Movement Disorders
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Guided Poster Tour 1
Atalaya Room, 24th Floor
Monday, June 14, 2010
14:00 – 15:30

Neuroimaging

581 Reduced dopamine transporter density in the ventral striatum of PD patients with impulse control disorders
R. Cilia, J.H. Ko, S.S. Cho, T. van Eimeren, G. Marotta, G. Pellecchia, G. Pezzoli, A. Antonini, A.P. Strafella (Toronto, Ontario, Canada)

609 Blinded analysis of conventional MR images in a cohort of pathologically confirmed parkinsonian illnesses at the QSBB
L.A. Massey, C.D. Micallef, D.C. Paviour, S.S. O'Sullivan, D.J. Burn, J.L. Holton, T.A. Revesz, A.J. Lees, N.C. Fox, H.R. Jager (London, United Kingdom)

616 Serotonin and fatigue in Parkinson's disease. An exploratory PET study
N. Pavese, V. Metta, S.K. Bose, K.R. Chaudhuri, D.J. Brooks (London, United Kingdom)

596 Olfactory impairment in early Parkinson's disease and white matter abnormalities in central olfactory areas. A voxel-based diffusion tensor imaging study
N. Ibarretxe-Bilbao, C. Junque, M.J. Marti, F. Valldeoriola, P. Vendrell, N. Bargallo, M. Zarei, E. Tolosa (Barcelona, Spain)

577 Hippocampal atrophy and ventricular enlargement in newly diagnosed Parkinson's disease; results from the Norwegian ParkWest study
M.K. Beyer, K. Hwang, S. Babakchanian, K.S. Bronnick, J.P. Larsen, O.B. Tysnes, J.L. Cummings, J.H. Morra, C.Y, L.G. Apostolova (Stavanger, Norway)

573 Magnetic susceptibility of substantia nigra in Parkinson's disease: A 7T *in vivo* MRI study
A. Lotfipour, S. Wharton, V. Gontu, S. Schwartz, A. Schafer, R. Bowtell, P. Gowland, D.P. Auer, N. Bajaj (Nottingham, United Kingdom)

576 Subthalamic-cortical resting state (fMRI-) functional connectivity is increased in early Parkinson's disease
S. Baudrexel, T. Witte, J.C. Klein, H. Steinmetz, R. Deichmann, R. Hilker (Frankfurt am Main, Germany)

593 How do the basal ganglia generate resting tremor in Parkinson's disease?
R.C. Helmich, M. Jansen, W.J. Oyen, I. Toni, B.R. Bloem (Nijmegen, Netherlands)

622 Microstructural white matter differences between dementia with Lewy bodies and Parkinson's disease with dementia
C. Sanchez-Castaneda, R. Rene, J. Campdelacreu, J. Gascon, M. Calopa, S. Jauma, M. Juncadella, C. Junque (Barcelona, Spain)

590 DTI and probabilistic tractography of the premotor to basal ganglia connections in healthy subjects and patients with Parkinson's disease
S. Groppa, T. Bustorf, C. Riedel, J. Volkmann, J. Herzog (Kiel, Germany)

Guided Poster Tour 2
Atalaya Room, 24th Floor
Monday, June 14, 2010
14:00 – 15:30

Parkinson's disease: Neuropharmacology

689 Long-term study on clinical benefits and quality-of-life of intraduodenal levodopa in routine care for a cohort of treatment-naïve patients with advanced Parkinson's disease
A. Johansson, N. Dizdar, T.B. Hauge, B. Holmberg, R. Jansson, J. Linder, H. Widner, S.E. Palhagen (Uppsala, Sweden)

696 Trehalose ameliorates dopaminergic and tau pathology in parkin deleted/tau overexpressing mice through autophagy activation
J.A. Rodriguez-Navarro, M.J. Casarejos, L. Rodriguez, A. Gomez, R.M. Solano, J. Perucho, A.M. Cuervo, J.G. Yebenes, M.A. Mena (Madrid, Spain)

707 In vivo evaluation of adenosine a_{2A} receptor availability in Parkinson's disease patients with and without levodopa induced dyskinesias studied with [^{11}C]SCH442416 PET
A.F. Ramlackhansingh, S.K. Bose, I. Ahmed, F.E.
Turkheimer, N. Pavese, D.J. Brooks (London, United Kingdom)

677 COMT Val(158)Met polymorphism determines entacapone efficacy on L-DOPA pharmacodynamics and pharmacokinetics in Parkinson's disease
J.-C. Corvol, C. Bonnet, F. Charbonnier-Beaupel, A.-M. Bonnet, E. Roze, A. Hartman, L. Lacomblez, J. Costentin, J.-S. Hulot, M. Vidailhet (Paris, France)

713 Transdermal nicotinotherapy: An ongoing study in patients with advanced Parkinson's disease
F. Grapin, G. Villafane, P. Cesaro, P. Maison, E. Itti (Creteil, France)

703 Adverse drug reactions to dopaminergic agonists: A study in the French pharmacovigilance database
S. Perez-Lloret, E. Bondon-Guitton, O. Rascol, J.-L.
Montastruc (Toulouse, France)

680 Safinamide reduces levodopa-induced dyskinesia in MPTP-lesioned primates while prolonging anti-parkinsonian efficacy
L. Gregoire, A. Roach, T. Di Paolo (Quebec, PQ, Canada)

690 **Can inhibition of fatty acid amide hydrolase (FAAH) provide a useful approach to reduce impulse control disorder and dopamine dysregulation syndrome in Parkinson's disease?**
T.H. Johnston, P. Huot, S.H. Fox, J. Wakefield, K. Sykes, W. Bartolini, G.T. Milne, J.P. Pearson, J.M. Brotchie (Toronto, Ontario, Canada)

687 **5-HT_{2A} receptor levels are increased in dyskinetic, MPTP-lesioned macaques**
P. Huot, T.H. Johnston, L. Winkelmolen, S.H. Fox, J.M. Brotchie (Toronto, Ontario, Canada)

682 **Mu-selective, but not non-selective, opioid receptor antagonism reduces L-DOPA induced dyskinesia in the MPTP macaque model of Parkinson's disease**
S.H. Fox, J.B. Koprich, T.H. Johnston, A. Goodman, B. Le Bourdonnec, R.E. Dolle, R.N. DeHaven, D.L. DeHaven, P.J. Little, J.M. Brotchie (Toronto, Ontario, Canada)

Guided Poster Tour 3
Atalaya Room, 24th Floor
Monday, June 14, 2010
14:00 – 15:30

Parkinson's disease: Behavioral disorders

283 **The relationship between mood and motor phenotype in Parkinson's disease (PD)**
D.J. Burn, S. Landau, J.V. Hindle, M. Samuel, K.C. Wilson, C.S. Hurt, R.G. Brown (Newcastle upon Tyne, Tyne and Wear, United Kingdom)

290 **Testing an aetiological model of visual hallucinations in Parkinson's disease**
D. Gallagher, A. Lees, A. Schrag (London, United Kingdom)

289 **Ophthalmic pathology and visual hallucinations (VH) in PD**
D. Gallagher, A. Spratt, A. Shah, F. Bremner, C. Davey, A. Lees, A. Schrag (London, United Kingdom)

304 **White matter lesions and depression in patients with Parkinson's disease**
I.N. Petrovic, N. Dragasevic, M. Svetel, V. Markovic, A. Tomic, M. Jecmenica-Lukic, T. Stojkovic, E. Stefanova, V.S. Kostic (Belgrade, Serbia, Serbia)

296 **Increased risk of developing depression for patients with Parkinson's disease (PD): A retrospective cohort study**
Y.-T. Hsu, Y.-W. Yang, C.-C. Liao, C.-Y. Hsu, C.-H. Tsai, F.-C. Sung (Taichung, Taiwan)

302 **'Walkabout': An unrecognized compulsive behavior in Parkinson's disease**
B. Pascual-Sedano, A. Gironell, C. Garcia-Sanchez, A. Campolongo, J. Pagonabarraga, J. Kulisevsky (Barcelona, Spain)

309 **Comparative neuropsychological profile of pathological gambling, hypersexuality and compulsive eating in Parkinson's disease**
G. Santangelo, C. Vitale, K. Longo, F. Verde, M. Rocco, A. Cozzolino, M. Picillo, M. Amboni, P. Barone (Naples, Italy)

312 **Behavioral, neuropsychiatric and cognitive disorders in parkinsonian patients with and without motor complications**
P. Solla, A. Cannas, C. Serra, L. Lavra, E. Costantino, F. Di Stefano, V. Piras, G. Floris, F. Marrosu, M.G. Marrosu (Monserrato, Cagliari, Italy)

292 **Frequency and type of impulse control disorders occurring in Parkinson's disease patients treated with dopamine agonists in a 2 year retrospective study**
A. Hassan, J.H. Bower, N. Kumar, J.Y. Matsumoto, R.D. Fealey, K.A. Josephs, J.E. Ahslkog (Rochester, Minnesota, USA)

Guided Poster Tour 4
Atalaya Room, 24th Floor
Monday, June 14, 2010
14:00 – 15:30

Tics/Stereotypies

1028 **Double-blind controlled randomized study of the use of levetiracetam to treat tics in children and adolescents with Tourette syndrome**
Y.M. Awaad, A.M. Michon, S. Minark, T. Rizk (Riyadh, Saudi Arabia)

1029 **Sensitivity to sensory stimuli is a common feature of Tourette syndrome, and is not a result of reduced detection threshold**
B.A. Belluscio, M. Hallett (Bethesda, Maryland, USA)

1033 **Cortical excitability in Tourette patients – differential effects of voluntary movements and median nerve stimulation**
S. Franzkowiak, B. Pollok, K. Biermann-Ruben, J. Paszek, G. Thomalla, A. Muenchau, A. Schnitzler (Duesseldorf, Germany)

1039 **Pitfalls in deep brain stimulation for treatment-refractory Tourette syndrome**
D. Servello, M. Sassi, S. Defendi, A. Brambilla, M. Porta (Milano, Italy)

1038 **Is it a tic? Twenty seconds to make a diagnosis**
J. Paszek, B. Pollok, K. Biermann-Ruben, K.R. Mueller-Vahl, V. Roessner, G. Thomalla, M.M. Robertson, M. Orth, A. Schnitzler, A. Muenchau (Duesseldorf, Germany)

1036 **Aripiprazole use in TS: A two year retrospective experience in 27 patients**
J.J. Juncos, G.J. Revuelta (Atlanta, Georgia, USA)

1030 Quantitative wearable monitoring of Tourette motor tics
M. Bernabei, E. Preatoni, M. Mendez, L. Piccini, M. Porta, M. Sassi, D. Servello, G. Andreoni (Milano, Italy)

1031 Dystonic tics in patients with primary tics disorders
J. Damasio, M.J. Edwards, A. Alonso, P. Scwingenschuh, K.P. Bhatia (London, United Kingdom)

1037 Major determinants of psychosocial and occupational disability in adult Tourette syndrome
D.G. Lichter, S.G. Finnegan (Buffalo, New York, USA)

1035 Stereotypies and repetitive motor behavior in patients with Alzheimer's disease who present spared vs. impaired executive functioning
E. Gleichgerrcht, A. Chade, M. Roca, T. Torralva, F. Manes (Capital Federal, Buenos Aires, Argentina)

Guided Poster Tour 5
Atalaya Room, 24th Floor
Tuesday, June 15, 2010
13:30 – 15:00

Basic Science

43 Comprehensive pathological analysis in MPTP-treated macaques reveal widespread synucleopathy and tauopathy
A. Vital, Q. Li, M.-H. Canron, P. Ravenscroft, M. Hill, E. Bezard (Bordeaux, France)

69 The PINK1/parkin-pathway links ubiquitin to damaged mitochondria for selective autophagy
S. Geisler, K.M. Holmström, D. Skujat, F.C. Fiesel, O.C. Rothfuss, P.J. Kahle, W. Springer (Tuebingen, Germany)

47 Reduced basal autophagy and impaired mitochondrial dynamics due to loss of Parkinson's disease-associated protein DJ-1
G. Krebiehl, S. Ruckerbauer, L.F. Burbulla, N. Kieper, B. Maurer, J. Waak, H. Wolburg, Z. Gizatullina, F.N. Gellerich, D. Woitalla, O. Riess, P.J. Kahle, T. Proikas-Cezanne, R. Krüger (Tubingen, Germany)

73 A new DBS clinical target for Parkinson's disease (PD) – mapping the caudal zona incerta (ZI)
M.G. Thomas, T. Chipungu, C. Watson, C.R.P. Lind (Perth, Western Australia, Australia)

56 Role of tau oligomers in Parkinson's disease and dementia with Lewy bodies
C.A. Lasagna-Reeves, B. Roi, M. Bakhoum, M.J. Guerrero-Munoz, D.L. Castillo-Caranza, R. Kayed, G.R. Jackson (Galveston, Texas, USA)

71 Proteasome inhibition in medaka brain induces the features of Parkinson's disease
R. Takahashi, H. Matsui, H. Itoh, Y. Taniguchi, H. Inoue, S.-I. Takeda (Kyoto, Japan)

46 Impaired mitochondrial stress response due to novel mutations in the mortalin/GRP75 gene in Parkinson's disease
L.F. Burbulla, C. Schelling, C. Schiesling, D. Ciceri, D. Woitalla, S. Jung, A. Nordheim, L. Schöls, O. Riess, R. Krüger (Tubingen, Germany)

50 Dopamine peroxidation in the pathogenesis of Parkinson's disease: New evidences in human cerebellum
A. De Iuliis, G. Arrigoni, P. Zambenedetti, G. Miotto, F. Vianello, P. Arslan (Padova, Italy)

51 CSF amyloid β 1-42 predicts cognitive decline in Parkinson's disease
A. Siderowf, S.X. Xie, H.I. Hurtig, D. Weintraub, J.E. Duda, A. Chen-Plotkin, L.M. Shaw, V. Van Deerlin, J.Q. Trojanowski, C.M. Clark (Philadelphia, Pennsylvania, USA)

45 Effects of inflammation on substantia nigra dopamine neurons
H.A. Boger, K.R.S. Reinert, A.-C. Granholm (Charleston, South Carolina, USA)

Guided Poster Tour 6
Atalaya Room, 24th Floor
Tuesday, June 15, 2010
13:30 – 15:00

Huntington's disease

257 Longitudinal analysis of intermediate CAGn repeat length expansion in the prospective Huntington's disease at-risk observational study (PHAROS)
K.M. Biglan, J. Jankovic, S. Eberly, E. Kayson, D. Oakes, A.B. Young, I. Shoulson, HSG PHAROS Investigators (Rochester, New York, USA)

255 Postural control in Huntington's disease – cross sectional results from the TRACK-HD study
N. Bechtel, R. Scahill, C. Jauffret, A. Sturrock, S. van den Bogaard, E. t'Haart, A. Patel, M.J. Say, J. Read, T. Acharya, D.R. Langbehn, H. Johnson, B. Leavitt, A. Durr, R.A.C. Roos, S.J. Tabrizi, R. Reilmann, the TRACK-HD Investigators (Muenster, Germany)

256 Evaluating methods to enrich clinical trial populations in individuals at-risk for Huntington's disease: The prospective Huntington's disease observational at-risk study (PHAROS)
K.M. Biglan, S. Eberly, D. Oakes, E. Kayson, J. Warner, A.B. Young, I. Shoulson, HSG PHAROS Investigators (Rochester, New York, USA)

270 Using the Mattis Dementia Rating Scale (DRS) to track cognitive change in Huntington's disease (HD)
S.L. Lessig, J.L. Goldstein, S. Edland, J. Corey-Bloom (La Jolla, California, USA)

272 **Therapeutic indications and prescription habits in Huntington's disease: Results from the REGISTRY observational study**
T.A. Mestre, M. Coelho, J.J. Ferreira, European Huntington Disease Network (EHDN) REGISTRY Study Group (Lisboa, Portugal)

264 **Sleep and sleepiness in Huntington's disease (HD): Effects on patient and caregiver quality of life**
R. Gupta, B. Ankush, L. Sue, S. Kathleen (Chicago, Illinois, USA)

265 **Pioglitazone ameliorates behavioral, biochemical and cellular alterations in quinolinic acid induced neurotoxicity: Possible role of peroxisome proliferator activated receptor-ϒ (PPARϒ) in Huntington's disease**
H. Kalonia, P. Kumar, A. Kumar (Chandigarh, India)

274 **Estimation of prevalence and molecular characteristics among Huntington's disease patients of Argentina**
E.M. Gatto, V. Parisi, G.G. Persi, J.L. Etcheverry, F. Leiguarda, A.P. López, V. Varela (Buenos Aires, Argentina)

259 **Cognition and brain metabolism of preclinical mutation carriers of huntington's disease: A follow-up study**
M. Dekker, J.C.H. van Oostrom, C.K. Jurgens, M.-N.W. Witjes-Ané, J.M. Spikman, R.A.C. Roos, K.L. Leenders (Groningen, Netherlands)

260 **Are gait and step initiation parameters early markers of Huntington's disease in presymptomatic mutation carriers?**
A. Delval, S. Bleuse, C. Simonin, M. Delliaux, B. Roland, L. Defebvre, K. Dujardin, P. Krystkowiak (lille, France)

Guided Poster Tour 7
Aguila Room, 24th Floor
Tuesday, June 15, 2010
13:30 – 15:00

Restless Legs Syndrome

1008 **Evidence for bilateral caudate nucleus involvement in PLMS: A case-study employing simultaneous EEG-EMG-fMRI**
N.M. Maurits, R.J. Renken, B.M. de Jong, J.H. van der Hoeven (Groningen, Netherlands)

1003 **Neurophysiological approach to the complex organization in spine: A study on F-wave duration and cutaneous silent period in patients with primary restless legs syndrome**
B. Isak, K. Uluc, C. Salcini, K. Agan, T. Tanridag, O. Us (Istanbul, Turkey)

989 **MEIS1 as a potential mediator of the RLS-iron pathology**
N. Silver, R.P. Allen, C.J. Earley (Baltimore, Maryland, USA)

998 **Impact of neuropsychiatric comorbidity on treatment success in restless legs syndrome**
J. Godau, N. Spinnler, A.-K. Wevers, C. Trenkwalder, D. Berg (Tuebingen, Germany)

990 **Evaluating a murine iron-deficiency (ID) model for RLS**
E.L. Unger, R.P. Allen, C.J. Earley (Baltimore, Maryland, USA)

1014 **Restless leg syndrome (RLS) by gender: The effects of hormones, life cycles and comorbidity in a female Sicilian cohort**
R. Silvestri, I. Aricò, R. Condurso, G. Mento (Messina, Messina, Italy)

1002 **Where is the core of the volcano? The undetermined origin of primary restless legs syndrome**
B. Isak, K. Agan, A. Pehlivan, K. Uluc, T. Tanridag, O. Us (Istanbul, Turkey)

1001 **Long-term safety and efficacy of rotigotine in patients with idiopathic RLS: 5-year results from a prospective multinational open-label follow-up study**
B. Hogl, C. Trenkwalder, D. Garcia-Borreguero, R. Kohnen, W. Poewe, K. Stiasny-Kolster, L. Bauer, A. Fichtner, E. Schollmayer, W. Oertel, for the SP710 Study Group (Innsbruck, Austria)

1017 **Is the restless legs syndrome (RLS) mediated by inflammatory and immunological mechanisms? RLS is associated with an increased prevalence of small intestinal bacterial overgrowth**
A.S. Walters, L.B. Weinstock (Nashville, Tennessee, USA)

994 **Neuroanatomical aspect of the dopaminergic diencephalospinal pathway in the non human primate: Potential implications for restless legs syndrome**
Q. Barraud, I. Obeid, I. Aubert, H. Contamin, W. Mazier, G. Barriere, F. Tison, E. Bezard, I. Ghorayeb (Bordeaux, France)

Guided Poster Tour 8
Aguila Room, 24th Floor
Tuesday, June 15, 2010
13:30 – 15:00

Neuropharmacology

650 **Synergistic anti-dyskinetic effect of topiramate and amantadine in the MPTP-lesioned non-human primate model of Parkinson's disease**
C. Kobylecki, A.R. Crossman, R. Paula (Manchester, Lancashire, United Kingdom)

645 **Reconstitution dilution volumes and botulinum toxin type A doses used to treat pediatric cerebral palsy in five EU countries**
S. Hall, J. Schwab, J. Mendoza, B. Zakine, C. Hubert (Brisbane, California, USA)

651 **Neuroprotection of pramipexole in UPS impairment induced animal model of Parkinson's disease**
C. Li, W. Xie, J. Jankovic, W. Le (Houston, Texas, China)

644 **The tolerability of rasagiline when used concurrently with serotonin reuptake inhibitors in Parkinson's disease: A retrospective analysis**
P. Ghosh, J. Winslow, C. Musleh, C. Gandhy, L. Bahroo, F. Pagan (Washington, District of Columbia, USA)

653 **Pardoprunox: Effects on motor and non-motor symptoms of Parkinson's disease**
A.C. McCreary, M. Jackson, C. Ashby, Jr, S. Rose, P. Jenner (Weesp, Netherlands)

649 **MAO-B inhibitors and dopamine agonists as initial treatment in Parkinson's disease: A naturalistic survey**
T. Keränen, T. Mattila, H. Kuusisto (Kuopio, Finland)

Guided Poster Tour 9
Atalaya Room, 24th Floor
Wednesday, June 16, 2010
13:30 – 15:00

Dystonia

195 **Identifying genetic risk factors of musician's dystonia**
A. Schmidt, K. Lohmann, C. Hemmelmann, H.-C. Jabusch, S. Winkler, S. Schreiber, E. Altenmueller, A. Ziegler, C. Klein (Luebeck, Germany)

194 **The syndrome of childhood-onset arm tremor followed by later development of cervical dystonia is a distinct dystonia subtype**
S. Schiebler, A. Schmidt, S. Zittel, T. Baeumer, C. Gerloff, C. Klein, A. Muenchau (Hamburg, Germany)

197 **Modulatory effects of 5Hz rTMS over the primary somatosensory cortex in focal dystonia – an fMRI-TMS study**
S.A. Schneider, B. Pleger, B. Draganski, C. Cordivari, J.C. Rothwell, K.P. Bhatia, R. Dolan (Luebeck, Germany)

182 **Linking DYT1 and DYT6 dystonia on the molecular level: Repression of *DYT1* gene expression by the transcription factor activity of THAP1 (DYT6)**
A. Osmanovic, S. Orolicki, D. Braunholz, A. Rakovic, T. Lohnau, M. Albrecht, G. Gillessen-Kaesbach, K. Lohmann, C. Klein, F.J. Kaiser (Luebeck, Germany)

198 **The blink reflex recovery cycle distinguishes patients with benign essential blepharospasm from patients with presumed psychogenic blepharospasm**
P. Schwingenschuh, P. Katschnig, J.T. Teo, M.J. Edwards, J.C. Rothwell, K.P. Bhatia (London/Graz, United Kingdom)

131 **Juvenile onset dystonia-parkinsonism associated with cerebral folate deficiency**
E. Baratelli, M. Edwards, M. Carecchio, P.R. Jarman, S.J.R. Heales, K.P. Bhatia (london, United Kingdom)

151 **DYT6 dystonia phenotype and the effect of deep brain stimulation**
J.L. Groen, K. Ritz, F.M. Contarino, B.P. van de Warrenburg, J.J. van Hilten, M. Aramideh, E.M. Foncke, R. Schuurman, J.D. Speelman, R.M.A. de Bie, F. Baas, M.A.J. Tijssen (Amsterdam, Netherlands)

184 **The D216H (rs1801968) polymorphism in the DYT1 gene: A potential susceptibility factor for familial dystonia in Argentinean cases**
C. Perandones, M. Irisarri, M. Caputo, M.T. Gomez, L.A. Pellene, C.Z. Salazar, F.E. Micheli, D. Corach (Ciudad Autonoma de Buenos Aires, Argentina)

146 **Secondary non response (SNR) to botulinum toxins type A (BoNT-A) in cervical dystonia (CD) patients: Definition and therapeutic strategies results from an international survey**
J.J. Ferreira, R. Bhidayasiri, C. Colosimo, M.J. Marti, B. Zakine, P. Maisonobe (Lisboa, Portugal)

185 **Prevalence of focal task-specific dystonia among professional musicians in a community-based study from Argentina**
E.M. Gatto, A. Chade, G. Persi, V. Parisi, A. Ayarza, M. Campuzano, S. García (Buenos Aires, Argentina)

Guided Poster Tour 10
Atalaya Room, 24th Floor
Wednesday, June 16, 2010
13:30 – 15:00

Genetics

856 **Parkinsonian features and motor network plasticity in LRRK2 patients and asymptomatic mutations carriers in comparison to sporadic PD and healthy controls**
K. Brockmann, A. Groeger, A. Di Santo, C. Schulte, A.-K. Hauser, D. Berg, T. Gasser (Tuebingen, Germany)

886 **Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease**
W. Satake, Y. Nakabayashi, I. Mizuta, M. Watanabe, A. Takeda, H. Tomiyama, K. Nakashima, K. Hasegawa, F. Obata, H. Kawakami, S. Sakoda, M. Yamamoto, N. Hattori, M. Murata, Y. Nakamura, T. Toda (Kobe, Japan)

871 **Genetic control of DNA methylation and expression in the context of neurological disease**
D.G. Hernandez, R. Gibbs, M.A. Nalls, S. Arepalli, M. Van der Brug, B. Traynor, S.B. Andrew (Bethesda, Maryland, USA)

894 **^{123}I-MIBG cardiac uptake and smell identification in patients with LRRK2 mutations**
F. Valldeoriola, C. Gaig, A. Muxi, I. Navales, P. Paredes, F. Lomeña, A. De la Cerda, M. Ezquerra, P. Santacruz, M.J. Marti, E. Tolosa (Barcelona, Catalonia, Spain)

890 **Studies of alpha-synuclein in brain samples from patients with Lewy body disorders carrying glucocerebrosidase mutations**
O. Goker-Alpan, J.H. Choi, B.K. Stubblefield, M. Cookson, G. Lopez, E. Sidransky (Bethesda, Maryland, USA)

863 **Genome-wide analysis and accuracy of self-reported data: The 23andMe Parkinson's disease project**
N. Eriksson, C. Do, A. Kiefer, J.M. Macpherson, K. Marton, J. Tung, L.S. Hon, B. Naughton, S. Saxonov, A. Wojcicki, J. Mountain (Mountain View, California, USA)

868 **Clinical manifestation of patients with Parkinson's disease carriers of "severe" mutations in the GBA gene**
E. Rozenberg, A. Mirelman, S. Levy, M. Kedmi, A. Orr-Urtreger, N. Giladi, T. Gurevich (Tel Aviv, Israel)

888 **Mutational screening of the coding regions of MEIS1 and BTBD9 in patients with restless legs syndrome**
E.C. Schulte, F. Knauf, P. Lichtner, T. Meitinger, J. Winkelmann (Munich, Germany)

893 **A new family with apparently dominant inheritance of PARK2**
F. Tison, N. Damon-Perriere, C. Cazeneuve, S. Lesage, P. Fernandez, A. Brice, W. Meissner (Pessac, France)

901 **The phenotypic spectrum of neurodegeneration associated to PLA2G6 mutations**
G. Zorzi, A. Giovannetti, F. Zibordi, V. Saletti, M. Sessa, S. Orcesi, M. Morbin, L. Chiapparini, B. Garavaglia, N. Nardocci (Milano, Italy)

Guided Poster Tour 11
Aguila Room, 24th Floor
Wednesday, June 16, 2010
13:30 – 15:00

Gene Therapies and Cell-based Therapies

249 **A phase I clinical trial on the safety and efficacy of ProSavin® a dopamine replacement gene therapy for Parkinson's disease (PD): An interim report**
B. Jarraya, H. Lepetit, S. Ralph, J. Miskin, J.-M. Gurruchaga, M. Vinti, G. Fenelon, P. Brugieres, K. Abhay, I. Gabriel, S. Boulet, C. Jan, S. Kingsman, P. Cesaro, P. Hantraye, P. Remy, K. Mitrophanous, S. Palfi (Paris, Creteil, France)

247 **Evidence of motor recovery after retinal pigment epithelial (RPE) cells implantation in the rat model of Parkinson's disease (PD)**
H. Gambhir, S. Vivekanandhan, V. Goyal, R. Mathur, M. Behari (New Delhi, Delhi, India)

248 **Investigation of optimal transduction targets in the nigrostriatal system for pleiotrophin gene therapy in a parkinsonian rodent model**
S.E. Gombash, T.J. Collier, B.F. Daley, S.L. Wohlgenant, N.D. Levine, B.T. Terpstra, R.J. Mandel, F.P. Manfredsson, C.E. Sortwell (Cincinnati, Ohio, USA)

253 **Restore neurotrophin signaling to enhance functional restoration following neural stem cell transplantation in Parkinson's disease**
K. Seth, A. Shukla, R.W. Ansari, R.K. Chaturvedi, A.K. Agrawal (Lucknow, UP, India)

251 **Therapeutic microinjection of autologous adult human neural stem cells and differentiated neurons for Parkinson's disease: Five-year post-operative outcome**
M.F. Levesque, T. Neuman, M. Rezak (Los Angeles, California, USA)

245 **Transgenic porcine xenografts: A model of brain immune response in parkinsonian primates**
R. Aron Badin, A. Padoan, M. Vadori, M. Boldrin, L. Chavicchioli, G.M. De Benedictis, F. Fante, M. Seveso, D. Sgarabotto, C. Jan, V. Daguin, P. Naveilhan, I. Neveu, J.P. Soulillou, B. Vanhove, M. Plat, F. Botte, F. Venturi, L. Denaro, R. Manara, P. Zampieri, D. D'Avella, D. Rubello, E. Ancona, P. Hantraye, C. Emanuele (Fontenay-aux-Roses, France)

246 **Derivation of dopaminergic neurons from human embryonic stem cells and IPS cells in animal-free conditions ready to use them in a treatment of Parkinson's disease**
S. Erceg, J. Kostic, V. Moreno-Manzano, M.A. Perez Arago, L.G. Maria, M. Ronaghi, P. Stojkovic, M. Stojkovic (Valencia, Spain)

250 **Enriching the environment for haematopoietic stem cell transplantation in MPTP-treated primates**
L.P. Kelly, M.B. Newman, R.A.E. Bakay (Chicago, Illinois, USA)

252 **Grafted serotonin neurons aggravate L-DOPA induced dyskinesia: In vivo evidence by microdialysis and [18F]fallypride PET imaging**
G. Sahin, S. Lavisse, L. Rbah, T. Bjorklund, M. Carta, L. Thompson, P. Hantraye, D. Kirik (Lund, Sweden)

254 **Vascular endothelial growth factor-B186 improves motor behavior in vivo in a rat model of Parkinson's disease**
X. Yue, T. Falk, S. Zhang, S.J. Sherman (Tucson, Arizona, USA)

Guided Poster Tour 12
Aguila Room, 24th Floor
Wednesday, June 16, 2010
13:30 – 15:00

Lewy Body Dementia and other dementias in movement disorders

911 **Extrapyramidal symptoms in frontotemporal dementia**
A.R. Chade, M. Roca, E. Gleichgerrcht, T. Torralva, F. Manes (Capital Federal, Buenos Aires, Argentina)

915 **Probable dementia Lewy body type is rare among Parkinson's disease patients**
J.M. Rabey, E. Dobronevsky, A. Miniovitz, T. Prokhorov (Zerifin, Israel)

917 **Parkinsonian features and apraxia in frontotemporal lobar atrophy behavioural variant (FTLA bv)**
S. Schmidegg, W. Struhal, S. Hoedl, C. Dorninger, M. Steffelbauer, M. Ortmayr, G. Ransmayr (Linz, Austria)

912 **Depression in dementia with Lewy bodies and Parkinson's disease dementia**
F. Fritze, U. Ehrt, D. Aarsland (Stavanger, Rogaland, Norway)

913 **Lack of beta-synuclein expression defines a specific group of dementia with Lewy bodies**
K. Beyer, M. Domingo-Sabat, L. Ispierto, C. Carrato, R. Alvarez, P. Latorre (Badalona, Spain)

916 **The SNCA locus in dementia with Lewy bodies**
A. Sailer, M. Kurzawa, P.F. Chinnery, I.G. McKeith, C.M. Morris, H. Houlden (London, United Kingdom)

Guided Poster Tour 13
Atalaya Room, 24th Floor
Thursday, June 17, 2010
13:30 – 15:00

Parkinson's disease: Clinical trials

376 **Pardoprunox in early stage Parkinson's disease: Results from two large studies**
C. Sampaio, J.B. Bronzova, R.A. Hauser, A. Lang, O. Rascol, S.V. van de Witte, A. Theeuwes (Lisboa, Portugal)

327 **A multi-center, placebo-controlled, double-blind trial to examine the safety and efficacy of pimavanserin in the treatment of psychosis in Parkinson's disease**
J.H. Friedman, B. Ravina, R. Mills, H. Williams, D. Bahr, P. Peters, F. Tison, D. Burn (Newcastle upon Tyne, United Kingdom)

359 **Safinamide as add-on to levodopa improves motor function without worsening dyskinesia in patients with mid-late Parkinson's disease**
C.M. Meshram, M. Bhatt, D. Chirileanu, P. Stanzione, V. Lucini, S.M. Rossetti, R. Anand, the Study 016 Investigators (Nagpur, India)

342 **Eighteen months of intervention with exercise improve functional mobility with maintenance of mental state in people with Parkinson's disease**
L.T.B. Gobbi, S. Gobbi, C. Teixeira-Arroyo, N.M. Rinaldi, F.A. Barbieri, E. Lirani-Silva, R.A. Batistela, M.P. Pereira, F. Stella (Rio Claro, Sao Paulo, Brazil)

351 **Fipamezole in the treatment of dyskinesia in advanced Parkinson's disease (FJORD study)**
P.A. LeWitt, R.A. Hauser, M. Lu, A.P. Nicholas, W. Weiner, N. Coppard, M. Leinonen, J.M. Savola (Southfield, Michigan, USA)

349 **The impact of left prefrontal repetitive transcranial magnetic stimulation on depression with Parkinson's disease: A randomized, controlled, double-blinded, single center study**
N. Kovacs, F. Nagy, Z. Aschermann, E. Balazs, E. Pal (Pecs, Hungary)

364 **Efficacy and safety of rotigotine transdermal application in levodopa-treated patients with Parkinson's disease (PD)**
M. Nomoto, T. Kondo, K. Hasegawa, M. Murata, N. Hattori, Y. Mizuno, Rotigotine Study Group (Tohon, Ehime, Japan)

367 **Safety and tolerability profile of the adenosine A_{2A} receptor antagonist BIIB014 in Parkinson's disease: Pooled analysis of two placebo-controlled 8-week studies**
S. Papapetropoulos, R. Borgohain, M. Kellet, N. Giladi, D. Tomic, A. Coppell, Y. Zhu, J. Barnard, L. Miller, G.N. O'Neill (Cambridge, Massachusetts, USA)

320 **Controlled study of intermittent theta-burst transcranial magnetic stimulation for the treatment of Parkinson's disease**
D. Benninger, B. Berman, E. Houdayer, N. Pal, D. Luckenbaugh, L. Schneider, S. Miranda, M. Hallett (Bethesda, Maryland, USA)

379 **Sustained efficacy and tolerability of pramipexole extended-release as adjunctive treatment in advanced Parkinson's disease**
A.H.V. Schapira, P. Barone, R.A. Hauser, Y. Mizuno, O. Rascol, M. Busse, L. Salin, M. Sohr, W. Poewe, in the name of the Pramipexole ER Studies Group (London, United Kingdom)

Guided Poster Tour 14
Atalaya Room, 24th Floor
Thursday, June 17, 2010
13:30 – 15:00

Parkinson's disease: Sleep Disorders

756 **Cyclic alternating pattern (CAP) in *de novo* Parkinson's disease**
R. Margis, R. Ferri, S.V. Schonwald, G.J.L. Gerhardt, C.R.M. Rieder (Porto Alegre, RS, Brazil)

759 **Effect of rotigotine on sleep and nocturnal symptoms in Parkinson's disease: RECOVER study**
C. Trenkwalder, B. Kies, M. Rudzinska, J. Fine, J. Nikl, D.L. Hill, T. Anderson, E. Surmann, J. Whitesides, B. Boroojerdi, K.R. Chaudhuri, on Behalf of the RECOVER Study Group (Kassel, Germany)

750 **Hallucinations and sleep disorders in Parkinson's disease: Ten year prospective longitudinal study**
C.G. Goetz, B. Ouyang, A. Negron, G.T. Stebbins (Chicago, Illinois, USA)

757 **Sleep-related falling out of bed (SFOB) in Parkinson's disease: A clinical marker of RBD?**
D.M. Wallace, D.Z. Carvalho, H. Moore, A. Pandey, F. Nahab, C. Singer (Miami, Florida, USA)

751 **A study of sleep problems in a community-dwelling cohort of people with PD**
R.W. Walker, A.R. Howells, I.L. Cookey, W.K. Gray (North Shields, Tyne and Wear, United Kingdom)

752 **Nighttime sleep and daytime sleepiness in idiopathic and genetic Parkinson's disease**
M. Kasten, V. Tadic, N. Brueggemann, A. Schmidt, L. Kertelge, C. Wisse, L. Drude, K. Lohmann, J. Hagenah, C. Klein (Luebeck, Germany)

755 **Does idiopathic restless legs syndrome protect against Parkinson's disease**
D.M. Elizabeth, W.G. Ondo (Houston, Texas, USA)

761 **Parkinson's disease patients: "Owls" or "larks"**
A. Videnovic, C. Noble, A. Marconi, T. Kuhta, C. Zadikoff, T. Simuni, P. Zee (Chicago, Illinois, USA)

753 **The impact of depression on sleep quality and excessive daytime sleepiness in Parkinson's disease patients**
N. Klepac, M. Titlic, D. Britvic, I. Lusic, L. Unusic (Zagreb, Croatia)

749 **Excessive daytime sleepiness in the MPTP non human primate model of Parkinson's disease**
Q. Barraud, V. Lambrecq, S. McGuire, M. Hill, F. Tison, E. Bezard, I. Ghorayeb (Bordeaux, France)

Guided Poster Tour 15
Aguila Room, 24th Floor
Thursday, June 17, 2010
13:30 – 15:00

Surgical Therapy: Parkinson's disease

766 **Quality of life after DBS STN in Parkinson's disease is related to the stimulation amplitude**
M. Baláz, M. Bocková, I. Rektor (Brno, Czech Republic)

814 **Effect of globus pallidus internus and/or pedunculopontine nucleus DBS on posture and gait ignition in advanced Parkinson's disease**
C. Schrader, H. Capelle, D. Dressler, A. Windhagen, J.K. Kraus, F. Seehaus (Hannover, Germany)

774 **Effects of pedunculopontine nucleus area stimulation on speech production in Parkinson's disease**
S. Pinto, A. Maillet, A. Ghio, M. Ferraye, V. Fraix, R. Espesser, S. Chabardès, E. Seigneuret, A.L. Benabid, B. Debû, P. Pollak (Grenoble, France)

807 **Factors related to extended hospital stays following deep brain stimulation for Parkinson's disease**
A. Mikos, J. Pavon, D. Bowers, K.D. Foote, A.S. Resnick, H.H. Fernandez, P. Thomas, C. Garvan, A. Roy, M.S. Okun (Gainesville, Florida, USA)

816 **Role of mesocorticolimbic dopaminergic denervation in postoperative apathy and depression in Parkinson's disease**
S. Thobois, E. Lhommee, H. Klinger, C. Ardouin, J. Xie, V. Fraix, C. Lagrange, E. Seigneuret, P. Mertens, S. Chabardes, G. Polo, D. Le Bars, P. Pollak, E. Broussolle, P. Krack (Lyon, France)

808 **Effect of subthalamic deep brain stimulation on acceleration of the swing phase of gait in Parkinson's disease**
F.J. Revilla, A. Duker, H.A. Miranda, M. Matthew, G. Mandybur, A. Espay, C. Cox, A. Bhattacharya (Cincinnati, Ohio, USA)

791 **Effects of chronic STN-DBS on the levodopa response: *Evidence for gain of long duration response***
C.S. Lee, S.-J. Chung, M.-J. Kim, S.-Y. You, S.-R. Kim, S.-Y. Chun (Seoul, Republic of Korea)

822 **Postoperative verbal fluency decline after subthalamic deep brain stimulation surgery correlates with laterality of the microlesion. Results of a prospective longitudinal study**
L. Wojtecki, L. Timmermamn, U. Habel, C. Reck, M. Suedmeyer, V. Sturm, F. Schneider, A. Schnitzler (Duesseldorf, Germany)

770 **Active contact location and acute mood response to STN DBS stimulation in Parkinson's disease**
M.C. Campbell, P.M. Weaver, H.M. Lugar, T.O. Videen, K.J. Black, J.S. Perlmutter, T. Hershey (St. Louis, Missouri, USA)

827 **Comparison of bilateral subthalamic deep brain stimulation (STN-DBS) and duodenal levodopa infusion (DLI) in advanced Parkinson's disease (PD) patients**
M. Zibetti, A. Cinquepalmi, S. Angrisano, C. Azzaro, L. Rizzi, M. Lanotte, L. Lopiano (Torino, Italy)

Guided Poster Tour 16
Aguila Room, 24th Floor
Thursday, June 17, 2010
13:30 – 15:00

Surgical Therapy: Other Movement Disorders

845 **Long term continuous deep brain stimulation to the internal globus pallidus in DYT1-gene positive dystonia induces lasting neural reorganization in the motor system**
D. Ruge, L. Cif, P. Limousin, V. Gonzalez, M.I. Hariz, P. Coubes, J.C. Rothwell (London, United Kingdom)

842 **Long-term clinical outcome in Meige syndrome treated with posteroventral lateral internal pallidum deep brain stimulation (GPi-DBS)**
R. Reese, D. Gruber, H. Bäzner, C. Blahak, H.-H. Capelle, D. Falk, J. Herzog, M.O. Pinsker, G.-H. Schneider,

C. Schrader, G. Deuschl, H.M. Mehdorn, A. Kupsch, J. Volkmann, J.K. Krauss (Kiel, Germany)

847 Pallidal deep brain stimulation may induce freezing of gait in patients with focal and segmental dystonia
C. Schrader, H. Capelle, T. Kinfe, C. Blahak, H. Baezner, D. Dressler, J.K. Krauss (Hannover, Germany)

828 Deep brain stimulation for segmental dystonia: Long-term (6-year) follow-up
C. Blahak, H.-H. Capelle, H. Baezner, T. Kinfe, M.G. Hennerici, J.K. Krauss (Mannheim, Germany)

829 Deep brain stimulation for camptocormia in dystonia and Parkinson's disease
H.-H. Capelle, C. Schrader, C. Blahak, T.M. Kinfe, W. Fogel, H. Baezner, J.K. Krauss (Hannover, Germany)

836 Two year experience with DBS for pediatric onset dystonias: Generator selection
W.A. Marks, J. Honeycutt, F. Acosta, Jr, M.A. Reed (Fort Worth, Texas, USA)

838 Rescue DBS leads: Tailoring deep brain stimulation (DBS) when clinical symptoms do not respond as anticipated
G. Oyama, K.D. Foote, N. Hwynn, C.E. Jacobson, P. Zeilman, J. Romrell, I.A. Malaty, H.H. Fernandez, R.L. Rodriguez, M.S. Okun (Gainesville, Florida, USA)

832 Steady or not following thalamic deep brain stimulation for essential tremor
N. Hwynn, C. Hass, P. Zeilman, J. Romrell, Y. Dai, S.S. Wu, K.D. Foote, S.H. Subramony, G. Oyama, F. Velez-Lago, H.H. Fernandez, A. Resnick, R.L. Rodriguez, I. Malaty, M.S. Okun (Gainesville, Florida, USA)

834 Generalized dystonia treated with bilateral pallidotomy and bilateral subthalamic deep brain stimulation
T. Mandat, H. Koziara, W. Bonicki, P. Nauman (Warszawa, Poland)

835 Comparison of merged CT analysis and direct MRI visualization of GPi lead placement for deep brain stimulation
W.A. Marks, J. Honeycutt, J. Paugh, R. Shivers, F. Acosta, Jr (Fort Worth, Texas, USA)

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POSTER SESSION 1

MONDAY, JUNE 14, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 14:00-15:30

ATAXIA

1

Clinical features and molecular genetics of autosomal dominant cerebellar ataxias in ethnic Bengalees

K.B. Bhattacharyya, R. Singh, S. Basu, A. Mishra, M. Seshadri (Kolkata, West Bengal, India)

Objective: The phenotype and genotype of Autosomal Dominant Cerebellar Ataxias (ADCA) vary with ethnicity. This work was undertaken to study the clinical features and molecular genetics of ADCAs in ethnic Bengalees in Eastern India.

Background: Though SCA2 has been reported as the commonest variety in India, the previous works did not take into account the question of ethnicity in their studies. The present study aims at looking into the frequency of the different varieties SCAs, specifically in the ethnic Bengalee population.

Methods: 14 Bengalee individuals, belonging to 14 families and 28 members in their families and 6 sporadic cases (Total 48) were examined clinically and a tentative diagnosis of ADCA was made. Neuroradiological and neuroelectrophysiological studies were performed in all the probands and in some selected members of the families. The genetic study was aimed at detection of trinucleotide repeat expansions of CAG/CTG and a control group of 80 randomly selected asymptomatic Bengalees. PCR application was performed for SCA1, SCA2, SCA3, SCA 6, SCA7, SCA8, SCA12 and SCA17.

Results: Genotype analysis identified SCA1 in 2, SCA2 in 2 and SCA3 in 5 patients among the 14 probands, while others were unclassified. Among the 28 family members, SCA1 was identified in 5, SCA2 in 5 and SCA3 in 9 subjects. Among the sporadic cases, SCA2 was identified in 2 and SCA3 in further 2 cases. One asymptomatic relative showed expansion for SCA3. There was significant inter- and intrafamilial heterogeneity in phenotypic expression of SCA3 cases and in one family, the same number of repeats was observed in two subjects, where they differed vastly in terms of the clinical severity and age of onset of the disease.

Conclusions: Our work suggests that in the ethnic Bengalee population, SCA3 outnumbers other varieties and therefore, this study is at variance with the generally accepted view that SCA2 is the commonest variety of ADCAs in India. It is also in agreement with another work performed on the same ethnic group.

2

Ataxia-telangiectasia: Mild and slowly progressive clinical presentation associated with two null *ATM* alleles

S. Chaal, A.M. Taylor, P.F. Worth (Norwich, Norfolk, United Kingdom)

Objective: To report a patient with complete loss of ATM function but a mild clinical phenotype.

Background: Ataxia Telangiectasia (AT) is an autosomal recessive disorder, characterized by oculocutaneous telangiectasia, progressive cerebellar ataxia, immunodeficiency, susceptibility to malignancy, and increased sensitivity to ionizing radiation. Classic forms of AT result from *ATM* mutations leading to complete loss of ATM function, while milder variant forms are associated with residual ATM activity in most cases.

Methods: Case report.

Results: We report a 40-year-old woman with a 30 year history of mild involuntary movements, who recently developed dysarthria and clumsiness. There is no history of recurrent infection, malignancy, infertility or signs of telangiectasia. She has generalized chorea, cerebellar signs, and upper limb dystonia. Abnormal tests: MRI showed cerebellar atrophy, raised alpha fetoprotein, increased chromosomal sensitivity to ionizing radiation, and complete absence of ATM activity. Consistent with this, genetic analysis showed compound heterozygosity for two known null mutations in *ATM*. The patient had an older brother with a history of involuntary limb movements from an early age with mild cervical dystonia developing in his early 40s. He died aged 49 from proven metastatic lung adenocarcinoma. DNA was not available.

Conclusions: Two null *ATM* alleles and resulting proven complete absence of ATM activity *in vitro* would predict a severe classic clinical form of AT. However, our patient's phenotype is restricted to early onset mild chorea, with a slowly progressive mild neurological phenotype emerging very much later in the 4th decade. Moreover, she has no other typical systemic features of AT. To our knowledge, this is the mildest clinical phenotype described in a patient with two null *ATM* mutations. Notwithstanding one previous report of 2 siblings with two null *ATM* mutations and a mild neurological presentation, both of these individuals had developed other significant neurological signs in their teens unlike this patient. This case broadens the clinical spectrum of AT and emphasises that ATM activity alone does not reliably predict clinical phenotype. Identifying presumed genetic or epigenetic modifiers in this patient may elucidate the pathophysiology of neuronal death/dysfunction in AT which remains poorly defined.

3

Diffusion tensor imaging (DTI) tractography in autosomal recessive cerebellar ataxias (ARCA)

M. Christophe, L.-B. Ouhaïd, A. Mathieu, K. Stephane, T. Christine (Strasbourg, France)

Objective: To use DTI tractography to study superior cerebellar peduncles (SCP), medial cerebellar peduncles (MCP), inferior cerebellar peduncles, and pyramidal tracts in patients suffering from distinct ARCAs.

Background: Classical brain MRI shows aspecific cerebellar atrophy in patients suffering from ARCAs, and cannot help distinguishing between the different causes of ARCA. Futhermore, some clinical data, found only in specific ARCA, has not yet been correlated with anatomical lesions. DTI tractography could be a way to do such correlations.

Methods: Twelve patients (3 ataxias with oculomotor apraxia type 1 (AOA1), 3 AOA 2, 3 Friedreich's diseases, 2 Autosomic Recessive Spastic Ataxia of Charlevoix Saguenay (ARSACS), 1 Ataxia with inherited vitamin E deficiency (AVED)) and 12 healthy subjects, underwent a 1.5 T brain MRI with diffusion echo planar spin echo sequences in 30 non colinear directions and acquisitions at b=o and b= 1000m.s^{-2}. Post treatment using the streamline method was held by defining 2 ROI perpendicular to the 4 studied tracts to achieve DTI tractography. The morphology and the mean Fractional anisotropy (FA) and apparent Diffusion coefficient (ADC) for each tract were evaluated.

Results: Increased ADC and decreased FA were observed in SCP, ICP and pyramidal tracts in all ACAR patients compared to control subjects. A specific morphological aspect was found only in ARSAC patients who showed a MCP hypertrophy contrasting with a thin pyramidal tract.

Conclusions: A decrease of FA in ICP and pyramidal tracts, found previously in Friedreich's disease, is not specific of this disease. DTI tractography revealed a specific aspect only in ARSACS, but complementary studies in greater groups of patients are necessary to improve this results.

4

Friedreich ataxia: Cognition and saccadic eye movement

J. Fielding, L.A. Corben, P.D. Cremer, L. Millist, D. Hocking, O.B. White, M.B. Delatycki (Notting Hill, Victoria, Australia)

Objective: To evaluate the higher-order or cognitive control processes involved in the generation of volitional saccadic eye movements in Friedreich ataxia.

Background: Friedreich ataxia (FRDA) is a multi-system neurodegenerative condition with characteristic ocular motor abnormalities including increased saccadic latencies, fixation instability, and impaired vestibulo-ocular reflexes.These are largely consistent with disruption to cerebellar circuitry. However, the cerebellum is becoming increasingly viewed as instrumental in the cognitive control of behaviour, its primary influence thought to involve cerebro-ponto-cerebello-thalamo-cerebral connections. It is therefore likely that the higher-order or cognitive control processes involved in the generation of more volitional eye movements are also compromised. This has not been previously investigated.

Methods: Using the scleral search coil technique, we evaluated a range of saccadic behaviours in 13 individuals homozygous for a GAA expansion within intron 1 of the FXN gene, contrasting performance with 13 age-matched neurologically healthy individuals.

Results: A broad range of deficits were revealed for FRDA individuals, beyond, and compounding the latency deficits previously identified. These deficits included attentional impairments, inhibitory dysfunction, increased saccadic latencies, altered velocity and gain profiles, and alterations to the main sequence of movement. Correlations between a number of ocular motor and clinical measures were also revealed.

Conclusions: Lateral aspects of the cerebellar hemispheres and the ventral portions of the dentate nucleus project to prefrontal and posterior parietal areas of cortex, regions crucial for more volitional saccadic behaviours. It is likely that deficits revealed here may be due to interruption in critical neural circuitry arising from these areas in FDRA. Correlations revealed between ocular motor measures, and performance on the Friedreich Ataxia Rating Scale as well as disease duration, suggest that these measures may be valuable biomarkers in FDRA, for use in monitoring disease progression or in clinical trials.

5

Clinical spectrum and neurophysiology in a German family with a novel SCA-14 mutation

C. Ganos, S. Zittel, C. Zühlke, V. Bernard, T. Bäumer, A. Münchau
(Hamburg, Germany)

Objective: To describe the clinical phenotype and neurophysiological findings in a German family with spinocerebellar ataxia type 14 (SCA-14).

Background: Families with SCA-14 have been reported harboring more than 23 different mutations of the Protein Kinase C γ gene (PRKGC). Typically, SCA-14 presents with early onset slowly progressive cerebellar ataxia.

Methods: Three SCA-14 mutation carriers (69 year old woman, her 46 year old son and her 43 year old daughter) were examined clinically and scored using the International Cooperative Ataxia Rating Scale (ICARS). Visual, auditory and somatosensory evoked potentials (VEP, AEP, Median- and Tibial-SSEP) were measured in all patients. Transcranial magnetic stimulation (TMS) protocols were performed in the son and daughter.

Results: A novel PRKCG mutation was found in the index patient and her two children. At protein level the 3 bp deletion results in loss of phenylalanine at position 48. All patients had childhood onset gait ataxia. Cerebellar dysfunction including gait ataxia, saccadic dysmetria and dysarthria was severe in the index patient (ICARS 58). She also had mild cervical dystonia (CD) and intermittent axial myoclonus. In addition to ataxia, the son (ICARS 35) also had mild CD and writer's cramp and the daughter (ICARS 28) mild CD and axial myoclonus. Evoked potentials were normal apart from prolonged central conduction time of tibial-SSEP in the index patient and her son. The duration of the contralateral silent period (cSP) in the right first dorsal interosseus muscle (FDI) at test stimulus (TS) intensities of 130% and 150% resting motor threshold (rMT) was increased in the son and the daughter. Also, duration of ipsilateral silent period (iSP) in the left FDI was increased in these patients at TS intensities of 150%.

Conclusions: This German SCA-14 family with a novel mutation presented with slowly progressive cerebellar ataxia, segmental dystonia and axial myoclonus. TMS showed abnormalities of intracortical and interhemispheric circuits in keeping with the view of SCA 14 as a multi-system neurodegenerative disease.

6

Vocal cords myoclonus, progressive ataxia and horizontal gaze palsy in a patient with olivary nuclei hypertrophy and posterior fossa malformation

P.S. Brito, J.A. Tenorio, C.O. Godeiro, Jr, J.B.R. Caldas
(Natal, RN, Brazil)

Objective: We present an unusual report of a patient with vocal cord myoclonus, progressive ataxia and horizontal gaze palsy associated with unique MRI abnormalities.

Background: Palatal tremor can be symptomatic or essential. Involvement of the larynx, either in its inner or outer part, is possible in both forms, although it is more frequent in symptomatic cases.

Methods: Case Report.

Results: A 61-year-old woman presented with ataxia and slurred speech. She had normal growth and development until age 25, when her gait became ataxic with frequent falls. Over the following years, her speech became slurred and she was unable to perform her professional activity of teaching Portuguese in high-school. There was no family history of a similar disease and no consanguinity. On neurological examination, she was alert, but with dysarthria and dysphagia. She scored 26 on the Mini-Mental State Examination. Muscle strength was normal, but she had generalized hyperreflexia with extensor plantar responses. On cerebellar examination, she had gait and limb ataxia. She had horizontal gaze palsy and slowed vertical saccades. Brain MRI showed arachnoids cyst surrounding the cerebellum, and extension of the cerebellar tonsils through the foramen magnum, what is suggestive of Chiari malformation. It disclosured abnormalities of the skull base and kinking of brain steam. There was also enlargement and increased signal intensity of both inferior olives. Nasolaryngoscopy with a flexible fibroscope showed bilateral myoclonus jerks close to the vocal cords. The patient did not complain of ear clicks and during examination via nasopharyngeal rout we did not observe palatal tremor, which could have been suppressed by muscular activity of mouth opening during direct via examination.

Conclusions: Laryngeal "myoclonus" without palatal tremor is unusual, but it has already been described. However, there is no previous report related to posterior fossa malformation. This case disclosures that not only an acute, but also a chronic and persistent insult to the brain steam may cause olivary abnormalities and palato-laryngeal tremor.

7

Aminopyridines correct presymptomatic neuronal dysfunction and improve late behavioral and cellular phenotype in a mouse model of spinocerebellar ataxia type 1 (SCA1)

R. Hourez, L. Servais, D. Gall, M. Pandolfo, S.N. Schiffmann
(Brussels, Belgium)

Objective: After characterizing an early dysfunction of Purkinje cells in a mouse model of SCA1, we tested whether potassium channels blockers of the aminopyridines family could improve neuronal dysfunction, motor behaviour and neurodegeneration in SCA1.

Background: SCA1 is a fatal incurable progressive cerebellar ataxia accompanied with loss of Purkinje cells and caused by an expanded polyglutamine tract in the protein ataxin-1. Mouse models of SCA1 display impaired motor performance ahead of loss or atrophy of Purkinje cells, suggesting that neuronal dysfunction may be important in the phenotype of SCA1.

Methods: Neuronal dysfunction was studied by electrophysiology combined with gene and protein expression studies. Aminopyridines (4-aminopyridine and 3.4diaminopyridine) were administered by sub-

cutaneous injection, either acutely (single injection) or chronically (implantation of osmotic Alzet pumps). Motor behaviour was assessed by accelerated rotarod, thin rod and grip strength tests. Cell atrophy was assessed by classical immunostainings or 3D reconstruction after intracellular dialysis with biocytin.

Results: We observed an early dysfunction of Purkinje cells characterized by a reduction in Purkinje cell firing rate (both in vivo and in slices) associated with a reduction in the efficiency of the main glutamatergic synapse onto Purkinje cells and with increased A-type potassium current. In acutely treated young SCA1 mice, aminopyridines normalize the firing rate of Purkinje cells and the motor behaviour of the animals. In chronically treated old SCA1 mice, 3.4-diaminopyridine improves the firing rate of Purkinje cells, the motor behaviour of the animals and partially protected against cell atrophy (as shown by measurement of molecular layer thickness, Purkinje cell volume and dendritic spines density) while no effect was observed on cell death. Chronic treatment with 3.4-diaminipyridine was associated with increased cerebellar levels of BDNF, the protection against atrophy of Purkinje cells could thus be provided by an increase in the production of growth factors secondary to the re-increase in electrical activity.

Conclusions: Our data suggest that aminopyridines might be proposed as a symptomatic and/or neuroprotective treatment in SCA1.

8

Protective effect of valproate on SCA3/MJD transgenic cell and drosophila models

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Objective: To evaluate the potential therapeutic roles of Valproate in SCA3/MJD transgenic cell and Drosophila models.

Background: It was shown that HDACIs had potential therapeutic roles in HD, DRPLA and SBMA. However, none have been reported to be involved in SCA3/MJD.

Methods: Immuno-Fluorescence and Western blot were used to study the effect of Valproate on the expression of polyQ expanded ataxin-3, H3 and H4 protein in SCA3/MJD cell model. Flow cytometry was used to study its effect on the apoptosis of wild-type and polyQ expanded ataxin-3. Drosophila models were constructed by GAL4/UAS system to observe its effect on the eye morphology under LM and SEM. Its effect on climbing ability and lifespan were also evaluated.

Results: Wild type and mutant type were found to scatter in nucleus or cytoplasm. Quantitative level of abnormal aggregations were analyzed to compare polyQ expanded ataxin-3 group with Valproate intervention group but found no significantly difference ($P>0.05$). Early apoptosis rate of pEGFP-N1-ataxin-3-68Q transfected cells was significantly higher than control group ($P<0.05$). After intervention, the early apoptosis rate of pEGFP-N1-ataxin-3-68Q transfected cells was significantly decreased, and the greater the dose, the lower the apoptosis rate. The empty pEGFP-N1 vector transfected cells and pEGFP-N1-ataxin-3-20Q transfected cells had the same expression of H3 and H4, whereas the pEGFP-N1-ataxin-3-68Q transfected cells had lower expression. After intervention,expression of H3 in pEGFP-N1-ataxin-3-68Q transfected cells was gradually increased. In Drosophila models, expression of MJDtr-Q78 protein resulted in progressive loss of pigmentation and collapse of the eye, decreasing of climbing ability and shortening of lifespan. The severity of the phenotype was relevant to the expression of MJDtr-Q78 protein. After intervention, the loss of pigmentation, collapse of the eye, and the climbing ability of Drosophila models were improved.

Conclusions: In SCA3/MJD cell models, Valproate can reduce the early apoptosis rate and increase the expression of H3 and H4 protein. In Drosophila models, proper dosage of Valproate has potential therapeutic effect by reducing loss of pigmentation and structural damage of eyes, improving climbing ability and extending lifespan.

9

SCA32: An autosomal dominant cerebellar ataxia with azoospermia maps to chromosome 7q32-q33

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Objective: To map and clone the disease-causing gene in an autosomal dominant cerebellar ataxia kindred with Azoospermia.

Background: The dominantly inherited spinocerebellar ataxias (SCA) are a clinically and genetically heterogeneous group of neurodegenerative disorders characterized by progressive imbalance, dysarthria and motor incoordination. Till now,at least 29 genetically distinct subtypes of SCA (SCA1-8, SCA10-23, SCA25-SCA31) in addition to DRPLA have been identified by genetic analysis. The gene and mutational mechanism responsible for at least 19 SCA subtypes and DRPLA has been elucidated.

Methods: Neurological and Urological examinations including brain MRI, IQ scores and testis biopsy were undertaken to evaluate the clinical features of the kindred. Cytogenetic and molecular genetic methods including chromosome Y microdeletion analysis, geneome-wide scanning, linkage analysis and mutation detection were applied to map and clone the disease-causing gene.

Results: A kindred with progressive ataxia was identified in which all affected males are infertile. The affected individuals, particularly females, have a broad range of age of onset. Detailed neuropsychological evaluations demonstrated cognitive impairment with borderline IQ scores for those with onset of ataxia before 40 years age. Magnetic resonance brain imaging demonstrates cerebellar atrophy. Affected males had testicular atrophy and azoospermia. Testicular biopsy from one sterile male demonstrated complete absence of germ cells and progenitors. A genome-wide genetic linkage scan located the novel disease locus to critical region of 0.989287 cM interval on chromosome 7q32-q33, flanked by rs3847110 (130,776313 bp) and rs2241728 (131,765600 bp), which recently has been assigned as SCA32 subtype by HGNC. We have identified a candidate gene and mutation that is expressed in cerebellum and testes, and provide evidence that the expression of this gene is altered in biopsied testes tissue. Additional expression studies are underway to confirm that this novel gene is responsible for this complex phenotype.

Conclusions: A novel SCA subtype was mapped to chromosome 7q32-q33 with a candidate gene and mutation, which will shed additional light into the pathogenesis of ataxia, as well as male infertility and mental retardation.

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Two in one: A case report of a patient with spinocerebellar ataxia types 2 and 10

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Objective: To report a rare case of the coexistence of two spinocerebellar ataxia (SCA) mutations in a single patient.

Background: The SCAs are a heterogeneous group of autosomal dominant neurodegenerative diseases characterized by progressive cerebellar ataxia and different genetic mutations. The presence of multiple SCA mutations within a single individual is extremely rare. Only three reports have described 2 coexisting SCA mutations within an individual, and in all of these, SCA8 mutations co-occurred with either SCA1, SCA3, or SCA6. We report the first case of SCA2 in combination with SCA10.

Methods: Case report of a patient at the Rush University Movement Disorders Clinic.

Results: The patient is a 48 year old male of Native American, French, and Mexican descent who presented with a seven year history of gait and limb ataxia. Neurological history and examination revealed executive dysfunction, dysarthria, slowed saccades, muscle cramps, and sensory neuronopathy (video available). Episodes of loss of awareness were reported, but EEGs were reported as negative. Brain MRI demonstrated severe cerebellar and brainstem atrophy. Genetic evaluation of the case revealed expanded repeats for SCA2

(abnormal allele CAG repeats 38) and for SCA10 (abnormal allele ATTCT repeats 1265). His mother and sister have gait and limb ataxia and also have SCA2 mutations, but were not previously tested for other SCAs; further evaluation is underway.

Conclusions: Our patient has a unique combination of genetic mutations for two different SCAs not previously reported, for SCA2 and SCA10. His clinical phenotype is largely consistent with SCA2, but his possible seizures and Mexican heritage suggest influences of SCA10. While the clinical and genetic effects of combined SCA mutations are unknown, his family, as well as others, provide opportunities to study gene interactions and clinical expression. Furthermore, finding two genetic mutations in a patient has important implications regarding counseling on genetic risk, testing, and prognosis.

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Chronic and progressive ataxia program: Results of the first 30 patients

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Objective: To systematize a diagnostic strategy and determine the most frequent genetic etiologies, we developed a multidisciplinary program for the study of chronic and progressive Ataxia in Argentina.

Background: Chronic and progressive Ataxias are a heterogeneous group of disorders caused by a vast number of different etiologies. Although there have been numerous advances in this field, it is still difficult to arrive to a definite etiologic diagnosis in these patients. Furthermore, the prevalence of different genetic alterations differs depending on the population that is being studied.

Methods: The chronic and progressive Ataxia Program is an ongoing epidemiologic registry of the clinical and molecular features of ataxic patients that are assisted in a tertiary center in Buenos Aires, Argentina. Neurologists, neurogenetics specialists, electrophysiologists, cardiologists, ophthalmologists are involved in the multidisciplinary assistance of these patients. Molecular studies were performed as previously described in the literature.

Results: From June 2008 to December 2009, 30 chronic and progressive ataxic patients were included. Among them, 20 cases were sporadic and the rest presented a positive family history of the disorder (one sibship suggestive of a recessive disorder and five multigenerational pedigrees suggestive of dominant disorders). We arrived to an etiologic diagnosis in eight patients: two sporadic cases and six familial cases. Of those, 3 subjects had Fiedreich Ataxia, four patients had Spinocerebellar Ataxia (SCA) type 2 and one had SCA 7.

Conclusions: This chronic and progressive Ataxia Program allowed us to study ataxic patients in a systematized way. We consider that it will improve our knowledge on the disease characteristics in Argentina. Preliminary results of the Ataxia Program are presented.

12

Antioxidants and other pharmacological treatment for Friedreich ataxia

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Objective: To examine the efficacy of antioxidants and other pharmacological treatment for Friedreich ataxia.

Background: Friedreich ataxia is a rare inherited, autosomal recessive, neurological disorder characterised initially by unsteadiness in standing and walking, slowly progressing to wheelchair dependency usually in the late teens or early twenties. It is associated with slurred apeech, scoliosis, pes cavus and heart abnormalities which may cause premature death in 60 to 80% of patients. There is no easily defined clinical or biochemical marker and no known treatment.

Methods: A search of the electronic databases Medline, Cochrane, Embase,and Cinahl was carried out. Publications since 1996 (when genetic diagnosis became available) were used where possible. References of all relevant articles were checked as well as all relevant conference proceedings. A search of Clinical Trials Registry of the US National Institute of Health (www.clinical trials.gov) was also undertaken. All randominsed clinical trials (RCT) or quasi-randomised trials which examined drug treatment in people with genetically confirmed Friedreich ataxia were examined. The primary outcome was change in ataxia rating scale as measured by the International Co-operative Ataxia Rating Scale (ICARS) after 12 months. Secondary outcomes included change in left ventricular heart mass as measured by magnetic resonance imaging or echocardiography.

Results: Over 10 studies used idebenone in the treatment of Friedreich ataxia but only one small randomised controlled trial with 29 participants using the synthetic antioxidant, idebenone, 5mgs/kg fullfilled the selection criteria set by this review.

Conclusions: No randomised clinical trial using idebenone or any other antioxidant, or any other pharmacological treatment has shown significant benefit on neurological symptoms associated with Friedreich ataxia. Idebenone, an antioxidant, has shown a positive effect on left ventricular heart mass but no research on the clinical relevance of this change has been done.

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Large normal polyQ runs underlies the highest prevalence of SCA2 in Cuba

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Objective: To test the hypothesis that the frequencies of normal alleles (ANs) with a relatively large number of CAG repeats (large ANs) are related to the prevalences of Spinocerebellar Ataxias.

Background: SCA2 reaches the highest prevalence in Cuba (43*100000 people) (1). In Huntington's disease, SCA1, SCA3, and SCA7 is largely known the arising of the *de novo* mutation from large ANs. However, in SCA2 is unclear the involvement of such alleles as reservoirs for pathological alleles.

Methods: Availability of large number of SCA2 and non SCA2 carriers chromosomes (N=2695) allowed us to perform a molecular an epidemiological based approach to decipher the possible cause of the high prevalence of SCA2 in Cuba. GeneSCAN and sequence analysis was performed aimed at estimate CAG size and STR haplotype around ataxin-2 CAG.

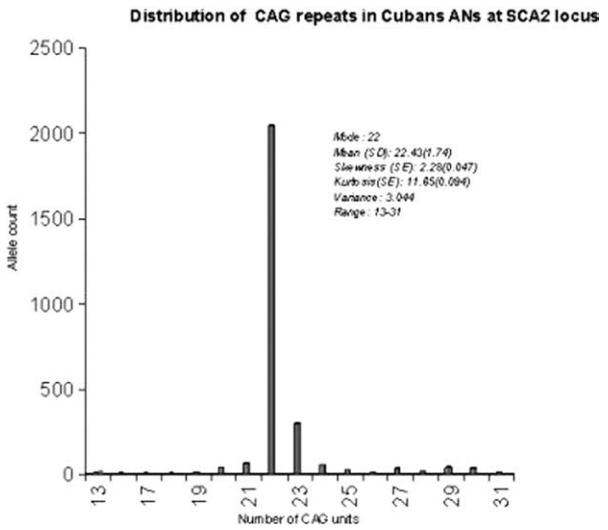

FIG. 1 (13).

Results: CAG mean was 22.43±1.74. CAG range extends from 13-31, encompassing 17 classes. Alleles with 13, 30, 31 CAG were exclusively linked with Cubans. Large alleles with >22CAG were overrepresented. SCA2 haplotype distribution was asymmetrical (Skewness: 2.28±0.047) toward large ANs. The frequency of such alleles was 0.19. Comparisson respecting other population disclosed high significant differences (*Cuba vs Caucasians:* $\chi^2=11.15$, $P=0.0000$). Genotypes distributions shows that large alleles only are linked with 22 CAG alleles and between it self. Large homoallelics genotypes were more frequent than short homoallelics ($\chi^2=23.30$, $P=0.0000$). Large ANs were enriched with the SCA2 STR haplotype 3-3-4 at *D12S1332-D121672-D12S1333* (P=0.0013).

Conclusions: The close correlations of the relative prevalences of SCA2 with the distributions of large ANs in Cuba, strongly support that large ANs contribute to generation of expanded alleles (AEs). 1. Velázquez Pérez L, Sánch ez Cruz G, Santos Falcón N, Almaguer Mederos L E, Escalona Batallan K, Rodríguez Labrada R, Paneque Herrera M, Laffita Mesa JM et al. Molecular epidemiology of spinocerebellar ataxias in Cuba: Insights into SCA2 founder effect in Holguin. Neuroscience Letters 454 (2009) 157–160.

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Neuropathy in spinocerebellar ataxia type 1, 2, 3 and 6

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Objective: To evaluate neuropathy in spinocerebellar ataxia (SCA) types 1, 2, 3 and 6, to decipher electrophysiological characteristics in different subtypes and to analyze nerve conduction parameters as potential biomarkers indicating disease progression.

Background: SCA comprises a group of neurodegenerative disorders of autosomal dominant inheritance and ataxia as key symptom. SCA does not necessarily mean that degeneration is restricted to spinocerebellar systems. Little is known about the impairment of peripheral nerves in SCA.

Methods: 162 patients with a mutation in the SCA 1, 2, 3, or 6 genes and 79 healthy controls were recruited in seven centers participating in the European SCA project (EUROSCA). Patients underwent a clinical and electrophysiological examination with motor nerve conduction studies of ulnar and tibial nerves and sensory studies of radial and sural nerves.

Results: 82% of SCA1 patients but only 22% of SCA6 patients presented with neuropathy by electrophysiological means. 63% of SCA2 patients and 55% of SCA3 patients were electrophysiologically diagnosed with neuropathy. Nerve conduction velocities were slower in SCA1 than in other subtypes. Mixed neuropathy was the most frequent presentation for SCA1, SCA2 and SCA3 patients, whereas SCA6 patients most frequently presented with mildly slowed conduction. Sensorimotor neuropathy was much more common than pure sensory or pure motor neuropathy in all SCA subtypes.

Conclusions: The present study proves peripheral nerves to be frequently involved by the neurodegenerative process in all subtypes of SCA but to be milder in SCA6 than in SCA1, 2 and 3. Electrophysiological analyses identified some characteristic findings suggesting a SCA subtype but also elucidated large overlap between different subtypes. At least in SCA3 sensory nerve action potentials and compound muscle action potentials correlate with disease duration and may serve as potential biomarkers for disease progression.

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Safety and tolerability of lithium carbonate in spinocerebellar ataxia type 1 (SCA1) patients: Lessons from a feasibility study

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Objective: The primary outcome of this study was side effect profile in patients with SCA1. Secondary outcome measures included: ICARS, SARA, BDI-II, ESS, MFAS, MMSE, time-up-and-go, tremor study and posturography. PEG board was used in a subset of patients.

Background: SCA 1 is an autosomal dominant neurological disorder caused by a trinucleotide repeat expansion encoding glutamine in the ataxin-1 gene in chromosome 6. Degeneration of neurons in the cerebellum, spinal cord, and brainstem result in a clinical presentation of progressive ataxia, speech difficulty and cognitive impairment. Based on an animal model study, lithium carbonate has been suggested to have neuroprotective properties.

Methods: Subjects with a molecular diagnosis of SCA1 were enrolled in this study. This study required four admissions to the NIH Clinical Center (titration phase, one and three month follow-up, and washout). Multiple rating scales were completed at each visit.

Results: Twelve subjects completed the study. Preliminary data review suggests moderate tolerability of lithium carbonate with lower serum levels in this population. An unexpected serious adverse event that required discontinuation and re-challenge with lithium (significant transaminase elevation) was observed in one patient. An additional patient, without prior history of liver disease, had a slight elevation of liver enzymes. 75% of the patients were able to complete the dose escalation and maintenance phase of the study but most required dosage adjustment to decrease untoward side effects. The most common side effects reported were tremor and worsening of balance. Other common complaints were lower extremity weakness and falls. Two patients developed hypothyroidism.

Conclusions: Lithium carbonate was moderately tolerated by this small cohort of patients with SCA1, following dose modification. However, many side effects associated with lithium were seen when taking into consideration the size of the sample group. Future analysis of secondary outcome measures from this trial may contribute to the determination of the best possible outcome measures for future efficacy trials.

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Electrophysiological parameters as preclinical and progression biomarkers of spinocerebellar ataxia type 2. A twenty years prospective follow up study

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Objective: To delineate the degenerative pattern in peripheral nerves in SCA2, to asses the predictive value of Electrophysiological parameters as progression markers and to correlate the progression velocity with CAG repeat.

Background: Different electrophysiological abnormalities in SCA2 patients have been characterized. Nevertheless, the progression of these alterations across time has not been studied in a definite sample of SCA2 patients.

Methods: Fifty five non-symptomatic first-degree relatives of SCA2 patients were studied 6 times during 20 years by motor and sensitive nerve conduction studies and multimodal evoked potentials as well.

Results: The most consistent findings were the reduction in amplitude in sensitive potentials and the increase in absolute latency of P40 component. Our data shown the structures of the nervous system are involved before any clinical sign appear. This allows us defining four stages in the evolution of this disease: 1st: normal electrophysiological parameters. 2nd: decrease in the amplitude of the sensitive potentials, increase in the absolute and interpeak latencies in the SSEPs, and abnormal morphology in the BSAEPs. 3rd: increase electrophysiological abnormalities, which correspond with the first clinical manifestation of the disease and 4th: both, peripheral and central afferent conduction blocks appear, expressed by absence of the response in sensory conduction nerve studies and in SSEPs. This classification of the disease in different stages allows to know the degenerative process

during the evolution of the disease of the afferent and efferent systems. Also, the existence of electrophysiological abnormalities in non-symptomatic subjects permits to choose the optimal moment for the evaluation of a specific therapeutic treatments.

Conclusions: Our electrophysiological results agree with the loss of ganglion cells in the dorsal root ganglia. This study have point out to a close association among CAG mutation and electrophysiological alterations, ending with a total blockade of the afferent conduction as a sign of severe neurodegeneration. The molecular substrate is linked with increase of ataxin-2 toxicity accounting for more neuronal neuronal loss in the Peripheral and Central Nervous System.

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Metabolic diseases revealed by cerebellar ataxia

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Objective: To describe four cases of cerebellar ataxia in teenagers or young adults and to emphazise red flags which led to the diagnosis of metabolic disorders

Background: The first diagnosis for cerebellar ataxia in young people is autosomal recessive Friedreich ataxia. However, some clinical or radiological signs can direct the diagnosis to some metabolic diseases for which a specific treatment is sometimes available.

Methods: We report clinical, radiological and biological data in four young patients who presented with a cerebellar ataxia due to 4 distinct metabolic disorders.

Results: Patient 1 was the only one issued from a consanguineous marriage. She was seen at age 20 but had since age 7, moderate ataxia and learning difficulties. Cerebral MRI showed diffuse demyelinisation. Organic acids chromatography led to the diagnosis of hydroxyl glutaric aciduria. Patient 2 had developed since age 11 bilateral cataract, ataxia, and behavioural disorders. At age 28, examination revealed polyneuropathy and xanthoma. MRI showed cerebellar T2 hyperintensities. Cholestanol level was increased leading to the diagnosis of cerebrotendinous xanthomatosis. Patient 3 developped ataxia at age 8, and at age 13 oculomotor disorders and cognitive impairment which led to Niemann Pick C diagnosis. Patient 4 had developed since age 3 moderate myoclonus. At age 17, were found a cerebellar ataxia and a hexosaminidase A and B deficit which directed the diagnosis to Sandhoff disease.

Conclusions: In front of a cerebellar ataxia in young patients, some of the red flags which can direct investigations to a metabolic disorder are : recessive inheritance, an onset in childhood, presence of other neurological signs (movement disorders, oculomotor abnormalities), extra neurological signs (xanthoma, splenomegalia.), behavioural disorders, bilateral MRI abnormalities. A precise clinico radiological phenotype can help to limit biological or genetical studies.

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Olfactory impairment in patients with spinocerebellar ataxias (SCA)

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Objective: To evaluate olfactory function in patients with autosomal dominant spinocerebellar ataxia.

Background: The main clinical manifestations of SCA result from the involvement of cerebellar structures but they often are present with extra-cerebellar features, including extrapiramidal signs. Cerebellar activity has been consistently observed in functional imaging studies of olfaction, but the anatomical pathways that lead to this connection have not yet been demonstrated. Hyposmia is a common finding in neurodegenerative diseases and co-occur with extrapiramidal features in Parkinson's disease (PD), multiple system atrophy and progressive supranuclear palsy. Previous studies showed olfactory deficit in SCA2, Friedreich's ataxia and in small groups of ataxia of varied causes. We have investigated olfaction in 32 SCA patients (including 11 patients with SCA10, which in Brazil presents with pure cerebellar features) and compared with control and PD subjects.

Methods: A previously validated translation of the 16 item smell identification test from Sniffin' Sticks (SS-16) was used to evaluate the sense of smell in 32 SCA patients and compared with groups of 106 PD patients and 119 healthy controls. Within the SCA group, we compared scores in 10 patients with SCA3 and 11 patients with SCA10 with the control subjects when adjusting for variation in age.

Results: When adjusted for age, the mean UPSIT score in SCA was higher than in PD ($p<0.001$, 95% CI for $\beta = -4.59$ to -2.42) and lower than in controls ($p=0.004$, 95% CI for $\beta = +0.52$ to $+2.70$). When adjusted for age, the mean UPSIT score in SCA10 was marginally lower than in controls ($p=0.046$, 95% CI for $\beta = -3.22$ to -0.03), and not different between SCA3 and controls ($p=0.50$).

Conclusions: Odor identification is diminished in SCA but not to the same extent as in idiopathic PD. The small number of patients provides marginal significance for the finding of hyposmia in SCA10, and further studies are warranted to confirm the presence of hyposmia in pure cerebellar ataxia.

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Clinical and genetic analysis of spinocerebellar ataxia in Mali

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Objective: To assess the frequency and clinical features of different types of hereditary spinocerebellar ataxia in Mali.

Background: Spinocerebellar ataxias (SCAs) are neurodegenerative disorders characterized by a clinical and genetic heterogeneity. They are caused by an expansion of unstable (CAG) triplets repeats in the genome. The relative frequencies of the different types of ataxias vary among geographic regions and ethnic groups. Data from African countries are very scarce.In this present report, we describe our clinical and molecular findings in 16 patients originating from Malian families, and suffering from progressive cerebellar ataxia syndrome.

Methods: A total of 33 individuals from five families were invited to participate in the study, after informed consent. The Ethics committee of the Medical school of Mali had approved the study design. The presence of progressive cerebellar ataxia has been considered as cardinal clinical symptom necessary for inclusion in the affected group. Clinical examination and detailed history of the onset, and progression of the disease were taken. Genetic profile of spinocerebellar ataxia was confirmed by molecular genetic testing.

Results: 16 Malians had received diagnoses of spinocerebellar ataxia. In 7 patients SCA type2 (CAG) mutation was expanded from 39 to 43 repeats.Spinocerebellar ataxia type 7 (CAG) mutation was confirmed in 6 patients. Mutations were expanded from 49 to 59 repeats. In 3 patients, Spinocerebellar type3 (Machado-Joseph disease) was diagnosed in only one family and CAG mutation was expanded to 73 repeats. The age of onset may correlate inversely with the number of CAG repeats in patients with SCA2 and SCA3/MJD disease.The most common manifestation was ataxia, followed by dysarthria and pyramidal symptoms. Other symptoms like bradykinesia, ophthalmoplegia, tremor were present.

Conclusions: Our findings sugested that the frequency of SCA2 and SCA7 were significantly higher than that of SCA3/MJD in Malian patients. Genetic testing is necessary to confirm the diagnosis. Further studies will be necessaty to confirm preliminary results.

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Effects of erythropoietin treatment on microvascularisation and metabolism of skeletal muscle in patients with Friedreich ataxia

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Objective: Aim of this study was to investigate effects of recombinant human erythropoietin (rhuEPO) treatment on numbers of endothelial progenitor cells (EPC) in the peripheral blood, microvascularisation and metabolism of skeletal muscle in Friedreich Ataxia (FA) patients.

Background: RhuEPO treatment increases frataxin levels, decreases oxidative stress parameters and improves clinical function in FA patients. The underlying mechanisms for these rhuEPO mediated effects are poorly understood at present. Since the pathological cascade in FA is not restricted to the central nerve system, we investigated effects of rhuEPO treatment on skeletal muscle in FA patients.

Methods: Seven genetically confirmed FA patients participated in this open clinical pilot trial. RhuEPO (5.000 international units) was administered subcutaneously 3 times per week over a total study period of 8 weeks. Patients had a muscle biopsy and magnetic resonance spectroscopy (MRS) of the gastrocnemius muscles before and after rhuEPO treatment. Additionally FACS (Fluorescence activated cell sorting) analysis of EPC were performed every 4 weeks during the study.

Results: Muscle biopsies of four FA patients revealed mild myopathic changes with type II fiber atrophy and sparse muscle fibers with internalized nuclei. Three FA patients displayed an atrophy of type I and II fibers as well as fiber type grouping indicating a neurogenic lesion. None of the patients had ragged red fibers and only one patient demonstrated single cytochrome C oxidase negative fibers. Assessment of number of capillaries per muscle fibre revealed an increased capillary density after rhuEPO therapy, although these values did not reach statistical significance. Numbers of EPC in the peripheral blood increased during rhuEPO treatment and returned to their baseline values four weeks after completion of the treatment period.

Conclusions: Our results indicate recruitment of bone marrow derived EPC in FA patients during rhuEPO therapy, which might induce neovascularization of skeletal muscle in FA. These effects could contribute to the previously observed clinical improvement in FA patients during rhuEPO treatment.

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Classification of cerebellar atrophy using voxel-based morphometry and SPECT with an easy Z-score imaging system

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Objective: The objective was to verify the utility of MRI voxel-based morphometry (VBM) in combination with single-photon emission computed tomography (SPECT) using easy Z-score imaging (eZIS) for diagnosing and classifying cerebellar atrophy.

Background: Classifying cerebellar ataxias in their early stages is therapeutically important. However,with conventional MRI and SPECT, accurate diagnosis and precise classification of cerebellar atrophy are often difficult.

Methods: We assessed gray matter atrophy using VBM and blood perfusion using SPECT with eZIS in fifteen patients with different types of cerebellar atrophy, such as the cerebellar variant of multiple system atrophy (MSA-C), spinocerebellar ataxia type 3 (SCA3), SCA6, and autoimmune cerebellar ataxia (AICA).

Results: In all five MSA-C patients, VBM imaging showed atrophy of the brainstem, the entire cerebellar vermis, and the cerebellar hemispheres, while SPECT using eZIS showed reduced perfusion in the same regions. Regarding SCA3, brainstem atrophy and reduced perfusion were recognized in two of the four patients, but none exhibited abnormal findings in the posterior lobe of the cerebellar vermis. SPECT showed that all four patients had obviously reduced perfusion in the anterior lobe of the vermis, but VBM demonstrated that there was no obvious atrophy of gray matter in any patient, meaning that the results of SPECT and VBM contradicted each other completely.All SCA6 and AICA patients exhibited atrophy and reduced perfusion in the cerebellar hemispheres but not in the brainstem. Only one AICA patient exhibited atrophy and reduced perfusion of the entire cerebellar vermis.

Conclusions: VBM clearly showed characteristic gray matter atrophy in the cerebellum and brainstem in different pathological conditions, thus indicating its high degree of utility in diagnosing and classifying cerebellar atrophy in combination with SPECT using eZIS.

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Distinct neurochemical profiles of spinocerebellar ataxias 1, 2, 6 and cerebellar MSA

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Objective: To determine if common spinocerebellar ataxias (SCAs) and cerebellar multiple system atrophy (MSA-C) can be distinguished based on neurochemical levels measured in the cerebellum and brainstem by high field magnetic resonance spectroscopy (MRS).

Background: Genetic testing for SCAs had a great impact in classifying these disorders although running the full profile of available tests is expensive and distinguishing the SCAs clinically is challenging. Imaging markers that can differentiate between ataxias could guide genetic testing for hereditary ataxias and help with diagnosis of non-hereditary ataxias. Most MRS studies of SCAs so far reported a decrease in the NAA-to-creatine ratio in patients, making the MRS findings non-specific. At higher fields MRS enables quantification of a neurochemical profile (Oz et al, Neurology, 2005, 64:434) which increases the potential for disease-specific MRS findings.

Methods: In this pilot, cross-sectional study, neurochemical profiles of patients with SCA1 (N=9, age 55±6 (SD) years), SCA2 (N=7, 51±7 years), SCA6 (N=5, 53±8 years), MSA-C (N=5, 55±3 years) and healthy controls (N=15, 52±8 years) were compared. Neurochemical profiles consisted of 10-13 metabolite concentrations measured from the vermis, cerebellar hemispheres and pons by proton MRS at 4 tesla. The Scale for the Assessment and Rating of Ataxia (SARA) was used to assess disease severity.

Results: The patterns of neurochemical alterations relative to controls differed between ataxia types. The best MRS predictors were selected by a tree classification procedure. Three MRS markers (NAA-to-myo-inositol ratio in the cerebellar hemispheres, myo-inositol levels in the vermis and NAA levels in the pons) lead to 89% accurate classification of all subjects. The differences between ataxias were not due to differences in disease severity because the SARA scores of patients overlapped considerably (SCA1: 9±4 (SD), SCA2: 10±4, SCA6: 16±1; MSA-C: 21±11). Pathological differences between different SCAs were likely the source of the different neurochemical alterations, e.g. lack of pontine involvement in SCA6 distinguished it from SCA1 and SCA2.

Conclusions: This study demonstrated the potential of high field MRS to differentiate ataxias based on neurochemical levels in affected brain regions.

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Assessment of posture using static posturography and accelerometry: Comparison of early stage Parkinson patients and elderly controls

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Objective: We hypothesize that accelerometry is able to differentiate between early stage Parkinson's disease (PD) patients and elderly controls more properly in comparison to static posturography.

Background: Our recent study showed that static posturography is not sufficiently sensitive tool for detection of postural instability in early stage PD patients (Valkovic et al. Mov Disord. 2009 Aug 15;24(11):1713-4.).

Methods: We assessed 12 healthy elderly controls (mean age 70.5 years) and 12 early stage PD patients (63.7 years). Each subject was tested in four basic sensory situations: upright stance on 1) firm floor, and 2) rubber foam, with their eyes a) open, and b) closed. Postural activity was measured by means of static posturography and two accelerometers placed over vertebrae L5 and T4. We evaluated amplitude and velocity parameters in x and y directions.

Results: Posturography revealed significant difference between both groups only in the most difficult situation, standing on rubber foam with closed eyes. However, analysis of sway activity recorded with accelerometers distinguished both groups in several parameters in each sensory situation. In all parameters of significant difference, patients had higher values than controls.

Conclusions: Accelerometry is able to differentiate between early stage PD patients and elderly controls better than static posturography. Supported by grants VEGA 2/7036/27, VEGA 1/0286/08 and SensAction-AAL 045622.

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Retinal nerve fiber layer (RNFL) and macular thickness decrease in spino-cerebellar ataxia (SCA) and multi-system atrophy type C (MSA-C)

J.H. Pula, V.L. Towle, C.M. Gomez (Chicago, Illinois, USA)

Objective: To evaluate the thickness of the retinal nerve fiber layer and macula by ocular coherence tomography (OCT) in patients with genetically confirmed SCA and MSA-C.

Background: RNFL and macular volumes are decreased in multiple sclerosis and other neurodegenerative diseases when tested using OCT. Forms of SCA have been associated with optic atrophy but quantitative measurements have not yet been reported.

Methods: Using fourier-domain OCT (Heidelberg, Spectralis), we measured the thickness of the peripapillary RNFL and peri-foveal retina (3 and 6 mm diameter regions) in both eyes for patients with SCA 1, 2, 3, 6 and MSA-C and correlated these to age and gender-matched controls. Eyes with ocular disease (glaucoma, age-related macular edema, high myopia) were excluded.

Results: The peripapillary RNFL and total macular volume (measured in a 3 mm diameter) are significantly thinner in all affected SCA and MSA-C groups versus controls based on 1 way statistical analysis of variance testing.

Conclusions: Our data suggest that the RNFL and macular volumes are thinner in SCA types 1,2,3 and 6 and MSA-C. Further evaluation may correlate RNFL or macular thickness with SCA type or number of repeats. Continued analysis is needed, as OCT could serve as a valuable secondary endpoint to track neurodegeneration in SCA and MSA-C.

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A novel mutation causing episodic ataxia type 2

D.E. Riley (Cleveland, Ohio, USA)

Objective: To report a case of episodic ataxia type 2 (EA2) caused by a novel mutation.

Background: EA2 is an autosomal dominant disorder characterized by adult-onset paroxysmal attacks of ataxia, vertigo, headache and nausea lasting minutes to days. Onset typically occurs in childhood or early adolescence (range 2-61 years). Frequency of attacks varies from 1-2/year to 3-4/week. Between attacks, individuals are initially asymptomatic but eventually typically develop interictal findings: nystagmus (90%), ataxia (80%), and dystonia (rare). EA2 is associated with mutations in the CACNA1A (calcium channel alpha-1A) gene containing 47 exons. More than 30 different CACNA1A mutations associated with EA2 have been reported.

Methods: Case report with genetic sequencing.

Results: A 52-year-old woman reported a 20-year history of episodes occurring 3-10 times per year, as follows. She awakens with a headache lasting 3-5 hours. During that time, her balance is "off". She may fall or "bang into things" sideways to either side. She may also have incoordination of her hands, or even a tremor. After symptoms resolve spontaneously, she feels fine. Outside of these episodes, she may stumble and trip, but suffers no falls. Family history was negative. On interictal exam, there was horizontal gaze-evoked nystagmus, dystonic hand "scooping" (wrist flexion with finger hyperextension), mild lower limb ataxia, worse on the left, and a wide-based gait with inability to walk in tandem fashion. MRI showed atrophy of the cerebellar vermis. Acetazolamide provided modest relief. CACNA1A gene sequencing detected a thymine-to-cytosine substitution at nucleotide position 859 in exon 6, resulting in an alteration of the amino acid sequence at position 287 from cysteine (a non-polar residue) to arginine (a polar residue).

Conclusions: A woman with typical paroxysmal and interictal findings of EA2 carried a previously unreported mutation in exon 6 of the CACNA1A gene. Mutations in numerous locations in this gene have been associated with EA2. The majority are nonsense mutations resulting in a truncated protein product; CACNA1A mutations appear to cause a loss of function. The EA2 patient reported here represents yet another example of the nonspecific nature of mutations underlying this genetic phenomenon.

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SCA15 is the most frequent form of autosomal dominant ataxia not caused by repeat expansions

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Objective: To assess the prevalence and phenotypic spectrum of spinocerebellar ataxia type 15 (SCA15) in German families with autosomal dominant cerebellar ataxia.

Background: Genetic diagnosis in spinocerebellar ataxias (SCAs) is a major challenge when common CAG repeat expansions have been excluded. To guide time- and cost-intensive analyses of the increasing number of SCA genes, more information about phenotypic characteristics and frequency distribution in different populations is highly warranted. SCA15 has recently been shown to be caused by multi-exon deletions of the ITPR1-gene.

Methods: A consecutive series of 274 ADCA families were recruited in the ataxia clinics at the Universities of Bonn and Tubingen. 69 families were negative for repeat expansions causing SCA1, 2, 3, 6, 7, and 17 and were screened for multi-exon deletions in the ITPR1-gene. To determine the most efficient diagnostic method for deletion detection two molecular-genetic techniques were used in parallel, namely multiplex ligation-dependent probe amplification (MLPA) and real-time PCR combined with copy number analysis by SNP array.

Results: SCA15 accounted for 1.8% (5/274) of all SCA families and for 7.2% (5/69) of SCA families negative for common repeat expansions, thus yielding SCA15 the most frequent form among SCAs negative for CAG repeat expansions. MLPA demonstrated less false positives and less false negatives and is more cost-effective than qPCR combined with SNP array. All SCA15 patients (n=10) presented with slowly progressive cerebellar ataxia, whereas marked postural, action and intention tremor often developed later in the disease. Other extra-cerebellar signs like e.g. pyramidal tract affection were infrequent. Cerebellar atrophy was uniformly most pronounced in the superior vermis and was present before patients regarded themselves as affected.

Conclusions: MLPA-screening for ITPR1 deletions should be considered in patients with slowly progressive SCA, vermal cerebellar atrophy and prominent tremor after common SCA repeat expansions have been excluded.

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Different age of GAA repeat expansion of Friedreich's ataxia patients in North and South Indian population with globally shared ancestral origin

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Objective: To estimate age of expanded GAA repeats using linkage disequilibrium (LD) pattern in closely linked markers in Indian Friedreich's ataxia patients.

Background: FRDA is a progressive recessive ataxia caused by expansion of GAA repeats in the range of 60 to 1200 in frataxin (FXN) gene on chromosome 9q13-q21.1.

Methods: Age estimation was carried out using 5 SNPs (FAD1, rs11145326, rs7861997, ITR3, and CS2) and a microsatellite marker FR6. The Haplotype AGCCC from 5 SNPs was reported earlier to be associated with FRDA mutation in Indian Populations (Mudila IS, MDS 2009). The FR6 has been previously implicated with expanded allele of German ancestry. The SNPs (CS2; ITR3; FAD1) have earlier been reported to be associated with GAA expanded alleles in the Caucasian population. We recruited 21 patients of north Indian (NI) and 8 patients of south Indian (SI) origin. 200 unrelated ethnically matched controls from both the population were also recruited for the study.

Results: It has been reported that LD is unlikely to be informative in regions less than 50-60 Kb,therefore age estimated using 2 SNPs (rs11145326 and FAD1) and FR6 for NI and SI were 15975±2850 and 5425±1750 years respectively. Nearly similar age of FRDA mutation has been reported from the western European population. Haplotype using 5 SNPs revealed that haplotype AGCCC is associated with 50% and 62.5% of expanded GAA allele in NI and SI population respectively. We observed 4 SNPs (FAD1, rs11145326, rs7861997 and ITR3) significantly associated ($p<10-6$) with expanded as well as LN allele in both NI and SI population, whereas CS2 is found to be significantly associated with FRDA families of NI only.

Conclusions: Result suggests common origin of all FRDA in India which is also shared with the Caucasian populations and origin of FRDA mutation is very ancient in India and arises from a pre-existing pool of permutation alleles introduce in India through European migration. Studies suggest that FRDA has been introduced more recently in SI population through admixture with a pre-existing population. The analysis suggest that the Indo-European populations of NI are genetically related to Caucasian populations.

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Variable phenotype and early infantile onset of spinocerebellar ataxia type 17 (SCA17) within a family cluster

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Objective: To characterise the clinical phenotype, show the range of movement disorder and describe the earliest reported case associated with genetically confirmed Spinocerebellar Ataxia type 17 (SCA17) in a family cluster.

Background: Spinocerebellar ataxia type 17 (SCA17) is a progressive neurodegenerative autosomal dominant cerebellar ataxia. SCA17 is caused by CAG/CAA repeat expansions within the TATA-binding protein (TBP) gene. The spinocerebellar ataxias are pleiomorphic conditions, but characterised by late onset ataxia. SCA17 has a wide variety of presentations and features, including ataxia, chorea, parkinsonism, dystonia and psychiatric disorders. As such, SCA17 may mimic a range of movement disorders including Huntington's disease, Parkinson's disease, multiple system atrophy and progressive supranuclear gaze palsy. Behavioural disorder and psychiatric presentation can dominate the clinical picture in some. There is some evidence for repeat length determining the age of onset of SCA17, with cases in the literature ranging from 3 to 73 years old, and with anticipation reported in some, but not all, families.

Methods: Case series of three patients from one family, who were examined and videoed in a movement disorder clinic. The cases were tested for a range of genetic disorders, including Huntington's disease, Fredreich's ataxia, SCA1, 2, 3, 6, 7 and 17. Cases were phenotyped using 3T MRI imaging and FP-CIT single positron emission tomography (SPECT).

Results: We describe a family with three genetically confirmed SCA17 cases where the presentations have been variable. One case presented with developmental delay aged 9 months: as far as we are aware, this is the earliest recorded case in the literature. The presentations vary between the family members: dystonia is present in all three members of the family, marked ataxia in 1 of 3, extensive chorea in 1 of 3 with mild chorea in another and no chorea in the oldest case. We describe in detail the clinical features of these three affected family members.

Conclusions: The cases presented here continue to broaden the clinical phenotype and age-range associated with polyglutamine expansion within the TBP gene.

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Spinocerebellar ataxia 12: Clinico-genetic features in 83 probands

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Objective: We report the phenotype among largest amongst the largest number of genotypically confirmed patients.

Background: SCA12 is an autosomal dominant cerebellar ataxia (ADCA) associated with an expanded unstable CAG repeat on chromosome 5q31-33.

Methods: 490 Indian families clinically diagnosed as ADCA phenotype were tested for expansion of CAG/CTG repeats at SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA12, SCA 17, Freiderich's and DRPLA loci.

Results: CAG repeat expansion associated with SCA 12 was identified in 83 probands. The expanded allele carried 45 to 69 CAG repeats (normal alleles 7 to 31 repeats). Age at onset of the disease was 26 to 67 years. 84% had dysarthria and 84% had mild to severe gait ataxia. Most (61%) had presented with upper extremity tremor as initial symptom and 60% were found to have brisk reflexes. In 43 of 51 patients there was evidence of sub clinical sensory or sensory-motor neuropathy while imaging of brain (CT/MRI) showed cerebellar as well as cerebral cortical atrophy in 71 of 83 cases. All the subjects belonged to an endogamous population.

Conclusions: SCA 12 accounts for about 9% of ataxia families and is emerging as second commonest cause of ADCA in Northern part of India. Although genotyping is essential for accurate diagnosis of ADCAs, those belonging to a particular community and presenting with hand tremors in a setting of milder ataxia with brisk reflexes, evidence of sub-clinical peripheral neuropathy and cerebral cortical and cerebellar atrophy can be suspected to have SCA12.

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Long-term effects of intensive coordinative training in degenerative cerebellar disease

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Objective: To evaluate long-term benefits and translation to real world function of physiotherapeutic training in patients with degenerative ataxia.

Background: Few clinical studies have evaluated physiotherapeutic interventions for patients with degenerative cerebellar disease. In particular, evidence for long-term effects and transfer to activities of daily life is still rare. We have recently shown that coordinative training leads to short-term improvements in motor performance, but long-term effects have remained unclear.

Methods: We assessed motor performance and achievement of individual daily life goals one-year after a four week intensive coor-

dinative training which was followed by a one year training program according to a homework protocol. Effects were assessed by clinical rating scales for ataxia, a goal attainment score assessing individual daily life goals and by quantitative movement analysis.

Results: Despite gradual decline of motor performance and worsening of ataxia due to progression of disease, improvements in motor performance and achievement of daily life goals persisted over one year. Long-term efficacy of coordinative training was determined not only by ataxia type (cerebellar vs. afferent), but also by training intensity.

Conclusions: Continuous training of whole body coordination exercises seems crucial for stabilizing improvements in patients with ataxia. We recommend professionally administered physiotherapy which focuses on whole body coordination exercises and which is complemented by home training as standard care in patients with degenerative ataxia.

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Transcranial sonography in spinocerebellar ataxia type 2

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Objective: To study the use of transcranial brain parenchyma sonography (TCS), in particular the echogenic signal in the substantia nigra (SN), in patients with spinocerebellar ataxia type 2 (SCA2).

Background: SCA 2 has recently been recognized as an uncommon cause of parkinsonism, an alternate presentation to the typical cerebellar disorders. Besides typical neuropathological changes in SCA 2, marked degeneration was also found in the SN.

Methods: Six consecutive and unrelated SCA2 patients without parkinsonian signs, 30 consecutive patients with Parkinson's disease (PD), and 30 healthy, age- and sex matched controls were prospectively studied with TCS according to a standardized protocol.

Results: Four (67 %) of the six SCA2 patients exhibited SN hyperechogenicity. In two patients, the hyperechogenicity was classified as moderate (unilateral in both) and in two as marked. Differences between the SN echogenicity of the SCA2 group or the PD group and controls were statistically significant (p [<] 0.001), while there was no difference between the two groups of patients.

Conclusions: Transcranial brain parenchyma sonography detects SN hyperechogenicity in the majority of patients with SCA2 without parkinsonian signs. It would be important to reproduce our TCS findings in a larger number of SCA2 patients, as well as to test their possible significance in differentiating SCA2 from other types of SCA.

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TARDBP accumulation on polyglutamine aggregates

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Objective: To clarify the importance of TAR DNA binding protein (TDP-43) on neurodegenerative disorders, we analyzed polyglutamine aggregation and TDP-43 accumulation in culture cells.

Background: TDP-43 accumulation was reported initially in amyotrophic lateral sclerosis and frontotemporal degeneration, followed by widespread neurodegenerative diseases; Alzheimer's disease, Parkinson's disease, Perry syndrome and etc. Mutations were also found in sporadic and familial ALS. Relationship between TDP-43 and polyglutamine diseases was observed in Huntington's disease and SCA3 pathology.

Methods: We cloned TDP-43 and inserted into a monomer DsRed vector. Polyglutamine clones were obtained from white blood cells of a SCA3 patient and inserted into blue fluorescent protein (BFP) vectors. Double transfection of the constructs into Cos7 cells and observed the distribution of TDP-43 and polyglutamine aggregates by a fluorescent microscope.

Results: Transfected TDP-43-mDsRed distributed cleary in nucei. BFP-polyglutamine formed aggragates in cytoplasm, which were also visualized by a phase contrast microscope simultaneously. Double labeling of polyglutamine aggregates by DsRed and BFP were observed in cytoplasm close to nuclei. Micro vesilcular movements in cytoplasm appeared actively similar to non-transfected cells.

Conclusions: This finding suggests that TDP-43 accumulates on polyglutamine aggregates for autophagic clearance of abnormal protein aggregates and maintaining of intracellular homeostasis in polyglutamine disease.

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Loss of CAA interruption in large normal alleles ATX2 is a risk factor to SCA2 gene instability: A haplotype and sequence based study in large Cuban kindreds

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Objective: To decipher the mechanism predisposing to SCA2 locus instability. 2) To identify other factor than CAG predisposing to SCA2.

Background: Strong linkage disequilibrium (LD) between SCA2 mutation and some STR alleles were found. CAG sequence analysis revealed new large alleles 30-31 CAG.

Methods: Methods: We carried out haplotype studies in 13 SCA2 pedigrees and 89 controls (n=132 chromosomes) using 6 microsatellite markers –STR- surrounding the mutant CAG.

Results: Results: Strong linkage disequilibrium (LD) between SCA2 mutation and some STR alleles were found. CAG sequence analysis revealed new large alleles 30-31 CAG. These alleles were either pure or lacked the most proximal 5' CAA interruption and were overrepresented respecting other alleles. We found strong association (p=0.0070) between allele 4 at D12S1672 marker and 22 CAG allele lacking 5'CAA (configuration 13+8). Alleles with CAG different of 22 repeat, and lacked of CAA interspersion were strongly associated (p=0.0000) with allele 4 of STR and the haplotype (3-3-4) (p=0.0013). Further tests narrowed this group to the 29-31 CAG range, showing association (p=0.0063) only with the haplotype 3-3-4 at D12S1332-D121672-D12S1333. Alleles with 29-31 CAG were unstable at somatic level (No. peaks = 3±0.18SEM, range 3-8 peaks) contrasting to stable chromosomes (No. peaks = 1±0.18 SEM, range 1-2 peaks) in our kindreds. These findings were strengthened by the fact that a pedigree with SCA2 haplotype and pure large allele (30CAG), show that along with an intergenerational increase in repeat size there was a horizontal increase in repeat size with the birth order of the siblings indicating an important role for parental age in repeat instability during transmission.

Conclusions: Conclusion: Large alleles are the principal source of SCA2 expansion. Somatic mosaicism in normal large alleles is a valuable predictor to determine predisposition to genetic instabilities. This is the first work uncovering the mechanism driving to genetic unstability at SCA2 locus.

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Polysomnographic characterization in the SCA2 mutation. A two years prospective follow up study

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Objective: To characterize the sleep pathology in SCA2 mutation by videopolysomnographic, also to check if the disorders appeared since preclinical stages of the disease and to identify therapeutic targets for treatment strategies.

Background: The sleep disorders are common complaints of SCA2 patients, fundamentally towards the final stages of the disease.

Methods: We analyzed thirty six genetically confirmed SCA2 patients, all with size SCA2 expansions (CAG 34 to 44), Thirty two presymptomatics with SCA2 polyglutamine expansions sizes (CAG 32 to 43) and thirty six sex-and age-matched healthy controls were stud-

ied by two all-ninght video polysomnographies and sleep interviews. The polyglutamine expansion size and the clinical score were obtained in all SCA2 mutation carriers and SCA2 patients respectively.

Results: Almost all patients and presymptomatics reported negated incidents of REM behavior disorders. Nevertheless, REM sleep was abnormal. The most striking at pathology of REM sleep was its significant reduction in 60% of SCA2 patients and presymptomatics, insufficient muscle atonia suggested subclinical RBD and decrease of REM density in the 32.3%. Abnormal motor control occurs in the 40% of patients. SCA2 patients and presymptomatics showed significant reduction of sleep efficiency and increase of arousal index and slow wave sleep. Central apnea appear in the 23% of these patients, but, not in the presymptomatic relatives. The most important findings in the prospective follow up study in the SCA2 patients were an increase in the PLMs sequences and index, a progressive reduction of the REM sleep and slow wave sleep and increased in the central apnea.

Conclusions: The most prominent PSG alterations in SCA2 are: REM sleep pathology, which precedes the disease onset, and Periodic legs movements. PLMs get worse Progressively, indicating an increase of PLMs index about 17.3 PLMs/sleep hours pers year. These stages correspond to the progressive atrophy from the pons, nigrostriatal projection, and locus ceruleus to the thalamus. PLMs are comorbid with ataxin 2 expansions perhaps proposing gene products interaction or trans-acting factors undescribed linked with nigro-striatal structures.

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An integrative characterization of SCA2 in Cuba: Epidemiological, genetic neurochemical and electrophysiological findings in 7 926 Cuban carriers

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Objective: To evaluate the clinical epidemiology, electrophysiological, molecular and neurochemical biomarkers of SCA2.

Background: Spinocerebellar ataxia type 2 is the second most frequent dominant ataxia worldwide. In Holguin, the stable prevalence of SCA2 along time, despite the existence of genetic anticipation is likely the result of the high frequency of large normal alleles with pure CAG, which represent reservoirs of mutated alleles, driving to the continuous raising of new SCA2 cases.

Methods: Availability of a high number of SCA2 carriers enables us to asses Clinical epidemiology, molecular, neurochemical and neurophysiological studies were done in all Cuban SCA2 families.

Results: The highest frequency of SCA2 mutation was observed in Holguin province, where the prevalence rate is 163.18 per 100 000 inhabitants. The genetic anticipation was observed in the 80% of transmissions and the expansions were presented in 89.02%. The neurochemical analyses demonstrated a significant decrease of CSF levels of Zn in patients. The neurophysiological studies showed the involvement of nervous structures since presymptomatic stages. The progression of these abnormalities was correlated with disease duration, polyglutamine expansion size and ataxia score. The polysomnographic recording showed the severe REM pathology with insufficient muscle atonia and periodic legs movements occurs in several cases. The electronystagmographical studies showed a significant reduction of maximal saccade velocity in patients and presimptomatic. MSV was negatively correlated with the polyglutamine expansion in both groups.

Conclusions: SCA in Cuba make up the highest prevalence in the world. Electrophysiological abnormalities of peripheral nerves and somatosensory pathways reflect an early and progressive axonal damage. REM pathology can be associated with the pons, nigrostriatal and thalamic degeneration and PLMs. MSV is the most important electrophysiological biomarker for genetic researches. Neurochemical results indicate an impairment of the microelements homeostasis in SCA2.

POSTER SESSION 1
MONDAY, JUNE 14, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 14:00-15:30

BASIC SCIENCE

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Aging augments expression of α-synuclein and endoplasmic reticular resident proteins GRP78 and Caspase12 in human nigral dopaminergic neurons

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Objective: To evaluate the age-related changes in expression of α-synuclein and endoplasmic reticular resident proteins GRP78 and Caspase12 in human substantia nigra pars compacta.

Background: Linear increase in α-synuclein expression and its misfolding as well as Lewy body formation result in loss of dopaminergic phenotype of the substantia nigra pars compacta neurons in aging and Parkinson's disease (PD). In experimental models of PD, GRP78 a neuroprotective endoplasmic reticulum (ER) chaperone protein targets misfolded proteins for degradation and prevents release of caspase12 from the ER. Although the expression of these proteins in animal models is known, there are no reports on their expression pattern in human SNpc.

Methods: On coronal cryosections of autopsied mid brains, we evaluated the expression of α-synuclein, caspase12 and GRP78 using immunohistochemical and stereological approaches, in adult and aging Asian Indians (n=31, 28GW-80yrs).

Results: Stereological quantification revealed that the number of α-synuclein and caspase12 immunoreactive neurons increased gradually with age whereas the number of GRP78 labeled neurons remained stable. α-synuclein immunofluorescence showed a statistically non-significant increase, contrary to linear rise reported in another study. Caspase12 expression was also cytoplasmic at all ages and the expression pattern was similar to α-synuclein. Conversely, GRP78 expression showed a significant age-related upregulation. Marinesco bodies were found at all ages studied, but an increase in their size and numbers was prominent after the sixth decade.

Conclusions: The mild increase in α-synuclein expression and presence of ubiquitinated marinesco bodies suggests age-related induction of protein misfolding. GRP78 upregulation indicates presence of ER stress in the aged brains. Since dopaminergic neurons are preserved in the aging Asian Indians, the logarithmic GRP78 upregulation could be a neuroprotective or modulatory response of the ER to protein misfolding. This possibly signifies better proteasome activity subsequent to initiation of unfolded protein response pathway in the Asian Indians and partly explains the lower prevalence of PD in them.

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Investigation of the role of tau gene transcriptional regulation in neurodegeneration

F.J. Anaya, J. Vandrovcova, A. Lees, R. de Silva (London, United Kingdom)

Objective: The aim is to test the hypothesis that the differential binding of tramscription factor (TF) complexes to the allelic variants of the SNPs in the MAPT promoter region forms the basis of the allele-specific differences in MAPT transcription that Dr. de Silva's group has observed in vitro and in vivo. The individual TFs would be plausible candidates for analysis of genetic variants that exacerbate or reduce these diffirences.

Background: The H1c sub-haplotype drives the association of the human Tau gene (MAPT) with increased risk of progressive supranuclear palsy, corticobasal degeneration and Alzheimer's disease. Two SNPs have been found as risk alleles which affect MAPT transcription and splicing. The objective of this project is to investigate MAPT transcription regulation and the precise role of the MAPT core promoter and predicted regulatory domains by identifying transcription factors (TFs) and TF complexes that bind to these domains.

Methods: We are using site-directed mutagenesis, promoter-luciferase- and electrophoretic mobility shift assays (EMSA) to assess the individual single nucleotide polymorphisms (SNPs) in the MAPT promoter, including a putative downstream enhancer containing one of the H1c-specific SNPs (SNP035). With immobilized double-stranded oligonucleotide probes (promoter trap) representing these regulatory domains we are affinity purifying TFs and TF complexes that bind to these domains to characterize them using gel electrophoresis and mass spectrometry (MS).

Results: Using site-directed mutagenesis in luciferase reporter vectors containing this conserved domain cloned downstream to the MAPT core promoter, we show that SNP035 is mainly responsible for the allele-specific elevation of MAPT promoter activity in vitro. With electrophoretic mobility shift assay (EMSA) we also observe quantitative allele-specific differences in intensity of bands representing TF complexes bound to the probes containing SNP035. On protein gels we observe quantitative allele-specific differences of discrete protein bands of promoter trapped TFs and have identified these proteins using ESI-MS/MS.

Conclusions: SNP035 was shown to attenuate promoter strength and to alter DNA-binding proteins' binding affinities and specificities These DNA-binding proteins have been identified using a mixture of proteomic approaches.

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Non-linear properties of the neuronal discharge in the globus pallidus of parkinsonian patients

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Objective: The objective of the present work is to calculate the embedding dimension in extracellular recordings of the Globus Pallidus of awake parkinsonian patients.

Background: Non-linear methods have been originally designed to consider the memory of a system (i.e., the specific order in which events take place). For this reason they seem promising for the study of temporal patterns present in time series. Non-linear properties have been found in extracellular recordings of the subthalamic nucleus and Globus Pallidus of awake Rhesus monkeys. In particular the approximate entropy (ApEn) has been calculated for interspike intervals time series and their gaussian surrogates and found different, which speaks in favour of the existence of a temporal order (Darbin, Soares, Wichmann, 2006). However, the calculation of ApEn depends on a correct estimation of the embedding dimension (Edim), which has not been done yet.

Methods: Ten interspike intervals (ISIs) time series obtained from extracellular recordings of the Globus Pallidus of 4 parkinsonian patients during functional surgery have been studied. The length of the series was 1530±925 ISIs (mean±SD). Edim was calculated with the method of false nearest neighbours (Andres, Irurzun, Mitelman, Mola, 2006) and compared against gaussian surrogates.

Results: We were able to successfully obtain Edim in all cases, with a value of 6±1. The dimension of the surrogates was significantly higher than for the original time series (13±2, $p<0.001$) indicating that the results obtained depend on the dynamical properties of the series (these are destroyed in the surrogates).

Conclusions: The series analysed show non-linear properties. Therefore, dynamical methods should be used for their study. The false nearest neighbour algorithm allows to successfully calculate Edim and might be useful for the calculation of ApEn.

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Rotigotine activates neurogenesis and improves hyposmia in a PD model

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Objective: We studied, if DA-depletion causes hyposmia via impairment of neurogenesis, and if treatment with the D3/D2/D1 DA-agonist rotigotine prevents these deficits.

Background: Hyposmia is common in Parkinson's disease (PD). Dopamine (DA)-depletion, a hallmark of PD, impairs precursor cell proliferation in the subventricular zone (SVZ), migration through the rostral migratory stream and integration in the olfactory bulb (Nat. Neurosci. 2004;7:726-35).

Methods: Experiment-1: We injected Wistar rats (n=26, 200-225 g) unilaterally with 4 μg 6-OHDA into the substantia nigra (SN). Two weeks thereafter, they received s.c. injections of a slow-release rotigotine preparation (0.1-5.0 mg/kg or vehicle) in 2-day-intervals for fourteen days. They were sacrificed 1 h after injection of 100 mg/kg BrdU. Experiment-2: We measured olfactory discrimination capacity (own vs. new scent, Biobserve Viewer-system) for 3 months in Wistar rats in the following groups (N=12-20/group): a. Normal controls b. Unilateral Bulbectomy c. Unilateral Bulbectomy + contralateral 6-OHDA d. Unilateral Bulbectomy + contralateral 6-OHDA + rotigotine (1.0 mg/kg in 2-day-intervals). e. Bilateral Bulbectomy

Results: Experiment 1: 6-OHDA-lesion reduced BrdU+ SVZ-cells (-35%, $p<0.05$ vs. unlesioned untreated controls). 1 mg/kg or more rotigotine increased BrdU+ SVZ-cells in 6-OHDA-rats (n.s. vs. unlesioned untreated controls). Experiment 2: Bilateral bulbectomy severely impaired odor discrimination (neg. control; $p<0.001$ vs. normal controls), but unilateral bulbectomy did not (pos. control; n.s. vs normal controls). 6-OHDA-lesion moderately impaired odor discrimination (PD-model; $p<0.05$). The impairment was restored by 1 mg/kg rotigotine (n.s. vs normal controls).

Conclusions: Rotigotine restored both deficit in BrdU+ SVZ-cells and odor discrimination in 6-OHDA-lesioned rats.

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Perception bias for acceleration in observed velocity change is less strong in Parkinson's bradykinesia

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Objective: To quantify a minimal observable velocity difference in Healthy Volunteers (HV) and patients with Parkinson's disease (PD) and investigate whether the magnitude of this interval is correlated with the velocity of movements in PD patients: bradykinesia.

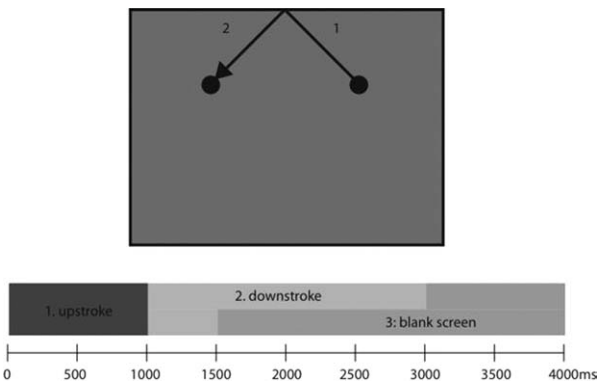

FIG. 1 (40).

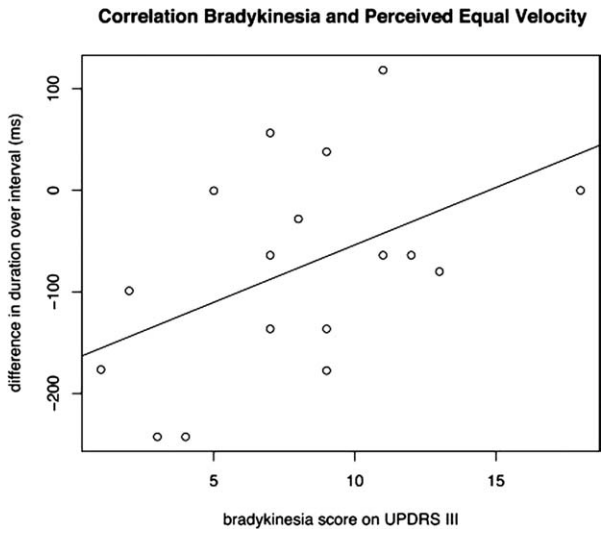

FIG. 2 (40).

Background: Estimating velocity implies the assessment of spatial displacement over time. In our previous fMRI experiment we obtained arguments that cerebral processing demarcates discrete intervals of minimal spatial change, associated with intrinsic cerebral processing time. The observed striatum contribution to such temporal measure was subsequently supported by the behavioural observation that PD patients showed a selective deficit in velocity estimation.

Methods: 19 Healthy Volunteers (HV) and 17 PD patients repeatedly judged change in velocity of a moving ball. Initial trajectory was always passed in 1s (same velocity), while velocity either increased or decreased with variable magnitudes at the point of rebound from the upper side of a monitor screen (Fig. 1). Trajectory lengths before and after rebound were the same. By pressing one of two buttons, subjects had to indicate whether they perceived the ball's velocity to either change or not.

Results: In our paradigm the threshold for detecting velocity change was around 0.014 rad/s in both the PD and HV group. Both groups perceived velocity as equal when the ball actually decelerated while unchanged velocity was perceived as acceleration. This reduced deviation of perceived velocity constancy in PD showed a positive correlation with the severity of bradykinesia (Fig. 2). The detection of velocity change could also be expressed as detected change in the duration of stimulus displacement. The threshold for discriminating velocity change was around 75ms in both groups.

Conclusions: The observed 'acceleration bias' might be explained by the 'flash-lag' effect in which the perception of successive locations of moving stimuli includes extrapolation over adjacent past and predicted locations. In this way the brain accomplishes 'real time' visuomotor control notwithstanding delays due to intrinsic cerebral processing time. In PD, visuomotor control might lack such small-scale feedforward processing, thus resulting in a slowing of movements: bradykinesia.

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Genes regulated in MPTP-treated macaques and human Parkinson's disease suggest a common signature in prefrontal cortex

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Objective: To study the transcriptional changes occurring in presymptomatic phase of Parkinson's disease (PD).

Background: The presymptomatic phase of PD is now recognized as a prodromal phase, with compensatory mechanism masking its progression and non-motor early manifestations, such as depression, cognitive disturbances and apathy. Those mechanisms were thought to be strictly dopamine-mediated until recent advances have shed light upon involvement of putative outside-basal ganglia, i.e. cortical, structures.

Methods: We took advantage of our progressive 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated macaque model to monitor whole genome transcriptional changes in several brain areas. Identified hits were then confirmed by qPCR in the prefrontal cortex of control and PD patients from the French Brain Bank.

Results: Our data reveals that transcriptomic activity changes take place from early stages, suggesting very early compensatory mechanisms or pathological activity outside the basal ganglia, including the PFC. Specific transcriptomic changes occurring in the PFC of fully parkinsonian MPTP-treated macaques have been identified. Interestingly, a large part of these transcriptomic changes were also observed in human post-mortem samples of patients with neurodegenerative diseases analysed by quantitative PCR.

Conclusions: These results suggest that the PFC is able to detect the progression of dopamine denervation even at very early time points. There are therefore mechanisms, within the PFC, leading to compensatory alterations and/or participating to pathophysiology of prodromal PD manifestations.

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Distribution of morphine immunoreactive cells in experimental and human Parkinson's disease

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Objective: To study the distribution, regulation and identity of the morphine-immunopositive cells in the Parkinson s disease brain.

Background: That morphine is endogenously synthesized in the central nervous system of vertebrates has recently been demonstrated and now receives considerable attention. The distribution and regulation of the morphine immunopositive cells in the brain is however unknown at this stage.

Methods: As other opioid peptides are strongly regulated in the basal ganglia of experimental and human Parkinson s disease, we here studied using immunocytochemistry the morphine immunoreactive cells in normal and Parkinson s disease-like conditions in the rat and non human primate models as well as in human Parkinson s disease. Animals of each species were divided into three groups, i.e. control non-lesioned, lesioned (unilaterally for rats and bilaterally for non human primates) and levodopa-treated lesioned.

Results: Morphine immunoreactive neurons are present in caude putamen, red nucleus, interstitial nucleus of Cajal, nucleus of Darkschewitsch and substantia nigra pars reticulata. Globus pallidus is devoided of morphine positive neurons. Immunoreactive neurons are uniformly scattered throughout the striatum and positive cell bodies are mostly of medium size. A marked increase in the labeling intensity of the neuropil and cell immunostaining in lesioned striatum was observed in comparison to the intact animals. In substantia nigra pars reticulata, some labelled neurons are large (30μm perikaryal diameter) and some are medium (15μm perikaryal diameter). Morphine immunoreactivity is also present in certain glial cells. Comparable data were collected in post-mortem tissues from control and parkinsonian patients.

Conclusions: The present study reveals the presence of morphine positive neurons in the brain and suggests that neurotoxin-induced and parkinson-induced lesion induce an upregulation of the morphine levels/immunoreactivity higher level in striatal neurons. Further studies are needed to identify the phenotype of these morphine immunoreactive neurons and to understand their role in the pathophysiology of Parkinson s disease.

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Comprehensive pathological analysis in MPTP-treated macaques reveal widespread synucleopathy and tauopathy

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Objective: To study the synuclein and tau expression pattern in untreated and levodopa-treated chronic MPTP-lesioned macaques.

Background: While the MPTP macaque model of PD is considered the gold-standard for validating symptomatic treatment, its relevance to the parkinsonian neurodegeneration is questioned. A few reports have investigated the expression, regulation and/or pattern of alpha-synuclein after MPTP exposure but they focused upon the substantia nigra, neglected other markers of neurodegeneration and were not controlled for dopamine replacement therapy.

Methods: A comprehensive neuropathological study was performed on 15 macaque monkeys, 6 controls (normal), 6 drug-naïve MPTP-lesioned (parkinsonian) and 3 levodopa-treated MPTP-lesioned (dyskinetic). Immunohistochemistry for alpha-synuclein, tau and glial fibrillary acidic protein (GFAP) were performed on neo-cortex (frontal, temporal, occipital), hippocampus, caudate-putamen, putamen-pallidum, thalamus, substantia nigra, pons, medulla oblongata and cerebellum (dentate nucleus).

Results: Our data reveals a widespread immunoreactivity for both alpha-synuclein and tau in several brain regions of the untreated MPTP-lesioned macaques. These include the substantia nigra, pons, medulla oblongata and cerebellum (dentate nucleus). GFAP staining was marked in the substantia nigra and pallidum. Interestingly, while the tauopathy was not corrected by the levodopa treatment, the immunostaining for alpha-synuclein was clearly reduced in the pallidum, pons, medulla oblongata and cerebellum but not in the substantia nigra.

Conclusions: This study extends the validity of the MPTP-lesioned macaque model of PD to pathological findings. In addition, it suggests that while alpha-synuclein increased expression is levodopa-insensitive in the substantia nigra, it is sensitive to dopamine replacement therapy in other brain regions. These data therefore offer a window for studying dopamine / synuclein interactions and their consequences upon widespread neurodegeneration.

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Inhibition of Ras-GRF1 signaling in the striatum reverts motor symptoms associated to L-dopa induced dyskinesia

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Objective: To demonstrate that inhibition of Ras-GRF1 reduces severity of L-dopa-induced dyskinesia (LID).

Background: LID is a common debilitating complication of the dopamine replacement in Parkinson's disease (PD). Recent evidence suggests that LID formation may be causally linked to abnormal long-term cellular adaptations in the basal ganglia, notably the hyperactivation of the Ras-ERK intracellular signaling cascade. To demonstrate whether a specific targeting of an upstream brain specific component of the Ras-ERK pathway may result in an effective therapy for LID, we have investigated the potential role of Ras-GRF1, a specific activator of the Ras proteins in neuronal cells of the central nervous system.

Methods: A combination of wild-type / genetically-modified mouse and macaque models of LID were used for behavioral, biochemical, molecular and electrophysiological investigations.

Results: In a validated neurotoxic mouse model of PD in which the LID analog abnormal involuntary movements (AIMs) can be induced by repeated L-dopa treatment, Ras-GRF1 deficient mice were significantly resistant to the development of dyskinesia. Furthermore, in a non-human primate (NHP) model of LID, Lentiviral Vectors (LV) expressing dominant negative forms of Ras-GRF1 cause a dramatic reversion of dyskinesia severity leaving intact the therapeutic effect of L-dopa.

Conclusions: These data not only confirm the crucial requirement of the Ras-ERK pathway in LID formation but also demonstrate a central role of Ras-GRF1 in governing critical aspects associated to dopamine-dependent adaptations in the striatum.

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Effects of inflammation on substantia nigra dopamine neurons

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Objective: The focus of this study is to assess time-dependent alterations in neuroinflammation, DAergic neurons, and neuronal signaling cascades in the SN following LPS administration.

Background: Inflammation has been implicated in the pathology of several neurodegenerative diseases, including Parkinson's disease (PD). Studies using the endotoxin lipopolysaccharide (LPS), a potent inflammogen, show that systemic insults can trigger prolonged microglial activation and pro-inflammatory cytokine production leading to delayed and progressive death of substantia nigra (SN) dopamine (DA) neurons, mimicking idiopathic PD.

Methods: In this study, high-dose LPS (5mg/kg, i.p.) or saline (0.9% NaCl) was administered to 8-month-old male c57Bl/6 mice. At 1hr, 3hr, 5hr, and 12hrs post-injection, the SN was assessed for tyrosine hydroxylase (TH, DAergic marker), Iba-1 (pan-microglial marker), phospho-Erk (signaling), and phospho-CREB (signaling).

Results: At 1, 3, and 5 hrs post-injection, high-dose LPS resulted in a significant reduction in SN TH-ir compared to saline controls, with a similar reduction in TH density observed at all 3 post-injection times. However, the high dose of LPS (5mg/kg) resulted in the greatest reduction of SN TH-ir at 12 hrs post-injection, compared to all other groups. In regards to neuroinflammation, the SN of high dose LPS-treated mice had an increase in microglia activation at all post-injection time points, with the greatest increase in activated microglia observed at 5 hrs post-LPS injection. By 12 hrs post-injection, high dose LPS-treated mice exhibited activated as well as reactive microglia; the latter are known to produce inflammatory cytokines that can result in toxic damage to neuronal populations.

Conclusions: These data demonstrate that the initial reduction in TH immunoreactivity observed after an LPS injection is not concomitant with morphological alterations in microglial cells. It is instead possible that the initial alteration in DA phenotype (TH reduction) may perpetuate an inflammatory response that persists and leads to further DAergic damage.

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Impaired mitochondrial stress response due to novel mutations in the mortalin/GRP75 gene in Parkinson's disease

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Objective: We identified human mortalin/GRP75 as a mitochondrial DJ-1-interacting protein that is responsible for cellular stress response and has been linked to Parkinson's disease (PD) pathogenesis due to significantly reduced levels in affected brain regions of PD patients. To define its relevance in DJ-1-mediated mitochondrial protection, we performed a detailed mutation analysis in 286 German sporadic and familial PD patients and functional studies in PD.

Background: There is strong evidence for a correlation of the susceptibility to PD with certain genetic factors. PD-associated proteins that are involved in the maintenance of mitochondrial homeostasis and oxidative stress response and lead, when mutated, to an increased

sensitivity for the onset of neurodegeneration. Loss of DJ-1 function leads to reduced mitochondrial membrane potential, suggesting a potential relevance of its interaction with the intramitochondrial stress response protein mortalin/GRP75 for mitochondrial homeostasis.

Methods: Via high throughput mutation screening and subsequent direct sequencing, we defined sequence variations and analyzed identified amino acid changes of the protein concerning differential interaction, mitochondrial morphology and function, ROS production and cell death in different cellular models. Two recently described mutations in the mortalin/GRP75 gene in Spanish PD patients were integrated in our functional analyses.

Results: One mutation in the mortalin/GRP75 gene, not present in more than 500 control chromosomes, lead to an amino acid exchange in a highly conserved region.We found no evidence for differential interaction of the mutant protein with DJ-1. However our functional studies argue in favour of subcellular mislocalization, a higher susceptibility towards proteolytic stress including impaired mitochondrial function as well as decreased cell viability caused by mutant mortalin/GRP75 in stably transfected cells. Similar results were obtained for the Spanish mutations.

Conclusions: The novel mutation in the mortalin/GRP75 gene links this mitochondrial protein with PD. Future studies focus on functional effects of the identified variant in neurons to determine the relevance of mortalin/GRP75 in neurodegeneration.

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Reduced basal autophagy and impaired mitochondrial dynamics due to loss of Parkinson's disease-associated protein DJ-1

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Objective: To analyse the role of DJ-1 in the regulation of mitochondrial and lysosomal function.

Background: Mitochondrial dysfunction and degradation takes a central role in current paradigms of neurodegeneration in Parkinson's disease (PD). Loss of DJ-1 function is a rare cause of familial PD. Although a critical role of DJ-1 in oxidative stress response and mitochondrial function has been recognized, the effects on mitochondrial dynamics and downstream consequences remain to be determined.

Methods: To determine the role of DJ-1 in PD, we used immortalized mouse embryonic fibroblasts from a DJ-1 KO mouse model and human fibroblasts from carriers of the E64D mutation in the DJ.1 gene. Mitochondrial and lysosomal function and morphology was studied using FACS-based analysis, quantitative morphology, life cell imaging and ultrastructure analysis.

Results: Using DJ-1 loss of function cellular models, we define a novel role of DJ-1 in the integrity of both cellular organelles, mitochondria and lysosomes. We show that loss of DJ-1 caused impaired mitochondrial respiration, increased intramitochondrial reactive oxygen species, reduced mitochondrial membrane potential and characteristic alterations of mitochondrial shape as shown by quantitative morphology. Importantly, ultrastructural imaging and subsequent detailed lysosomal activity analyses revealed reduced basal autophagic degradation and the accumulation of defective mitochondria in DJ-1 KO cells, that was linked with decreased levels of phospho-activated ERK2.

Conclusions: We show that loss of DJ-1 leads to impaired autophagy and accumulation of dysfunctional mitochondria that under physiological conditions would be compensated via lysosomal clearance. Our study provides evidence for a critical role of DJ-1 in mitochondrial homeostasis by connecting basal autophagy and mitochondrial integrity in Parkinson's disease.

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Urate attenuates H2O2-induced neurotoxicity in a dopaminergic cell line

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Objective: To evaluate the effect of urate and its precursor inosine on H2O2- and 6-OHDA-induced neurotoxicity.

Background: Recent data have correlated higher levels of urate, an antioxidant and inosine metabolite, with a decrease risk of developing Parkinson's disease (PD) and with a slower progression of PD symptoms. Moreover in vitro studies have shown that urate increases viability of dopaminergic neurons and reduces glutamate-induced neuronal death.

Methods: The MES23.5 cell line was treated with 200 uM H202 or with 50 uM 6-OHDA in presence of urate (0 - 100 uM) or inosine (0 - 1000 uM). Cell viability was assessed by the MTT test and intracellular dopamine content was measured by HPLC system at different times of treatment.

Results: At 24 h of treatment cell viability was decreased by 60 % ($P<0.01$) and by 50 % ($P<0.01$) in 200 uM H202- and 50 uM 6-OHDA-treated cells, respectively. At the same time point dopamine content was decreased by 65 % ($P<0.01$) in H2O2-treated cells. In 6-OHDA-treated cells dopamine depletion occurred at 3 h of treatment with a reduction of about 47% ($P<0.01$). 100 uM urate and 100 uM inosine tended to increase cell viability by 37 % and 45% in H202- treated cells, but they showed no effect on 6-OHDA-treated cells. Moreover urate and inosine significantly increased dopamine content of about 77% ($P<0.01$) and 29% ($P<0.05$) in H2O2-treated cells, respectively.

Conclusions: These data suggest that inosine and urate attenuate functional deficits and possibly cell death induced by oxidative stress in a cellular model of PD.

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Gene expression induced by L-DOPA in the striatum in 6-hydroxydopamine-lesioned mice

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Objective: To identify genes regulated by L-DOPA in a mouse model of PD.

Background: One major hypothesis is that L-DOPA induced dyskinesia (LID) in Parkinson's disease result from an aberrant transcriptional program induced by L-DOPA in the striatum. Genes deregulated by L-DOPA and responsible for LID development remain unknown.

Methods: Mice with unilateral injection of 6-hydroxydopamine in the striatum were compared to sham-operated animals. After 3 weeks, mice were treated with 20 mg/kg L-DOPA + 12 mg/kg benserazide and sacrificed 0, 1, 3 and 6 hours post L-DOPA injection ($n = 3$–6 per group). Total RNA from striata were extracted and hybridized on cDNA beadchips (Illumina MouseWG-6 v2.0). Gene expression analysis was carried out using BRB array tools, an open source software using R (http://linus.nci.nih.gov/BRB-ArrayTools.html).

Results: 257 genes were significantly deregulated by L-DOPA along time (F test, $p<0.01$, 216 upregulated and 41 down-regulated). Using a Self Organizing Tree Algorithm (SOTA), we identified 4 clusters corresponding to upregulated genes at 1 h (19 genes), 3 h (51 genes), 3-6 h (127 genes) and 6h (19 genes). As expected from previous studies, Fos belonged to the 1h-cluster (+ 26-fold change, $p=0.0026$) whereas Fos-b upregulated in the 3h-cluster (+ 14-fold change, $p=0.0003$). Gene ontology analysis showed an enrichment in genes belonging to the MAPK signaling pathway (enrichment ratio (ER)=34, $p=0.003$), transmission of nerve impulse (ER=4, $p=0.01$) and regulation of transcription (ER=1.5, $p=0.03$). In addition, genes involved in cytoskeletal remodeling were upregulated.

Conclusions: Our results support the hypothesis that one of the major effects of L-DOPA in the dopamine-denervated striatum is the activation of the MAPK pathway through the dopamine/glutamate

signaling cascade. Most of the L-DOPA-induced genes were regulators rather than effectors of these cascades suggesting that deregulation mechanisms may play a key role in the induction of LID.

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Dopamine peroxidation in the pathogenesis of Parkinson's disease: New evidences in human cerebellum

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Objective: In order to investigate on the metabolism of dopamine (DA) occurring in human cerebellum, we analysed this brain region by using the in gel-detection of DA peroxidizing activity, by us set out, combined with mass spectrometry (MS) analysis. Parallely, we assayed, by HPLC-ED, DA levels in cerebellar tissues in comparison with DA levels in midbrain tissue.

Background: The cerebellum is a brain area not traditionally considered dopaminergic, but it contains neuronal elements, which are indicative of dopaminergic neurotransmission. We have reported on in gel-detection of a DA peroxidizing activity from human midbrain tissue, by using DA and hydrogen peroxide as substrates. This enzymatic reaction, analysed by MS, revealed the presence of proteins that may play a role in neurodegenerative disease, highlighting a possible functional link among DA redox cycle and protein metabolism.

Methods: After separating protein mixtures from human normal cerebellum homogenates on two sets of identical native gels, one gel set was subjected to specific activity staining by using DA and hydrogen peroxide and the second set of gels was stained with Coomassie Blue. The reactive gel bands were analysed by MS. As blank sample a colorless band was cut, immediately below the reactive band.

Results: A strong red-orange activity band, similarly to that previously developed from human midbrain tissue, appeared in human cerebellar total vermis, cortex and central white matter. MS analysis of the specific activity bands identified, along with proteins of glucose metabolism, some peroxiredoxines: Prx-1, already described in the previous study, Prx-2, Prx-6 and DJ-1. Notwithstanding the presence of peroxidative enzymatic activity, DA concentrations assayed in cerebellar tissues were lower if compared to midbrain tissue.

Conclusions: Dopamine peroxidizing activity was detected in cortex, total vermis and white matter from human cerebellum. Cerebellar peroxidative reaction, revealed, like the peroxidative reaction from midbrain, the presence of some proteins, peroxiredoxins and DJ-1, interplaying with the oxidative metabolism of DA. Our results suggest a possible cerebellar dopaminergic system, highlighting new perspectives of investigation in the pathogenesis of Parkinson's disease.

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CSF amyloid β 1-42 predicts cognitive decline in Parkinson's disease

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Objective: To examine the ability of cerebrospinal fluid (CSF) levels of amyloid beta 1-42 ($A\beta_{1\text{-}42}$), p-tau-181 and total tau to predict future cognitve decline in Parkinson's disease (PD) patients with prospective longitudinal assessment.

Background: Cognitive decline associated with Parkinson's disease is common and highly disabling. Biomarkers that inform risk for cognitive decline would be a useful addition to the clinical management of this disease.

Methods: Forty seven patients with PD were enrolled in this study and 43 had at least one longitudinal follow-up evaluation. CSF collected at baseline and cognition was assessed at baseline and at annual follow-up visits using the Mattis Dementia Rating Scale (DRS-2). CSF was tested for $A\beta_{1\text{-}42}$, p-tau-181 and total tau levels using the Luminex xMAP platform. Mixed linear models were used to test for associations between baseline CSF biomarker levels and change in cognition over time.

CSF biomarkers as predictors of deterioration on the DRS-2

CSF biomarkers	Estimated effects on baseline DRS-2	Estimated effects on annual DRS-2
$A\beta_{1\text{–}42}$	−0.0038 (0.02); p=0.835	0.040 (0.013); p=0.002
Tau	0.008 (0.046); p=0.857	−0.0031 (0.035); p=0.928
p–tau_{181p}	0.133 (0.11); p=0.261	−0.069 (0.083); p=0.401
tau/$A\beta_{1\text{–}42\ ratio}$	1.23 (4.74); p=0.797	–4.47 (3.70); p=0.227
p–tau_{181p}/$A\beta_{1\text{–}42\ ratio}$	16.86 (11.6); p=0.154	−12.25(7.85); p=0.118

Results: Lower baseline CSF $A\beta_{1\text{-}42}$ levels were strongly associated with more rapid cognitive decline. Compared to subjects with higher CSF $A\beta_{1\text{-}42}$ levels, subjects with CSF $A\beta_{1\text{-}42}$ at or below 192 pg/mL declined an average of 5.20 (95% CI 1.53, 8.86, p=0.01) points per year more rapidly on the DRS-2 after adjustment for age, disease duration and baseline cognitive status. CSF tau and p-tau-181 levels were not significantly associated with cognitive decline.

Data are shown as β (SE). For the first column, each coefficient (β) represents the difference in baseline DRS-2 score per one point difference in biomarker. For the second column, coefficients represent the difference in annual rate of change of the DRS-2 for each one point change in the biomarker.

Conclusions: Our data show that CSF $A\beta_{1\text{-}42}$ is an independent predictor of cognitive decline in PD patients. This biomarker may provide clinically useful prognostic information, particularly if combined with other risk factors for cognitive impairment in PD.

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The role of disturbed innate immunity linked to toll-like receptor 4 (TLR4) in α-synucleinopathies

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Objective: To determine the role of TLR4 on microglial function in response to α-synuclein.

Background: The pathological hallmark of α-synucleinopathies are α-synuclein-positive cytoplasmic inclusions spread throughout the neurodegenerating CNS. Microgliosis commonly accompanies neurodegeneration in α-synucleinopathies and is considered a possible mediator of the disease process. Up-regulation of TLR4/CD14 has been reported in human MSA and PD/DLB brains as well as in murine transgenic models of neuronal and oligodendroglial α-synucleinopathy (Stefanova et al., 2007, Letiembre et al., 2007), however the role of innate immunity in these disorders remains unexplored.

Methods: Immortalised murine microglial cell line BV-2 and primary murine microglia (P1-3) were used for all the experiments. The role of TLR4 was assessed by either using blocking antibodies, or preparing cell culture from TLR4 deficient mice. FACS analysis, immunocytochemistry and fluorescence microscopy were applied to characterise microglial activation and phagocytosis in response to fibrillar α-synuclein.

Results: Preliminary results suggest effects of α-synuclein on microglial activation and phagocytosis that is partly mediated through TLR4 and may be relevant to degeneration in α-synucleinopathies.

Conclusions: The current studies provide new insights into the role of innate immunity in α-synucleinopathies and define further pathogenic mechanisms that may play a role in neurodegeneration and identify potential novel therapeutic targets.

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Toe-clearance while stepping over obstacles of different heights is not influenced by dopaminergic treatment in Parkinson's disease

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Objective: To compare the influence of dopaminergic replacement on toe-clearance regulation while stepping over different obstacles.

Background: L-dopa can improve hypometric movements (e.g. stride length) in Parkinson's disease (PD). Attentional strategies such as verbal instruction and visual cues also normalize gait parameters. However, there are no studies showing how dopamine influences regulation of how we step over obstacles of different height. Toe-clearance (vertical distance between toes to the superior edge of obstacle) is a measure that describes the relationship between safety and energy economy, while also providing an opportunity to examine sensorimotor integration in PD.

Methods: Twelve participants with PD [UPDRS III: 43.5(Off) 29.7(On)] and twelve age, sex and height matched participants were recruited from the community. PD participants were collected 12 hours after L-dopa withdrawal and 1 hour after medication. Kinematic data was collected using two digital video cameras. Obstacles were normalized by the lateral maleolus to the ground distance (low obstacle) and by the half of knee joint distance to the ground (High obstacle) of each participant.

Results: No significant influence of dopamine was identified for toe-clearance for either limb (Lead Limb: 1st to cross - $F_{1,11}=2.302$; p= 0.157; Trail Limb: 2nd to cross - $F_{1,11}=0.376$; p= 0.552). No differences were identified between the PD On and Control groups ($F_{1,22}=1.368$; p= 0.255). An obstacle main effect showed that all participants cleared the higher obstacle with a significantly greater clearance (approximately 19% to 21% compared to lower obstacles) in all statistical comparisons (Off x On - Lead Limb: $F_{1,11}=22.14$, p=0.001 ; Trail Limb: $F_{1,11}=6.98$, p=0.023 / On x Controls – Lead Limb: $F_{1,22}=22.74$, p=0.001; Trail Limb: $F_{1,22}=14.27$, p=0.001).

Conclusions: The lack of a group and/or dopaminergic effect suggests that obstacle clearance is not mediated by basal ganglia pathways. The requirement to clear an obstacle may be similar to visual cues, allowing patients to overcome hypometria and behave much like healthy control participants.

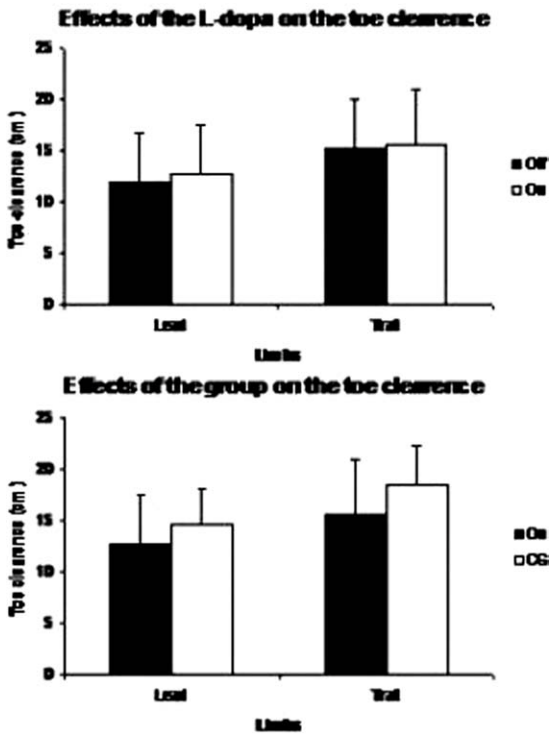

FIG. 1 (53).

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Nestin protein is expressed in striatal astrocytes in the acute though not the chronic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model

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Objective: To evaluate nestin expression in striatal astrocytes in two different MPTP mouse models.

Background: Nestin is a marker of neural progenitor cells in the developing central nervous system and is replaced by glial fibrillary acid protein (GFAP) following their differentiation into mature astrocytes. Nestin reexpression has previously been detected in neostriatal astrocytes in acute and subacute MPTP mouse models. A neurotrophic role for these nestin expressing astrocytes was postulated.

Methods: The acute (4 IP injections of 20mg/kg MPTP every 2 hours) and chronic (1 IP injection of 4mg/kg MPTP daily, for 20 days) MPTP models were induced in 25 and 26 C57/bl mice, respectively. Nineteen mice served as overall vehicle controls. Pathology was studied at 1-3-7-14-21 and 1-7-21-42-63 days post-last-injection (PLI), respectively. Single immunohistochemistry for Tyrosine-hydroxylase (TH), GFAP and nestin, as well as double immunofluorescence for nestin-GFAP were performed. Immunopositive cells were counted per mm^2 of substantia nigra (SN) and striatum. Striatal TH-immunoreactivity was semi-quantitatively evaluated.

Results: There was a significant reduction in the mean number of TH+ neurons in SN of both acute ($P<0.001$) and chronic ($P<0.05$) models on day 1 PLI. It stabilized thereafter in the acute model but upturned to control levels in the chronic model. Striatal TH-immunoreactivity significantly decreased in both models ($P<0.001$), upturning 2 months PLI in the chronic model. In the acute model, GFAP+ astrocytes significantly increased in both SN and striatum ($P<0.001$); specifically, striatal astrocytosis reached a peak on day 3 PLI and never returned to control levels. In chronic model, the number of astrocytes marginally increased, at days 42 and 63. Nestin reactive astrocytes were detected only in the striatum of the acute model ($P<0.001$).

Conclusions: Nestin reactive astrocytes are regionally detected in the striatum, at day 3 PLI only in the acute MPTP model.

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Deficiency in the Nrf2 transcription factor but not in its target gene heme oxygenase-1 sensitizes to MPTP

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Objective: To compare neuronal damage and neuroinflammation in Nrf2 and heme oxygenase-1 (HO-1) knockout mice in the subacute MPTP model of Parkinson's disease (PD).

Background: The transcription factor Nrf2 and its target gene products, including HO-1, elicit an antioxidant response that may have therapeutic value for PD. However, iron released from HO-1-mediated heme degradation might promote oxidative stress, leading to detrimental effects. Before targeting Nrf2 for PD therapy it is imperative to determine if HO-1 is neurotoxic or neuroprotective in the basal ganglia.

Methods: Both genetic backgrounds were submitted to intraperitoneal injection of of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) for five consecutive days. Protein and immunohistochemical analysis of gliosis and dopaminergic nigroestriatal degeneration, HPLC determination for dopamine, and iron deposits were evaluated.

Results: Nrf2-knockout mice exhibited increased gliosis and dopaminergic degeneration, compared to wild type littermates, as determined by immunohistochemical staining of tyrosine hydroxylase in striatum and substantia nigra and by HPLC determination of striatal dopamine and DOPAC. On the other hand, the severity of degeneration in HO-1-null mice was neither increased nor reduced compared to their wild type littermates.

Conclusions: The fact that HO-1 deficient mice were similarly sensitive to MPTP as wild type mice suggests that HO-1 does not protect or enhance the sensitivity to neuronal death in Parkinson's disease. Moreover, these results suggest that Nrf2, capable of activating not only HO-1 but also other antioxidant genes, is more efficient than HO-1 for cytoprotection in MPTP-treated mice. Therefore, the pharmacological or genetic intervention on Nrf2 may provide a neuroprotective benefit as add on therapy with current symptomatic protocols.

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Role of tau oligomers in Parkinson's disease and dementia with Lewy bodies

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Objective: To characterize tau oligomers in PD and DLB.

Background: Although tau pathology is a prominent feature of progressive supranuclear palsy (PSP), its involvement in disorders usually regarded as primarily synucleinopathies, such as idiopathic Parkinson's disease (IPD) or dementia with Lewy Bodies (DLB), is less well characterized. Nonetheless, recent genome wide association screens have suggested that tau polymorphisms may be found in a substantial proportion of sporadic IPD cases. An emerging view in neurodegeneration is that visible aggregates such as neurofibrillary tangles (NFT) themselves are not toxic; rather, aggregates of a size intermediate between monomers and NFT- so-called tau oligomers- are pathogenic.

Methods: We generated and characterize a novel monoclonal antibody specifically recognizing tau oligomers, tau oligomer monoclonal antibody (TOMA). We used this antibody to characterize tau oligomers in post mortem brain tissue from PD and DLB as well as brains from mouse models for PD.

Results: Elevated levels of tau oligomers were detected in PD and DLB brains and in the brains from young PD mouse models. These data demonstrate that tau oligomers play a crucial role in these disorders and validate them as a potential target for PD therapeutics.

Conclusions: One potential mechanism for formation of tau oligomers in IPD and DLB is by seeding with oligomeric alpha-synuclein; we are using dual transgenic fly models to demonstrate enhanced synergistic toxicity of tau and alpha-synuclein when expressed in dopaminergic neurons, as well the effects of alpha-synuclein on tau conformation and vice versa. These efforts should yield novel insights into the interplay between alpha-synuclein and tau in pathogenesis of movement disorders.

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Alpha-synuclein oligomers in Parkinson's disease (PD) and Lewy body dementia (DLB)

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Objective: To study the formation of alpha-synuclein oligomers and pore-like structures *in vitro* and *in vivo*.

Background: Aggregation of α-synuclein has been linked to the pathogenesis of neurodegenerative diseases such as Parkinson's disease (PD), Lewy Body dementia (DLB) and other synucleinopathies. Increasing evidence suggests that alpha-synuclein pre-fibrillar oligomers and annular protofibrils, rather than mature fibrils, are the pathogenic species in PD.

Methods: We used novel conformation specific antibodies to study the formation of alpha-synuclein oligomers and annular protofibrils from wild type and the disease related alpha-synuclein mutants A30P, A53T and E46K, and to examine their toxicity to cultured cells. Moreover, we investigated these structures in brains from PD and DLB.

Results: Alpha-synuclein disease related mutations promote the formation of toxic oligomer in vitro. Our data show elevated levels of these pre-fibrillar intermediates in PD and DLB brains as compared to age matched controls.

Conclusions: Our results suggest that targeting these toxic structures with conformation specific antibodies/intrabodies has potential as a disease modifying treatment for PD and other synucleinopathies.

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Progressive loss of dopaminergic function that is dose dependant in an AAV1/2 rat model of Parkinson's disease α-synucleinopathy

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Objective: To examine the effects of AAV1/2 delivery of A53T α-synuclein on dopaminergic function in the nigrostriatal system according to dose and time.

Background: A central pathological feature of Parkinson's disease is the presence of α-synuclein aggregates in DA neurons of the SN. Previously, we have shown, in rats, that 3 weeks after viral vector delivery of human mutated α-synuclein (A53T) to the SN, results in nigrostriatal pathology. However, the control vector used, GFP, also produced degeneration (titer, 5.1 x 10exp12 gp/mL). In the current study we have defined preparations of active and control vector to reliably attribute degenerative effects to α-synuclein.

Methods: Chimeric AAV1/2s (A53T α-synuclein, GFP, or empty vector [EV]) were delivered to the SN of rats in 2 concentrations (1.7 x 10exp12 or 5.1 x 10exp11 gp/mL). At 3 and 6 weeks, behaviour was examined in the cylinder task, followed by post-mortem analyses including: SN TH cell counts, striatal TH optical density, striatal DA neurochemistry, and examination of axon and cell morphology.

Results: We report that at the higher 1.7 x 10exp12 gp/mL concentration, only AAV A53T, not GFP or EV, showed significant signs of nigrostriatal pathology. At 3 weeks, in the striatum, dystrophic neurites had developed, DA turnover was increased ($P<0.05$), and TH was reduced ($P<0.05$). Signs of dysfunction progressed as shown at 6 weeks by a marked presence of dystrophic neurites, TH cell loss in the SN ($P<0.05$), a reduction in striatal DA ($P<0.01$) and TH-ir ($P<0.05$), and a greater increase in DA turnover ($P<0.05$). At 3 weeks there was a significant degree of forelimb asymmetry in the cylinder task ($P<0.01$) that persisted through 6 weeks ($P<0.01$). Post-mortem measures in the lower 5.1 x 10exp11 gp/mL condition (A53T synuclein) revealed similar alterations, at 3 weeks, that resolved by 6 weeks.

Conclusions: AAV1/2 delivery of A53T α-synuclein produces degenerative changes along the nigrostriatal path that is dose and time dependent. The progression of DA and behavioural deficits in this model provide a platform for evaluating novel treatments directed at preventing and/or reversing PD α-synucleinopathy. These data highlight the need to characterize the dose of AAV being utilized to avoid potential non-specific effects.

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Antibodies to melatonin in patients with multiple system atrophy

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Objective: The aim of our research was to measure the level of antibodies to melatonin (AM) in the serum and cerebrospinal fluid (CSF) samples in the patients with different types of multiple system atrophy.

Background: Multiple system atrophy (MSA) is a progressive neurodegenerative disorder characterized by symptoms of autonomic nervous system failure such as fainting spells and bladder control problems, combined with motor control symptoms such as tremor, rigidity, and loss of muscle coordination. MSA affects both men and women primarily in their 50s and 60s. Melatonin is a hormone produced in the brain by the pineal gland, from the amino acid tryptophan. The synthesis and release of melatonin suggests the involvement of melatonin in circadian rhythm and regulation of diverse body functions.

Methods: AM were obtained by separation of Ig G serum fractions from the rabbits immunized by N-acetyl-5-methoxytryptamine,

wich is melatonin chemical substrate. AM was measured by flow cytometry in serum and cerebrospinal CSF samples. We studied the levels of MA in 12 patients with olivopontocerebellar atrophy (OPCA), characterized by progressive ataxia; 10 patients with Striatonigral degeneration (SND), predominating Parkinson's-like symptoms; and 15 patients with Shy Drager syndrome (SDS), characterized by parkinsonism plus a more pronounced failure of the autonomic nervous system. Control group was comprised by serum of 35 healthy donors, and CSF from 12 patients operated with umbilical hernia.

Results: Results The AM levels were increased in the serum of 76% of OPCA patients, 86% SND patients, and 69% SDS patients. The AM levels in CSF samples were increased in 85 % OPCA patients, 78% SND patients, and 88% SDS patients in comparison with a median control values.

Conclusions: Many biological effects of melatonin are produced through activation of melatonin receptors, while others are due to its role as a pervasive and powerful antioxidant, with a particular role in the protection of nuclear and mitochondrial DNA. In animal models, melatonin has been shown to ameliorate glutamate induced neuronal death, possibly due to its antioxidant effects. There is no discovered cure for MSA. Since the data obtained in differentt MSA patients suggest an increased immune response to melatonin, these finding could be used in a future study of a new approaches for MSA syndromes therapy.

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Levodopa and pramipexole induce different striatal expression profiles in an animal model of parkinsonism

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Objective: To compare the gene expression profiles induced by L-dopa or pramipexole (PRA) in the lesioned striatum of rats with a moderate lesion of the nigrostriatal pathway.

Background: Both L-dopa and PRA are widely used Parkinson's disease (PD) clinics. Initially L-dopa works sufficiently against the symptoms of PD but after some years of treatment dyskinesias appear. Lower risks of dyskinesias are observed when D2 dopamine receptor agonists are used. PRA has been successfully used to treat the symptoms of PD at its early stages but their therapeutic benefit tends to be less when compared to L-dopa. Although there have been several studies published on the gene expression profile induced by the nigrostriatal dennervation and by L-dopa therapy in patients, and in animal models, only a few have dealt with the gene expression profile induced by dopamine agonists.

Methods: Rats with severe motor deficiencies were randomly assigned to receive during 3 weeks water, L-dopa 170 mg/kg (LL), or PRA 3.5 mg/kg (LP). Normal rats were treated with water (control group). Drugs were dissolved in the animal's drinking water. The doses employed were chosen to be capable of causing comparable improvement of contralateral forepaw akinesia in the cylinder test. Messenger RNA was isolated from the lesioned striata to interrogate Affymetrix Rat Gene 1.0 ST. The probes sets were summarized and normalized by the Robust Multichip Average algorithm. Differentially expressed genes between conditions and controls were determined using the empirical Bayes moderated t-test in the Bioconductor package Linear Models for Microarray Data. All analyses were performed using the open-source R programming environment in conjunction with the open-source Bioconductor software.

Results: Microarray profiling identified several genes that were differentially expressed between the LL and the LP groups. Sets of co-regulated genes are visualized in a heatmap. Between these genes we have identified some dopamine related genes and genes related to mitochondrion, ribosomal and proteosome function.

Conclusions: We hope to further identify key transcripts and metabolic pathways related to the therapeutic effects, as well as those possibly related to neuroprotection, plasticity and dyskinesias.

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The formation of pore-like amyloid aggregates in movement disorders

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Objective: To analyze amyloid pore-like structures in Parkinson's disease (PD), Lewy Body dementia (DLB) and Supranuclear Palsy (PSP).

Background: Proteins associated with neurodegenerative diseases such as beta-amyloid and alpha-synuclein have the tendency to form pore like amyloid structures (annular protofibrils). Disease related mutations in these proteins have been shown to increase the formation of pore like structures. *In vitro* these pores are heterogeneous and cause ion homeostasis and the leakage of proteins from vesicles and cells.

Methods: We used novel antibodies to study the formation of amyloid annular structures in Parkinson's disease (PD), Lewy Body dementia (DLB) and Supranuclear Palsy (PSP).

Results: Systematic analysis of brains from PD, DLB and PSP patients showed the presence of alpha-synuclein annular aggregates, and unexpectedly revealed the presence of tau annular protofibrils as well; these novel tau-containing structures were widespread and associated with different cell types, including astrocytes and oligodendrocytes. Thorough examination of these intracellular tau aggregates demonstrate that they have a pore like structure, are partially phosphorylated, and heavily ubiquitinated.

Conclusions: That pore like structures are normally associated with membranes suggests that tau aggregation might impair cellular ion homeostasis. In addition, these ubiquitinated tau aggregates might affect the efficiency of the ubiquitin-proteasome system and lead to the accumulation of other misfolded proteins.

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α-Synuclein oligomers induced by trivalent metal ions – a distinct particle species with pivotal role in the pathogenesis of syncleinopathies?

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Objective: To analyze the aggregation pathways of α-synuclein (α-syn) induced by various metal ions and to characterize the molecular properties of the resulting aggregates.

Background: Parkinson's disease (PD) is characterized by the formation of fibrillar α-syn aggregates. Small aggregates, termed oligomers, are thought to be the principal toxic aggregate species in PD. Several lines of evidence implicate iron ions in the pathogenesis of PD. Recently, we could describe an iron dependent two step α-syn aggregation pathway that leads to detergent resistant aggregates that form pores in biological membranes and share structural properties with α-syn oligomers that can be found *in vivo*.

Methods: Using single particle-based methods such as scanning for intensely fluorescent targets (SIFT) we analyzed aggregation pathways and oligomer formation of α-syn. Aggregate characterization was complemented by thioflavin T fluorescence, circular dicroism and by electron microscopy.

Results: Trivalent ions as Fe^{3+}, Al^{3+}, Gd^{3+}, Ti^{3+} and Tb^{3+} at low micromolar concentrations dramatically increased aggregation of α-syn and induced immediate formation of relatively SDS-resistant α-syn oligomers. In presence of divalent metal ions such as Mg^{2+}, Mg^{2+}, Cu^{2+}, Zn^{2+} and Fe^{2+}, formation of this aggregate species was not detectable. Under control conditions, α-syn at 50μM formed fibrils within 48 to 96 hours. Divalent metal ions did not show any impact on fibril formation and β-sheet formation. In contrast, oligomeric α-syn aggregates induced by trivalent metal ions did not show molecular properties of fibrils. In their presence the formation of typical α-syn fibrils was suppressed. Iron induced oligomers form pores in biological membranes and bind to lipid vesicles. In contrast to monomeric α-syn and fibrillar aggregates formed in presence of diva-

lent metal ions, only oligomers induced by trivalent ions were able to bind to POPC lipid vesicles. Based on the formation of potentially toxic aggregates, we developed a high-throughput aggregation assay for the identification of anti-aggregative compounds.

Conclusions: Our results shed light on the formation and biochemical properties of toxic α-syn oligomers in neurodegenerative diseases and provide new approaches for drug-development.

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Anti-dyskinetic effects of piribedil on levodopa-induced dyskinesia in the unilaterally 6-OHDA-lesioned rat model of Parkinson's disease

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Objective: This study aimed to investigate the anti-dyskinetic effects of piribedil using unilaterally 6-OHDA-lesioned rats that received chronic administration of levodopa.

Background: A central problem in the long-term treatment of Parkinson's disease (PD) with levodopa (L-DOPA) is the development of dyskinesias. There is evidence that $alpha_2$-adrenoceptor antagonists attenuate these disabling side effects. The D_2/D_3 dopamine agonist piribedil, which is effective in treating all major symptoms of PD, displays antagonist properties at $alpha_2$-adrenoceptors.

Methods: Unilaterally 6-OHDA-lesioned rats (12.5 mg 6-hydroxydopamine; -2.8 mm from bregma, 2 mm lateral, 9 mm ventral) were treated i.p. twice daily with levodopa methylester (12.5 mg/kg) and benserazide (3.25 mg/kg) for 20 days. At day 21, five minutes before administration of levodopa, rats were either treated i.p. with saline or 5, 15 and 40 mg/kg piribedil. The anti-dyskinetic effect of piribedil was assessed by measuring the levodopa-sensitized contraversive circling response and levodopa-induced characteristic abnormal involuntary movements (AIMs).

Results: Pre-treatment with 5 and 40, but not 15 mg/kg of piribedil, led to a reduction of contralateral turning behaviour and AIMs scores for axial dystonia, orolingual and forelimb dyskinesia compared to the vehicle group. This bell-shaped dose response may be the result of a partial antagonism of piribedil at $alpha_2$-adrenoceptors.

Conclusions: This data suggest a role for piribedil in the treatment of patients with late stage PD and efficacy of piribedil in treatment of levodopa-induced dyskinesias.

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Effect of amitriptyline on PC12 cells after copper intoxication

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Objective: To evaluate the effect of amitriptyline on PC12 cells in a copper intoxication model.

Background: ATP7B-deficient LEC rats are a genetic animal model of Wilson's disease (WD). Amitriptyline has been shown to protect these rats from liver cirrhosis, presumably by the inhibition of apoptosis caused by the activation of acid sphingomyelinase and release of ceramide. Since WD patients run the risk of a neurological deterioration at the beginning of a decoppering therapy or may still feature residual neurological symptoms during long-term treatment, it is appealing to speculate that the widely-used antidepressant amitriptyline may also have some protective effect in the central nervous system in WD.

Methods: A copper intoxication model was established in PC12 cells, a neuronal model cell line. Cell survival after the administration of copper w/ and w/o amitriptyline was quantified by MTT tests. Apoptosis was investigated using a Cell Death Detection ELISA (Roche).

Results: The simultaneous administration of 30 μM amitriptyline led to an increased survival of PC12 cells two (30±11% vs. 11±4%, p=0.04) and four (25±7% vs. 9±3%, p=0.03) days after intoxication of PC12 cells with Cu(2)Cl. Preliminary results from the Cell Death Detection ELISA confirmed that amitriptyline prevented apoptosis in these cells.

Conclusions: This in vitro study indicates that amitriptyline may have some potential in the treatment of neurological WD. However, further basic research has to be conducted before any clinical investigation may appear justified.

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Pharmacological enhancement of phosphatase-mediated alpha-synuclein dephosphorylation is protective in transgenic mice

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Objective: To evaluate the impact of modulating the phosphorylation state of alpha-synuclein on the phenotype of alpha-synuclein transgenic mice in a proof-of-principle study.

Background: alpha-Synuclein, which is a major component of Lewy bodies and Lewy neurites, is hyper-phosphorylated at serine 129 in Parkinson's disease and other alpha-synucleinopathies. Phosphorylated alpha-synuclein also accumulates in dopaminergic neurons of transgenic mice that express human alpha-synuclein. Drosophila and cell culture studies suggest that this post-translational modification promotes the toxicity of alpha-synuclein. Here we focused on enhancing the de-phosphorylation of alpha-synuclein as a neuroprotective therapeutic strategy. Protein phosphatase 2A (PP2A) is the major serine/threonine phosphatase in the brain. We have extracted a small molecule (SIG-1012) from coffee that promotes PP2A activity in vitro and in vivo.

Methods: alpha-Synuclein transgenic mice were placed on SIG-1012 containing feed or control chow upon weaning. Motor behavior was assessed every three months and brains were analyzed at 9 months of age. The study was done according to the NIH guide for the use of laboratory animals and under an approved protocol.

Results: Significant improvement in behavioral performance was noted in treated mice compared to the control group in the open field horizontal activity test at 3 months of age, on the rotarod at 3 months and 6 months, and in nest building at 9 months. Western blot analysis and immunohistochemical studies of brain tissue revealed significant decrease in phospho-serine 129 alpha-synuclein but no change in total alpha-synuclein. SIG-1012 treatment also produced the expected changes in brain PP2A. (An earlier analysis of the results from this study was presented at the Society for Neuroscience meeting 2009.)

Conclusions: These results demonstrate that enhancing PP2A activity by SIG-1012 is effective in de-phosphoryating alpha-synuclein in the mouse brain. This pharmacological approach also protects the mouse brain against alpha-synuclein mediated behavioral deficits.

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Phenotypic and behavioural assessment and MPTP sensitivity of LRRK2 kinase dead transgenic mice

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Objective: To further understand the biological function(s) of LRRK2 we generated LRRK2 "kinase dead" mice and carried out a range of behavioural studies.

Background: The leucine-rich repeat kinase 2 (*LRRK2)* gene contains 51 exons and its encoded protein is unusually large (2527 amino acids). LRRK2 autosomal dominant mutations are responsible for PARK8-linked PD (Paisan-Ruiz et al., 2004; Zimprich et al., 2004). *LRRK2* mRNA is expressed throughout the brain and in some other organs. Despite intensive study little is known about the biological substrates and true physiological role of LRRK2. In the last year a number of groups have started to report data on LRRK2 transgenic mice that express various pathological (G2019S or R1441C) forms of LRRK2 using BAC, Thy-1, or endogenous promoters.

Methods: In the present studies we have generated a D2017A knock-in (KI) mutation which is expressed under the control of the endogenous regulatory elements. Homozygous *LRRK2* D2017A KI mice are viable and fertile and appear grossly normal. We then tested these

mice (12 months of age) in a battey of behavioural assays and explored their sensitivity to MPTP (20 mg/kg i.p x 7 doses every other day).

Results: Detailed behavioural phenotyping indicated that both heterozygous and homozygous mice had no functional deficits as assessed using a battery of behavioural tests (basal locomotor activity, grip strength, pole test, balance beam and static rod performance). The mice also showed no altered locomotor responses when challenged with apomorphine or amphetamine and also exhibited no altered sensitivity to MPTP as assessed using neurochemistry and immunocytochemistry when compared to Wt controls. These data indicate that inhibiting the kinase activity of LRRK2 does not appear to effect motor function or balance in C57Bl6 mice and that treatment with MPTP produces similar neurotoxicity in both Wt and LRRK2 "kinase-dead" mice.

Conclusions: These data suggest that it is possible to inhibit LRRK2 kinase activity without producing overt side effects. The data also suggest that the physiological and pathological mechanisms involving LRRK2 kinase activity are different and independent to those pathways triggered by mitochondrial inhibition with neurotoxins such as MPTP.

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Withdrawn by Author

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Subthalamic nucleus deep brain stimulation in a rat model of parkinsonism: Effects on brain derived neurotrophic factor within the basal ganglia and motor cortex

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Objective: To determine the impact of deep brain stimulation of the subthalamic nucleus (STN-DBS) on brain derived neurotrophic factor (BDNF) levels in the basal ganglia and motor cortex.

Background: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become a popular surgical treatment for Parkinson's disease and preclinical evidence has demonstrated its neuroprotective potential. However, the mechanism by which DBS exerts its therapeutic benefits is unknown and moreover, the clinical use of STN-DBS has proceeded without a complete understanding of its effects on the trophic environment within the basal ganglia and other target structures of the STN.

Methods: Electrodes were implanted unilaterally in the STN in rats made parkinsonian with a progressive 6-hydroxydopamine lesion as well as unlesioned rats. Two weeks after STN electrode implantation continuous high frequency stimulation was initiated for 2 weeks. BDNF protein levels were determined via ELISA and levels of BDNF mRNA were determined via qPCR. Structures evaluated included the subthalamic nucleus (STN), substantia nigra (SN), globus palidus externa and interna (GPe and GPi), striatum (STR), and M1 motor cortex.

Results: STN DBS induced a significant increase in BDNF protein bilaterally in the nigrostriatal system and in the contralateral M1 cortex. qPCR results revealed a unilateral increase in BDNF mRNA in the GPe but not the STN. qPCR analysis of BDNF mRNA in additional structures in both lesioned and unlesioned animals is ongoing.

Conclusions: The upregulation of BDNF may play a role in the long-term therapeutic efficacy and potential neuroprotective effects of STN-DBS.

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The PINK1/parkin-pathway links ubiquitin to damaged mitochondria for selective autophagy

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Objective: Identification of the molecular and cellular mechanisms of selective mitochondrial autophagy and the contribution to the pathogenesis of Parkinson's disease (PD).

Background: PD is the most common neurodegenerative movement disorder. Mutations in PTEN-induced putative kinase (PINK1) and PARKIN are the most frequent causes of recessive PD. Although underlying disease mechanisms are largely unknown, two major cellular dysfunction have been implicated in the pathogenesis of PD: mitochondrial dysfunction and oxidative stress as well as alterations of protein turnover and the resulting proteotoxicity.

Methods: To identify key players of selective mitochondrial autophagy, a combination of biochemical, cell biological and genetic methods was employed. For this, human non-neuronal and neuronal cells were used as well as "humanized" *C. elegans* as an *in vivo* screening system.

Results: Here, we discovered important mechanistic steps of a PINK1/Parkin-directed pathway linking mitochondrial damage, ubiquitination and selective autophagy. PINK1 kinase activity and its mitochondrial localization sequence are prerequisites to induce translocation of the cytosolic E3 ubiquitin ligase parkin to depolarized mitochondria. Subsequently, parkin mediates the formation of two distinct poly-ubiquitin chains linked via lysine-63 and lysine-27. In addition, the autophagic adaptor p62/SQSTM1 is recruited to mitochondrial clusters and is essential for clearance of mitochondria. Strikingly, we identified the voltage-dependent anion channel (VDAC) 1, as a target for Parkin-mediated lysine-27 poly-ubiquitination and mitophagy. Moreover, pathogenic parkin mutations interfere with distinct steps of mitochondrial translocation, ubiquitination and/or final clearance via mitophagy.

Conclusions: Thus, our data provide important functional links between PINK1, parkin and selective autophagy of mitochondria implicated in the pathogenesis of PD. Moreover, we have established an *in vivo* screening system to identify modulators of mitophagy. Reference: Geisler, S., Holmström, K.M., Skujat, D., Rothfuss, O.C., Fiesel, F.C., Kahle, P.J. and Springer, W. (2010) PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. Nat Cell Biol, Vol. 12 (2).

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Disturbance of innate immunity linked to toll-like receptor 4 promotes neurodegeneration in a transgenic α-synucleinopathy model

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Objective: To determine the role of toll-like receptor 4(TLR4) on neurdegeneration in an α-synucleinopathy mouse model of multiple system atrophy (MSA).

Background: α-synuclein (AS)-positive glial cytoplasmic inclusions (GCIs) are the pathological hallmark of MSA. Microgliosis commonly accompanies neurodegeneration in MSA as demonstrated by post-mortem studies and in vivo PET imaging. We have recently shown up-regulation of TLR4 in human MSA as well as in a transgenic mouse model of primary oligodendroglial α-synucleinopathy, however the role of innate immunity remains obscure.

Methods: We used (PLP)-AS mice with oligodendroglial AS expression and normal TLR4 expression (AS,TLR4$^{+/+}$) and (PLP)-AS mice with deletion of all 3 exons of the TLR4 gene (AS,TLR4$^{-/-}$). Genotypes were determined by tail clip PCR. Mice were characterized at 6 months of age. The animals underwent motor behavior evaluation by flex field activity test, pole test, and beam walking test. Brains were subjected to neuropathological analysis. Cytokine levels in the brain were determined by FACS analysis. ELISA was used to measure transgenic AS in brains of AS,TLR4$^{+/+}$ and AS,TLR4$^{-/-}$ transgenic mice.

Results: We found augmented locomotor deficits in AS,TLR4$^{-/-}$ mice, which correlated with elevated loss of dopaminergic SNc neurons, accompanied by reduced microglial and astroglial activation

and decreased nigral levels of GM-CSF. AS,TLR4$^{-/-}$ mice showed increased density of GCI-like aggregates and significantly increased brain protein levels of transgenic AS as compared to AS,TLR4$^{+/+}$ transgenic mice.

Conclusions: The current study suggests an important link between AS maintenance and innate immunity. These results may serve to define potential novel therapeutic targets in MSA and other α-synucleinopathies. This study is supported by grant of the Austrian Science Foundation (FWF) P19989-B05.

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Proteasome inhibition in medaka brain induces the features of Parkinson's disease

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Objective: To investigate whether administration of proteasome inhibitors to the cerebrospinal fluid space of medaka fish leads to the development of Parkinosn's disease (PD)-associated phenotype characterized by selective degeneration of dopaminergic neurons and inclusion body formation.

Background: Recent findings suggest that a defect in the ubiquitin-proteasome system plays an important role in the pathogenesis of PD. A previous report (McNaught et al., Ann Neurol 2004) demonstrated that rats systemically administered with proteasome inhibitors exhibited PD-like clinical symptoms and pathology. However, because these findings have not been consistently replicated, this model is not commonly used to study PD.

Methods: Proteasome inhibitors including lactacystin and epoxomicin and 6-hydroxydopamine were injected into the cerebrospinal fluid space of medaka fish using glass micropipette. Behavioral analysis and biochemical as well as neuropathological analysis of the drug-treated medaka fish were performed.

Results: After administration of proteasome inhibitors into the medaka brain, selective dopaminergic and noradrenergic cell loss was observed. Furthermore, treated fish exhibited reduced spontaneous movement. Treatment with proteasome inhibitors also induced the formation of inclusion bodies resembling Lewy bodies, which are characteristic of PD. Treatment with 6-OHDA also induced dopaminergic cell loss but did not produce inclusion bodies.

Conclusions: Non-selective proteasome inhibition replicates the cardinal features of PD: locomotor dysfunction, selective dopaminergic cell loss, and inclusion body formation.

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Allantoin is the neuroprotective metabolite of inosine in a rodent model of Parkinson's disease

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Objective: To determine the metabolite involved in the neuroprotective effect of systemically administered inosine in the 6-hydroxydopamine (6-OHDA) model of Parkinson's disease (PD).

Background: Inosine treatment provides neuroprotection in animal models of stroke, yet inosine has not been examined in PD models. Additionally, the metabolite responsible for inosine-mediated neuroprotection has not been examined. In humans uric acid (UA) is the end product of inosine metabolism whereas in most other mammals, UA is metabolized to allantoin via urate oxidase. Inosine, UA or allantoin may be responsible for inosine-mediated neuroprotection.

Methods: For neuroprotective and plasma purine studies rats received subcutaneous matrix-driven pellets (200 mg total dose) for compound delivery. Groups included inosine, inosine plus an urate oxidase inhibitor, allantoin, or no pellets. Pellet surgery occurred prior to striatal 6-OHDA infusion. Rats were tested for forelimb asymmetry at baseline and four and six weeks post surgery. The striatum was analyzed for dopamine (DA) biochemistry and the substantia nigra (SN) was processed for tyrosine hydroxylase immunohistochemistry.

Results: Inosine and allantoin treatment ameliorated forepaw asymmetry ($p<0.001$). Blocking the conversion of UA to allantoin completely eliminated this effect. Inosine and allantoin treatment resulted in sparing of DA neurons in the SN ($p=0.02$). Blocking the metabolism of UA to allantoin abolished this effect. Levels of DA and its metabolites in the striatum did not differ between groups. Allantoin treatment elevated whole brain allantoin levels ($p=0.008$).

Conclusions: Our results show allantoin is a potent neuroprotective compound in a PD model and suggests that allantoin is the neuroprotective metabolite of inosine. The permeability of the BBB to allantoin points to its potential as a non-invasive neuroprotective therapy for PD.

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A new DBS clinical target for Parkinson's disease (PD) – mapping the caudal zona incerta (ZI)

M.G. Thomas, T. Chipungu, C. Watson, C.R.P. Lind (Perth, Western Australia, Australia)

Objective: To create a detailed map of the primate caudal ZI deep brain stimulation (DBS) target for PD and locate the concordant cytoarchitectural region within the rodent ZI.

Background: The caudal ZI may be a safer and more effective target than the subthalamic nucleus (STN) for DBS in patients with PD and can be accurately targeted with MRI-directed guide tube technique being pioneered in Australia. Thus understanding the composition and function of ZI subregions is becoming critical. In contrast to the STN, the ZI differs markedly between rodents, primates and humans. It is much larger and fundamentally shaped differently in rodents than primates, including humans. For functional information to be translated between rodent and primate studies it is necessary to identify concordant cytoarchitectural regions within the rat, non-human primate, and human ZI.

Methods: Photomicrographs of rat and marmoset sections stained for: parvalbumin, calbindin, calretinin, Nissl substance, neurofilament protein, TH, NADPH diaphorase, and ACh have been selected containing the ZI and surrounding nuclei and printed at a magnification of x72. A grid was placed over each section and the immunohistochemical profile determined by grading the immune-positivity of each of the neurotransmitter markeras either: no staining (−), low (+), medium (++), or high (+++) staining.

Results: Parvalbumin, SMI32, and calretinin have proved the most useful markers in delineating sub-regions in the primate ZI. The primate caudal ZI is composed of a unique combination of neurotransmitter cell types that most closely correlates to the dorsal region of the rodent ZI. The sub-regions in proximity to the ZI DBS electrode contacts in primates have been correlated to the rat.

Conclusions: This project has been designed to characterise the rodent, marmoset and human caudal ZI DBS target which may lead to improved insight into this novel DBS target. The findings should underpin development of stereotactic neurotransmitter-specific surgical therapies in the future.

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Substance P antagonists reduce onset of experimental L-DOPA induced dyskinesia

E. Thornton, M. Hassall, R. Vink (Adelaide, South Australia, Australia)

Objective: To determine if the neuropeptide substance P plays a role in the onset of experimental L-DOPA induced dyskinesia.

Background: Substance P (SP) is an excitatory neurotransmitter that is highly expressed by striatal medium spiny projection neurons in the direct pathway of the basal ganglia (BG). It is decreased within BG nuclei in late stage Parkinson's disease (PD), however it returns to near normal levels with L-DOPA/benserazide treatment. Despite direct

pathway hyperactivity being implicated in the development of L-DOPA induced dyskinesia, and the expression of NK1 (SP) receptors on all of the BG output nuclei, it has yet to be determined if SP plays a role in this debilitating consequence of L-DOPA treatment.

Methods: Male Sprague-Dawley rats (n=40) underwent a stereotaxic lesion with 6 OHDA into the medial forebrain bundle (MFB) before being treated with L-DOPA (6mg/kg) + benserazide (15mg/kg) once daily to induce dyskinesia. A subset of animals was co-treated with the SP, neurokinin 1 (NK1) receptor antagonist N-acetyl-L-tryptophan (NAT; 0.5mg/kg and 5mg/kg). All animals were then assessed twice weekly using the abnormal involuntary movement score to determine the severity of dyskinesia. Dopaminergic degeneration and SP expression were also assessed.

Results: A threshold of 80% dopaminergic cell loss was required in the ipsilateral substantia nigra for the development of L-DOPA induced dyskinesia in the 6 OHDA MFB model of PD. Combined treatment with NAT produced a significant ($p=0.017$) reduction in the development of dyskinesia, with less than 50% of treated animals demonstrating dyskinetic movements. In particular, NAT treatment was very effective in preventing the onset of mild to moderate dyskinesia.

Conclusions: We conclude that SP is a factor in the onset of L-DOPA induced dyskinesia, and although further clarification of it's exact role is required, the use of a SP NK1 receptor antagonist may provide a novel therapeutic approach for the prevention of dyskinesia in PD.

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Accelerometer-based automated ambulatory-assessment of mobility in Parkinson's disease

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Objective: The goal of this work is to develop an automated, ambulatory and objective method for assessing mobility in PD patients, based on a body-worn sensor. To this end, we investigated accelerometer-derived measures that evaluate the quality and consistency of the walking pattern to identify which measures discriminate between control and PD groups and associations with clinical measures.

Background: Objective measures for quantifying at-home motor and ADL performance and abilities are lacking. Such measures could be used to help monitor the response to therapeutic interventions, on/off fluctuations, and disease progression in an objective and accurate manner.

Methods: 38 patients with PD (mean age 66.8±5.9 yrs; H&Y stage 2.7±0.5) and 17 healthy controls (CO) (mean age: 70±8.8 yrs) wore a 3D-accelerometer on the lower back while performing activities of daily living (ADLs). The walk followed a set pattern and included traversing several hallways, walking in an outdoor area, stairs, browsing at a book store, and returning to the lab. Derived measures included average step duration, step variability, and the frequency, amplitude, width and slope of the main (dominant) harmony of the power spectral density in the locomotion and Freezing Of Gait bands (0.5-3hz, 3-8hz respectively), in all 3 accelerometer axes.

Results: The amplitude and slope were significantly ($p<0.05$) lower in the PD group, compared to CO, in both frequency bands, while the width of the dominant frequency was significantly higher, in all axes. No significant difference was found in the main frequency. UPDRS motor scores were significantly correlated with the amplitude, width and slope for the vertical and anterior-posterior axes. PD patients took more steps.

Conclusions: Accelerometer parameters that reflect the quality and consistency of ADL performance are sensitive to PD and are associated with PD motor symptoms. These measures may serve as complementary bio-markers of PD to augment the objective evaluation of disease progression and functional independence.

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Caloric restriction protects against ageing diseases via NAD(H) and methyl pathways: Confirmation from pellagra

A.C. Williams (Birmingham, United Kingdom)

Objective: Experiments suggest longevity and immunity from diseases of ageing involve energy NADH pathways and NAD consuming SIRTs/PARPs. Real life confirmation needs correlation with the nicotinamide/NAD deficiency disease, pellagra. Other redox and methyl perturbations including dietary over-supply may have "mirror-image" effects.

Background: Longevity and freedom from diseases of ageing is manipulatable in the laboratory by caloric restriction and ecological or genetic manipulations that affect energy or NAD consuming SIRT/PARP or methylation pathways in many species, including primates. Adjusting nicotinamide and methyl-status protects against disease whether in genetic or toxic, traumatic or anoxic models. Pellagra takes on new significance as sub-clinical pellagra may never have been eliminated and an over supply of nicotinamide may be toxic.

Methods: Review pellagra.

Results: Pellagra caused poor development, premature ageing and death. Dementia and a whole range of neuro-psychiatric syndromes were present. Parkinsonism with non-motor features was common. Symbiotic infections were attempts to boost host NADH/nicotinamide. Metabolic disturbance was common. Addiction including to nicotine was frequent. Pathologically a range of degenerative findings were described with lipofuscinosis suggesting radical attack and amyloidosis demonstrating lost protein homeostasis. Findings that included inflammatory and cancerous changes were likened to premature ageing. Low meat diets would also reduce methionine and choline intake. Nicotinamide and nicotine are catabolised by a methylation pathway so high intakes would disturb methylation status: nicotinamide inhibits SIRT/PARP paths so dietary dose levels that are neither too low or too high may be necessary for optimal homeostasis, without taking emergency measures such as autocarnivory or reverting to fermentation, in ageing and degenerative circuits. An L-DOPA responsive akinetic model of nicotinamide toxicity has recently been reported.

Conclusions: Pellagra confirms the importance of energy supply, NAD consumer and methyl paths in disease of ageing circuitry. Optimal dose ranges of nicotinamide & calories producing NADH and methyl-group precursors matched to demand ie mental and physical exercise and repairs, with toxicity at either end provides (epi)genomic, metabolic and proteomic stability and robustness against ageing diseases.

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Glial cell line-derived neurotrophic factor protects midbrain dopaminergic neurons against lipopolysaccharide neurotoxicity in the striatum-midbrain organotypic culture

B. Xing, T. Xin, R. Hunter, Y. Chen, L. Zhao, G. Bing (Dallas, Texas, USA)

Objective: To evaluate if 1) glial cell line-derived neurotrophic factor (GDNF) protects dopaminergic neurons against lipopolysaccharide insult in the striatum-midbrain organotypic cultures and 2) whether its neuroprotection is associated with inhibiting microglia-mediated nitric oxide (NO) generation.

Background: Parkinson's disease (PD) is featured by the progressively selective dopaminergic neuronal degeneration in the substantia nigra of the midbrain, and aberrant activated microglia-mediated neuroinflammation has been implicated in this process. GDNF has a neuroprotective and restorative effect on the nigral dopamine system in various animal PD models, and a line of evidence suggested that its neuroprotection might be related to inhibiting neuroinflammation.

Methods: Striatum-midbrain organotypic cultures were prepared from postnatal day 2-3 Spraque Dawley rats. Various doses of lipopolysaccharide (10, 20, 40, or 80μg/ml) was administered after 12 days, alternatively, the cultures were treated with GDNF (20ng/ml) 1hr before treatment. Immunocytochemistry of tyrosine hydroxylase (TH) and OX-6 were performed to demonstrate TH-positive neurons and activated microglia, respectively. The production of NO was

assessed by the accumulation of nitrite in culture supernatants using the colorimetric reaction of the Griess reagent, and immunoblot of phosphoinositide 3-kinase (PI3K) was performed.

Results: Seventy-two hours exposure to different doses of lipopolysaccharide markedly induced the loss of TH positive neurons and microglia activation, in contrast, pretreatment with GDNF significantly protected neurons and inhibited microglia activation accompanied with decreased NO production. In addition, the expression of PI3K was reduced in lipopolysaccharide-treated group and GDNF reversed this effect.

Conclusions: The results demonstrate that GDNF blocked some but not all of the cytotoxic activity of lipopolysaccharide in the organotypic culture and suggest that GDNF protects dopaminergic neurons by suppressing microglia activation and excessive NO production via increasing the activity of PI3K pathway.

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Striatal neurotransmitter release-related presynaptic proteins in L-dopa induced dyskinesia in 6-hydroxydopamine model of parkinsonism

G. Yalcin Cakmakli, A. Vural, E. Eren Kocak, B. Elibol, E. Saka (Ankara, Turkey)

Objective: To study the role of striatal presynaptic proteins in the pathogenesis of L-dopa induced dyskinesias (LIDs) in PD.

Background: In PD, L-dopa-induced motor fluctuations and dyskinesias incapacitate patients as much as the disease itself. Many studies demonstrated that postsynaptic alterations and striatal synaptic plasticity are main changes leading to LIDs. However, there is evidence that presynaptic mechanisms are also involved in this process.

Methods: To induce LIDs, 6-hydroxydopamine injected rats were treated chronically with L-dopa/ benserazide for 21 days, b.i.d. The control group included rats with parkinsonism treated with saline and normal rats treated with saline or L-dopa/ benserazide. Behaviours of rats were videotaped and analysed once in every 3 days according to dyskinesia scoring scale. Striatal tissue was analysed with immunofluorescence staining and immunoblotting to explore alterations in expression of presynaptic proteins, secretogranin 2 (SG 2), synaptophysin (Syp) and synaptotagmin 7 (Syt 7).

Results: As expected LIDs developed only in denervated rats treated with chronic L-dopa. Severity of LIDs increased throughout the treatment period. Immunofluorescence and immunoblotting studies for tyrosine hyroxylase confirmed total depletion of dopaminergic neurons which was also strongly and negatively correlated to severity of LIDs. In immuoblotting, striatal SG 2 and Syp, but not Syt7 levels were found to be increased in parkinsonian rats. Chronic L-dopa treatment further increased SG 2 in denervated striatum. Besides, severity of LIDs was clearly correlated with levels of SG 2 expression. Although not quantitated, increased expression of these presynaptic proteins in denervated striatum was also evident in immunofluorescence studies.

Conclusions: These findings suggest functional relation of changes in expression of striatal presynaptic proteins and LIDs. Further studies are needed to find out molecular mechanisms linking increased SG 2 expression and LIDs.

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The effects of α-synuclein overexpression in neural stem cells

T. Yasuda, M. Tani, H. Hayakawa, N. Hattori, Y. Mizuno, H. Mochizuki (Sagamihara, Kanagawa, Japan)

Objective: To evaluate the effect of α-synuclein (αSyn) accumulation in neural stem cells in vitro and in vivo.

Background: αSyn is a key protein in Parkinson's disease (PD), and its abnormal accumulation is implicated only not in the loss of dopaminergic neurons in the substantia nigra but also in impairment of olfactory bulb (OB) in PD. Reduction of neural stem cell (NSC) generation could potentially lead to olfactory dysfunction, which is commonly associated with and precedes the motor symptoms by several years in PD.

Methods: We investigated neurosphere formation in vitro and migration of NSCs in vivo after transduction of αSyn-encoding retroviral vector to identify the function of αSyn in the NSCs.

Results: Overexpression of αSyn caused less effective formation of neurospheres and induced morphological changes. Fluorescence-activated cell sorting showed diminished NSC cell cycle progression induced by overexpression of αSyn. Intriguingly, suppression of NSC migration along the rostral migratory stream was observed when the αSyn-encoding vector was directly injected into the SVZ of mice in vivo.

Conclusions: The present study demonstrated that accumulation of αSyn in NSCs exhibited a cell-autonomous influence on the generation of neural progenitors, suggesting that effective elimination of toxic species of αSyn could pave the way to halt and possibly reverse the clinical symptoms of the patients with PD.

POSTER SESSION 1
MONDAY, JUNE 14, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 14:00-15:30

CHOREAS (NON-HUNTINGTON'S DISEASE)

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Acute chorea caused by myelinolysis of lenticular nucleus in a patient with renal failure under dyalisis therapy. Case report and review of literature

R. Buzo, I. Amorin (Montevideo, Uruguay)

Objective: To inform about a non-frequent neurological complication in patients under hemodialysis: extrapontine myelinolysis with extrapyramidal manifestations. To provide an update on similar reports in the literature on the subject as well as on speculations on the possible causes of the disorder.

Background: Osmotic demyelination or myelinolysis is a complication typically associated to the rapid correction of sodium in patients with hyponatremia; the pontine topographic localization is the most usual form. Pontine as well as extrapontyne myelinolysis is a complication described in patients with renal failure under hemodialysis treatment; lenticular topography along with chorea is rare.

Methods: We present a case which was studied by Nuclear Magnetic Resonance (NMR) of the skull while the follow-up was recorded on videos. A literature review for related publications was performed using the PUBMED/Medline databases.

Results: Acute chorea due to myelinolysis in the lenticular nucleus is a neurological complication to be taken into account in patients under hemodialysis treatment. Although the cause is still unknown, it is speculated that it may be related to sudden variations in natremia during dialysis.

Conclusions: Acute chorea due to myelinolysis in the lenticular nucleus is a neurological complication to be taken into account in patients under hemodialysis treatment. Although the cause is still unknown, it is speculated that it may be related to sudden variations in natremia during dialysis.

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Rat striatal infusion of antibodies from sydenham's chorea (SC) patients

F. Doyle, F. Cardoso, C. Olortegui, F. Dias, C. Lopes, L. Lopes, M. Mendes, R. Tavares, A. Camargos (Belo Horizonte, Minas Gerais, Brazil)

Objective: To assess the biological effect of antibodies from SC patients.

Background: SC is the neurological manifestation of rheumatic fever. The following findings support immune mechanisms as responsible for the pathogenesis of SC: symptoms improvement with immunomodulatory therapy; anti-basal ganglia antibodies present in the serum and CSF; increase of Th2 cytokines in serum and CSF of patients. However, it remains undetermined whether these antibodies have a biological effect. The gold standard for establishing the auto-immune nature of a given condition, passive transfer, has not been achieved in SC.

Methods: SC was diagnosed according to previously published criteria (Cardoso et al, 1999). Sera from four patients with active chorea and four healthy subjects were drawn and antibodies were purified by immunoaffinity chromatography using Protein A-sepharose. Five rats underwent 6-OHDA lesion of the SNc, followed by positive response (≥50 contra lateral rotations per 30 minutes) to 0,1mg/kg apomorphine (Brit. Pharmaceuticals Ltd.). The animals received intrastriatal infusion of antibodies through mini osmotic pumps (Alzet) during 48h. Four rats received patients antibodies and one rat received the pool of healthy subjects antibodies. Animals were video recorded during 30 minutes before antibody infusion (BAI), 24 hours (24hAI) and 48 hours (48hAI) after infusion initiation. Rotational movements were registered. Differences between BAI X 24hAI and BAI X 48hAI were calculated using the T-Student test.

Results: The mean number of contra lateral rotations (CLR) after apomorphine test was 156,8 (SD 101,81). The mean number of CLR of rats that received SC antibodies before infusion, 24 hours and 48 hours after infusion initiation were, respectively, 7,5 (SD 11,840, 7,5 (SD 6,85) and 2,25 (SD 3,20). For the rat that received antibodies from healthy subjects it was 0,-1 (one ipsil. rotation) and 0. Comparing BAI X 24hAI and BAI X 48hAI, no significant differences were found (p=0,5 and 0,22 respectively).

Conclusions: In the present model, we were not able to demonstrate any significant biological effect of the antibodies derived from sera from SC patients. Our results may reflect methodological limitations of our study or genuine lack of pathogenic value of the antibodies.

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A family with female prevalence of "benign" paroxysmal kinesigenic choreoathetosis

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Objective: To evaluate the family presentation of a paroxysmal kinesigenic choreoathetosis (PKC).

Background: PKC is a rare disorder, characterized by brief involuntary dyskinetic attacks triggered by sudden voluntary movements. PKC occurs sporadically or as an autosomal-dominant (AD) familial trait with variable penetrance. PKC usually affects male more than female subjects but this higher male-to-female ratio was not recently found in familial cases. No gene are actually identified.

Methods: We observed a 17-years old girl with a suggestive history for PKC and an AD trait transmission of the disturb in our family. The patient and her mother were investigated with cerebral MRI, EEG recordings, video poligraphic recordings, and genetic analysis.

Results: A female prevalence of the paroxysmal attacks was found. Since her childhood, the patient referred that her right feet blocked from 5 to 30 sec in concomitance with a sudden voluntary movement and she described some "compensatory strategy" to diminish the disturb. The mother presented a choreo-athethosis movement of an hemibody; she actually is on carbamazepine treatment. Her aunt suffered from PKC (disappeared after the first pregnancy) and migraine with aura. Cerebral RM and EEG recordings of the patient and her mother were normal. She underwent two diurnal video-polygraphic recordings during which she presented a transitory plantar flexion of the anterior part of the right feet cracking a varism posture suddenly passing from sitting to stand up or a valgism posture in the reverse without another EEG abnormalties. Molecular analysis (still in progress) of C.F. and her mother's DNA was performed for the two candidate genes: GLUT1, ATP1A2. If no mutations will be identified, we will perform a linkage analysis focused on chromosome 16 on the whole family.

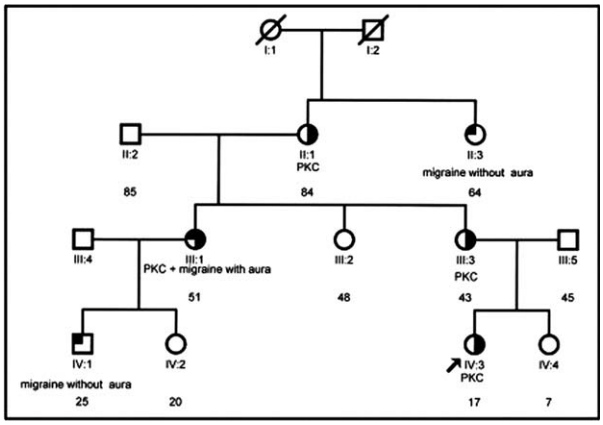

FIG. 1 (82).

Conclusions: Our family represent a case of PKC with AD familial transmission, variable expressivity, female presence and a benign course of the disturb. The video-polysographic recordings confirm the paroxystical kinesigenic semeiology of the attacks. We are still waiting for DNA analysis.

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Acquired hepatocerebral degeneration: Presentation of eight patients

R.J. Giannaula, J.C. Maiques, J.C. Giugni, A. Alfonso, N. Mrtinez Tamborini, B.P. Borrego Guerrero, G. Orzuza (Buenos Aires, Argentina)

Objective: To describe the characteristics of 8 patients with Acquired Hepatocerebral Degeneration (AHD).

Background: AHD is a heterogeneous disorder usually related to chronic liver disease. It can be recognized by the appearance of cognitive dysfunction, movement disorders (chorea, dystonia, parkinsonism), cerebellar symptoms or myelopathy. MRI scans may reveal T1 lenticular hyperintensity that may also involve the pituitary gland, caudate, subthalamus and red nucleus. Cerebral and cerebellar atrophy may be observed as well. Manganese buildup or several toxic substances might be responsible for the symptoms.

Methods: We assessed 8 patients (2 men, 6 women), ages raging from 50 to 73 years (mean age 65). The underlying liver diseases were: type C hepatitis: 2 patients, autoimmune hepatitis: 1 patient, cirrhosis due to alcohol use: 4, primary biliary cirrhosis: 1.

Results: Patients presented confusional syndrome (6), asterixis (3), orofaciolingual dyskinesias (3), asymmetric parkinsonism (1), chorea (1). They all had bilateral T1 putaminal hyperintensity signal. Response to lactulose and neomicine was satisfactory in 4 cases.

Conclusions: Liver diseases may be associated with different movement disorders, with cerebral lesions that suggest the underlying cause.

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Hyperglycemia associated with basal ganglia lesions and movement disorders

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Objective: To present eight patients with movement disorders associated with hyperglycemia and basal ganglia lesions.

Background: Hyperglycemia is a metabolic disorder that has been associated with hyperkinetic involuntary movements secondary to basal ganglia lesions as shown on CT scans or MRIs. Postmenopausal women are more commonly affected by this rare condition. It may be related to a diminished GABAergic inhibition over the thalamus, which in combination with the striatal lesions might enhance the inhibition over the subthalamic nucleus, leading to the hyperkinetic movements.

Methods: Two males and 5 females, ages raging from 48 to 89 years, presented with hemibalism or hemichorea, and a 66 years old female suffered from acute dystonic movements in both upper and lower limbs and neck. All patients underwent laboratory assessments that revealed glycemia values above 310 mg/dl. In five of them, brain MRIs showed T1 hyperintense lesions involving the basal ganglia. In two patients the CT scans revealed hyperdense lesions in the basal ganglia. Lesions were unilateral in 5 patients and bilateral in 2. No lesions could be demonstrated in the patient with dystonic symptoms.

Results: The 8 patients recovered completely. All of them underwent insulin therapy and their blood sugar levels went back to normal. Six patients didn't recquire any other treatment. One patient needed additional therapy with haloperidol, and another patient with severe hemibalism, underwent stereotactic contralateral thalamotomy with successful results.

Conclusions: Movement disorders associated with hyperglycemia are an unusual manifestation of diabetes mellitus. Prognosis is usually good. Glycemia control not always improves symptoms. This possibility should be remembered in diabetic patients with movements disorders.

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Severe hyperglycemia induced hemichorea-hemiballismus with a dramatic response to tetrabenazine

S.A. Kareus, K. Jefferies, J.J. Steffens, J.C. Wagner (Salt Lake City, Utah, USA)

Objective: To discuss a case of severe disabling chorea-ballismus which was the presenting feature of diabetes. We will also discuss treatment options for this patient as well as his dramatic response to tetrabenazine.

Background: Hyperglycemia induced hemichorea-hemiballismus is a rare but established complication of poorly controlled hyperglycemia. It has been reported as the presenting feature of hyperglycemia. Tetrabenazine, an inhibitor of the vesicular monoamine transporter 2 (VMAT2) membrane transport protein, is useful in the treatment of hyperkinetic movement disorders, and has recently been approved by the FDA for use in the treatment of Huntington's chorea.

Methods: We obtained video footage of the patient prior to the initiation of tetrabenazine, and after tetrabenazine had reached a therapeutic dose.

Results: Tetrabenazine resulted in a dramatic reduction in this case of severe disabling chorea-ballismus.

Conclusions: Hyperglycemia induced hemichorea-hemiballismus is often difficult to treat. Neuroleptics have traditionally been used in the past, as well as deep brain stimulation in one severe refractory case. This case demonstrates the beneficial use of tetrabenazine in the treatment of hyperkinetic movement disorders, in particular hemichorea-hemiballismus secondary to hyperglycemia.

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Acoustic analysis of prosody in dysarthric speech: A comparison of populations with basal ganglia disturbances

T. Machado, F. Cardoso, R. Rothe-Neves (Belo Horizonte, MG, Brazil)

Objective: To compare prosody in subjects with hypokinetic and hyperkinetic dysarthrias.

Background: Despite investigations of speech in neurological disorders have been largely carried out, there are few studies comparing directly prosody in different basal ganglia disorders.

Methods: We studied 27 subjects with Parkinson's disease (PD), persistent Sydenham's chorea (SC) and Huntington's disease (HD) which demographic data are indicated below.

TABLE 1 (86). *Demographic data of subjects*

N	Mean age (years)±SD	Schooling (years)±SD	Diagnosis (years)±SD
SC (13)	19.38±2.17	7.15±0.76	9.9±2.1
HD (07)	48.43±7.14	9.29±1.25	2.3±0.5
PD (07)	55.86±4.61	6.43±1.45	9.7±1.9

PD patients were evaluated OFF and ON, and had peak-dose dyskinesia in the latter condition. Acoustic analysis, performed with the software Praat®, assessed reading of a standard text. Descriptive statistic analyses were performed, as well as Pearson and Spearman correlations, regression, variance and discriminant analysis.

Results: The descriptive analysis appears in table below.

TABLE 2 (86). *Descriptive analysis of prosody*

	Total time of speech - seconds (±SD)	Total time of breaks - seconds (±SD)	Speech rate - syllables/ seconds (±SD)	F0 – Hz (±SD)	Intensity - dB (±SD)
SC	132.15±11.99	46.74±7.33	0.32±0.02	217.29±14.51	43.31±0.62
DH	263.48±63.24	148.95±60.29	0.66±0.14	221.20±25.47	40.66±1.04
PD OFF	169.75±46.63	74.50±35.52	0.41±0.10	163.42±9.68	43.24±0.91
PD ON	154.32±47.25	58.28±38.22	0.37±0.10	189.38±19.06	45.22±l0.86

F0=fundamental frequency.

Only the PD ON group showed positive correlations between the total time of speech (p=0.010), average duration of pauses (p=0.003) and the motor impairment (UPDRS). The other parameters of prosody did not correlate with the other specific global motor scale. In the discriminant analysis, the variable that best discriminates the groups were speech rate (p=0.016) and minimum intensity (p=0.041).

Conclusions: We have demonstrated that speech prosody of HD, PD and SC is similar, with the exception of the speed which is faster in HD hyperkinetic condition.

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Chorea gravidarum in patients with Sydenham's chorea

D.P. Maia, P.G. Fonseca, S.T. Camargos, M.C. Cunningham, F.E. Cardoso (Belo Horizonte, Minas Gerais, Brazil)

Objective: To study the clinical features in a cohort of patients from a Movement Disorder Clinic with Chorea Gravidarum (CG) that have rheumatic fever as primary disease and its relationship to Sydenham's chorea (SC).

Background: Chorea is characterized by brief, abrupt involuntary movements resulting from a continuous flow of random muscle contractions. When the onset of chorea overlaps with pregnancy it has been called CG. Although the first description of chorea with onset during pregnancy was made by Horstius in 1661, its etiology remains unknown, but recurrence of SC is often implicated as the underlying cause. Recent articles about CG are scarce and consist of single case reports.

Methods: Prospective follow-up of all patients with CG seen at the Movement Disorders Clinic of the Federal University of Minas Gerais (MDC-UFMG) from 07/1993 through 11/2009. The following parameters were analyzed: age and gestational age at onset; topo-

graphic distribution of chorea; severity of chorea on UFMG SC rating scale, resolution of the movements, clinical and laboratory evidence of streptococcal infection or acute rheumatic fever, presence of rheumatic valvulopathy, clinical and laboratory evidence of systemic lupus erythematosus, primary antiphospholipid antibody syndrome and syphilis.

Results: CG was diagnosed in 15 of 64 female subjects (29,68%) with history of previous Sydenham chorea seen during the study period at the MDC-UFMG. Among the patients with Sydenham chorea and pregnancy, 78,9% developed CG. The median age at onset and gestational age at onset were, respectively, 18,25 years (range 13-26) and 10 weeks (range 4–24). In 9 patients remission occurred after delivery. No clinical or laboratory evidence of acute RF or streptococcal infection was present in any patient. There was no clinical or laboratory evidence of systemic lupus erythematosus, primary antiphospholipid antibody syndrome and syphilis.

Conclusions: Our results suggest that CG is a common occurence in patients with SC. Moreover, they suggest that CG is not caused by an acute infection or immune response but rather results from hormonal changes acting on a previously injured basal ganglia. These findings extend our previous observation that SC may cause persistent brain changes.

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Withdrawn by Author

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Multiple sclerosis presenting as acute hemi-chorea

A. Schteinschnaider, G. Vazquez, C. Romero, J. Correale (Buenos Aires, Argentina)

Objective: To report an uncommon cause of hemichorea.

Background: Hemi-chorea is an uncommon movement disorder in childhood, where vascular etiology should be initially considered.

Methods: A previously healthy 10-year-old boy presented with acute onset of involuntary movements in the right side of the body with brachial predominance. Movements were mainly continuous and undulating, were exacerbated by fatigue and stress and ceased during sleep. Findings on neurological examination: hemi-chorea in the right side of the body, with low muscle tone and ipsilateral increased stretch reflexes, right Babinski sign and subtle signs of hemiplegic gait.

Results: Brain MRI: focal faintly hyperintense lesion in left globus pallidum on diffusion weighted imaging, other focal subcortical hyperintense lesions in both semi-oval centers and predominantly in the left corona radiate on FLAIR and T2-weighted images. No gadolinium enhancement. Normal magnetic resonance angiography. Spinal MRI: hyperintense spinal cord lesion on D6 on T2-weighted images and STIR, without contrast enhancement. Visual and auditory evoked potentials: normal. CSF Isoelectrofocusing: positive, fractionated CSF IgG with normal plasma IgG. Cardiologic evaluation: normal. Collagenogram and thrombophilic profile: normal. The patient was suspected of having an initial event of childhood Multiple Sclerosis, and received methylprednisolone pulse therapy recovering ad integrum. During the next three years he had 2 relapses meeting clinical and radiological criteria of multiple sclerosis.

Conclusions: This case shows an unusual presentation of childhood multiple sclerosis. Demyelinating diseases should be considered in patients with hemi body chorea after ruling out other more frequent causes.

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Paroxysmal kinesigenic dyskinesia with interictal myoclonus/dystonia in a family with infantile seizures and migraines: A case report

I. Subramanian, R. Hamill (Los Angeles, California, USA)

Objective: To report on a case of paroxysmal kinesigenic dyskinesia (PKD) and interictal myoclonus and dystonia in a patient with a family history of migraine and infantile seizures who has been treated successfully with carbamazepine.

Background: PKD has been described in patients with family histories of migraines and infantile seizures. PKD has also recently been reported in two patients who had dystonia and myoclonus in between their episodes of PKD. Successful treatment of PKD has been seen with carbamazepine.

Results: Case Report: A 21 year old female presents with a 10 year history of episodes of abnormal movements triggered by initiation of movement. These episodes would last upto 30 seconds and would occur at times multiple times per day. They would occur more often starting on the right side of the face and involve the right side of the body and then spreading to the left side. She had a past medical history of seizures that remitted as an infant. She also had a family history of infantile seizures and migraines on her paternal side and in her brother. On examination she was noted to have myoclonus and some mild dystonic posturing of her hand. An MRI of the brain was normal. She was tried on carbamazepine at a dose of 100 mg/day and has not had any further episodes of dyskinesia since the drug was initiated. Her myoclonus and dystonia are improved somewhat on examination but still are persistent but not troublesome to the patient.

Conclusions: To our knowledge this is the first case of PKD with a family history of infantile seizures and migraine with interictal myoclonus and dystonia that has been reported. Our case was robustly responsive to carbamazepine. This case expands the phenotype of PKD.

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Hemichorea-hemibalism related to basal ganglia astrocytoma ipsilateral

M. Velez, M. Flores, H. Heinicke (Lima, Peru)

Objective: Hemichorea and hemibalism are related with the presence of contralateral subtalamic nuclei of Luys (STN) injury. However, cases with ipsilateral of STN or internal globus pallidus (iGP) injury are been reported (1). We present a patient with hemichorea-hemibalism related with brain tumor ipsilateral.

Background: Cases of hemichorea and hemiballism associated with ipsilateral cerebral lesions are been reported, with doubts about their validity because the underlying mechanism are not clear.

Methods: A 42 years-old male patient, without previous personal or familiar medical history who eleven days before his admission, presents abnormal movement in left side body that compromise talking, driving, without compromise balance or swallowing, get worse with stress, and disappear during the sleep. During the exam, patient was awake and his behavior was puerile. Pyramidal or cerebellar signs were not present. Chorea compromise head, trunk, left arm and leg 3/4, difficulting talk and walk, and disappear during rest. Palsy up vertical gaze was present.

Results: CT scan showed a left capsule thalamic hipodense lesion with mass effect that compresses ipsilateral ventricule. MRI showed unspecific lesions in basal ganglia, left corona radiata, pons and cerebral peduncles. Stereotactic surgery biopsy showed anaplastic astrocytoma grade III WHO.

Conclusions: Movement disorders in tumours of the basal ganglia have been described in a very short range. We present a patient with anaplastic astrocytoma and ipsilateral hemichorea-hemibalism like initial symptom. Reference: 1. Krauss JK, Pohle T, Borremasn JJ. Hemichorea and Hemiballism Associated With Contralateral Hemiparesis and Ipsilateral Basal Ganglia Lesions. Movement Disorders 1999;14(3):497–501.

POSTER SESSION 1
MONDAY, JUNE 14, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 14:00-15:30

CLINICAL ELECTROPHYSIOLOGY

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Cognitive event-related potentials and ERD/S – an intracerebral subthalamic nucleus and globus pallidus internus study

M. Bockova, J. Chladek, P. Jurak, J. Halamek, M. Balaz, I. Rektor (Brno, Czech Republic)

Objective: We studied the appearance of cognitive event- related potentials (ERPs) and event- related de/synchronizations (ERD/S) in the subthalamic nucleus (STN) and globus pallidus internus (GPi).

Background: ERPs and ERD/S in alpha and beta frequency range were analysed in four Parkinson's disease patients and one generalized dystonia patient undergoing deep brain stimulation (DBS).

Methods: A visual three-stimulus protocol was used. The frequent (70%) stimulus (without required response) was a small blue circle; the target (15%, with motor response) stimulus was a larger blue circle; the distractor (15%, without required response) stimulus was a checkerboard.

Results: A specific positive ERP peak around 200 ms and low alpha frequency ERS were detected from STN as a response to distractor stimuli in three Parkinson's disease patients and also in the Gpi in generalized dystonia.

Conclusions: The STN and Gpi are involved in cerebral network processing orienting response and attentional processes.

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Memory enhancement in Alzheimer's disease after daily transcranial direct current stimulation

P.S. Boggio, R. Ferrucci, F.C. Mameli, M. Vergari, D. Martins, O. Martins, F. Fregni, S. Marceglia, E. Scarpini, A. Priori (Milan, Italy)

Objective: To assess whether daily tDCS can induce prolonged cognitive improvement in patients with Alzheimer dementia (AD).

Background: Previous studies assessed the effect of tDCS on memory in patients with Parkinsons disease (PD) and AD. These studies showed that, immediately after a single session of anodal tDCS, PD and AD patients improve their memory performance. These results on acute effects of tDCS prompt the development of new experimental protocols for investigating the effects of prolonged treatment with anodal tDCS.

Methods: Fifteen patients with AD were enrolled in two centers. The cognitive functions were evaluated before and after the treatment with tDCS using four different tasks: Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-cognitive sub scale (ADAS-cog), visual recognition task (VRT) and visual attention task. tDCS was delivered bilaterally by a direct constant-current electrical stimulator connected to a pair of sponge electrodes: two scalp electrodes placed over the temporal regions (T3 left side; T4 right side) and the stimulation reference electrode placed over the right deltoid muscle. The stimulating current was anodal DC at 2 mA intensity, delivered for 30 minutes for five consecutive days.

Results: Two-way ANOVA (tDCS*Time) showed that tDCS induced significant changes in the accuracy of VRT ($p=0.04$). Performance changes after anodal and sham stimulation were 8.99% and -2.62% as compared to baseline. Also, we found a significant VRT change of 11.4% and -7.5% for anodal and sham tDCS, respectively, after four weeks at the end of tDCS sessions as compared to baseline. tDCS failed to change ADAS-cog, MMSE, and the visual attention task.

Conclusions: Our results showed an enhancement of visual recognition memory that persists for at least four weeks after the end of five consecutive daily sessions of anodal tDCS over temporal areas of the cerebral cortex. This long-lasting effect could reflect the impact of this technique on long-tem potention (LTP) even in a progressive, degenerative disease and could be relevant also for memory in PD.

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Intermittent theta burst stimulation improves bradykinesia in Parkinson's disease – preliminary results

S.R. Filipovic, N. Kresojevic, A. Kacar, I. Petrovic, M. Ljubisavljevic, V.S. Kostic (Beograd, Serbia)

Objective: To evaluate the potential of intermittent theta burst stimulation (iTBS) to improve motor impairments and in particular bradykinesia in patients with Parkinson's disease (PD).

Background: The iTBS, a non-invasive transcranial magnetic stimulation method, has been shown to increase excitability and activation in targeted areas of motor cortex. Decreased activation of motor cortex due to impaired impulses from basal ganglia is physiological model behind bradykinesia and hypokinesia in PD. Hypoactivation of the motor cortex was found on functional brain imaging in PD patients without medication.

Methods: We conducted an open administration of iTBS (80% active motor threshold; 2-s trains of iTBS are repeated every 10 s for a total of 190 s – 600 pulses) to seven patients with akinetic-rigid type of PD (Hoehn and Yahr stage when off, 2 and 3). Motor performance was evaluated using Purdue peg-board (the number of pegs arranged in 30 s) and a ballistic task (the time to achieve 20 go-and-back movements with the index finger between two targets fixed 30 cm apart, as fast as possible) before iTBS administration (B), immediately after (T0), and at 30 (T30) minutes following iTBS. In addition, motor cortex excitability was assessed by measuring size of the motor evoked potentials (MEP) following single pulses of transcranial magnetic stimulation (TMS) over targeted cortical area, at the same time points. The study sessions were organised while patients were on their usual medication, during their typical on phase.

Results: The MEP increased following iTBS to $116.5\pm14.8\%$ at T0, and $148.8\pm26.9\%$ at T30. In parallel with this, there was progressive increase of number of pegs arranged from 8.1 ± 2.7 at B to 9.2 ± 1.8 at T0 and 9.8 ± 2.4 at T30; while time to complete ballistic task shortened from 27.0 ± 7.7s at B to 22.6 ± 5.1 at T0 and 22.1 ± 6.3 at T30. Patients did not report any adverse effects following iTBS.

Conclusions: Our data suggest potential positive effects of iTBS on motor speed and dexterity in patients with PD, which parallel increase in motor cortex excitability induced by the method. Based on these results, a larger-sample double-blind, placebo-controlled trial of iTBS in PD is planned to better assess potential beneficial effects of iTBS and to distinguish them from placebo effects.

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Neurophysiological features of hemiballismus

A.D. Ha, N. Mahant, V.S.C. Fung (Westmead, New South Wales, Australia)

Objective: We report three cases of hemiballism with their associated radiological and neurophysiological findings.

Background: Hemiballismus is a rare hyperkinetic disorder, characterized by irregular, large amplitude involuntary movements of the limbs.[1] It is typically associated with a lesion in the contralateral subthalamic nucleus. The pathophysiological mechanisms underlying the expression of these involuntary movements are poorly understood, and there have been few neurophysiological recordings of hemiballismus[2].

Results: Case 1: A 57 year old man developed hemiballismus of his right upper and lower limb two days after the onset of headache and vomiting. CT brain revealed a left subthalamic haemorrhage. Surface EMG recordings revealed intermittent movements associated with bursting of 200-1000ms duration. Proximal muscles tended to be more active than distal muscles. Case 2: A 56 year old man developed the onset of right sided hemiballismus approximately thirty minutes following a fall with pre-syncopal symptoms. CT and MRI brain revealed an infarct involving the left subthalamic nucleus and inferior globus pallidus. Surface EMG recordings showed near continuous bursting in all muscles varying between 200 to 1000ms duration, with the pattern being approximately equally divided between co-contracting and alternating activity. Case 3: A 68 year old woman presented with left sided hemiballism/hemichorea, in the setting of hyperosmolar non-ketotic hyperglycemia. MRI Brain revealed T2 hyperintensity in the putamen and associated diffuse putaminal enhancement. Surface EMG recordings revealed bursts of variable amplitude and duration ranging from 100ms to over 1500ms. More proximal muscles did not show any consistent pattern of activation between agonists and antagonists, with largely independent bursts in each muscle with occasional co-contraction.

Conclusions: Hemiballismus in the setting of acute basal ganglia pathology is associated with a characteristic pattern of EMG activity. Neurophysiological studies reveal irregularly timed, variable and at times prolonged EMG bursts ranging from 100-1500ms involving predominantly the proximal muscles, at times co-contracting but frequently isolated in an agonist without involving the antagonist. We suggest that unopposed and prolonged EMG bursting in joint agonists without antagonist activity underlies the characteristic rapid flailing movements of hemiballismus.

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The effect of simultaneous repetition of unrelated finger movements on SI in the motor system: Comparison between non-musician and professional pianists

S.Y. Kang, S.-K. Song, J.E. Lee, H.-W. Shin, Y.H. Sohn (Seoul, Republic of Korea)

Objective: To explore the effect of muscle overuse on SI, we measured changes in SI after short-term exercise with repetition of two different types of finger movements.

Background: Surround inhibition (SI) is a neural mechanism by which desired neural processes can be adjusted by suppression of unwanted, neighboring neural activity for the selection of the proper neuronal response. Disturbed SI in the motor system could account for dystonia. Dystonia may be more pertinent clinically to impaired SI. FHD usually develops following a period of highly repetitive movements that typically require extreme motor precision. I hypothesize that repetitive exercise of unrelated finger movements can lead to disturbed SI, which could provide physiological evidence to support the potential contribution of muscle overuse to the development of FHD.

Methods: Right-handed healthy non-musicians and professional pianists participated in this study. We studied changes of SI in the motor system with transcranial magnetic stimulation technique after a short-term exercise with simultaneous repetition of unrelated finger movements or repetition of single finger movements.

Results: Motor evoked potentials (MEPs) were suppressed in the little finger muscle (abductor digiti mini; ADM) during flexion of the index finger muscle (flexor digitorum superficialis; FDS). After short-term exercise, MEPs of the ADM were no longer suppressed but instead were enhanced during the flexion of the FDS in non-musician healthy volunteers. Exercise comprising simultaneous ADM and FDS movements produced significantly larger and longer-lasting enhancements than those of the ADM movement alone. In professional pianists, on the contrary, alterations in SI after both types of exercise were similar.

Conclusions: This study provides neurophysiological evidence that repetitive practice of unrelated finger movements can disturb SI. The finding that the effect of exercise types on SI are different between non-musicians and professional musicians supports the hypothesis that neurophysiological mechanisms regulating SI in professional musicians may be different from those in non-musicians, probably due to previous long-term practice of unrelated finger movements.

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Neuromyotonia: A case series from northwest India

A. Panagariya, H. Kumar, D. Khandelwal, P. Dubey, B. Sharma (Jaipur, India)

Objective: To describe 27 case of neuromyotonia from northwest India.

Background: Neuromyotonia is a syndrome of spontaneously occurring muscle activity of peripheral nerve origin. The abnormal activity is characterized electromyographically by doublet, triplet or multiplet single unit discharges that have a high intraburst frequency, the frequency of the bursts themselves being irregular. The long-term prognosis for individuals with the disorder is uncertain. This is the largest series of cases of neuromyotonia from India.

Methods: Patients were recruited from the Neurology outpatient service of this large super specialty centre of northwest India over a period of five years. Twenty old cases (published) and seven new cases were studied. Patients who presented with the complaints of pain, stiffness and twitching with or without autonomic symptoms were clinically analyzed in detail with the help of a proforma. Electromyography was done for neuromyotonic discharges.

Results: Most of the patients were young adult male. Almost all the patients complained of pain started with calves pain and autonomic symptoms. Clinical examination revealed undulating movements of calves and or generalized limbs. EMG of such patients always revealed doublets and triplets. 12 of the 20 old and all new cases had irritability, sleep disorders, restlessness and peculiar worried and pinched facies. 80% of old cases and all new cases had autonomic involvement in the form of excessive sweating. Only one new case had history of familial disease to his two sons. Clinical examination revealed normal power and sensations. Deep tendon reflexes were normal or diminished. Nerve conduction studies and

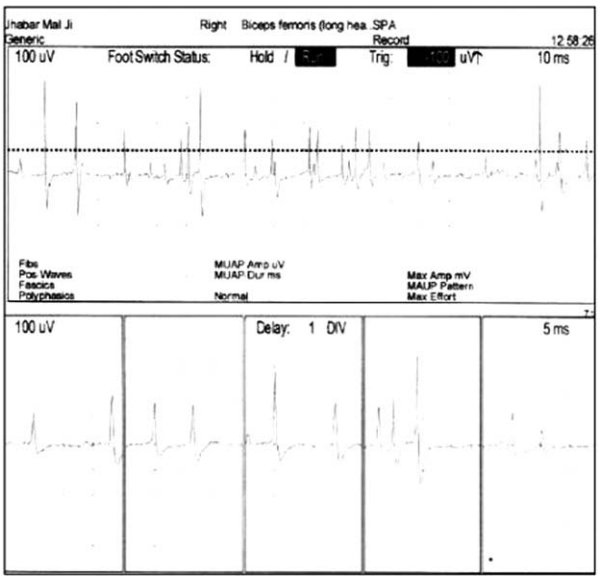

FIG. 1 (97).

CSF examinations were normal. Responses to anticonvulsants were partial in controlling pain stiffness and undulating movements. All the patients received IV methylprednisone except two cases who received IVIG. There was complete recovery in most of the cases.

Conclusions: Neuromyotonia is a rare neuromuscular disorder of young adults caused by hyperexcitability and continuous firing of the peripheral nerve axons that activate muscle fibers. Symptoms, which include progressive muscle stiffness, continuously contracting or twitching muscles, cramping and increased sweating. Prognosis was found favourable as contrast to the literature. In addition to symptomatic treatment disease modifying treatment can be given in the form of IV methylprednisolone or IVIg.

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Dysfunction of cortical inhibitory circuits in stiff-man syndrome

S.D. Kim, S. Vucic, M.C. Kiernan, V.S.C. Fung (Sydney, New South Wales, Australia)

Objective: To assess the pathophysiological mechanism underlying clinical features in Stiff man syndrome (SMS) using novel threshold tracking TMS techniques.

Background: SMS is a rare autoimmune disorder characterised by persistent stiffness with superimposed episodic muscle spasms. Although dysfunction of GABA-ergic inhibitory circuits have been established in SMS, the pathophysiological mechanisms underlying the development of symptoms remain to be fully elucidated. The function of GABA-ergic circuits may be assessed clinically using transcranial magnetic stimulation (TMS). Specifically, the function of cortical $GABA_A$ intracortical circuits is indicated by short interval intracortical inhibition (SICI), as measured by the paired-pulse paradigm, while the integrity of $GABA_B$ circuits is reflected by the cortical silent period (CSP) duration. Using the constant stimulus paired-pulse TMS technique, motor cortex hyperexcitability was reported in SMS. However, the relationship of cortical hyperexcitability with clinical manifestations of SMS remained obscure.

Methods: Cortical excitability studies were undertaken in 2 SMS patients, using a 90 mm circular coil, and results were compared to 62 normal controls. SICI was assessed with the conditioning stimulus (CS) intensity set to 70% of resting motor threshold (RMT), while CSP duration was assessed with stimulus intensity set to 140% RMT. Motor evoked potentials were recorded over the abductor pollicis brevis muscle. SMS disease severity was assessed using the distribution of stiffness index and heightened sensitivity scale.

Results: SICI was significantly reduced in SMS patients compared to controls (averaged SICI patient 1, -0.36%; patient 2, -4.8%; controls, 10.6±0.5%). In addition, CSP duration was significantly reduced in SMS patients compared to controls (patient 1, 116 ms; patient 2, 106 ms; controls, 210.2±3.1 ms). The extent of SICI and CSP reduction was greater in patient 2, who exhibited more severe disease.

Conclusions: These findings suggest that both $GABA_A$ and $GABA_B$ cortical circuits are dysfunctional in SMS, and that this dysfunction in inhibitory circuitry may underlie the development of clinical features in SMS. As such, the threshold tracking TMS technique may be an important aid in monitoring disease severity and response to therapy in SMS, especially in clinical drug trials.

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Contrasting effects of single dose L-DOPA on LTP and LTD-like plasticity of motor cortex in drug-naïve Parkinson's disease

A. Kishore, T. Joseph, S. Meunier (Trivandrum, Kerala, India)

Objective: To test the effect of single dose L-DOPA on LTP and LTD-like plasticity of motor cortex (M1) in denovo cases of early asymmetric PD.

Background: A single dose of L-dopa restores the defective LTP-like plasticity in patients with advanced PD on chronic L-dopa treatment. The effect on L-DOPA on LTP and LTD-like plasticity in drug-naïve PD is not reported so far.

Methods: Intermittent theta burst stimulation (iTBS) and continuous theta burst stimulation (cTBS) were used to induce LTP and LTD-like plasticity respectively, in M1 cortex in 10 healthy volunteers and M1 of the more affected hemisphere of 10 patients with early asymmetric denovo PD. The tests were done both in untreated state and 1 hour after a single dose of L-dopa (100mg) on 2 separate days. Mean values of MEP were measured immediately after TBS and every 10 minutes till 30minutes after both TBS protocols.

Results: LTP-like plasticity was significantly reduced when compared to controls only immediately after the intervention ($p<0.04$) but not later, while LTD–like plasticity was significantly impaired ($p<0.01$) when compared to controls. Even though patients showed good improvement in clinical signs following a single dose (100mg) of L-dopa, only LTD improved after L-DOPA but not LTP-like plasticity. There were no significant differences in the baseline MEPs or thresholds of excitability of M1 cortex of the groups.

Conclusions: LTD-like plasticity is significantly impaired in M1 cortex of early PD and improves with single dose L-DOPA. LTP-like plasticity is less severely affected in early stages, is poorly responsive to single dose L-DOPA and probably requires chronic exposure to be modulated by exogenous L-DOPA. The implications of these differences in response to acute dosing with L-DOPA need to be studied further.

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Botulinum toxin injections reduce cortical plasticity in patients with cervical dystonia

M. Kojovic, A. Caronni, M. Bologna, K. Bhatia, J. Rothwell, M. Edwards (London, United Kingdom)

Objective: To investigate the effect of Botulinum Toxin (BT) injections to the neck on cortical plasticity of hand muscles in cervical dystonia.

Background: Injections of BT are thought to ameliorate dystonic symptoms by blocking the neuro-muscular junction and weakening contraction of the muscle. Here we asked whether BT injections also affect the level of sensorimotor cortical plasticity, since enhanced plasticity in clinically affected as well as unaffected body parts is one of the pathophysiological hallmarks of dystonia.

Methods: We applied a rapid paired associative stimulation (rPAS) protocol to induce plastic changes in primary motor cortex (M1) hand area of 12 patients with cervical dystonia before, 1 and 3 months after BT type A neck injections. Patients were clinically assessed followed by rPAS. M1 excitability was probed by measuring TMS-evoked motor evoked potentials (MEPs) before, 30 and 60 min after rPAS. We also measured MEP recruitment curves, short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), short afferent inhibition (SAI) and long afferent inhibition (LAI) in several hand muscles. Results were compared using two-way repeated measures ANOVA.

Results: The effect of rPAS was highly suppressed 1 month after injections. Before BT, rPAS significantly facilitated MEPs in abductor pollicis brevis (amplitude 30 min after rPAS: 178% of pre-rPAS MEP), but one month after injection this effect was abolished (95%), while at 3 months it had partially recovered (134%). BT had no effect on MEP recruitment, SICI, ICF, SAI or LAI. The amount of facilitation produced by rPAS was positively correlated with the time after previous injection and with the dystonia score ($p<0.01$).

Conclusions: BT reduced the effect of rPAS in cervical dystonia. This could result from the change in afferent input from the neck. The effect size correlates with clinical improvement and may indicate an additional mechanism of BT action.

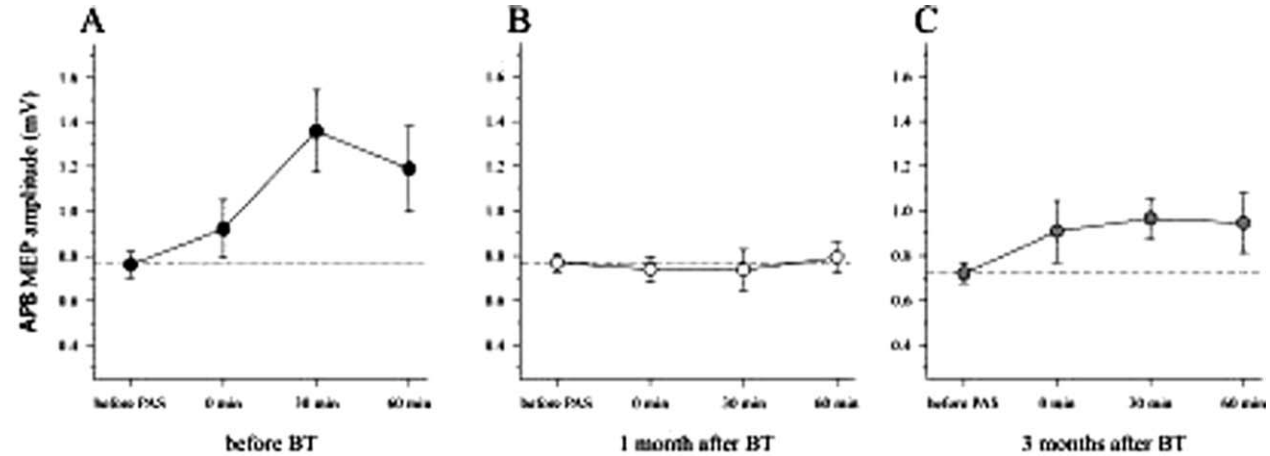

FIG. 1 (100).

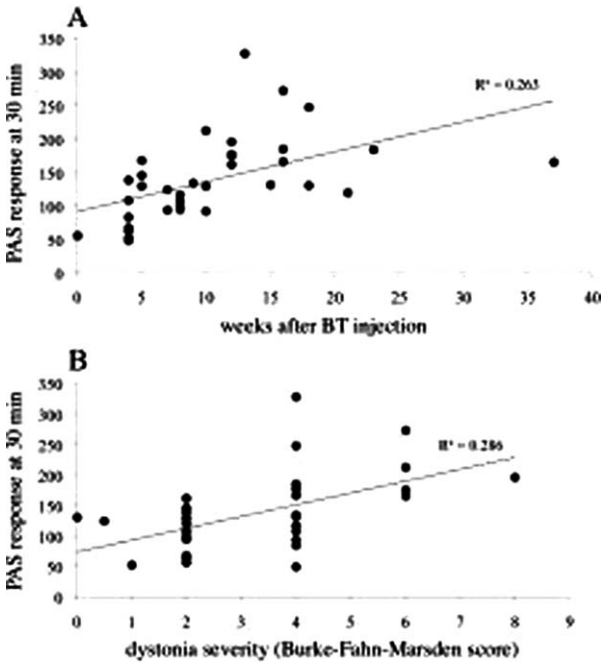

FIG. 2 (100).

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Transcranial magnetic stimulation in therapy of psychogenic neurological symptoms: Two case reports

N. Kresojevic, I. Petrovic, A. Tomic, M. Svetel, S. Radovanovic, V. Kostic (Belgrade, Serbia)

Objective: To present effect of transcranial magnetic stimulation (TMS) on psychogenic neurological symptoms (PNS).

Background: Clinical presentation of psychogenic disorders varies and sometimes it could be very disabling. Distractibility, variability and response to placebo are important characteristics of PNS. The prognosis for functional recovery is variable and relatively poor. Recent reports of TMS usage for psychogenic disorder treatment and spectacular improvement of neurological symptoms after TMS sessions, encouraged us to use TMS for our patients.

Methods: We present two patients: patient 1: 52 year-old female with 10 months history of psychogenic blepharospasm and patient 2: 24 year-old male with previous history of psychogenic seizures and actual psychogenic hemiparesis which compromised his walk. During single pulse stimulation we used A and B side of round coil alternately, placed over vertex. The intensity of stimuli at first was 30%, later increased for 10% and it was finished at stimulus intensity of 80% (in total twelve single pulses were applied).

Results: Patient 1: There was no obvious effect during stimulation. Patient felt weak after stimulation and felt to sleep. After four hours she wake up without any neurological complains. Three months follow up period showed intermittent mild right eyelid problem without functional disabilities. Patient 2: Effect was immediate, he could walk independently. Six months after stimulation, he reports occasional mild walking difficulties which didn't influence his daily activities. Interestingly, he didn't have seizures during this period.

Conclusions: Although psychiatric therapy should be essential for PNS, symptomatic and physical therapy are substantial in prevention of extreme consequences. It is possible that placebo could be underlying mechanism of our TMS protocol. If so, we assume that in more functionally impaired patient this therapy could be more effective. We propose TMS to be a part of the therapy in PNS patients if there are no contraindications since it is safe, non invasive and doesn't produce side effects.

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Isaac's syndrome – case report and electroneuromyographic changes after administration of phenytoin

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Objective: To report a case of Isaac's syndrome with clinical improvement after administration of phenytoin attested by electroneuromyography.

Background: Isaac's syndrome is characterized by gradual onset of muscle stiffness at rest, with continous twitching with cramps following voluntary contractions due to delay in muscle relaxation (pseudomyotonia). Clinical myokymia is defined as a wave-like rippling of muscle or motor unit discharges in doublets or triplets and neuromyotonia, a delayed muscle relaxation or high-frequency electroneuromyographic discharges. It represents an alteration in excitability of the terminal portions of motor axons. The symptoms of muscle contraction are often accompanied by profuse sweating and persist during sleep. Electrophysiologically, the hallmark of the syndrome is the presence of continous motor unit activity. Fasciculations and grouped high-frequency discharges are evident on electromyography. Phenytoin can be successful in abolishing clinical symptoms.

Results: Partial suppression of continuous electrical activity and less frequent bursts of motor units of normal appearance and bizarre

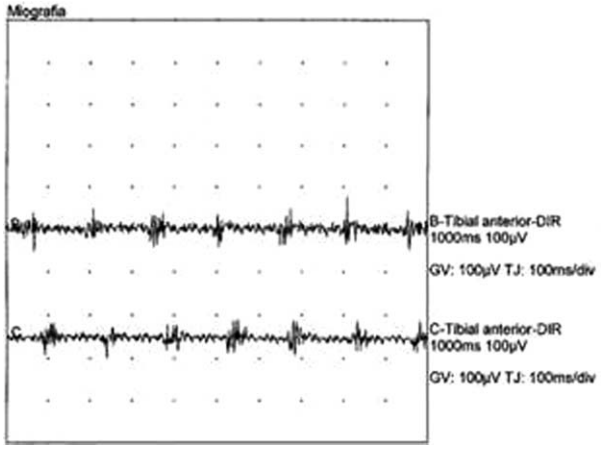

FIG. 1 (102).

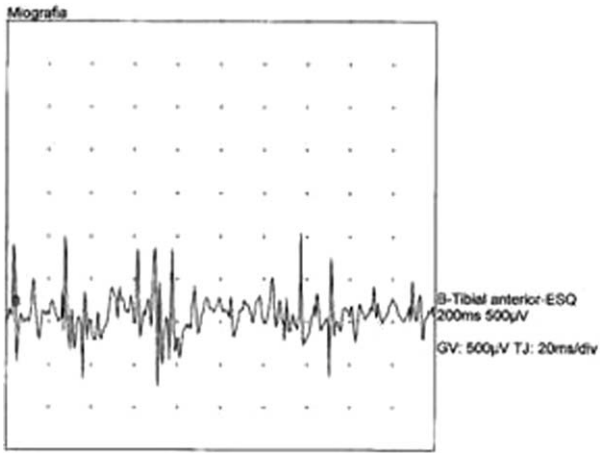

FIG. 2 (102).

high-frequency (150-300 Hz) discharges (figure1), after phenytoin (figure2).

Conclusions: Phenytoin is markedly efficient on the treatment of Isaac's syndrome, improving clinical and electroneuromyographical outcomes.

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tDCS for hyperkinetic movement disorders? A report of 4 cases

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Objective: We studied the effects of cathodal transcranial direct current stimulation (tDCS) over the motor cortices in two patients with focal hand dystonia (FHD) and two patients with Tourette syndrome (TS).

Background: Since weak electrical currents applied to the brain induce prolonged excitability changes in humans, we have proposed tDCS as a possible method of non invasive brain stimulation for modulating cortical excitability in patients with hyperkinetic disorders. In particular, cathodal tDCS is reported to inhibit brain areas below the stimulating electrode.

Methods: Cathodal and sham tDCS were applied in two different sessions comprising 5 consecutive days of daily stimulation (2mA-15 min for TS and 20 min for FHD) of the motor cortices. Patients were evaluated through disease-specific rating scales, through paper-and-pencil tasks, and subjective evaluation of general wellness.

Results: In both TS patients, whereas sham tDCS left the number of tics unchanged, cathodal tDCS (of the motor area controlateral to the most affected body side) consistently decreased total number of motor tics by a maximum of 60% and total number of phonic tics by a maximum of 40%. In both FHD patients, bilateral cathodal tDCS over the motor areas induced a sensation of general wellness and improved symptoms (for example: VAS percentage change sham vs cathodal for pain/no pain right hand patient 1, 130 vs 37%; patient 2, 0 vs 0%; pain/no pain left hand patient 1, 20 vs 6,8%; patient 2, 0 vs 0%). Paper and pencil task for qualitative tremor analysis (Copy of an Archimedes spiral) confirmed that cathodal tDCS was able to reduce tremor, whereas sham tDCS did not (Patient 1: C-tDCS vs S-tDCS: -37,5 vs 162%; patient 2: -75 vs 25%). tDCS effects on tremor persisted for approximately 10 days after the end of the entire 5-days session (Patient 1: C-tDCS vs S-tDCS: -37vs 60%; patient 2: -75 vs 0%).

Conclusions: Our preliminary results suggest that cathodal tDCS could have improved hyperkinetic symptoms in patients by recovering an inadequate inhibition of motor cortices responsible for excessive excitation.

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EMG pattern mining for tremor types recognition

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Objective: To develop a classifier for automatic recognition of different tremor types using Support Vector Machine (SVM) modeling and ensemble learning of the extracted electromyographic (EMG) features from subjects performing motor tasks.

Background: Tremor detection and its proper identification are crucial in prescribing the appropriate therapy to lessen its deleterious physical and emotional impact. EMG pattern mining can be a useful diagnostic aid for an objective identification of the different tremor types.

Methods: Eighteen normal subjects (mean age 44.9 years, range 17-70 years) and 20 tremor patients (mean age 53.75, range 22-71 years) participated in the study. The tremor types included 6 Essential tremor, 7 parkinsonian tremor, and 7 others (physiological, cerebellar, Holme's, and psychogenic). Fourteen EMG channels (7 per upper limb) were recorded from each subject while performing 15 motor tasks. The EMG signals were band-pass filtered (Butterworth, 10-500hz) and the following features were extracted: zero crossing; mean absolute value; variance; and mean spectral density. The features were then transformed into components by Independent Component Analysis. Two-stage modeling was performed using SVM ensemble to 1) discriminate tremor from normal, and 2) classify tremor types. The ensemble's voting weights were optimized by Monte Carlo simulation and its final prediction was determined by majority voting. Performance evaluation to estimate the ensemble's prediction accuracy used leave-one-out cross-validation.

Results: The best ensemble for stage 1 achieved 84.21% accuracy (32/38). Three SVMs were used with the following EMG channels and motor tasks: 1) biceps (finger tapping), 2) extensor indicis (loading test on outstretched forearm), 3) abductor pollicis brevis (hand at rest). For stage 2, the best ensemble achieved 80% accuracy (16/20). It was composed of four SVMs. All used line drawing tasks with the following EMG channels: extensor carpi radialis, triceps, and flexor carpi ulnaris.

Conclusions: We have shown the feasibility of developing robust classifiers to discriminate different tremor types. Our results suggest that good classification accuracy can be achieved even with just a small subset of motor tasks and EMG channels, which can help streamline and objectify tremor diagnosis.

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Boosting brain excitability by transcranial high frequency stimulation in the ripple range

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Objective: To test the effects of high frequency transcranial alternating current stimulation (tACS) applied in the ripple range, in a frequency-dependent fashion on cortical excitability.

Background: Two distinct populations of high frequency oscillations called ripples (80 -200 Hz) and fast ripples (250 -500 Hz) have been reported in animals and humans. Higher frequencies in the ripple range are intensively used in deep brain stimulation for treatment of Parkinson's disease and recently received attention as a possible correlate to epileptic activity. Here, for the first time we have tested the effects of 80, 140 and 250Hz oscillations on motor evoked potential (MEP) amplitude.

Methods: Subjects received on separate days AC- (80Hz, 140Hz, 250Hz,) and sham stimulations in a randomized order. Stimulation was delivered by a battery-driven electrical stimulator (NeuroConn GmbH, Ilmenau, Germany) through conductive-rubber electrodes. To detect changes of excitability MEPs of the right first dorsal interosseus muscle (FDI) were recorded during and following stimulation of its motor-cortical representation field by single-pulse tarnscranial magnetic stimulation (TMS). For the TMS train during the AC stimulation, the MEPs were subdivided into successive groups of 15, each covering a time range of 1 min, and the means for each group were calculated. Following stimulation, 20 single test-pulse MEPs were recorded at, i.e., 0, 5, and 10 min after stimulation and then every 10 min up to 60 min.

Results: Using tACS we could immediately increase motor cortex (M1) excitability as measured by TMS during 140 Hz stimulation with an induced aftereffect of 1 hour. Controls by sham and 80 Hz stimulation were without any effect. Furthermore, 250 Hz was effective only with a delayed induction and reduced duration. Interestingly, in our study, 140 Hz stimulation excitatory after-effects are not sensitive to the physiological state of stimulating neurons.

Conclusions: In summary we were able to show that high frequency stimulation enhances human M1 excitability in a frequency-dependent fashion. Our findings are expected to be of importance to engender research in several directions. It represents a further step to more targeted plasticity modulating protocols and also may have important implications for neurological disease accompanied by pathological oscillations and motor deficits.

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Plastic changes in human motor cortex induced by repetitive Aδ laser inputs paired with transcranial magnetic stimulation

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Objective: To investigate whether repetitive Aδ nociceptors activation paired with transcranial magnetic stimulation (TMS) induces changes in human primary motor cortex (M1) plasticity.

Background: Laser evoked potentials (LEPs) can be elicited by cutaneous activation of Aδ nociceptors. LEPs consist of an N2-P2 vertex complex generated by anterior cingulate and insula area, and an earlier bilateral N1 component generated by secondary sensory cortex (SII). When TMS is delivered 0-100 ms after N1, a transient inhibition in M1 occurs. The reduction of motor evoked potentials (MEPs) amplitude is due to a cortical collision in M1 between Aδ inputs and TMS.

Methods: Fifteen healthy subjects were studied with a conditioning-test paradigm. Test stimulation consisted of 20 single TMS pulses delivered over the left M1 at intensity able to evoke at baseline MEPs of about 1 mV in right hand abductor digiti minimi (ADM) muscle. We determined the laser perceptive threshold (LPT) as the lowest intensity at which the subjects perceived at least 50% of the stimuli. We then delivered 15 laser stimuli over the back-hand ulnar region at intensity twice the LPT. The conditioning stimulation consisted of 60 laser stimuli paired with TMS at interstimulus interval of N1 peak latency + 50 ms, and at 0.1 Hz (laser-paired associative stimulation, L-PAS). MEPs were analyzed before and at 5-90 minutes after conditioning. To exclude changes in spinal excitability we tested in five subjects the effect of L-PAS on MEPs elicited by cortical anodal stimulation. Repeated measures analysis of variance (ANOVA) was used in the statistical analysis. Tukey honest significant difference test was used for post hoc analysis.

Results: One-way ANOVA showed a significant effect of factor intervention ($F\ 7.98=3.79$; $p=0.01$). Post hoc analysis showed that L-PAS significantly increased MEPs size at 20-60 minutes after conditioning ended. Conversely, L-PAS left MEPs evoked by cortical anodal stimulation unchanged ($F\ 7.28=2.03$; $p=0.1$).

Conclusions: L-PAS induces plastic changes in M1 through SII-to-M1 connections suggesting a role for the nociceptive pathway in modulating the plasticity of human motor cortex.

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Spontaneous neuronal firing in the subthalamic nucleus in dystonia differ from those in Parkinson's disease

P. Zhuang, M. Hallett, S. Guo, Y. Zhang, J. Li, Y. Li (Beijing, China)

Objective: To explore spontaneous neuronal activity in the subthalamic nucleus in patients with dystonia and Parkinson's disease.

Background: Deep brain stimulation (DBS) in the subthalamic nucleus (STN) is used to treat both dystonia and Parkinson's disease (PD). Different motor symptoms in dystonia and PD have been ascribed both to different mean rates or patterns of neuronal firing.

Methods: Microelectrode recording of STN neuronal activity were obtained during stereotactic surgery for the implantation of DBS electrodes in 14 patients with PD and 8 patients with idiopathic dystonia. Electromyography on the contralateral limbs to surgery was simultaneously performed. Single unit analysis, interspike intervals (ISI) and coefficient of variation (CV) of the ISI were performed. ISI histograms were constructed to evaluate the neuronal firing pattern. ANOVA and Chi-square test were employed to compare the neuronal firing in the STN between two patient groups.

Results: Sixty five STN neurons were identified from patients with dystonia, including 16.8% neurons with tonic firing and 83.2% neurons with irregular discharge. One hundred and five STN neurons were identified from patients with PD, including 19.4% tremor-related neuronal activity, 55.6% neurons with tonic firing and 25.0% neurons with irregular discharge. The mean spontaneous firing rate recorded from dystonia patients was lower than in PD patients ($p<0.001$, mean$\pm$SD: 27.2 $\pm$11.8 Hz vs 39.6$\pm$13.6 Hz). Furthermore, STN neurons fired in a more irregular pattern consisting of more frequent and longer pauses in dystonia compared to PD; this was confirmed by CV ($P<0.001$, mean$\pm$SD: 1.96$\pm$0.86 vs 1.20$\pm$0.28).

Conclusions: The data suggest that both alteration in firing rate and firing pattern in STN might underlie the differing motor symptoms associated with the two movement disorders.

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Quantitative assessment of dystonia in children with early onset primary dystonia

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Objective: To quantify movement disorder in dystonic children by acquisition of kinematic data and muscle activity during unconstrained movemnts of upper limbs and to correlate these measurements with the clinical scales.

Background: Precise measurements of a movement disorder is crucial to assess efficacy of any treatment in dystonia, especially in the pediatric population, due to the lack of validated rating scales and to the great variability of the phenomenology of dystonia and its effect on motor function.

Methods: Nine children with primary dystonia (2 DYT1 positive and 7 negative, age range:10 -17) and matched control children are included in the study. Kinematic parameters (duration of movement,

excursion of joint angles, intra-subject repeatability, end-effector path, peak velocity, smoothness, inter-segmental coordination, coefficient of variation) and EMG data (presence and measurement of co-contraction) during unconstrained movements of upper limbs (reaching and writing) were recorded using a portable 3D motion capture and a electromyographic system integrated and synchronized. Data were statistically analyzed (student t-test and Pearson correlation). The BFMDRS was administered at time of testing.

Results: Reaching protocol: There was no difference in peak velocity between patients and control s Coefficient of variation (CV) on coordination parateters, velocity and acceleration control was higher for dystonic children and it correlated with the measurements of the BFMDRS. Co-contraction of antagonist muscles was not constantly present in dystonic children and did not correlate with the severity of dystonia. Writing protocol: CV was higher in patients, with no correlation with the clinical scales.The coordination detriment was mainly due to the output trajectory (written path) decoupled from the lomb involved joints trajectories.

Conclusions: Dystonic children showed greater variability of movements. There was no difference in the velocity, and co-contraction was not a constant feature. Both protocols were easily applicable and reproducible in children, and pointed out different defict aspects.

POSTER SESSION 1

MONDAY, JUNE 14, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present:14:00-15:30

DRUG-INDUCED MOVEMENT DISORDERS

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Parkinsonism induced by cyclosporin A: A serie of three cases

P. Antonio, D.F. Oriol, H.-V. Jorge, C. Antonio, A.-S. Jose
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Objective: To present the clinical and neuroimaging features of a serie of three patients that developed a parkinsonian syndrome after beginning treatment with Cyclosporin A.

Background: Cyclosporin A is a drug used as immunosuppressive treatment to prevent organ transplant rejections. In 40% of patients, it has been associated with different neurological side effects as headache, epileptic seizures, disorientation or mild action tremor. Nevertheless, a parkinsonian syndrome caused by this drug is uncommon.

Methods: Among all patients referred to our Movemet Disorder Unit in the past two years, we detected three patients with parkinsonian syndromes suspected to be induced by Cyclosporin A. Brain MRI and brain SPECT with ioflupan (DATscan) were performed in all patients. Patient 1: A 71-year-old male with hepatic cirrhosis received a liver transplant in 2004 and started treatment with Cyclosporin A. Four years later developed a bilateral parkinsonian syndrome and a gait disturbance. Patient 2: 80-year-old male treated with Cyclosporin A since 1992 after a liver transplant for hepatic cirrhosis caused by hepatitis C virus. He was referred to us because a restly tremor, bradykinesia, and bilateral rigidity appeared in the last months. Patient 3: A 64-year-old male received treatment with Cyclosporin A for a cutaneous pemphigoid. Four years later, he developed bilateral restly tremor and bradykinesia.

Results: Neuroimaging studies did not reveal any significant findings. In three cases, a brain SPECT with ioflupan (DATscan) was normal. Cyclosporin A was removed and changed to another immunosuppressor drug and it was followed by an improvement of the extrapyramidal syndrome in all cases.

Conclusions: Cyclosporin A can occasionally induce a parkinsonian syndrome even years after its beginning. We notice the importance of its detection, because its change to another immunosuppressor can improve the extrapyramidal symptomatology.

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Schizophrenia and Parkinson's disease: An unfrequent association revisited

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M. Perez Ackly, R. Diaz, F. Alvarez, M.M. Esnaola y Rojas
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Objective: To describe two cases of possible Parkinson's disease (PD) associated with a long history of schizophrenia. To discuss on the efficacy of the apomorphine test and to present a video recording of the motor response.

Background: Drug induced parkinsonism (DIP) is the second most common cause of parkinsonism in older individuals after PD, and in patients chronically exposed to neuroleptics, it is the most frequent diagnosis when developing parkinsonism. However, the occurrence of PD in schizophrenic patients is rare and the pathophysiology unclear.

Methods: Two male patients with a long history of schizophrenia were referred to the movement disorder clinic for evaluation of unilateral hand tremor and bradikynesia and unilateral hand and chin tremor. Patients underwent an apomorphine test (AT) and a transcranial sonography (TCS).

Results: Patient A was a 63 years (ys) old man, with a 20 ys history of paranoid schizophrenia, who developed right upper limb tremor and marked bradykinesia in 2000. He received haloperidol for 15 ys, trifluoperazine for 10 ys, clozapine 100mg/day for 1 year and quetiapine 150mg/day since June 2009. Relevant clinical features were marked hypomimia, bradykinesia and gait disorder, and unilateral and persistent left hand and foot tremor. A TCS was normal. An AT revealed a basal UPDRS III=74, after 2 mg=44, markedly improving bradykinesia, gait and tremor. Patient B was a 64 ys old man, with a 15 ys history of paranoid schizophrenia, who developed right hand and chin tremor two ys ago and minor bradykinesia. The patient received haloperidol for 13 ys, trifluoperazine 5 mg for 6 ys, olanzapine 5 mg for 2ys, and quetiapine 200mg/day. A TCS showed a hyperechogenic mesencephalic area (20 mm2), and an AT showed a basal UPDRS III=20, after 1 mg=11, markedly improving hand and chin tremor.

Conclusions: A positive motor response to apomorphine in parkinsonism of schizophrenic patients exposed to neuroleptics may suggest a possible coexistance of PD. Clinical features such as bradykinesia and unilateral and persistent hand tremor are not frequently associated with parkinsonism of schizophrenic patients treated with neuroleptic drugs.

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Withdrawn by Author

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The efficacy of alpha lipoic acid (thiogamma) in treatment of movement disorders induced by manganesese

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Objective: The aim of the study was to evaluate the efficacy of the Alpha Lipoic Acid in patients with Manganese-Induced Encephalopathy (MIE).

Background: Manganese-Induced Encephalopathy (MIE) induced by intravenously injected self-prepared drug "ephedrone", comprising manganese, water, and potassium permanganate is resistant to antyparkinsonian medications.

Methods: 20 patients with MIE were evaluated and divided into 2 groups: 1st group (11 patients) received Alpha Lipoic Acid (ALA) (THIOGAMMA, WÖRWAG Pharma GmbH., Germany) and 2nd group (9 patients), received standard treatment. 600 mg ALA were used intravenously every day during 20 days and then treatment continued 600 mg p.o. once daily during 2 months. All the patients were men, aged from 21 to 50 years. The mean time of "ephedrone" abuse was about 1 year. PD symptoms were assessed before the treatment, after 3 months of treatment. Follow up investigation was made after 6 months of treatment. UPDRS scale, Tinnetti Scale, Hamilton Depression and Anxiety Scale (Ham-D,Ham-A) were used.

Results: The analysis carried out has shown reduction of symptoms of parkinsonism after treatment in the 1st group (in 7 cases) as well as reduction of Ham-D and Ham-A scores (in 5 cases). In the 2nd (3 cases) group such improvement was seen in 3 cases after the 3 months of treatment. On the follow up in the 1st group the symptoms of parkinsonism are worsening without apparent cause in the 2 patients, who had long history of drug addiction.

Conclusions: It seems that thiogamma improves the general status of the patients as well as walking and speech. This preliminary data need further confirmation.

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Multi-centre survey of new patients referred from primary care with parkinsonism – what proportion are on medications which can cause drug induced parkinsonism?

V.R. Lyell, E.J. Henderson, D.J. Ahearn, D.G. MacMahon (Bristol, United Kingdom)

Objective: To establish what proportion of new referrals with suspected parkinsonism are taking medications that can induce drug induced parkinsonism (DIP).

Background: After idiopathic Parkinson's disease (IPD), prescribed medications may be the second most common cause of parkinsonism (Barbosa, Mov Disord 2006;21:800-8). A history of antipsychotic or dopamine depleting drug use precludes the diagnosis of IPD according to the UK Brain Bank criteria and causative drugs should be identified and discontinued as drug induced parkinsonism (DIP) can be reversible. A previous series (Stephen, Lancet 1984;2:1082-3) found 51% of patients referred to a geriatric department with parkinsonism were taking implicated drugs. Prochlorperazine then accounted for 43% of the culprit medications, without apparent indication.

Methods: Participants on the 15th BGS Parkinson's Academy collected data from 17 UK secondary care centres. All new referrals from the community requesting a movement disorder opinion on tremor or parkinsonism were considered, but excluded if no adequate drug history was available.

Results: Data was collected on 328 patients (56% male; median age 76 [range 19-95]). 12% (38/328) were being prescribed medications that could precipitate DIP. The single commonest was prochlorperazine (12/38, 32%). Typical antipsychotics made up the majority (16/38, 42%) followed by atypical antipsychotics (7/38,18%) with the remainder being metoclopramide (4/38, 11%), amiodarone (3/38, 8%), lithium (3/38, 8%), antihistamines (promethazine and cinnarizine) (3/38, 8%) and valproate (2/38, 5%). An equal number of men and women were taking implicated medications. It was not possible to review outcomes in this study, but many patients will improve on cessation of such drugs, while others may show typical idiopathic disease on longer follow-up.

Conclusions: An important minority (12%) of new referrals from primary care to specialist PD services in the UK are being prescribed drugs implicated in DIP. Some may be necessary to the management of other significant conditions. However, 25 years on from Stephen's series the predominance of prochlorperazine (32%), which is prescribed mainly for relatively trivial indications and for which alternatives are readily available, is concerning.

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Differential diagnosis of Parkinson's disease and drug-induced parkinsonism with TCS: A population-based study

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Objective: To determine the diagnostic accuracy of midbrain hyperechogenicity as assessed by transcranial sonography (TCS) for the differential diagnosis of Parkinson's disease and drug-induced parkinsonism (DIP) in the general population.

Methods: As part of an ongoing prospective population-based study of carotid atherosclerosis and stroke risk (the Bruneck study), a total of 574 men and women aged 55-94 years underwent an examination with TCS (follow-up rate 86.2%). The diagnosis of PD was based on UK Brain Bank Criteria. Drug induced parkinsonism was diagnosed according to criteria published previously (*Schrag et al., 2000*). Transcranial sonography (TCS) was performed (2.5MHz transducer, Logiq 7, GE) by one experienced examiner from both sides using the temporal approach to display the butterflyshaped mesencephalon. Echogenic areas of both sides were analyzed separately. To compare areas of echogenicity and the prevalence of hyperechogenicity between groups, the side of greater value of SN echogenicity of each subject was used for statistical analysis. Based on a ROC analysis between healthy controls and patients with PD, hyperechogenicity is defined as an area of echogenic signal of 0.18 cm^2 or greater at least on one side.

Results: 15% of the study population had no sufficient acoustic bone window or had no TCS due to institutionalization (n=12). Of the subjects with sufficient acoustic bone window, 17 subjects had a diagnosis of clinically definite PD (age 79 years, SD 8; females n=7) and 7 subjects had a diagnosis of DIP (age 68 years, SD 11; females n=5), respectively. Area of midbrain echogenicity in PD patients (0.23 cm^2, SD 0.07) was significantly increased compared with the DIP group (0.17 cm^2, SD 0.07; Mann-Whitney-Test, $p<0.05$). One (14%) of the DIP patients had SN hyperechogenicity as compared to15 (88%) of the patients with PD (Chi-square-Test, $p<0.01$). Thus, sensitivity of TCS to differentiate between PD and DIP was 88%, the specificity was 86%. The positive predicitive value of TCS for PD was 94%, the negative predicitive value was 75%.

Conclusions: TCS may help to differentiate between patients with Parkinson's disease and those with drug-induced parkinsonism.

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Acute, severe tardive dyskinesia precipitated by armodafinil use

R. Marcus, S. Baser, M. Sunseri, R. Pfeiffer (Pittsburgh, Pennsylvania, USA)

Objective: To present a case of acute, severe tardive dyskinesia precipitated by armodafinil use.

Background: Armodafinil, a stimulant, is commonly used to treat narcolepsy and refractory obstructive sleep apnea. It is the R-enantiomer of modafinil, in which orofacial dyskinesia has been reported as an adverse reaction in 1-2% of patients during clinical trials. We describe the first case of severe, acute tardive dyskinesia precipitated by armodafinil.

Methods: Case study with review of relevant literature provided. We present a 60 year old Caucasian male with narcolepsy, refractory obstructive sleep apnea, and gastroesophageal reflux disease who was prescribed armodafinil for his sleep disorder. For the past fifteen years, he had been taking metoclopramide, a gastroprokinetic agent with a well known side effect of tardive dyskinesia, which he had tolerated well.

Results: Videotapes to be presented. Within three weeks of starting armodafinil, the patient developed severe orofacial, trunk and limb dyskinesias. Despite discontinuation of both armodafinil and metoclopramide, the patient's symptoms persisted. Amantadine, an NMDA channel inhibitor, was added, with subsequent improvement of movements.

Conclusions: Our case suggests that armodafinil use may trigger the onset of severe tardive dyskinesia associated with chronic use of metoclopramide. To our knowledge, no prior cases of acute tardive dyskinesia have been reported with armodafinil.

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Tardive syndromes in children and adolescents

M. Rotstein, T. Pearson, P.E. Greene, S. Fahn (New York City, New York, USA)

Objective: To describe the clinical spectrum of tardive syndromes in children and adolescents.

Background: Tardive syndromes result from exposure to dopamine receptor blocking agents (DRBA), and include oral-buccal-lingual dyskinesia ("classic" tardive dyskinesia), tardive dystonia, tardive akathisia and withdrawal emergent syndrome (WES). Tardive syndromes are reported to be less common in children than in adults, and have not been described extensively in children.

Methods: A retrospective review of patients diagnosed with tardive syndromes starting before 20 years of age, evaluated at a movement disorders center between 1976 and 2009.

Results: Of 20 children identified, 13 were male. The age at symptom onset was 13.5±4.5 years (range 4.7 to 19.9 years). Tardive symptoms included akathisia (50% of children), dystonia (45%), oral-buccal-lingual dyskinesia (35%), WES (30%), and chorea (20%). More than one feature was present in 50% of patients. There was a history of abnormal development in 75%. Common psychiatric diagnoses were Pervasive Developmental Disorder (55%) and Attention Deficit Hyperactivity Disorder (50%). Indications for DRBA treatment were aggressive behavior (60%), hyperactivity (45%) tics (35%) and mood disorders (25%). 50% of children were exposed to multiple DRBA's. Risperidone was the cause in the 55% of patients; other DRBA's implicated were haloperidol (30%), aripiprazole (20%), pimozide (10%), chlorpromazine (10%), and olanzapine (5%). The length of drug exposure before the emergence of tardive symptoms ranged from 3 months to 8 years (mean: 32 months). In the 6 patients with WES, symptoms resolved after an average of 2.5 months. Of the 14 other patients with tardive syndromes 12 had persistent symptoms for the duration of follow-up, ranging from 9 months to 10 years. Significant improvement was noted in only 40% of these patients despite treatment. Treatment included discontinuation of the causative drug, symptomatic treatment (e.g. benzodiazepines, anticholinergics), dopamine depleting agents, and occasionally reintroduction of a DRBA.

Conclusions: Tardive syndromes do occur in children. Some childhood tardive syndromes, such as WES, are self-limited, but some children suffer persistent symptoms which may be treatment-resistant and cause significant morbidity.

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High resolution tracking of motor complications in Parkinson's disease

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Objective: Our goal is to develop a wearable sensor system that can automatically monitor the presence and severity of motor signs of Parkinson's disease (PD), motor fluctuation in response to anti-Parkinson's medication, and the mobility status of the patient; all with high temporal resolution from normal unconstrained activities.

Background: Self-report instruments offer limited temporal resolution necessary to capture the rapid and unpredictable changes in PD motor complications. Current prototype wearable monitors offer the advantages of objectivity, portability, and operator-independent measurement. However, they have not progressed in capturing motor activity status to a resolution of less than 30-minute epochs.

Methods: We have developed a sensor technology that combines electromyographic (EMG) and accelerometer (ACC) data acquisition into a single wireless sensor. This technology is being used to acquire and analyze data from multiple sensors from n=22 patients with advanced PD during unconstrained activity in a simulated home environment. Videotaped data were recorded and annotated to serve as the gold-standard for algorithm assessment.

Results: Algorithms have been implemented using a custom blackboard-based signal processing architecture coupled with feature extraction procedures and time-dependent neural networks. Training of the algorithms from a sub-set of the data (ACC signals from 4 sensors) has succeeded in providing 1 s. temporal resolution for identifying mild to severe motor signs of PD (*Tremor and Freezing*), motor complications of anti-PD medication (*Dyskinesia*) and mobility status (*sit, stand, walk, lie down*) with better than 90% accuracy.

Conclusions: Results to date support the likelihood of achieving a high-resolution and accurate monitoring system for Parkinson's disease. *This work was supported in part by grant # EB007163 from the NIH/NIBIB.*

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Tardive akathisia successfully treated with electro-convulsive therapy (ECT)

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Objective: To describe two cases of tardive akathisia successfully treated with electro-convulsive therapy.

Background: Akathisia comes from the Greek word meaning "unable to sit still". Patients afflicted with this condition describe an inner feeling of restlessness or discomfort that manifests with movements such as squirming, pacing, rocking, or even moaning. The condition is frequently iatrogenic in origin and presents in both an acute and a tardive form. The tardive form is often co-morbid with other tardive syndromes, and similarly persists or even worsens after the offending agent has been removed.

Methods: Tardive Akathisia causes significant distress among patients, but has been notoriously difficult to treat. We present details of two cases who initially failed treatment on Reserpine and Tetrabenezine and were then treated successfully with ECT.

Results: In the first case, a 49 year old woman with tardive dyskinesia and tardive akathisia after Haldol exposure underwent ECT with complete remission of her akathisia. This improvement was maintained as late as 5 years following her treatment. The second case was a 54 year old woman who developed tardive akathisia after Mellaril exposure. She was treated with ECT and remained symptom-free at follow-up three weeks later. In neither case were there long-term side effects of ECT reported.

Conclusions: To our knowledge, there has only been one previously published case of ECT treating tardive akathisia[1]. Although further studies are needed, given these combined reports, ECT should be considered as a treatment option for tardive akathisia, particularly in those patients who have not responded to standard medication management or who are intolerant of side-effects. Hermesh H, Dov A, Friedberg, G, Lapidot, M, and Munitz, H. Electroconvulsive therapy for persistant neuroleptic-induced akathisia and parkinsonism: A case report. Biol Psychiatry 1992; 37:407-411.

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Tardive dyskinesias associated with citalopram and escitalopram

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Objective: To report cases of tardive dyskinesia (TD) that appeared after exposure to citalopram or escitalopram, without exposure to other dopamine- receptor blocking agents (DRBAs).

Background: Tardive dyskinesias, often consisting of oral/buccal/lingual dyskinesias (OBLD), chorea, retrocollis, and repetitive hand movements, are associated with exposure to DRBAs, although they have been reported after exposure to selective serotonin reuptake

inhibitors (SSRIs) as well. TD has not previously been reported after isolated exposure to citalopram or escitalopram.

Methods: Case reports.

Results: Case#1: A 77-year-old man with a history of anxiety and depression developed involuntary movements after 16 months of exposure to citalopram. He had no prior exposure to DRBAs or SSRIs. Exam revealed blepharospasm, OBLD, chorea in the limbs, hand stereotypies, and akathisia. The citalopram was discontinued gradually; 2 months later he had occasional finger-rubbing and OBLD, and 9 months later rare tongue-popping and finger-rubbing. Case#2: A 43-year-old woman with no psychiatric or past medical history was started on escitalopram for anxiety; 6 months later she developed severe jerky retrocollis and facial dystonias. The escitalopram was withdrawn, but the movements persisted. Her cervical dystonia responded somewhat to injections of botulinum toxin; her facial movements improved with TBZ, but this had to be withdrawn due to severe depression. Case#3: An 83-year-old man with cognitive impairment and depression developed involuntary movements of the lower face after 18 months of treatment with escitalopram. He had no exposures to DRBAs. Examination revealed OBLD, hand stereotypies, and parkinsonism (shuffling gait, reduced armswing, postural instability). Escitalopram was tapered off and venlafaxine was started. One year later, examination revealed improved OBLD with occasional tongue-popping, jaw-opening dystonia, and finger-rubbing.

Conclusions: Citalopram and escitalopram are highly selective SSRIs, without known activity at any subtype of dopamine receptors. We report three cases of involuntary movements with phenomenology indistinguishable from classic TD, all of which developed after exposure only to citalopram or escitalopram. These reports and evidence from animal models support the role of the serotonergic system in the development of TD.

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Peripheral blood RNA gene expression profiling in illicit methcathinone users reveals effect on immune system

K. Sikk, S. Koks, U. Soomets, L.C. Schalkwyk, C. Fernandes, S. Haldre, S.-M. Aquilonius, P. Taba (Tartu, Estonia)

Objective: In the present study we analyzed gene expression networks related to the chronic abuse of methcathinone.

Background: In recent years, a syndrome of hypokinesia, dysarthria, dystonia and postural dysfunction has been reported in drug addicts in several countries, who have intravenously injected a "designer" methcathinone prepared from pseudoephedrine (Sudafed tablets), potassium permanganate, and acetic acid. An extrapyramidal syndrome in methcathinone (ephedrone) users has been attributed to manganese (Mn) intoxication. Molecular mechanisms underlying combined Mn and methcathinone neurotoxicity are poorly understood.

Methods: We analyzed gene expression profiles of peripheral blood from 20 methcathinone users and 20 matched controls using Affymetrix GeneChip Human Gene 1.0 ST Arrays. Gene expression profile data was analyzed by Bayesian modeling. Functional annotation of the enriched gene sets was used to define changed genetic networks. In order to verify the microarray results, we chose eight genes from the list of genes with most significantly different expression and performed quantitative real-time (RT) PCR.

Results: 326 out of 28,869 analyzed genes showed statistically significant differential expression with False Discovery Rate (FDR) below 0.05. Quantitative RT-PCR confirmed differential expression for most of the selected genes. Functional annotation and network analysis indicated that most of the genes were related to activation "immunological disease, cellular movement and cardiovascular disease" gene network (enrichment score 42). A similar functional difference was also evident when we compared patients according to the injection status (past or current users).

Conclusions: Methcathinone abusers have characteristic blood transcriptional pattern that is mostly caused by their HIV and HCV infections. However, drug abuse itself has similar effects on transcriptome and further compromises the immune system of patients.

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Acute effects of methcathinone and manganese in mice: A dose response study

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Objective: To determine (1) the tolerance of methcathinone in mice as a single substance and as a part of a psychoactive drug and (2) to determine a dose of manganese that produces symptoms of intoxication in mice to be able to design an animal model of manganism.

Background: Injection of a designer drug made by mixing and heating pseudoephedrine, potassium permanganate, vinegar and water produces an extrapyramidal syndrome with parkinsonism, dystonia, gait and balance disorders similar to manganism. Its abuse has become a problem in several countries around the world. The exact mechanism of the drug's neurotoxicity and the role of its individual components is not well understood.

Methods: Groups of 14 male C57B6 mice were injected intraperitoneally with (1) the previously mentioned drug mixture containing an estimated 10, 25, 50, 100 or 150mg of methcathinone and respectively 1.6, 3.8, 6.9, 17.1 and 22.6mg of manganese per kg of body weight; (2) 10, 25, 50, 100, 150, 200 or 300mg of pure methcathinone per kg of body weight; (3) 10, 25 or 50mg of manganese per kg of body weight. Locomotor activity of the animals was measured for 30min after the injection, various symptoms and time of death were recorded.

Results: The drug mixture containing 150mg/kg and 100mg/kg of methcathinone resulted in lethal outcome for 92.9% and 47.3% respectively. With 300mg/kg and 200mg/kg of pure methcathinone the mortality rate was 100% and 50% respectively. Doses of methcathinone above 100mg/kg produced epileptic seizures in 74% of the animals. Lower doses (10 and 25mg/kg) of methcathinone had a strong stimulating effect, while the intermediate doses did not differ significantly from the control. Manganese did not prove to be lethal in doses up to 50mg/kg, but induced behavioral inhibition on the animals.

Conclusions: Our data suggests that, in order to produce symptoms in mice, relatively high doses of methcathinone and manganese have to be used. As part of the drug mixture it appears that a smaller amount of methcathinone already has a strong effect suggesting that the other components of the mixture potentiate the effect of methcathinone.

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A case of manganese toxic encephalopathy

Y.A. Trufanov, T.V. Mironenko (Lugansk, Ukraine)

Objective: Manganese Toxic Encephalopathy (MTE) is being increasingly recognized as a cause of parkinsonism, due to injection of ephedrine-like medication.

Background: We present a case of MTE recently seen at our institution.

Methods: A previously healthy 27-year-old man presented with weakness in the extremities, gait impairment, occasional falls, and memory impairment.

Results: Starting in 2001, the patient used an intravenous drug solution prepared from "Coldact Flu Plus" (phenylephrine hydrochloride 25 mg, chlorpheniramine maleate 8 mg, paracetamol 200 mg) with the daily dosage of 10-50 pills and the additives: manganese, vinegar and water. Within 9 months of beginning drug injection, he began developing bradykinesia, leg weakness, gait impairment, and memory dysfunction. In spite of discontinuation of the drug use in 2002, worsening of the neurological symptoms were observed for the next 4 years. Current examination revealed left sided bradykinesia and rigidity, right sided hemiparesis, and bilateral upgoing toes and hyperreflexia. Treatment consisted with physiotherapy, baclofen and piracetam with minimal improvement. Some improvement was seen in cognitive function resulted in his returning to work in 2006.

Conclusions: This case demonstrates the typical course and progression of neurological symptoms following chronic intravenous ingestion

of ephedrine-like medications. The neurological syndrome may continue to advance slowly even after a complete discontinuation of the drug.

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Amantadine-induced myoclonus in Parkinson's disease: A new case report

F. Viallet, D. Gayraud (Aix en Provence, France)

Objective: To describe a new case report of amantadine-induced myoclonus with 3 video recordings of challenge, dechallenge and rechallenge with amantadine prescribed for l-dopa-induced dyskinesias in a patient with advanced Parkinson's disease (PD).

Background: To date, amantadine-induced myoclonus has been rarely reported (Pfeiffer, Mov Disord. 1996;11:104-106), restricted to the vocal tract in a 69 year-old patient with PD of 5 years duration. More recently, 3 other cases with generalised myoclonus have been described (Matsunaga et al, Neurology 2001;56:279-280) in elderly PD patients with less than 5 years duration.

Methods: Case report: In this 74 year-old female PD patient, the disease had started 19 years earlier. The UPDRS motor score was 25/108 in OFF state (after 12h of l-dopa withdrawal) and 12/108 in ON state (1h after oral intake of 250mg of l-dopa) with peak-dose dyskinesias at 11/28 (Goetz score). The MMS was scored at 30/30 and Mattis DRS at 140/144. Amantadine had been introduced since 1 year at 300 mg/day, then providing a partially successful reduction of dyskinesias with some hallucinations and balance disorders after 6 months: the l-dopa daily dosage was 600mg with 16mg/day of Ropinirole and 25 mg/day of Clozapine.

Results: During January 2009, some episodes of confusion occurred and Rivastigmine was added (4.6 mg/day), then reducing hallucinations and confusion. 1 month later, a generalised myoclonus was clearly observed with dysarthria due to vocal myoclonus (1st video): the role of amantadine was suspected and it was stopped. 1 week later, the myoclonus disappeared, but the dyskinesias worsened (Goetz score at 17/28) whereas the UPDRS motor score was 14/108 (2nd video): the patient asked for taking again amantadine and it was restarted at 300 mg/day. After 1 month, the patient was hospitalised because of falls due to generalised myoclonus (3rd video) and amantadine was stopped again and further restarted at 100 mg/day, then providing a sufficient reduction of dyskinesias and only a mild myoclonus. The renal function (serum creatine level) was normal.

Conclusions: This clinical observation illustrates a new case of amantadine-induced myoclonus. In a recent paper (Nishikawa et al, parkinsonism Relat Disord. 2009;15: 351-353), the adverse reactions as myoclonus and confusion have been attributed to excessive plasma concentration (over 3000 ng/ml) due to renal insufficiency.

POSTER SESSION 1
MONDAY, JUNE 14, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 14:00-15:30

DYSTONIA

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Paroxysmal dystonia in Devic's disease

L. Abaroa, N.S. Garretto, T. Arakaki, S.A. Rodriguez, L.I. Melamud, O.D. Garcea, A.M. Villa (Buenos Aires, Argentina)

Objective: Movement disorders (MD) have been described in demyelinating diseases, specially in multiple sclerosis (ME). Paroxysmal dystonia, also called tonic spasm (TS) is the most frequent MD in ME. Only few cases have been reported in Devic's disease (DD) albeit it's frequently referred by these patients. For this reason, we decided to study more deeply the characteristics of this abnormal movement in DD.

Background: It has been suggested that spinal cord pathology predominantly affecting the inhibitory interneurones may result in abnormal activation of the antagonistic muscles resulting in dystonic-athetotic posturing. Even though the pathophysiological mechanisms of TS remain unclear, the most widely accepted hypothesis is that they occur by a transversely spreading ephaptic activation of axons within a demyelinating plaque, at any level in a motor path.

Methods: We recruited 19 patients (P) with DD followed in the Demyelinization Section of our hospital. Eigthteen women; aged between 23-53 ys. We performed them an interview, a physical exam and reviewed their clinical records. Three patients with TS were excluded because of irregular follow up.

Results: Fourteen /16 P developed TS during their illness. Of the two P without spasms, one had miasthemia gravis, and the other one had a very benign disease. Most spasms involved an hemibody or lower extremities. Trunk, neck and face were also affected in 3 P with a more severe disease. Twelve /14 had sensory symptoms preceding or accompanying the TS, tipically a burning pain. Triggers usually were sudden movements and emotions. The severity, frequency and duration of the TS were worst during disease relapses. No correlation was observed between the severity of the spasms and spasticity (Modified Ashworth scale). Coexisting spasms and hypotonia was observed during acute myelitis. All P, except one, required pharmacological treatment. Most of them were treated with low doses of carbamazepine with excellent response. Acetazolamide was used in 2 P also with good results.

Conclusions: The frequency of paroxysmal dystonia in this group of patients was high and the severity was worst during active disease. Spasms occurred in a stereotypical fashion and sometimes were disabling, but with good response to pharmacological treatment. Carbamazepine proved to be an effective drug.

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Antigenicity differences between two brands of botulinum toxin A

F. Adib Saberi, H. Bigalke, D. Dressler (Hamburg, Germany)

Objective: We wanted to test the antigenicity of the two different botulinum toxin (BT) type A drugs Botox® and Xeomin®.

Background: Botox® and Xeomin® differ in their specific biological activity and in their content of complexing proteins. Both factors may influence antigenicity. We compared the antigenicity of both drugs in a patient with complete antibody induced therapy failure.

Methods: A 58 year old female with severe craniocervical dystonia was treated for 1417d with Botox® (Allergan, Irvine, CA, USA, 100MU in 1.0ml 0.9% NaCl/H20, specific biological activity 60MU/ng botulinum neurotoxin, complexing proteins present, number of injection series 14, interinjection interval 109±27d, mean dose 577±82MU, no booster injections) before she developed complete subjective and objective therapy failure. Electromyography did not show a drug response and the mouse diaphragm assay revealed a BT antibody titre of 7mU/ml. After the BT therapy was stopped for 1875d the BT antibody titre had disappeared and BT therapy was restarted with Xeomin® (Merz Pharmaceuticals, Frankfurt/M, Germany, 100MU in 1.0ml 0.9% NaCl/H20, specific biological activity 167MU/ng botulinum neurotoxin, complexing proteins removed).

Results: During 703d of Xeomin® treatment (number of injection series 8, interinjection interval 100±17d, mean dose 405±14MU, no booster injections) there was no subjective or objective therapy failure, electromyography showed normal drug response and the BT antibody titre remained negative.

Conclusions: Lack of BT antibody formation in a patient who previously responded with complete antibody induced therapy failure to

Botox® indicates a lower antigenicity of Xeomin®. Whether this is caused by lack of complexing proteins or by an improved specific biological activity remains unclear.

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Successful treatment in primary blepharospasm and hemifacial spasm by botulinum toxin A

S. Aiba, M. Tatsumoto, K. Hirata (Tochigi, Japan)

Objective: The purpose of the study is to evaluate the efficacy and side effects of botulinum toxin A (BTA) in different injected points.

Background: BTA injections into the orbicularis oculi muscle and other surrounding muscles have been demonstrated to be the effective treatment for blepharospasm and nearly 80% of patients receiving injections show good results. The location of the injection sites influenced both the effectiveness of BTA treatment and incidence of local complications. Therefore the sites of injections were a matter of debate for blepharospasm.

Methods: Thirty patients with blepharospasm (n=5) and hemifacial spasm (n=25) investigated in this retrospective study. Of these 30 patients, 9 were male and 21 female. Their age ranged from 41 to 86 years (mean age: 63.5 years). BTA was given by subcutaneous injections of 2.5 U each located at the corrugator supercilii muscle and/or procerus muscle and/or nasalis muscle. We changed a needle diameter size in 30-gauge from 26-gauge for the pain reduction of the patients and also revised a treatment attitude in sitting position from recumbent for bleeding reduction by the treatment. Follow up visits were performed four weeks after the injections.

Results: The average self-rating score after the treatment was 76 points (range 60-100) out of 100 points. By the change of the needle diameter size, pain by injection was improved 18 patients (60%), no change in 11 patients (37%), and was aggravated one patient (3%). As for the local bleeding, 28 patients (93%) were reduction and two patients (7%) were no change. With posture of the treatment, 28 patients (93%) chose for sitting position not recumbent.

Conclusions: The location of the injection sites around the orbicularis influenced the effectiveness of BTA treatment for patients with blepharospasm and hemifacial spasm. Moreover, we could reduce the side effect of the patients by changing a needle diameter size and treatment posture.

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Isolated eye lid opening apraxia with remarkable response to L-DOPA. Case report and review of literature

I. Amorin, R. Buzo, D. Salinas (Montevideo, Uruguay)

Objective: To report a case of isolated eye lid opening apraxia, sensitive to DOPA and to search previous reports on this entity.

Background: Eye lid opening apraxia is a rare condition described in Progressive Supranuclear Palsy, Huntington's disease, Blepharospasm and other extrapyramidal disorders. When this is not taken into account, it is usually confused with Myasthenic Ptosis or considered as a disorder of psychogenic nature. Isolated eyelid-opening apraxia levodopa responsive is reported for R. Dewey in 1994.

Methods: A video record of the patient was made before and after the treatment with L-DOPA. She was also studied with structural and functional neuroimaging. We made a one year follow-up. The literature review consisted of a search of cases in papers indexed in the PUBMED/Medline database.

Results: In our case the apraxia have a remarkable response to L-dopa.

Conclusions: Isolated eye lid opening apraxia is a rare entity causing inability in certain cases since it can provoke functional blindness. It is an entity which should be included among the disorders responsive to L-DOPA.

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Focal dystonia affecting shoulder muscles (dancing scapula)

K. Asanuma, T. Sakamoto, T. Sakamoto, A. Miyashiro, H. Shimazu, R. Kaji (Tokushima, Japan)

Objective: To describe rare cases of focal dystonia affecting shoulder muscles that causes dancing or flying-like unique movement of the scapula.

Background: Focal dystonia often involves facial muscles (blepharospasm or Meige's syndrome) or upper extremities in task-specific manner (writer's cramp, musician's cramp, etc). Reports of shoulder muscle (or upper limb girdle) dystonia are rare.

Methods: Case report of 5 patients with shoulder dystonia from Japanese. They complained about uncomfortability with involuntary shoulder movement in one side in which sustained or repetitive twisting muscle contractions were seen. One patient (65 years old at onset, male) was a forestry worker using chain-saw and has a past history of hand-arm vibration syndrome. Second patient (61 years old at onset, female) was a school employee and has no apparent past history, however winged scapula was found in the affected side on close medical examinations. The 3rd patient was 14years old school girl without past disease. Her symptom occurred after a hard athlete training and gradually worsened. The 4th patient developed the symptom after amputation of forearm due to osteosarcoma in her seventies. Te 5th patient was a left-handed engraver and developed symptom in the left shoulder in her forties.

Results: VIDEO showed unique dancing or flying like movement of the scapula or shoulder. Botulinum toxin was more or less effective. Correlations between the onset of the symptom and injury/inflammation in the shoulder were also suspected.

Conclusions: These cases represent focal dystonia that uniquely involves shoulder muscles causing "dancing scapula".

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Transcranial magnetic stimulation (TMS) studies in secondary dystonia

C. Trompetto, L. Avanzino, L. Marinelli, L. Mori, M. Bove, G. Abbruzzese (Genova, GE, Italy)

Objective: To examine cortico-spinal excitability in a group of patients with dystonia secondary to focal lesions of the basal ganglia (BG).

Background: Excessive motor cortical activation due to a dysfunction of the cortico.striatal-cortical circuits is likely to play a major role in the pathogenesis of dystonia. TMS studies support the hypothesis that primary dystonia is due to inappropriate disinhibition of the motor cortex, whereas few TMS data are available in dystonia secondary to focal lesions.

Methods: 6 patients with single lesions in the BG and contralateral upper limb secondary dystonia were studied. 3 patients presented with dystonic spasms (Group A: putamen/caudate lesions), the others presented with myoclonic dystonia (Group B: pallidum/substantia nigra/thalamus lesions). For the FDI muscle of both sides we measured: latency, threshold and size of motor evoked potentials (MEPs); MEP and contralateral silent period (CSP) recruitment curves; CSP duration/MEPs area ratio; short intracortical inhibition (SICI).

Results: MEP threshold and central latencies were normal. SICI was not different between sides. MEP size and CSP duration increased significantly with increasing stimulation intensity in either side of both groups. The increase was similar in both sides of group B, while MEP recruitment curve was significantly steeper in the affected side of Group A with a smaller CSP duration/MEP area ratio.

Conclusions: Patients with a lesion in the afferent part of the BG show increased cortico-spinal excitability and a reduced excitability of intracortical circuits in the affected upper limb. Patients with a lesion in the efferent part of the BG did not show any sign of hyperexcitability in the affected muscles. Different pathophysiological mechanisms underlie dystonia secondary to lesions in various parts of the BG.

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Disabling head tremor in a patient with *DYT1* mutation

J.-H. Bae, J.-H. Lee (Busan, Republic of Korea)

Objective: To report a male patient with *DYT1* primary torsion dystonia who had severe head tremor in the absence of relevant cervical dystonia.

Background: Tremor in *DYT1* dystonia is usually dystonic tremor or rarely isolated postural hand tremor. Head tremor accompanying cervical dystonia is known to be a feature in some patients. However, disabling head tremor in the absence of relevant cervical dystonia has rarely been described in *DYT1* dystonia.

Methods: Routine laboratory tests were all normal as well as measurements of serum ceruloplasmin, CK, and lactate levels. Electroencephalography and brain MRI were unremarkable. Genetic studies for the mutation of *DYT1* gene were performed.

Results: 52-year-old man developed dystonic twisting his right foot especially while walking at mid 30s. Dystonia spread progressively over 10 years to involve the left foot. At the same time, he noted head tremor, which worsened progressively, leading to severe problems in eating and drinking since 5 years ago. On examination, the patient had a coarse, slow (3-4Hz), complex head tremor, with a combination of 'yes-yes' and 'no-no' oscillations, worsening on turning his head to right or left. There was no apparent neck deviation. He got some relief by holding her forehead lightly, resting his head against the back of a chair, or lying down. Various medical treatment including trihexyphenidyl, clonazepam, and propranolol were ineffective. Alcohol also failed to provide any benefit. Genetic testing confirmed the three-bp GAG deletion in the *DYT1* gene (904_906delGAG).

Conclusions: Although co-occurrence of essential tremor was a diagnostic consideration, some of the clinical features shown by this patient would be quite unusual for such a diagnosis. He used maneuvers to attenuate the head tremor, which were similar to 'sensory tricks' observed in patients with cervical dystonia. There was also striking change in his tremor on his head position, which is typical of dystonia. Isolated head tremor associated with these features may be initial manifestation of cervical dystonia. In these cases, neck deviation did not become apparent for many years, and eventually developed obvious cervical dystonia. Therefore, long-term clinical follow-up will confirm the nature of his head tremor.

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Juvenile onset dystonia-parkinsonism associated with cerebral folate deficiency

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Objective: To report a new association between a juvenile onset dystonic-parkinsonian condition with an isolated cerebral folate deficiency.

Background: Cerebral folate deficiency is due to a deficient transport of folate in the CSF which can be acquired, due to auto-antibodies against folate receptor, or primary sometimes due to identified genetic cause e.g. folate receptor 1 (FOLR1) mutation. Typically onset is in early infancy with agitation, insomnia, deceleration of head growth, psychomotor retardation/autism, hypotonia and later spasticity, ataxia, dyskinesia, gait/speech disturbances, and epilepsy. After age 6 years, visual/hearing problems may develop. Extrapyramidal features are not commonly reported.

Methods: We present two cases with a dystonic-parkinsonian condition with adolescent onset. Case 1 at the age 16 years developed leg dystonia and parkinsonism. There was past history of epilepsy and family history of epilepsy and young onset dystonia-parkinsonism in two uncles on the maternal side. Levodopa (400 mg/day) was beneficial but produced dyskinesias. Ropinirole 3 mg/day was also helpful but discontinued due to behavioural side effects. Case 2 presented similarly but also had autism and a positive family history for deafness. A complete diagnostic workup was performed (routine blood tests, acanthocytes, thyroid function, brain and spinal MRI, CSF pterins and folate, CSF monoamine metabolites, muscle biopsy, gene analyses -frataxin, GCH1, DYT1, DRPLA, mitochondrial genes, POLG, PEO1, LRRK2, Parkin, FBX07- and in case 1 a DaT-Scan).

Results: Only CSF methyltetrahydrofolate was low with normal serum folate levels. In case 1 CSF folate was 20 nmol/L (46-160), serum 3,8 ng/mL (2,3-17,6). In case 2 they were 21 nmol/L and 9,9 ng/mL. Common mitochondrial mutations were excluded and muscle biopsy was normal. All gene analyses performed were negative. DAT-Scan showed reduced tracer uptake bilaterally. Case 2 was treated with supplemental folate but did not have benefit.

Conclusions: To our knowledge this is the first report of an association between a dystonic-parkinsonian syndrome related to cerebral folate deficiency and should be kept in mind in young onset dystonia-parkinsonian conditions.

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Striatal dopaminergic function in writer's cramp

B.D. Berman, P. Herscovitch, M. Hallett, K. Simonyan (Bethesda, Maryland, USA)

Objective: Examine striatal dopaminergic function during symptomatic and asymptomatic motor tasks in patients with Writer's Cramp (WC) using [11C]raclopride (RAC) PET imaging.

Background: WC is a task-specific dystonia characterized by excessive muscle contractions while writing. The pathophysiology is unknown, although a role for dopamine is implicated.

Methods: 8 WC patients (50.9±11.2, 3F) and 8 matched controls (51.4±8.7, 3F) underwent 2 RAC PET scans that included 50 min of rest followed by either 50 min of a 5-finger tapping task or 50 min of speech production (sentence repetition). Patients had no dystonia at rest and had normal laryngeal function. No subject was taking medication known to affect dopaminergic function. RAC binding potential (BP) was determined as the ratio of concentrations in regions with (putamen [Put] and caudate nucleus [CN]) and without (cerebellum) specific binding, and task-induced effects were estimated as percent change in RAC BP between a resting baseline and task production. Statistical significance of BP changes was assessed using t-tests ($p<0.05$).

Results: WC patients reported mild to moderate cramping during tapping, but there was no significant difference between numbers of taps compared to controls (787±156 vs. 797±75). At rest, RAC BP was not significantly different between patients and controls. In controls, RAC BP was significantly reduced during tapping (R/L Put: 4.7%/5.7%, R/L CN: 5.8%/9.8%, all $p<0.02$) and during speech (R Put: 9.0%, R/L CN: 6.4%/11.1%, all $p\leq0.008$). In patients, RAC BP was less prominently decreased during tapping (R/L Put: 2.3%/3.7%, R/L CN: 5.1%/4.5%), and was significantly different from rest only in the L Put ($p=0.04$) and R CN ($p=0.02$). During speech, RAC BP in patients was also less prominently decreased, but was significantly different from rest in the R/L Put (3.8%/3.9%, $p<0.01$) and R/L CN (3.5%/6.3%, $p<0.007$). Between-group differences showed a trend in the R CN during tapping ($p=0.09$) and speech ($p=0.06$), and significant differences in the R Put ($p=0.002$) and L CN ($p=0.03$) during speech.

Conclusions: WC patients showed normal levels of striatal dopamine release at rest, but decreased release during symptomatic finger tapping and asymptomatic speech production. Dopaminergic dysfunction independent of the type of motor task being performed may underlie the pathophysiology of this disorder.

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CD-PROBE (cervical dystonia patient registry for observation of BOTOX® efficacy) — CD impact on quality of life (QOL) and patient reported outcomes (PRO)

M. Kurth, C. Adler, C. Comella, D. Charles, J. Jankovic, M. Stacy, M.F. Brin, L.M. Boo (Irvine, California, USA)

Objective: Interim report on the impact of onabotulinumtoxinA (BOTOX®) on QOL and PRO in patients with cervical dystonia (CD).

Background: CD-PROBE is an ongoing registry intended to understand the use of onabotulinumtoxinA (BOTOX®) in CD treatment across a broad range of physicians.

Methods: Multicenter, prospective, observational study. Inclusion criteria: a) botulinum toxin (BoNT) naïve, b) new to practice or c) if previously received BoNT, >16 weeks post last injection. Subjects are followed over 3 treatment cycles and evaluated at time of injection and 4-6 weeks post-injection. Efficacy measures: Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), Pain Numeric Rating Scale (P-NRS), Cervical Dystonia Impact Profile (CDIP), Healthcare Utilization and Work Productivity Questionnaire, Clinician and Patient Global Impression of Change (CGIC, PGIC).

TABLE 1 (133). *Physician CD severity ratings correlate to TWSTRS and CDIP subscales*

	Mild	Moderate	Severe
Number of Patients	96	105	15
TWSTRS-Total	32±12*	43±11	48±16
TWSTRS-Severity	14±4*	20±4**	23±5
TWSTRS-Disability	8±6*	12±6	15±8
CDIP-Total	414±123*	460±128	490±142
CDIP-Head/Neck Sx	61±16*	73±19	82±18
CDIP-Annoyance	53±21*	59±21	65±27
CDIP-Social Function	42±23*	54±22	63±23

* $p<0.05$ (mild-moderate, mild-severe); ** $p<0.05$ (moderate-severe).

PGIC and all domains of CDIP showed continued improvement throughout 2 treatment cycles.

TABLE 2 (133). *Patient rated global impression of change*

PGIC	4-6 weeks Post-Injection 1 (Peak 1, N=173)	Injection 2 (N=81)	4-6 weeks Post-Injection 2 (Peak 2, N=53)
Very much improved	11%	11%	13%
Much improved	34%	36%	30%
Minimally improved	32%	37%	43%
No change	14%	12%	9%
Minimally worse	4%	4%	0%
Much worse	5%	0%	2%
Very much worse	1%	0%	2%

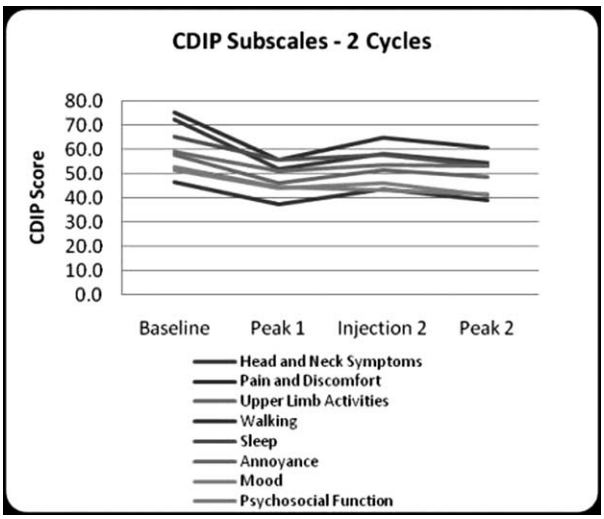

FIG. 1 (133).

Results: As of December3,2009, 224 subjects were enrolled (females=79%, Caucasians=96%). Mean age is 57±15 (20-90) with symptom onset at 48±17 (0-82) years. Mean time from symptom onset to diagnosis 6±9.5 (0-48) years; mean time to first treatment 0.9±3.5 (0-31) years after diagnosis. There were 220, 86, and 20, subjects who received 1, 2 or 3 injections, respectively. Baseline mean TWSTRS=38.5±13.0, CDIP total=442±129. Physician rated CD severity correlated with TWSTRS and CDIP subscales.

At baseline 194 of 218 (89%) subjects reported P-NRS>0. After 1 injection, mean P-NRS decreased from baseline P-NRS=6.0±2.5 to 4.2±2.8 after 1 injection (N=153; 66% improved, 12% unchanged, 22% worsened). After 2 injection cycles, P-NRS decreased from 6.9±2.4 to 4.4±3.0 (N=44; 73% improved, 16% unchanged, 11% worsened). The correlations between P-NRS and TWSTRS-Pain (r=0.79), P-NRS and CDIP (r=0.54), and TWSTRS-Pain and CDIP (0.65) were high at baseline ($p<0.0001$ for all 3).

Conclusions: Repeated injections of onabotulinumtoxinA results in significant and sustained relief of CD associated pain. PRO improved over 2 treatment cycles.

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Two adult cases of congenital muscular torticollis successfully treated with botulinum toxin type A

M. Bouchard, O. Suchowersky (Calgary, Alberta, Canada)

Objective: To describe two adult patients with congenital muscular torticollis (CMT) successfully treated with botulinum toxin type A.

Background: CMT is a common congenital musculoskeletal anomaly involving shortening and fibrosis of the sternocleidomastoid muscle (SCM), usually treated in infancy. If CMT is not corrected early, facial asymmetry may develop. Facial asymmetry, head tilt since infancy, absence of head tremor, lack of sensory tricks and constant abnormal head posture helps in differentiating CMT from idiopathic cervical dystonia in adults. The best treatment for adult-persistent CMT is uncertain. There is scarce literature concerning the use of botulinum toxin in such patients.

Methods: Two case reports.

Results: Patient 1 had a delayed diagnosis of CMT in adulthood following clinical deterioration after a car accident. Patient 2 was diagnosed at birth with CMT, which did not regress despite physiotherapy. With time, the patient developed pain and discomfort in the posterior neck and shoulder. In both patients, examination showed limitation in cervical movements with a prominent cord-like SCM and ipsilateral facial asymmetry. There was no head tremor. Both patients responded well to botulinum toxin injections into posterior cervical muscles (range 25 to 55 units), with improvement in pain, tightness and cervical mobility. Both patients have had repeat injections for up to 4 years.

Conclusions: The majority of CMT resolve completely within the first year of life either spontaneously or with physiotherapy. In infants with persistent CMT, surgery is usually recommended. The treatment for CMT persisting in adulthood is not clear. We found a single case series describing the use of botulinum toxin in adult-persistent CMT, with only 33% moderate improvement (Collins and Jankovic, Neurology 2006). Both of our patients reported good improvement in neck pain, tightness and mobility with botulinum toxin injections, emphasizing the fact that botulinum toxin can work and should be tried in adult CMT patients.

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The utility of visual, tactile and mixed tasks in the determination of temporal discrimination thresholds in adult-onset primary torsion dystonia

D. Bradley, N. Mulrooney, R. Whelan, R. Walsh, R. Reilly, S. Hutchinson, S. Hutchinson, M. Hutchinson (Dublin, Ireland)

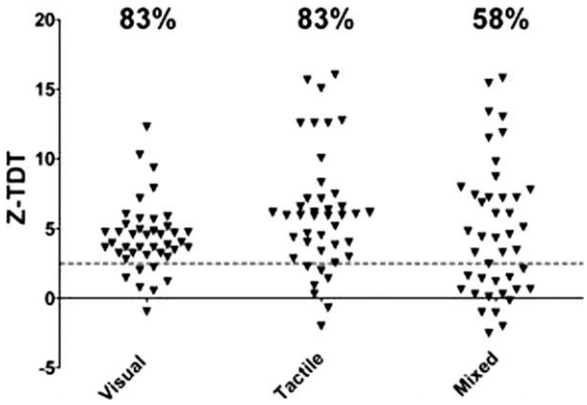

FIG. 1 (135).

Objective: To compare the utility of visual, tactile and mixed temporal discrimination threshold (TDT) tasks in adult-onset primary torsion dystonia (AOPTD) patients and first degree relatives.

Background: AOPTD is autosomal dominant with markedly reduced penetrance. Sensory abnormalities in unaffected relatives may indicate non-manifesting gene carriage - an ideal endophenotype should be detected in 100% of patients and 50% of first degree relatives. The TDT is the shortest time interval at which two stimuli are detected to be asynchronous.

Methods: TDTs were examined in 42 AOPTD patients (29 with cervical dystonia, 13 with writer's cramp), 48 first degree relatives and 51 controls using visual (2 LED lights), tactile (non-painful electrical stimulation) and mixed (1 LED, 1 electrical) stimuli.

Results: The mean TDT in controls <50 years was 24.45ms and >50 years was 30.87ms. The upper limit of normal was defined as control mean +2.5 SD. In AOPTD patients, the visual task detected abnormalities in 35/42 (83%), the tactile task in 35/42 (83%) and the mixed task in 30/42 (58%); the mixed task was statistically less sensitive than the other two (p=0.001). The abnormality rates in unaffected relatives using the visual, tactile and mixed tasks were 23/48 (48%), 20/48 (42%) and 22/48 (46%) respectively. Specificity was 100% for all 3 tasks. Comparing cervical dystonia (CD) and writer's cramp (WC) patients, abnormal visual TDTs were seen in 25/29 (86%) CD and 10/13 (77%) WC patients, abnormal tactile TDTs were found in 25/29 (86%) CD and 10/13 (77%) WC patients, and abnormal mixed TDTs were detected in 21/29 (72%) CD and 9/13 (69%) WC patients.

Conclusions: The visual and tactile tasks found to be more sensitive than the mixed task which could be omitted in practical application of the endophenotype in genetic studies. The tasks performed similarly in CD and WC patients.

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The temporal discrimination threshold in patients with sporadic adult-onset primary torsion dystonia and their first degree relatives

D. Bradley, N. Mulrooney, R. Whelan, R. Reilly, S. Hutchinson, F. Molloy, M. Hutchinson (Dublin, Ireland)

Objective: To assess the frequency of temporal discrimination threshold (TDT) abnormities in sporadic adult-onset primary torsion dystonia (AOPTD) patients and their first degree relatives.

Background: AOPTD is autosomal dominant; the large numbers of apparently sporadic cases may reflect low penetrance (12-15%). Sensory abnormalities in unaffected relatives may indicate non-manifesting gene carriage. An ideal endophenotype in an autosomal dominant disorder should be found in 100% of cases, 50% of first degree relatives and no control subjects. The TDT is the shortest time interval at which two stimuli are detected to be asynchronous.

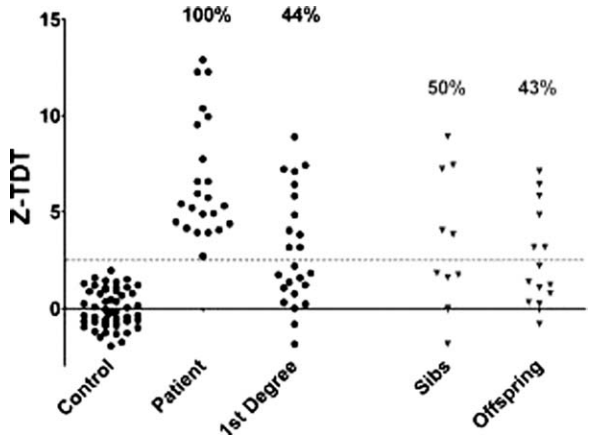

FIG. 1 (136).

Methods: TDTs were examined in 23 sporadic Cervical Dystonia patients, 24 of their first degree relatives (10 siblings and 14 offspring) and 51 controls using visual (2 LED lights), tactile (non-painful electrical stimulation) and mixed (1 LED, 1 electrical) stimuli.

Results: The mean TDT in controls <50 years was 24.45ms and >50 years was 30.87ms. The upper limit of normal was defined as control mean +2.5 SD. In the 23 Cervical Dystonia patients, TDT abnormalities were detected in 100% of cases. Abnormal TDTs were found in 11/24 (44%) of first degree relatives (5/10 siblings and 6/14 offspring). None of the control subjects had abnormal TDTs.

Conclusions: The frequency of abnormalities in sporadic patients and relatives approach the ideal values for an autosomal dominant endophenotype; this supports the hypothesis that all of these cases are genetically determined with poor penetrance of the phenotype.

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The utility of temporal discrimination threshold testing in different adult-onset primary torsion dystonia phenotypes

D. Bradley, N. Mulrooney, R. Whelan, R. Reilly, S. Hutchinson, F. Molloy, M. Hutchinson (Dublin, Ireland)

Objective: To examine the frequency of abnormal Temporal Discrimination Thresholds (TDTs) in various adult-onset primary torsion dystonia (AOPTD) phenotypes.

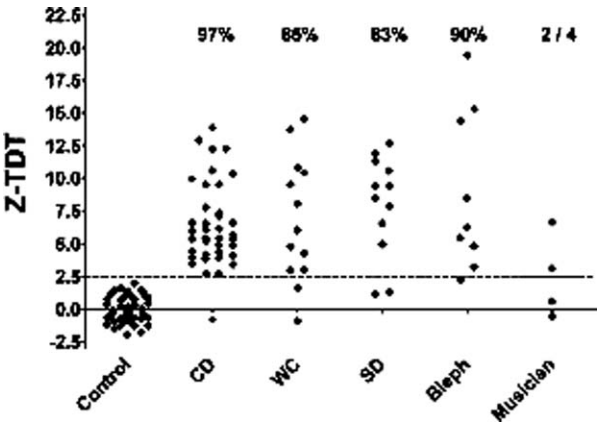

FIG. 1 (137).

Background: AOPTD is autosomal dominant with significantly reduced penetrance. Sensory abnormalities are a marker of basal ganglia dysfunction in these patients and may be used as an endophenotype. The temporal discrimination threshold (TDT) is the shortest time interval at which two stimuli are detected to be asynchronous. The comparative utility of TDT testing in different types of AOPTD is of interest in planning genetic studies.

Methods: TDTs were examined in 38 Cervical Dystonia (CD), 13 Writer's Cramp (WC), 12 Spasmodic Dysphonia (SD), 10 Blepharospasm (BEB) and 4 Musician's Dystonia Patients as well as 51 healthy control participants. Measurements were taken using visual (2 LED lights), tactile (non-painful electrical stimulation) and mixed (1 LED, 1 electrical) tasks.

Results: The mean TDT in controls <50 years was 24.45ms and >50 years was 30.87ms. The upper limit of normal was defined as control mean +2.5 SD. Abnormal TDTs were seen in 37/38 (97%) of CD, 11/13 (85%) of WC, 10/12 (83% of SD), 9/10 (90%) of BEB patients and 2/4 Musicians. None of the control subjects had abnormal TDTs.

Conclusions: The frequencies of abnormalities in CD, WC, SD and BEB patients are comparable. Musicians may represent a different or heterogeneous pathological group.

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Botulinum toxin type A and cervical dystonia: Seven years follow up

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Objective: The objective of our study was to document the effects of long-term BoNT/A treatment in CD patients.

Background: Cervical dystonia (CD) is the most common form of dystonia. Most cases are idiopathic and focal injections with botulinum toxin A (BoNT/A) are the treatment of choice. As in most chronic disorders, long term treatment is required but individual clinical response may vary depending on the natural history of the disorder and patients immunological and clinical profile.

Methods: Fifty-eight patients with idiopathic CD were recruited from the Movement Disorders Clinic of Hospital de Clinicas of the Federal University of Paraná from March 2001 to May 2002. A standardized protocol was used to gather information regarding response to the BoNT/A (efficacy and security). Twenty-eight of these subjects were available for re-assessment after seven years. During this period, all underwent regular treatment with BoNT/A injections performed service staff members. Clinical information of patients and CD severity (TWSTRS and VAS) on baseline assessment (2001-2002) and on follow up (2008-2009) were compared.

Results: There was a significant motor improvement as detected by the TWSTRS scale scores, used to analyze clinical severity (19.6±6.6 and 17.7±4.8; $p<0.05$). There was no improvement regarding cervical pain severity ($p=0.43$). Two patients, one with hemidystonia and another with segmental dystonia (cervical and cranial), spread their dystonic symptoms to a generalized form. There were no changes in the presentation in 10 (37.8%) patients. Eight (28.6%) presented reduction in topographic distribution. Five (16.8%) patients had a drastic change in symptoms predominant pattern and laterality, while other, less precise modification patterns were described in five (16.8%) patients.

Conclusions: BoNT/A was effective and safe long-term therapy to CD.

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CD-PROBE (cervical dystonia patient registry for observation of BOTOX® efficacy) — preliminary safety data

D. Charles, C. Adler, C. Comella, J. Jankovic, M. Stacy, M. Kurth, M.F. Brin, L.M. Boo (Nashville, Tennessee, USA)

Objective: Interim safety report of onabotulinumtoxinA (BOTOX®) in patients with cervical dystonia (CD).

Background: CD-PROBE is an ongoing registry intended to understand the use of onabotulinumtoxinA (BOTOX®) in CD treatment across a broad range of physicians.

Methods: Multicenter, open-label, prospective, observational study. Inclusion criteria: a) botulinum toxin naïve, b) new to practice or c) if previously received botulinum toxin (BoNT) trial, >16 weeks post last injection. Subjects are followed over 3 treatment cycles and evaluated at time of injection and 4-6 weeks post-injection. Data collected: subject and practice demographics, CD classification/severity, Toronto Western Spasmodic Torticollis Rating Scale, Pain Numeric Rating Scale, Cervical Dystonia Impact Profile, Healthcare Utilization and Work Productivity Questionnaire, BoNT/A injection regimens, Clinician and Patient Global Impression of Change, and adverse events.

Results: As of December 3,2009, 224 subjects were enrolled (females=79%, Caucasians=96%). Mean age is 57±15 (20-90) with symptom onset at 48±17 (0-82) years. Mean time from symptoms onset to diagnosis is 6±9.5 (0-48) years and mean time to first treatment is 0.9±3.5 (0-31) years after diagnosis. There were 220, 86, and 20, subjects who received 1, 2 or 3 injections, respectively. 34 adverse events (AEs) were reported by 21 subjects (9.5%) with 1 unrelated serious AE (fever with hospitalization). Ten subjects (4.5%) reported 17 related AEs, as determined by investigators, all rated as mild or moderate (N): dysphagia 2.3% (5), neck weakness 2.3% (5) with only 1 case experiencing weakness after injections 1 and 2, headache 0.9% (2), nausea 0.5% (1), pruritus 0.5% (1), and decreased saliva 0.5% (1). All but 2 patients recovered, while only 1 reported AE improved and 1 (dysphagia) remained unchanged upon study exit. Out of 28 withdrawals, 5 (2.3%) were due to AEs (3 for neck weakness).

Conclusions: Preliminary safety information suggests that repeated injections of onabotulinumtoxinA are well tolerated with a low rate of AEs.

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Thalamic deep brain stimulation for writer's cramp; a case report

C.B. Cho, K.J. Lee (Seoul, Korea)

Objective: Recently, DBS appears to be a safe and effective therapeutic option for dystonia. We report a case of writer's cramp treated successfully by thalamic stimulation.

Background: Dystonia is the term for a set of disorders characterized by abnormal postures and unwanted muscle spasms that interfere with motor performance. By definition, writer's cramp is a task-specific focal hand dystonia. It is characterized by an abnormally tight grip while writing with progressive difficulty in performing the task as writing continues. Non-surgical treatment included oral medications, sensorimotor training, immobilization, physical rehabilitations and botulinous toxin injections, but the symptom recurrence is the rule. Siegfreid introduced firstly stereotactic thalamotomy as a treatment for writer's cramp. After that, successful treatment by thalamotomy was reported in patients with writer's cramp.

Methods: A 36-year-old female suffered from right hand tremor and dystonia aggravated especially during the writing task. She has been treated through drug medication for one year, but drug adverse effects made having medication difficult. We performed left thalamic DBS for right focal hand dystonia. Magnetic resonance images were obtained and the stereotactic target was chosen at 2 mm posterior to the mid-intercommisural point, 0.5 mm dorsal to the intercommisural line and 13.5 mm lateral to the midline. According to Schaltenbrand-Wahren atlas, magnetic resonance image guided visual targeting and intra-operative microelectrode recording, we confirmed the accurate targeting point for ventral thalamic nucleus.

Results: During operation, we confirmed her remarkably improvement of writing by thalamic stimulation. Therefore we decided to

connect the Vo DBS lead with an implantable pulse generator without test simulation period. She exhibited no surgery-related complications. Her immediate post-operative BFMDR scale demonstrated 1 compared with pre-operative BFMDR scale 4. Her BFMDR scale demonstrated 1 at 3 and 12months after the surgery. Post-operative brain CT revealed the accurate electrode implantation for pre-operative targeting point.

Conclusions: Thalamic stimulation appears to be an effective and safe treatment for writer's cramp. In regard of targeting area, although extensive cases need to be reported, we assure that thalamic Vo complex is a valuable therapeutic target for writer's cramp.

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Validation of a cervical dystonia questionnaire (CDQ)

A.L. Davidson, C. Hunter, J. Jankovic (Houston, Texas, USA)

Objective: To evaluate the reliability and validity of a short, self-administered questionnaire regarding symptoms of cervical dystonia (CD), also termed spasmodic torticollis (ST).

Background: The prevalence of CD or ST, or both, is estimated to be 390 per 100,000 (Jankovic et al parkinsonism and Related Disorders, 2007), but epidemiological studies have been hampered by a lack of reliable instruments that identify individuals with CD symptoms with high sensitivity and specificity. A previously reported instrument, the Beth Israel Dystonia Screen (BIDS) was developed primarily to enhance ascertainment of affected individuals within families and its specificity was not assessed in a population of non-CD movement disorder (Saunders-Pullman et al. Neurology, 2005).

Methods: We administered a 5-question Cervical Dystonia Questionnaire (CDQ) to 98 patients seen in the Baylor College of Medicine Movement Disorders Clinic. Patients were diagnosed with CD or some other movement disorder by a movement disorder specialist. Responses were analyzed individually for sensitivity, specificity, positive and negative predictive value (PPV, NPV), and for ability to distinguish patients with CD using Pearson's chi-square test or Fisher's exact test. Reliability of the instrument was evaluated using Cronbach's alpha. Factor analysis of the tetrachoric correlation matrix was used to determine Eigenvalues for principal factors.

Results: All questions showed statistically significant ability to distinguish CD from other movement disorders. Specificity, sensitivity, PPV and NPV ranged from moderate (66.7% sensitivity for question 1b) to complete (100% sensitivity for question 1a) (Table 1). Cronbach's alpha for the mean of the standardized items was 0.887. Factor analysis generated an Eigenvalue for factor 1 of 4.29, with other factor Eigenvalues less than one (0.41 to 0.05). Receiver Operating Characteristic analysis (ROC) indicated that for a cut-point of 3 or greater on the summary score, sensitivity was 94.9% and specificity was 88.1% (Figure 1).

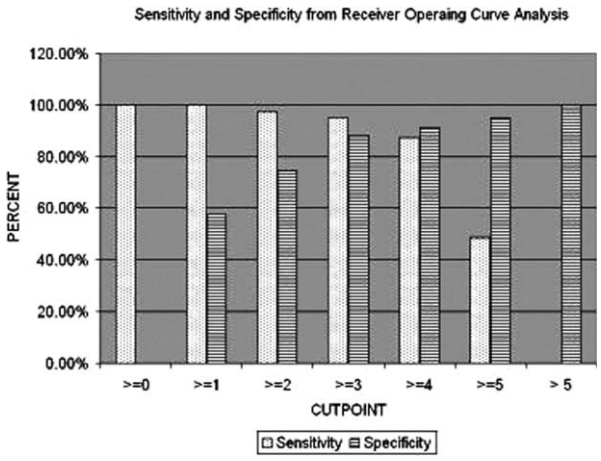

FIG. 1 (141).

TABLE 1 (141). *Summary and analysis*

	Cervical Dystonia (N=39	Other (N=59)	p-value (Pearson's χ^2)	Sensitivity Pr(+|A)	Specificity Pr(-|N)	Positive Predictive Value Pr(A|+)	Negative Predictive Value Pr(N|-)
Sex: M/F	9/30	27/32	0.032				
Age at Survey (±SD)	60.6 (11.1)	55.6 (19.9)	0.154				
# Pts answering "yes" to questions/total in category							
Q1a (Neck/head tilting)	39/39 (100%)	18/59 (30.5%)	<0.001	100%	69.5%	68.4%	100.0%
Q1b (Head shaking/ jerking)	26/39 (66.7%)	13/59 (22.0%)	<0.001	66.7%	78.0%	66.7%	78.0%
Q1c (Neck pain)	30/39 (76.9%)	9/59 (15.3%)	<0.001	76.9%	84.7%	76.9%	84.7%
Q2 (Ever told had CD)	36/39 (92.3%)	9/59 (15.3%)	<0.001	92.3%	84.7%	80.0%	94.3%
Q3 (Receiving tx for CD)	36/39 (92.3%)	6/59 (10.2%)	<0.001	92.3%	89.8%	85.7%	94.6%
Cronbachs Alpha	Item-Test Corr.	Alpha					
Q1a (Neck/head tilting)	0.8472	0.8572					
Q1b (Head shaking/jerking)	0.7102	0.9012					
Q1c (Neck pain)	0.8014	0.8729					
Q2 (Been told had CD)	0.8792	0.8457					
Q3 (Being treated CD)	0.9138	0.8325					
Test Scale		0.8874					
Factor Analysis: Principal Factors	Eigenvalue	Proportion	Cumulative				
Factor 1	4.299	0.8579	0.8579				
Factor 2	0.4088	0.0818	0.9415				
Factor 3	0.2420	0.0484	0.9899				

Conclusions: Our study provides evidence that the CDQ is a valid instrument that reliably differentiates patients with CD from other movement disorders. Further testing in a more diverse patient population is needed to determine whether the CDQ will be a useful screening tool in future epidemiological studies.

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Treatment of Wilson's disease with ammonium tetrathiomolybdate: Experience in 3 cases with neurological symptoms

O. De Fabregues, A. Palasi, J. Gamez, A. Callen, J. Hernandez-Vara, M. Duero, C. Auge, J. Alvarez-Sabin (Barcelona, Spain)

Objective: To report our experience with TTMo in WD.

Background: Wilson's disease (WD) is an inherited disorder of copper metabolism caused by a mutation in the ATP7B gene. Firstly described as a lethal neurological and hepatic familial disease, now it has different drug therapies. However, neurologic deterioration and severe adverse reactions have been reported with penicillamine and trientine which require the use of other drugs such as ammonium tetrathiomolybdate (TTMo).

Methods: These 3 patients with WD with neurologic impairment were treated with TTMo 120 mg / day for 8 weeks. All patients were clinically assessed with the UWDRS neurological subscale and GAS for WD, video and neuroimage, before and 6 months after treatment. Drug adverse events were evaluated by hematologic and biochemical measures and clinical follow-up.

Results: Different reasons for TTMo treatment: neurological deterioration with penicillamine, intolerance to conventional treatment

and neurologic presentation of WD. Effectiveness: no patients had neurological deterioration. All patients had clinical improvement with UWDRS average drop of 34 points (improvement of 64%) and 14 points GAS for WD (47% improvement). Well tolerated in 2 cases, treatment lasted 8 weeks more in 1 case, 1 case had elevated transaminases that cause dose reduction and transient suppression. Improved neuroimaging in 2 cases. Subsequent clinical evolution: moderate neurological sequelae 2 and mild 1 case, 1 death unrelated to treatment.

Conclusions: Treatment of the WD with neurological symptoms is a challenge issue. Concern is made on penicillamine and trientine as first line treatment election. TTMo is an effective well tolerated therapeutic alternative even though its contraindications need to be clarified.

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Successful treatment of Wilson's disease dystonia with botulinum toxin

O. De Fabregues, A. Palasi, A. Callen, J. Hernandez-Vara, J. Alvarez-Sabin (Barcelona, Spain)

Objective: To report a case of WD dystonia which was successfully treated with botulinum toxin A (BTA) injections.

Background: Progressive hepatolenticular degeneration or Wilson's disease (WD) is an inherited disorder of copper metabolism caused by a mutation in the ATP7B gene. Neurological signs mainly include akinetic-rigid and dystonic syndromes, tremor and ataxia. Firstly described as a lethal neurological and hepatic familial disease, now it has different drug therapies. However, treatment of the WD with neurological symptoms is currently a challenge issue.

Methods: A 38-year-old woman was diagnosed of WD in 1985. She was initially treated with penicillamine which was changed to trientine in 1988 because of lupus-like syndrome. In 2007 she developed a progressive parkinsonian syndrome and dystonia that required ammonium tetrathiomolybdate and zinc therapy. She improved clinically but due to persistent bilateral leg dystonia we tried botulinum toxin, with a dose of 1000 U BTA (Dysport) in the bilateral extensor hallucis longus, flexor hallucis brevis, abductor hallucis and abductor digiti quinti muscles with EMG guidance.

Results: Two weeks later, she noted a functional improvement allowing footwear to be worn comfortably and a reduction in symptoms, with decreased spasm, pain relief and improvement of contractures. Two additional injections of 500 U BTA were given at four-monthly intervals with good effect. No adverse event was reported. She is now neurologically stable.

Conclusions: BTA injections in the involved muscles should be considered as a treatment option in WD dystonia management that can be followed by marked functional improvement and reduction of systemic drugs. In our patient, significant improvement started 2 weeks after the injections and lasted about 4 months.

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Family-based case-control study of coffee drinking in primary late-onset dystonia

R. Di Fede, P. Girlanda, R. Liguori, D. Martino, L. Santoro, G. Defazio (Bari, Italy)

Objective: To determine whether people with primary late-onset dystonia are less likely to report a history of coffee intake than their unaffected first-degree relatives.

Background: Previous studies suggested that environmental factors may contribute to the development of primary late-onset dystonia. Recently, an inverse association between coffee drinking and cranial dystonia was found in a case-unrelated control study.

Methods: In a matched case-control study of 140 families, individuals with primary late onset dystonia (n,.180) were compared to unaffected first-degree relatives controls (n. 306). Information on coffee drinking history was collected by a structured interview. Conditional logistic regression analysis examined the relationship between coffee drinking and dystonia while controlling for confounding by age and sex.

Results: Ever coffee drinking were significantly inversely associated with dystonia (Odds ratio=0.4, 95% confidence interval 0.2 to 0.6, $p<0.01$). The association was not modified by recency of exposure. Stratifying case and control relatives by cranial and extracranial dystonia yielded a significant association of coffee drinking with both groups.

Conclusions: Individuals with primary late-onset dystonia are less likely to have drunk coffee regularly than their unaffected relatives. This association was detected even thoughun affected relatives are more likely to be overmatched for environmental exposures than unmatched case and control groups.

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A transversal and longitudinal MRI-VBM study in patients with primary adult-onset cervical dystonia

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Objective: To evaluate by voxel based morphometry (VBM) the volume of gray matter (GM) in patients with cervical dystonia (CD) at baseline and after a follow-up period of 5 years.

Background: CD may be secondary to lesions in the basal ganglia or in other structures of the central nervous system but in the majority of cases conventional neuroimaging tecniques do not reveal any brain lesions. The use of non-conventional neuroimaging techniques, however, by detecting abnormalities in brain areas that may be functionally involved in the pathophysiology of primary dystonia is increasingly challenging this conclusion.

Methods: Nineteen CD patients (15 women, 4 men, mean age 53.2 ± 11.2 years) and twenty-eight healthy subjects (HS) (17 women, 11 men; mean age 47.5 ± 15.6 years) were enrolled in the study. Twelve of the nineteen patients were studied at baseline and again about five years after. All the subjects were imaged with a 1.5T scanner with a 3D-T1-weighted sequence on 150 contiguous axial 12 mm-thick sections. SPM5 was used for statistical analysis.

Results: VBM analysis revealed a significant regional GM volume reduction in the left caudate head and left putamen, and in the premotor and primary sensory motor cortices bilaterally in CD patients compared with HS. This finding did not correlate with patient age, severity or duration of disease. The voxelwise longitudinal analysis showed a significantly decreased regional GM volume in the left somatosensory cortex (p corrected<0.05 at the cluster level) at follow-up than at the baseline.

Conclusions: The GM abnormalities we found suggest a loss of neuronal density in the caudate, putamen and somatosensory cortex in CD patients. The finding of statistically significant differences in local GM volumes in the same group of patients over a long time suggest that in CD patients there is a progressive, albeit slow, process of neuronal loss within the sensory motor cortex.

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Secondary non response (SNR) to botulinum toxins type A (BoNT-A) in cervical dystonia (CD) patients: Definition and therapeutic strategies results from an international survey

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Objective: To define criteria for SNR to BoNT-A in CD patients and to describe therapeutic practices.

Background: CD is the most common of the focal dystonias. BoNT-A preparations are the treatment of choice for CD. CD is a

chronic disease making long-term efficacy of BoNT-A of the utmost importance. Unfortunately some patients develop SNR to BoNT-A. An appropriate definition as well as an overview of therapeutic practices are needed to address it.

Methods: We conducted a retrospective survey based on the experience of neurologists from 9 countries. A 17-item questionnaire assessed physician's definition for SNR (based on clinical examination, diagnostic test(s), BoNT-A dosing), incidence of SNR and therapeutic practice in case of SNR.

Results: 57 neurologists from Czech Republic, France, Italy, Poland, Portugal, Romania, Russia, Spain and Thailand completed the questionnaire. 96% of physicians had more than 5 years of experience. To define SNR, an insufficiently improved posture is considered to be more relevant (98% of physicians) than pain (86%), and is assessed more frequently with the TWSTRS (71%) than the Tsui scale (54%).The most frequently used diagnostic test is the frontalis test (68% physicians). Antibody testing is performed by 13% of physicians. 3 consecutive injection cycles are appropriate to define SNR (55% of physicians). Shorter intervals between cycles are not considered as a relevant factor. Overall, physicians considered that 5.9% (median) of their patients treated in 2008 became secondary non responders to BoNT-A. In case of SNR, physicians target new muscles (91%, using EMG: 86%), and/or increase the dose of BoNT-A (89%). Switching to BoNT-B, deep brain stimulation (DBS) and optimization of physiotherapy are considered by 64%, 73% and 98% of physicians respectively.

Conclusions: According to this international panel of neurologists, SNR could be defined by an insufficiently improved posture after 3 injection cycles. A large majority of this panel targets new muscles, often using EMG, and/or increases the dose of BoNT-A if SNR occurs. Alternatives are BoNT-B, DBS and optimization of physiotherapy.

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Tensor threads in blepharoespasm: A potential therapeutical approach manipulating sensory tricks? A case report

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Objective: To present a severe case of blepharospasm with partial and short duration response to botulinum toxin chemodenervation who experimented an enhacing effect of effectiveness and duration of the therapeutical response after the application of Tensor Threads with aesthetics purposes.

Background: Botulinum Toxin is the mainstay treatment for Blepharospasm. Sensory trick is an important clinical phenomenon and is characteristic of dystonia, described as an activity or sensory stimulus that reduces symptoms.

Methods: Case report.

Results: A 60-year-old Caucasian woman with idiopathic blepharospasm treated since 2004 with botulinum toxin with moderate response of short duration (less than two months) who underwent last year the aesthetic procedure of Tensor Threads with the goal of eliminating wrinkles. After this, in the last two infiltration the efficacy of the respone to botulinum toxin have been increased to 100% and the duration prolonged to 6 months.

Conclusions: The application of Tensor Threads is a revolutionary technique developed by Drs Zulamanizde consists in introducing polypropylene threads underneath the skin through the zone that presents the relaxation. This procedure is done under local anesthesia in an outpatient facility. The proposed mechanism could be related to modulation of the somatosensory cortex by the tissue traction by the tensor threads, similar to a 'sensory trick'. Severe cases of blepharospasm resistant or with partial or unsatisfactory duration of response to botulinum toxin represent a challenging clinical problem and could be benefitted from this simple procedure.

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Screening for THAP1 mutations (locus DYT6) in a cohort of 114 patients with primary dystonia

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Objective: To evaluate the (1) frequency of *THAP1* (locus DYT6) mutations in a cohort of 114 European patients with generalized, segmental or focal primary dystonia and (2) to describe the mutational and clinical spectrum of *THAP1* mutations carriers.

Background: Dystonia is a group of movement disorders characterized by involuntary muscles contraction resulting in abnormal movements or postures. This affection is highly heterogeneous from both clinical and genetic standpoints. To date, up to 18 loci were described and 10 genes identified. Mutations in *THAP1* (DYT6) coding for "a thanatos associated protein" were recently associated with early onset primary dystonia characterized by prominent cranial or neck involvement. However, the clinical and mutational spectrum of *THAP1* mutations carriers are still poorly known.

Methods: *THAP1* gene was sequenced in a cohort of 114 caucasian index cases selected in our database. All the patients have early onset (<26 years old) generalized, segmental or focal dystonia and were negative for for the 3 bases pair deletion in exon 5 (c.907_909delGAG) of *TOR1A* gene (DYT1). Medical records were reviewed and clinical data, including age, localization of the dystonia at onset, clinical phenotype of the dystonia at the time of diagnosis and additional neurological features were extracted.

Results: We identified 5 novel heterozygous mutations (2 missense and 3 small deletions) in 5 index cases (4.5% of patients). Three cases were sporadic and 2 were familial leading to 6 *THAP1*-positive patients available for clinical analysis. Mean age at onset was 14 years [range 9–20]. Disease usually started in the neck (4/6). Cranial muscles with speech impairment (5/6) or neck (5/6) dystonia were the most frequently involved sites. Dytsonia was generalized in 4/6 patients and remained segmental or focal in 2/6 after a median of 16 years follow-up. Myoclonus was observed in 2 patients.

Conclusions: Although rare, *THAP1* mutations are associated with various forms of primary dystonia. We confirm that onset in the neck and prominent involvement of cranial muscles are useful clinical clues to point to this gene.

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Safety and efficacy of repeated NT 201 (botulinum neurotoxin type A free from complexing proteins) injections of patients with blepharospasm

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Objective: To assess the long-term safety and efficacy of NT 201 [botulinum neurotoxin type A (BoNT/A) free from complexing proteins] in an open-label extension study in blepharospasm.

Background: NT 201 has shown comparable efficacy and safety to onabotulinumtoxinA (Botox, Allergan, USA) in treating blepharospasm when used in a 1:1 dosing.

Methods: Patients with blepharospasm who completed a placebo-controlled, double-blind study of NT 201 ($\leq$20-weeks) in 29 centers in US and Canada, could enter an open-label extension phase and were treated with NT 201 (up to 50 U per eye; $\leq$5 injection intervals) over 1 year (48-weeks + maximum of 20-week follow-up). Injection intervals were at least 6 weeks, with a mandatory visit 6 weeks after each injection. The injection intervals were chosen at the patient's and physician's discretion. Outcome measures included the Jankovic Rating Scale (JRS) severity subscore, the JRS frequency subscore, the JRS sumscore, and the frequency of adverse events (AEs).

Results: A total of 102 patients entered the extension phase. The mean total dose ranged from 64.7 to 72.7 Units and the mean cumulative dose was 276.7 Units. All JRS scores were significantly

improved at 6 weeks after each injection ($p \leq 0.001$; vs prior visit JRS score) as well as at the study termination of the OLEX phase ($p < 0.001$; vs the JRS score prior first injection at baseline extension visit). During the extension period, 81/102 patients (79.4%) experienced ≥ 1 AE. The most frequently reported AEs were ptosis, dry eye, nasopharyngitis, visual disturbance, and upper respiratory tract infection. No serious AEs were considered to be related to NT 201. The overall incidence of AEs decreased from the first to the fifth injection, indicating no cumulative effect with repeated doses.

Conclusions: Repeated treatments with NT 201 were effective and well tolerated in the long-term (>48 weeks) treatment of patients with blepharospasm.

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Bilateral masseter and temporalis hypertrophy with an outstanding response to botulinum toxin

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Objective: To report a case of bilateral masseter and temporalis hypertrophy responsive to botulinum toxin type A.

Background: Hypertrophy of masseter and temporalis muscles, bilateral or occasionally unilateral, was first described by J.W. Legg in 1880. It is not gender-specific and occurs usually between the ages of 20 and 40 years. The underlying etiology has been attributed to chronic bruxism, masseteric hyperfunction, and parafunctional jaw habits. Conservative treatment is via occlusal splints and administration of muscle relaxants. Surgery involves partial resection of the masseter and bony prominence in the mandibular angle region. As botulinum toxin chemodenervation has been used to successfully treat dystonia and other conditions of muscle hyperactivity, it has been hypothesized that it could also be used to treat temporalis and masseter hypertrophy.

Methods: Retrospective chart review.

Results: A 39 year old female with a six-year history of pain, swelling, and heaviness on both sides of her face. After an extensive cardiac workup, she was diagnosed with bilateral temporalis and masseter hypertrophy. She received botulinum toxin A (BTX-A, BOTOX®) injection to the temporalis and masseter muscles with good clinical outcome. However, she had syncope associated with injection, ultimately requiring sedation at the time of the procedure. During her two pregnancies, she experienced remission of facial pain and stopped BTX-A injections. She presented to our clinic approximately 2.5 years after her last BTX-A injection. She was uncomfortable, experiencing facial heaviness, facial pain, and headache. She was initially injected with 100 units of BTX-A, which produced a partial response, with persistent pain when chewing and talking. Three months later, she was injected with an increased dose of BTX-A, 165 units. This produced an excellent clinical response, with decreased hypertrophy of temporalis muscles and decreased facial discomfort. Four months since her last treatment, she continues to receive clinical benefit.

Conclusions: Temporalis and masseter hypertrophy is an uncommon disorder that can cause significant pain and affect quality of life. Local injection of BTX-A is a minimally-invasive therapeutic alternative to surgery or medication treatment. BTX-A injection was effective and well-tolerated in our patient.

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DYT6 dystonia phenotype and the effect of deep brain stimulation

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Objective: Here we assess the frequency and phenotype of *THAP1* mutation carriers in a large Dutch cohort of late-onset (>26 years) cervical dystonia (n=333), writer's cramp (n=55) and early-onset dystonia (n=67) patients. We describe the effect of GPi-DBS in 4 DYT6 dystonia patients.

Background: Mutations in THAP1, a gene encoding a nuclear pro-apoptotic protein, have been associated with DYT6 dystonia. First reports on the phenotype of DYT6 dystonia show an early onset dystonia with predominant craniocervical and laryngeal involvement. The response on GPi-DBS is not reported as yet.

Methods: All patients were previously examined by a movement disorder specialist and diagnosed with pure dystonia based on the accepted criteria. Disease severity in segmental and generalized dystonia patients was scored with the Burke–Fahn–Marsden dystonia rating scale. All patients were screened for mutations in *THAP1* (exon 1-3), including the entire 5' untranslated region (UTR) and 500 bp of the 3' UTR, and at least 50 base pairs of the upstream and downstream intronic sequences that flank each exon. Sequences were analyzed using CodonCode software.

Results: Overall, 3 new heterozygous mutations were detected in the early-onset group causing generalized dystonia with profound oromandibular and laryngeal dystonia in all but one patient. Two DYT6 families are identified, showing a heterogeneous phenotype. Four DYT6 patients were treated with GPi-DBS with moderate to good response on distal and cervical dystonia. Rare synonymous variations were identified in conserved regions of THAP1, two in the late-onset cervical dystonia group and one in the control group.

Conclusions: Patients with non-synonymous mutations in *THAP1* show an early onset segmental or generalized dystonia with profound oromandibular and laryngeal involvement. The effect of GPi-DBS in DYT6-patients is beneficial for distal dystonic features, while the prominent speech symptoms respond less. No non-synonymous mutations were found in patients with late-onset focal dystonia in Dutch population.

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Rimabotulinum toxin B dosing in cervical dystonia: How much is too much?

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Objective: To report a patient with cervical dystonia (CD) receiving higher dosages of Rimabotulinum toxin B (Rbtx) relative to that utilized in clinical trials, with continued clinical benefit, absence of side effects, and no evidence of immunogenicity.

Background: Rbtx has been definitively established in multiple randomized, controlled clinical trials as an effective and safe treatment for CD. The pivotal trials used in establishing the efficacy of Rbtx in CD utilized a maximum dosage of 10,000units. Subsequent studies in CD patients have demonstrated similar safety and efficacy utilizing up to 28,000units in a single treatment session. Concerns of utilizing higher dosages of Rbtx in CD include dry mouth, dysarthria, and dysphagia, as well as the risk of developing neutralizing antibodies against Rbtx.

Methods: Case report.

Results: A 66yr old woman developed CD and dystonic head tremor in mid-2004. Examination revealed marked hypertrophy of both SCM muscles, and muscle stiffness over posterior neck muscles. The predominant abnormal head and neck movement was torticollis to the right, elevation of the right shoulder, and a lateral head tremor. Rbtx injections were initiated in 2005, all under EMG guidance, starting with a dosage of 4000 units, which resulted in a dramatic reduction in pain. Subsequent Rbtx injections have continued every 12 weeks at gradually escalating dosages with continued and consistent improvement in both the dystonia and pain. She has achieved maximal clinical benefit with the following regimen: Left SCM:7000u; Right SCM:6500u; Right splenius capitis:2000u; Right levator scapulae:3500u; Right trapezius:10,000u; Left trapezius:7500u; Total: 36,500u. She continues to report exceptional clinical improvement, and consistently denies noting any dry mouth, dysphagia, dysarthria, or loss of benefit.

Conclusions: Rbtx can be used effectively and safely in CD at dosages beyond those used in clinical trials. While experience from a single case report cannot be extrapolated to the general population, our data will hopefully assist in developing future clinical trials on Rbtx and other types of botulinum toxin to expand our knowledge of these exceptional treatments available for CD. Although such high dosages can be safe in at least some individuals, continued clinical vigilance for potential side effects should always be maintained as the dosage of Rbtx is modified.

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Safety and efficacy of repeated NT 201 (botulinum neurotoxin type a free from complexing proteins) injections of patients with cervical dystonia: A first long-term safety analysis

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Objective: To assess the long-term safety and efficacy of NT 201 (botulinum neurotoxin type A (BoNT/A) free from complexing proteins) in an extension study in cervical dystonia.

Background: NT 201 has shown comparable efficacy and safety to onabotulinumtoxinA (Botox, Allergan, USA) in treating cervical dystonia when used in a 1:1 dosing. So far more than 76000 patients worldwide have already been treated with this compound.

Methods: Patients with cervical dystonia who completed a placebo-controlled, double-blind study of NT 201 ($\leq$20-week) in 37 US centers, could enter an extension phase and were treated with NT 201 (120 U or 240 U; $\leq$5 injection intervals) over 1 year (48 weeks + 20-week follow-up). Injection intervals were at least 6 weeks, with a mandatory visit 4 weeks after each injection. The injection intervals were chosen at the patient's and physician's discretion. Outcome measures included the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and the frequency of adverse events (AEs).

Results: A total of 217 patients entered the double-blind extension, and a first long-term safety analysis was performed on 153 patients. The mean duration before re-injection was 10.0 ($\pm$2.4) to 14.5 ($\pm$5.9) weeks. TWSTRS-Total score was significantly improved at 4 weeks after each injection ($p \leq 0.05$ vs injection visit score) as well as at the study termination visit (12–13 weeks after the final injection) versus the first injection visit of the extension phase ($p < 0.001$). During the extension period, 118/153 patients (77.1%) experienced $\geq$1 AE (120 U group, 70.7%; 240 U group, 83.3%). The most frequently reported AEs were dysphagia, neck pain, and sinusitis. No serious AEs were considered to be related to BoNT/A. The overall incidence of AEs reduced with each injection interval, indicating no cumulative effect with repeated doses.

Conclusions: Repeated treatments with NT 201 were effective and well tolerated in the long-term (>48 weeks) treatment of patients with cervical dystonia.

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An unusual presentation of dystonia in Lubag's syndrome

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Objective: A case report to highlight a rare presentation of dystonia in X-linked dystonia-parkinsonism.

Background: X-linked recessive dystonia-parkinsonism (XDP), DYT3 or Lubag syndrome, is a neurodegenerative disorder of dystonia and parkinsonism endemic to the island of Panay in the Philippines. Affected males usually present in with focal dystonia that later gives way to parkinsonian symptoms. Dystonia may respond to pharmacological intervention such as zolpidem, trihexyphenidyl chloride, and benzodiazepines. A few patients have undergone deep brain stimulation with benefit.

Results: Case Report: We present the case of a 32 year-old man with a family history of X-linked dystonia parkinsonism whose initially presented with dystonia of the respiratory muscles. He first noted difficulty in speaking long sentences but otherwise had preserved exercise tolerance. Over the course of the following three weeks, he developed severe episodic bouts of dyspnea that interfered with speaking, eating, and physical exertion. An extensive cardiopulmonary work up revealed only mild abnormalities of the arterial blood gas. Within six weeks, the dyspnea was continuous. At eight weeks, he began to feel painless neck spasms, especially when upright, that were associated with simultaneous contraction of the biceps and triceps. All movements abated with sleep. He had lost 35 pounds in four months due to the exacerbation in respiration when both eating as well as sitting upright. He had negligible benefit from medical therapy, including trihexyphenidyl chloride, clonazepam, baclofen, zolpidem and carbidopa/levodopa. All studies confirmed the diagnosis of thoracoabdominal dystonia.

Conclusions: This case represents an unusual presentation of dystonia that began in an episodic fashion and affected primarily the respiratory musculature including the intercostals and abdominal muscles. He was diagnosed with throacoabdominal dystonia after involvement of trapezii, biceps, and triceps produced more characteristic movements. Our patient had minimal benefit from pharmacologic interventions; as his symptoms continue to progress, we consider surgical intervention as well. Two case studies report benefit from bilateral pallidal electric stimualtion. Pallidal DBS may offer therapeutic benefit for medically refractory secondary dystonia.

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A multicentre open study on the treatment of heterogeneous subtypes of cervical dystonia with botulinum toxin a (500 units Dysport®)

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Objective: The aim of this study was to compare the effectiveness and safety of a standard initial dose of 500 units Dysport® in the treatment of the most frequent subtypes of cervical dystonia (CD), i.e. predominantly torticollis or laterocollis, including additional symptoms such as shoulder elevation or tremor.

Background: Botulinum toxin type A is a first line therapy for CD. Nevertheless, there are only few studies available in the treatment of heterogeneous subtypes of CD. In this study, substantial data on a large representative group of out-patients in specialized clinics could be gained.

Methods: Between November 2004 and January 2008, 516 *de novo* patients with CD were recruited by 81 study sites in Germany and Austria. The investigators could choose among 12 injection protocols, with a muscle selection based on clinical assessments following the Tsui rating scale. This regimen allowed an individual yet standardised therapy and provided a structure of twelve CD subgroups for inter-individual treatment comparison.

Results: Dysport® treatment led to a clinically relevant and statistically significant decrease of the total Tsui score at week 4 and, to a lesser extent, still at week 12. This decrease in the total Tsui score was statistically not different between both CD main subtypes. An equal improvement of disease related quality of life, as assessed by the CDQ-24, could also be observed. The patient diaries reflected the positive effects on day to day function and activities, pain reduction and duration. All in all, the treatment was generally well tolerated and similar in patients with torticollis or laterocollis.

Conclusions: This study with a large patient population provides valuable insights for optimal initial treatment of heterogeneous subtypes of CD.

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Patients with primary cervical dystonia have evidence of deficits in praxis

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Objective: To uncover evidence of higher motor dysfunction in patients with primary cervical dystonia using a battery test of praxis.

Background: Functional imaging and electrophysiological data from patients with primary dystonia reveal widespread abnormalities in brain areas associated with higher motor functions, but to date there has been little investigation of the functional consequences of these abnormalities.

Methods: We assessed praxis in 13 patients with primary cervical dystonia without hand involvement and 29 age and sex matched controls. We used a semi-quantitative praxis assessment combining timed tests of meaningful and meaningless movements with copying of transitive and intratransitive hand movements and pantomime of tool use. Control tasks included evaluation of motor speed and strength, and a number of additional cognitive tasks.

Results: Patients made significantly more errors in copying meaningless gestures and were slow in the performance of meaningless sequences of hand movements. Production of meaningful intratransitive gestures, pantomiming object use, and performance on control tasks was normal.

Conclusions: This is the first study to confirm a discrete deficit in praxis that appears to be specific for the execution of novel movements. This study provides evidence of functional impairments related to higher motor order brain areas as part of the widespread pathophysiological abnormalities seen in primary dystonia.

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Ventral premotor-motor interaction in surround inhibition and movement preparation in focal hand dystonia

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Objective: To assess whether intracortical circuits between the ventral premotor cortex (PMv) and the primary motor cortex (M1) are involved in surround inhibition.

Background: PMv plays a key role in voluntary motor control, especially in visuomotor transformations and coordination of grasping movements. Focal hand dystonia (FHD) represents abnormal posturing due to sustained muscle contractions. It as been established that surround inhibition (SI) is diminished in FHD. SI is the decreased excitability in a cortical area surrounding an activated one. Cortical mechanisms responsible for SI are not known. Here, we hypothesize that PMv might be a generator of SI.

Methods: Single and paired pulse transcranial magnetic stimulation (TMS) was applied during different phases (rest, 100 ms before EMG onset, 50 ms before EMG onset and first EMG peak) of an index finger movement in FHD patients and controls. Right abductor pollicis brevis (APB), a surrounding, non-synergistic muscle, was used as target muscle. Sub-threshold conditioning TMS was applied to PMv 6 ms before M1 stimulation.

Results: SI was present during movement initiation only in the control group. PMv stimulation induced a premotor-motor inhibition (PMI) at rest in controls but not in patients. During movement initiation, PMI decreased in controls whereas patients showed an abnormal facilitation of the motor evoked potentials over the APB. In controls, a transient premotor-motor facilitation was found 100 ms before EMG onset.

Conclusions: Ventral PMI does not play a key role in SI in normal subjects since it was not enhanced during movement initiation. However, our results show that FHD patients have a lack of PMI and that movement initiation is accompanied by an abnormal facilitation of M1. Thus, the deficiency of SI in patients could be due in part to an abnormal facilitation of the premotor-motor excitatory circuits. Results in the control group show that PMv might exert a facilitatory influence on M1 during movement preparation. This facilitation is absent in the patient's population. These results bring more information on the impairment of motor preparation in FHD and are coherent with a previous EEG study demonstrating a decrease of beta event-related desynchronization before movement in FHD.

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The use of low-dose botulinum toxin for hereditary geniospasm – a review of this rare dystonia

L.J. Jaffe (San Diego, California, USA)

Objective: To identify the optimal treatment and dosing for Hereditary Geniospasm. This abstract was presented at the 19th World Congress of Neurology on 29th October 2009, Bangkok, Thailand with the following title: Use of low-dose botulinum toxin for hereditary geniospasm - a review of this rare dystonia not reported in Asians.

Background: First described in 1894 by Massaro, Hereditary Geniospasm (HG) is recognized as dystonic movement of always bilateral mentalis muscles beginning in early childhood or infancy, continuing through life, provoked by emotional stress, occasionally causing great social concern, with Autosomal Dominant transmision, responsive to botulinum toxin injections. We present a girl with the classic presentation who we treated with low dose toxin and followed for 10 years.

Methods: A review of the world literature was undertaken to see how neurologists treat this rare hereditary dystonia. Since its availability became more widespread, botulinum toxic has been shown to be the most effective treatment. Dosing of 20, 25, and 30 units in each mentalis muscle is described in the literature. Also noted in the review was that this rare disorder has not been reported in Asian populations.

Results: Articles published from 1971 to 2009 describe HG occuring in European and North American families with 1 reported case from Peru and Argentina each. Cases in the Australian and Turkish populations have been reported. Genetic linkage at the 9q13-q21 locus has been shown in >38 families (2008) and there has been 1 new mutation case described in the Autosomal Dominantly-inherited disorder. Our patient was from a large affected family of Mexican ancestry. She reponded well to 7.5u injected into each mentalis muscle. The effect lasted approximately 5 years after the first treatment and 3 years after the second.

Conclusions: Hereditary Geniospasm can be easily recognized. The disorder can be treated effectively with occasionally low doses of botulinum toxin, occasionally with prolonged effect. The reasons for no reported cases of HG in Asian populations is unclear.

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BONTA without complexing proteins in spasmodic torticollis: No secondary treatment failure after three years

W. Jost (Wiesbaden, Germany)

Objective: Secondary treatment failure is a serious clinical concern. In Germany, BONTA without complexing proteins has been licensed for the treatment of spasmodic torticollis and blepharospasm for >4 years.In contrast to other botulinum toxin products it is free from complexing proteins, a property that could reduce or even prevent the formation of neutralising antibodies. When investigating neutralising antibodies, secondary treatment failure is regarded as the crucial parameter. Based on our experience, antibodies develop relatively soon and secondary treatment failure can be identified within the first three years. It would be a crucial clinical benefit, if neutralising antibodies would not occur with a product of equal efficacy.

Methods: All de novo patients suffering from spasmodic torticollis which were treated with BONTA without complexing proteins were documented. Patients were analysed retrospectively if they were treated for 3 years and at least 12 times. Those who reported a decrease in or loss of clinical effect after initially responding to the treatment were to be regarded as secondary treatment failures. These patients were to be tested for neutralising antibodies.

Results: 21 patients (13 females) with idiopathic spasmodic torticollis were included. Mean age was 48.7 years. The mean dose per injection after 3 years of treatment was 179 (±39) units and the mean cumulative dose was 2167 (±485) units. The patients received

an average of 12.8 injections (approximately every 3 months). No dose increase was required. We did not observe any cases of secondary failure and therefore none of the patients were tested for neutralising antibodies.

Conclusions: None of the patients in this series of 21 patients treated with Xeomin for spasmodic torticollis experienced a secondary failure of therapy. Should Xeomin® induce lower rates of neutralising antibodies, the recommendation to keep to a minimum interval of 3 months between injections could become less stringent.

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Rechargeable deep brain stimulator (DBS) ACTIVA RC for childhood dystonias: A one year experience

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Objective: To evaluate indications, reliability, recharging compliance, complications and parental satisfaction related to the Activa RC Deep Brain Stimulator.

Background: DBS is a recognised method of treatment for primary and secondary dystonia. The size of non-rechargeable batteries has limited their use in small children under 20 kg. Our severe dystonias have required battery replacement every 20-24 months with worsening dystonia towards the end of battery life. The Medtronic Activa RC was launched in Europe in autumn 2008.

Methods: An ACTIVA RC was implanted in 25 children and young people (mean age 9.25 years; range 4.25 – 19 years) between December 2008-9 including 16 primary GPi DBS operations and 9 as battery replacements. 17 cases (11 first implants, 6 replacements) with 3-12 months follow up (mean 7 months) were invited to complete an audit on maintenance and parental satisfaction.

Results: Of 15/17 completed surveys, 1 battery replacement was removed due to infection (5.8%). Self resolving early seroma occurred in 3 cases (17%). The recharging kit was replaced due to recharging difficulties in 2 cases (11%). 1 stimulator was inadvertently switched off for 2 months by a parent. Parents and carers were responsible for recharging in most cases, but one 7-year old began recharging herself a few months post-implant. The Activa RC was recharged daily in 40%, every 2 days in 33% and every 3 and 5 days in 13% of cases respectively. Recharging times were as follows: 46% below 30 minutes, 79% below 1 hour. The recharging harness was used regularly only in 13% and not at all in 73%. 86% responders did not consider recharging a burden. Overall 93% of families would recommend rechargeable stimulators because of smaller size and longer lifetime.

Conclusions: The ACTIVA RC offers a reliable stimulation with a low rate of complications and is suitable for children with dystonia. Recharging times were longer than initially anticipated by the manufacturer due to our higher parameters of stimulation A smaller harness size or other means of maintaining connection during recharging would be useful for children. Avoiding 2-yearly battery replacements significantly reduces DBS expense, risk of infection and re-operative morbidity.

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Mental rotation of body parts and sensory temporal discrimination in fixed dystonia

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Objective: To further explore the pathophysiology of fixed dystonia.

Background: Fixed dystonia without evidence of basal ganglia lesions or neurodegeneration is an uncommon but severely disabling condition typically affecting young women following a minor peripheral injury. There is continued controversy as to whether isolated fixed dystonia is of psychogenic origin. In fact, a substantial proportion of patients were found to fulfill the diagnostic criteria for psychogenic dystonia or somatization disorder. Electrophysiological techniques such as short intracortical inhibition, cortical silent period and a plasticity inducing protocol have revealed similarities but also differences compared to classical mobile dystonia. To further explore the pathophysiology of fixed dystonia we compared mental rotation of body parts and sensory temporal discrimination in 11 patients with fixed dystonia, 11 patients with classical mobile dystonia and 10 healthy controls.

Methods: In the mental rotation task subjects were presented with photos of left or right hands, feet and the head of a young women with a black patch covering the left or the right eye in 6 different orientations. Subjects had to verbally report the laterality of the presented stimuli. To assess sensory temporal discrimination subjects were asked to discriminate whether pairs of visual, tactile or visuotactile stimuli were simultaneous or sequential (temporal discrimination threshold) and in the latter case which stimulus preceded the other (temporal order judgement).

Results: In keeping with previous reports our fixed dystonia group was characterized by female gender, age at onset in the fourth decade and a precipitating peripheral injury in eight out of 11 patients. As well as confirming the presence of abnormalities in both methods in patients with mobile dystonia, we found that mental rotation was also impaired in patients with fixed dystonia. Both groups had a comparable level of performance for all body part rotations tested.

Conclusions: Possible explanations for this deficit may include the influence of the abnormal body posture itself, a shared predisposing pathophysiology for mobile and fixed dystonia, or a body image disturbance. These findings add information to the developing pathophysiological picture of fixed dystonia.

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A case with X-linked dystonia-parkinsonism (XDP:DYT-3) improved by bilateral pallidal stimulation

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Objective: To evaluate the efficacy of deep brain stimulatin in patients with X-linked dystonia-parkinsonism (XDP:DYT-3).

Background: X-linked dystonia-parkinsonism (XDP:DYT-3), first reported by Dr.Lee et al in 1976, is characterized by the clinical onset of facial and cervical dystonia followed by parkinsonism, and is limited incidence in the Philippines. We examined a Filipino whose grandfather is a Japanese. He was diagnosed as having DYT-3 in Manila; his maternal uncle showed similar involuntary movements with bradykinesia. His involuntary movements, which are generalized dystonia, were refractory and he wished to be treated by deep brain stimulation (DBS) to continue his occupation.

Methods: The patients was 46-year-old Filipino and his mother was born in Bacolod City where the incidence of DYT-3 is high. From his forties, involuntary movements such as grimacing and rotating cervix to the right side appeared. After the onset of the initial symptoms, he gradually experienced difficulties in speech, writing, and walking. He showed tremor and rigidity on the left side. He was diagnosed as having DYT-3 in Manila and was administered levodopa, clonazepam, anticholinergic drug or injected with botulinus toxin; however, the effect was minimal. Bilateral pallidal DBSs (GPi- DBS) were performed in July 2008. The operation was carried out general anesthesia.

Results: After starting the stimulation, phasic dytonic movements including facial dystonia were improved in a few days and cervical dystonia and dysphonia were also improved. The condition of bilateral DBS were monopolar stimulation using contact 1 located at the center of the GPi, 90us, 160Hz. His BFM score was improved by 90%. He no longer has involuntary movements and will return to his job in January 2009.

Conclusions: This is the first report of patients with DYT-3 treated with GPi DBS in Japan. His dystonic movements were well controlled following GPi-DBSs. The dystonia associated with DYT-3, as well as familiar dystonia, was improved by the GPi-DBS at our hospital.

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Swallowing induced laryngo-pharyngeal dyskinesia – a variant of PKD?

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Objective: To document two unusual cases of swallowing induced laryngo-pharyngeal dyskinesia presenting as dysphagia and their response to Carbamazepine.

Background: Paroxysmal Kinesogenic Dyskinesia (PKD) is a rare disorder characterized by brief and frequent episodes of abnormal involuntary movements, triggered by sudden activities. The triggering activities can be variable and the dyskinesias usually involve limbs of one or the other side. We present two cases of focal PKD where act of swallowing induced abnormal laryngo-pharyngeal movements.

Methods: Case 1: An 80 years old gentleman presented with dysphagia of one year duration. He also complained of involuntary eye closure during act of swallowing. Electrophysiological study ruled out neuromuscular disorders and neuroimaging was normal for age. Clinical examination and video fluoroscopy revealed multiple rapid, laryngo-pharyngeal movements lasting for 2-4 seconds after each attempt to swallow. Case 2: A 90 years old female presented with chronic cough, dysphagia and frequent episodes of choking. Extensive evaluation for the cough was done previously and no respiratory or throat pathology was found. Clinical examination and video fluoroscopy revealed rapid laryngo-pharyngeal movements lasting for upto 5 seconds after each swallow. Some of the attempts to swallow were followed by cough.

Results: Carbamazepine was started in both these cases considering a focal form of PKD, where an act of swallowing induced the abnormal laryngo-pharyngeal movements. Both of them showed remarkable improvement in swallowing after one week of starting the drug. The swallowing induced laryngo-pharyngeal movements decreased significantly and that was shown objectively on video fluoroscopy. Involuntary eye closure in the first patient and chronic cough in the second patient also reduced after starting carbamazepine. Involuntary eye closure was possibly a sensory trick patient used to facilitate swallowing and chronic cough could be the result of micro-aspirations associated with the abnormal movements.

Conclusions: We present two cases of carbamazepine responsive, focal form of PKD where act of swallowing induced abnormal laryngo-pharyngeal movements and resulted in dysphagia. If recognized, this entity can be treated effectively.

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Generalized dystonia revealing a hydrocephalus

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Objective: A 77 year-old woman developed a generalized dystonia 8 months after radio-surgery for an acoustic neuroma. Further examinations revealed an active normal pressure hydrocephalus. Once a ventriculo-peritoneal shunt has been performed, the dystonia completely recovered.

Background: Dystonia is a movement disorder characterized by involuntary and sustained muscle contractions that produce abnormal postures. It is mostly induced by striatal lesions. The usual manifestations of normal pressure hydrocephalus are characterized by the association of gait disturbances, cognitive impairment and sphincter dysfunction.

Methods: A 77 year-old woman presented to our service with 1 month history of gait disturbances, falls and cognitive impairment. Her medical history included acoustic neuroma treated with radio-surgery 8 months earlier. After admission in our department, a rapid impairment of clinical status occured, leading to an "astasia-abasia" phenotype, associated with cognitive impairment and urinary retention. Moreover, she presented a generalized dystonia. Afterwards, the patient progressively became unable to walk and talk. The brain CT Scan showed a tetraventricular dilatation. The MRI confirmed cerebral ventricular dilatation without obstacle or ventricular compression and showed significant signs of transependymal resorption. There was no cortical or basal ganglia abnormal signal. The flow MRI confirmed the disturbances of cerebro-spinal resorption suggesting a felting of the subarachnoid spaces.

Results: The patient was treated by ventriculo-peritoneal shunt with a positive effect on symptoms. Dystonia completely recovered a few days after the surgery. She was able to walk with unilateral support and language disorders completely disappeared. However, a spatiotemporal disorientation remained. The MMS was impossible before the surgery, and it was 15/30 high after the surgery. Five months after the ventriculo-peritoneal shunt, the flow MRI was normalized.

Conclusions: To our knowledge, this is the first case of generalized dystonia secondary to hydrocephalus. The complete regression of dystonia after shunt confirms the link between hydrocephalus and dystonic movements. The mechanism remains unkown, it could be related to an impaired resorption of cerebrospinal fluid near the caudate nucleus or a mass effect exerted by the ventricules on the basal ganglia.

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A rare sequence variant in intron 1 of THAP1 is associated with primary dystonia

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Objective: To examine the THAP1 c.71+9C>A sequence variant in subjects with primary dystonia and normal controls.

Background: Recently, numerous THAP1 sequence variants have been linked to primary dystonia. In a previous study of 1210 subjects with dystonia and 600 controls, we identified an Intron 1 variant of THAP1 (c.71+9C>A) in 7 subjects with dystonia and 1 control.

Methods: High resolution melting was performed in 1508 subjects with mainly adult-onset primary dystonia and 1520 normal controls. Samples with shifted melting curves were sequenced in the forward and reverse directions. To evaluate the effects of the c.71+9C>A variant on transcription, relative quantitative real-time PCR was performed using leukocyte RNA harvested from Ambion LeukoLOCK filters.

Results: Thirteen subjects harbored the c.71+9C>A variant, 11 with dystonia (11/1508) and 2 normal controls (2/1520) [P=0.011]. Anatomical distribution included cervical dystonia (N=3), laryngeal dystonia (adductor subtype, N=3), masticatory dystonia (jaw opening, N=1), blepharospasm (N=1) and unclassified dystonia (N=3). Age of dystonia onset ranged from 25 to 66 yrs (mean=52 yrs). Two probands had a family history of dystonia. In comparison to controls with no identified THAP1 sequence variants, the c.71+9C>A sequence variant was associated with an elevated ratio of isoform 1 (3 exon variant) to isoform 2 (2 exon variant).

Conclusions: Our data indicate that the c.71+9C>A Intron 1 THAP1 variant is associated with adult-onset primary dystonia and alters THAP1 splicing.

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Developmental expression of THAP1 in the rat nervous system

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Objective: To investigate the expression of THAP1, a transcription factor associated with DYT6 dystonia, during development of the rat nervous system.

Background: An abundant collection of *THAP1* sequence variants is associated with primary dystonia. THAP1 dystonia shows significant heterogeneity in anatomical distribution and age of onset. In extra-neural tissues, THAP1 plays a critical role in transcriptional regulation in the context of cell proliferation and pRb/E2F cell cycle pathways. In neural tissues, little is known about the development expression of this transcription factor.

Methods: Immunohistochemistry, double-label fluorescent cytochemistry and quantitative Western blot analysis were performed to inspect THAP1 expression in brain, spinal cord and dorsal root ganglia (DRG) from the early postnatal period through adulthood.

Results: THAP1 immunoreactivity (IR) was present in brain, spinal cord and DRG at Postnatal Day 7 (P7), P14, P21, 2 months and 6 months. In brain, THAP1 was present in cerebral cortex, hippocampus, striatum, brainstem and cerebellum. Western blot analysis using β-tubulin as the loading control showed that THAP1 expression was highest in early development, particularly in cerebellum at P7. In cerebellar cortex, THAP co-localized with calbindin-IR. THAP1-IR was prominent in the perikarya and proximal dendrites of Purkinje cells at early postnatal time-points. In contrast, THAP1-IR was more diffusely distributed throughout the dendritic arbors of adult Purkinje cells producing a moderately strong diffuse staining pattern in the molecular layer. At all time points, nuclear IR was weaker than cytoplasmic IR. In a subset of Purkinje cells, THAP1-IR appeared concentrated near the nuclear envelope.

Conclusions: The transcription factor THAP1 is diffusely distributed in neural tissues and concentrated in cerebellar cortex. In cerebellar cortex, the vast majority of THAP1-IR was localized to Purkinje cells. Our data suggests that THAP1 may contribute to the developmental maturation of the neural tissues and signaling in adult Purkinje cells.

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Combination of botulinum toxin A (BTXA) and phenol to cervical dystonia (CD) case report

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Objective: We report a case of CD treated with combination of BTXA and phenol injection (PI) in a patient who had already received BTXA treatment without any satisfactory great improvement.

Background: CD is a movement disorder characterized by sustained cervical muscle contractions resulting in twisting and repetitive movements or abnormal postures. Oral drugs and a rehabilitation program have been used to treat this disease, but with unsatisfactory results. BTXA is the treatment of choice but some patients do not respond completely and remain with residual movements.

Methods: Case report.

Results: A 38 year-old black female started to present insidious tremors in the cephalic segment worsening over a period of several years, which were associated with involuntary movements such as head and neck torsion (cervical rotation to the left w/ anteversion). Etiologic investigation was negative. Treatment with drugs shows no benefits and several BTXA injections left the patient with some residual torsion. After electrophysiological muscle study we classified the involuntary muscle hyperactivity according to its intensity and duration. BTXA (BOTOX®) was injected into muscles which showed impairment of degrees 4, 3, and 2: Right Sternocleidomastoid (SCM), Right Splenius Capitis, Left Splenius Capitis, Left Semispinalis Capitis, Right Superior Trapezius, Right Scalenus Medius. One month after BTXA, the patient showed improvement in her preexisting condition, particularly regarding pain. The clinical evaluation, however, showed persistent SCM hyperactivity and limited rotational movement of the neck. A therapeutic test with 1% Xylocaine at the right spinal accessory nerve was performed, and a satisfactory response, with release of cervical movement, was observed. Subsequently, 5% Phenol was prepared and 1.5 ml was injected into the spinal accessory nerve. PI response showed a major improvement in the range of cervical motion over a period of 6 months.

Conclusions: We suggest that the PI may be an adjunctive treatment for CD when there are residual muscle movements and BTXA reapplications are not still recommended. Trials with this treatment are indicated in order to evaluate the role of PI combined with BTXA in CD.

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Diagnostic heterogeneity and clinical complexity of primary and secondary dystonias presenting to a national paediatric complex motor disorders service

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Objective: To describe the commonest causes of dystonia presenting to a national complex motor disorders service for consideration of possible deep brain stimulation (DBS), intrathecal baclofen (ITB) pump implant or alternative management.

Background: Dystonia is increasingly considered to represent excessive cerebral plasticity and inadequate inhibition. Globus pallidus internus DBS may work by facilitating a more functional plasticity-to- inhibition ratio. Movement disorders in children present a significant diagnostic and management challenge. Expectations and goals for children with perinatal or infantile-onset dystonias (with no previous motor repertoire) may differ considerably from those for movement disorders related to later-onset primary or secondary dystonias. Referrals for DBS require careful diagnostic and phenotypic classification of the underlying disorders for appropriate clinical decision-making and counselling.

Methods: Consecutive referrals 2007-9 to the paediatric Complex Motor Disorders Service and Functional Neurosurgery for possible DBS, ITB or alternative medical advice were classified according main diagnostic category.

Results: The commonest aetiologies in 174 referrals are given in the table 1 in order of frequency.

Conclusions: Dystonia-dyskinesia secondary to prematurity represents the commonest group (18%), followed by HIE (13%), neurometabolic disorders including NBIA (12%) and primary dystonias (14%). The remaining cases have miscellaneous 'orphan' causes. This case-mix complexity requires an experienced multidisciplinary service for diagnostic and clinical assessment, goal-setting and post-intervention review. Careful clinical assessment complemented by radiological and neurophysiological methods aimed at defining minimal cerebral destruction together with realistic goal-setting and outcome measures will help refine the selection criteria and prognosis for DBS in these children and young people.

TABLE (168). *Paediatric movement disorders by diagnosis*

Broad Diagnosis	Total	%
Ex Preterm Birth	32	18
Perinatal HIE	22	13
DYT1 Negative Primary Dystonia	15	9
Acquired brain injury beyond the neonatal period	12	7
Neurodegeneration with Brain Iron accumulation (NBIA-1) PANK2 disease	10	6
Neuro-metabolic	10	6
Hemidystonia	9	5
Dystonia Myoclonus	4	2
DYT1 Positive Primary Dystonia	4	2
Kernicterus	3	2
Dopa Responsive Dystonia	2	1
Miscellaneous	51	29

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Abdominal paroxismal dysnesis or "belly dance" syndrome: Presentation of two different cases

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Objective: Description of two cases of Abdominal Dyskinesia with different characteristics.

Background: Abdominal Paroxismal Dyskinesias are infrequent movement disorders. They can start in childhood of idiopathic type (which can be sporadic or familiar) or in adulthood, where they usually are a secondary to a recognizable cause. Some cases are described as diaphragmatic flutter, a rare presentation of this kind of disorder, and are associated with dyspnea or thoraxic pain. When the movement starts in the epigastrium and it extends to the abdominal wall with epigrastric pulsations of 5 to 10 waves per inspiration, in which intercostals muscles and the diaphragm are used. This local, unvoluntary, stereotyped movement disorder produces (because of its prolonged evolution) muscular pain in the affected area. Early diagnosis of it makes possible the use of therapy and to avoid psychological consequences.

Methods: Report of two Abdominal Paroxismal Dyskinesia.

Results: The clinical characteristics of both cases are the following: FIRST CASE Male, 27 years-old, with history of simple abdominal contusion, starts having spasmodic movements that, at first, are recognized as hiccups and becomes chronical with wavy movements of the abdominal wall. Multiple drugs were used, with no effects. 3mm of fractionated Clonazepam a day are used to diminish the intensity of the movement. The patient is pending for the use of botulinum toxin. SECOND CASE Female, 23 years-old. She previously used neuroleptic drugs (metoclopramide, cinnarizine). The patient presented two independent episodes of prolonged and painful wavy spasms of the abdominal wall. This is treated with intravenous benzodiazepine (continuous drip of midazolam and lorazepam, respectively) stopping the movements after 48 hrs.

Conclusions: So far, there is no determined cause for this movement disorder, but there is evidence that it could be due to a channelopathy, which would explain their positive response to anticonvulsant drugs. Various therapies have been tried with varying results, among which are the uses of carbamazepine, reserpine, tetrabenazine, clonazepam, trihexyphenidyl or levodopa, leading to botulinum toxin. The abdominal location and movement characteristics of these cases are described as Belly Dance Syndrome and must be identified by their unique characteristics and confirmed by electromyography diaphragm and abdominal wall.

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Battery life in paediatric patients receiving pallidal deep brain stimulation (DBS)

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Objective: To determine the battery life in clinical practise of non-rechargeable neurostimulator devices currently used in the treatment of paediatric dystonia.

Background: The finite longevity of the non-rechargeable batteries that power implantable neurostimulators such as the Kinetra and Soletra systems necessitates their periodic replacement. In addition to the inconvenience and operative risks this exposes patients to there is also a financial burden given the costs of these units. In adult patients receiving DBS for the treatment of Parkinson's disease mean battery lives of almost 4 years have been reported. In the treatment of dystonia a shorter battery life can be predicted due to the higher energy consumption resulting from the higher settings needed to obtain symptomatic benefit. Paediatric patients may potentially require numerous battery changes over their treatment lifetime. Small benefits in battery life could accumulate considerably over this time period.

Methods: The length of time from initial insertion until the time of neurostimulator replacement due to battery failure was measured in all children receiving pallidal DBS during the first 5 years of our clinical service.

Results: A total of 14 patients required battery replacements, with 5 patients requiring replacements on a second occasion. On 5 occasions bilateral Soletra® units were replaced. The other 14 replacements were of Kinetra® stimulators. Overall, the mean time from insertion to replacement due to battery failure was 24.6 months (range 15.9 to 33.9 months). There was no apparent difference between Soletra® and Kinetra® longevity.

Conclusions: Battery longevity appears to be comparatively short for implantable neurostimulators currently used in the treatment of paediatric dystonia. Our provisional findings suggest a comparable longevity with adult patients. This short battery life would result in numerous battery changes over the paediatric patient life-time. These findings high-light the potential benefits of the recently introduced rechargeable Activa RC® neurostimulator device.

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Botulinum toxin (BoNT) therapy for focal hand dystonia (FHD) – 10 years or longer follow-up

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Objective: To assess the safety and efficacy of BoNT therapy in FHD with treatment duration of 10 years or more.

Background: FHD is a focal dystonia with task specificity. BoNT therapy is an established therapy for FHD, with proven but variable efficacy. Prior studies from our group and others have explored the efficacy and safety of this therapy, but no studies have to date followed a large number of patients for 10 or more years.

Methods: Retrospective study of cases in our standardized BoNT injection record database. Benefit from the each treatment was assessed on a subjective scale from 0 to 4, based on % restoration of normal function. Weakness was assessed on a similar scale. Demographic, clinical and treatment characteristics were analyzed and t-tests and Pearson correlations were used with a threshold of $p<0.05$.

Results: 20 of the 214 FHD patients in our database had a follow-up of 10 years or longer (range 10-17). 5 patients were professional musicians with dystonia related to the professional activity, and most of the others had writer's cramp. We found large variability in the inter-injection intervals. The musicians were statistically more likely to wait longer between injections than non-musicians (19.9 ± 12.4 months vs 7.7 ± 2.3 months, $p<0.002$). There was a trend for the shorter intervals to be associated with greater benefit at each visit. The average benefit from the injections and the average weakness were in the moderate range, with a trend for larger magnitude of benefit in women. The dose increased over time based on response and the patient's needs. The dystonia pattern and other clinical characteristics did not predict the response or side-effects in our cohort. No serious side-effects occurred and no patients developed antibody-mediated resistance.

Conclusions: This is the longest reported period of BoNT treatment in the largest FHD patients cohort. There is large variability in the inter-injection intervals, especially for musicians, partly by choice of timing injections around performances, given the task specificity. BoNT therapy for FHD remains safe and effective after more than a decade of treatment. Most patients obtain benefit in the moderate range, and the amount of benefit is likely derived multi-factorially and difficult to predict. No significant side-effects emerge, and the risk of developing immunity is low.

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Highly task-specific oromandibular dystonia in speech

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Objective: To report a patient showing oromandiblular dystonia on only specific articulation.

Background: Task-specific dystonia is focal dystonia characterized by excessive muscle contractions during selective motor performance. It is often associated with highly skilled, overlearned, and repetitive movements such as writing, or playing musical instruments. The dystonia occurs whenever patients carry out any action of the specific tasks. For example, patients with writer's cramp develop dystonia with any kind of writing, irrespective of the types of characters. It has not been reported that patients develop dystonia only with exclusive component of the specific task, which can be called highly task-specific.

Methods: Case description.

Results: A 35-year-old, right-handed woman visited our clinic for the evaluation of frequent tongue bite due to involuntary oromandibular contraction of two months while speaking. The past medical and family history was unremarkable. She denied trauma history or exposure to neuroleptics. She was a telephone operator for 10 years. She complained that her involuntary movement developed while she pronounced specific sound such as 'u' or 'g'. Otherwise, she did not have any problem to speak. Prior her visit to our clinic, dental evaluation was performed, but did not find any abnormality. Brain magnetic resonance imaging and laboratory tests showed normal results. Detailed neurological examination with the help of a speech-language pathologist (H.K.) revealed an isolated, highly task-specific oromandibular dystonia. There was no weakness of tongue and facial muscles. Her phonation and consonance was normal. On articulation, her speech intelligibility was normal, but articulation accuracy was decreased with open vowel sound. The articulation accuracy of the other sound was normal. She could sing normally. She reported her articulation was improved with chewing gum. We also found that tongue pressor in her mouth could alleviate her focal dystonia remarkably. During the 9-month follow-up period, she was treated with procyclidine, baclofen, and clonazepam and reported mild to moderate improvement without progression.

Conclusions: It is an illustrative case that task-specific dystonia can occur with very selective action of task.

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Central and extrapontine myelinolysis with severe dystonia after resolution of quadraparesis

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Objective: To describe a rare presentation of extrapontine myelinolysis (EPM), initially masked by quadraparesis and vegetative state.

Background: Central pontine myelinolysis (CPM) and EPM are well known demyelinating syndromes following hyponatremia. There are rare case reports of movement disorders associated with CPM and EPM with parkinsonism, dystonia, choreoathetosis, or ataxia. MRI findings typically include T2 hyperintensities of the caudate and putamen, sparing the globus pallidus (GP).

Methods: We describe the clinical, radiographic and laboratory findings in a patient with CPM and EPM.

Results: A 49 year-old man with alcoholism presented to an outside hospital with shortness of breath and confusion. He had quit drinking 3 weeks prior and was recently noted to drink excessive amounts of water. He became more altered and was intubated for oxygen desaturations to 80%. Sodium was <100. After extubation he was in a persistent vegetative state with quadraparesis and required a G-tube. MRI showed diffuse cerebral atrophy with increased signal in the brainstem thought to be a small infarction. Increased symmetric T2 signal was noted in the bilateral basal ganglia but was felt to be not significant. Over the next 2.5 years, his cognitive and motor symptoms improved. He could walk with support and speak. However, he developed dysarthria and abnormal movements of his face, trunk and limbs. A repeat head CT was read as unremarkable and he was referred for suspected psychogenic movements, prompting a referral to our clinic. His current exam (3 years after initial presentation) revealed dysarthria, asymmetric orofacial dystonia, truncal and limb ataxia, limb spasticity, and severe dystonic posturing of the right more than left hand. On re-examination of the initial MRI, symmetrical T2 hyperintensities are noted in the bilateral caudate and putamen, as well as the central pontine region.

Conclusions: This is a rare case of severe CPM/EPM with the full spectrum of clinical findings; initially presenting with altered consciousness and quadraparesis followed by asymmetric dystonia, dysarthria, spasticity and ataxia. The patient's long history of alcoholism and global cerebral atrophy likely contributed the severity and nature of his symptoms.

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Use of an interactive voice response system by patients with blepharospasm receiving repeated injections of NT 201 (botulinum neurotoxin type A free from complexing proteins)

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Objective: To assess the efficacy of repeated injections of NT 201 [botulinum neurotoxin type A (BoNT/A) free from complexing proteins] using an Interactive Voice Response System (IVRS) in patients with blepharospasm enrolled in a double-blind, placebo-controlled and open-label extension study.

Background: NT 201 has shown comparable efficacy and safety to onabotulinumtoxinA (Botox, Allergan, USA) in treating blepharospasm when used in a 1:1 dosing.

Methods: Patients with blepharospasm who completed a placebo-controlled, double-blind study of NT 201 ($\leq$20-week) and one injection cycle of an open-label extension phase. Patients were treated with NT 201 (up to 50 U per eye) or placebo during the first injection cycle and with NT 201 (up to 50 U per eye) during the second injection cycle. Injection intervals were at least 6 weeks, with a mandatory visit 6 weeks after each injection. The injection intervals were chosen at the patient's and physician's discretion. An IVRS was established for the daily assessment of the patient diary of the Jankovic Rating Scale (JRS) severity subscore, the JRS frequency subscore and the JRS sum score. The patients had to call a toll-free number every day in the morning. A IVRS (available in all relevant languages) guided the patient through the assessment of both JRS subscores. If the patient had not performed the scoring in the morning, the diary system contacted the patient to evaluate the outstanding data.

Results: 109 patients were randomized. Data were available for 99 patients for the placebo-controlled phase (67 patients received NT 201 and 32 patients received placebo) and for 93 patients of the extension phase. During both injection cycles mean changes in the JRS sum scores for NT 201 patients decreased markedly after 6 weeks ($p <= 0.009$, ANCOVA). Changes were more clearly demonstrated with the severity subscore than with the frequency subscore. Independent physician assessment of the placebo-controlled phase and IVRS data correlated positively at all visits.

Conclusions: Analyses of the JRS IVRS data indicate that the therapeutic effect of repeated treatments with NT 201 was clearly demonstrated through interactive patient assessment.

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Paroxysmal kinesigenic dyskinesia: The Cleveland clinic experience and literature review

K. Menezes, A.D. Rothner (Cleveland, Ohio, USA)

Objective: To review The Cleveland clinic experience with PKD and compare it with a Literature review in relation to the following (1) How common is epilepsy is in these patients (2) The age of onset of Epilepsy in relation to the movement disorder (3) The yield of

various available tests in diagnosis (4) The response to treatment (5) The natural history of this condition.

Background: Paroxysmal Kinesigenic Dyskinesia is a condition that often goes misdiagnosed formany years. There is no definite protocol for working up these patients and EEG is often unhelpfull. Family often have questions regarding the natural history of this disease and its relationship to epilepsy.

Methods: IRB approval for this study was obtained. Data was extracted from the patient medical records. A literature review was performed using Pubmed Key words: Paroxysmal Kinesogenic dyskinesia and paroxysmal Kinesigenic choreoathetosis.

Results: Twenty one Cleveland Clinic (CCF) cases and 357 cases from the literature were reviewed. The age of onset of CCF group versus Literature: 11.47 and 11.08. Epilepsy was seen in 23.8% versus 31.7%. Diagnosis was made in 1.42 years at CCF versus 4.8 years in Literature. Interictal EEG was positive in 14.28% versus 3.79%. Video EEG was positive in 0% vs. 5.12%. Nuclear scans were positive in 0% versus 100%. Family history was positive in 40% versus 57.87% in Literature. Anticonvulsants were 100% effective versus 88.34%. Remission was seen in 5% vs. 71.11%.

Conclusions: Most PKD presents at age less than 20. Cases may be familial, sporadic or symptomatic. Response to antiepileptics is 100% effective. Spontaneous remission may occur. Despite intense efforts no single gene has been identified. Nuclear scans suggest an abnormality in the caudate nucleus and may be more helpful than video EEG in diagnosing this condition. Movement disorders specialists should be aware of this condition and its physiology so as to limit unnecessary testing, prevent delay in diagnosis and unnecessary morbidity in these patients.

TABLE (175). *Results*

	Cleveland Clinic	Literature review
Number of patients	21	357
Males to females	18/3 (6:1)	210/97 (2.1:1)
Family history of PKD	8/20 (40%)	180/311 (57.87%)
Epilepsy seen in	5/21 (23.8%)	74/233 (31.7%)
Age of onset of movement disorder (Years)	2.5-16y Mean11.47y	1-39y Mean 11.08y
Age at onset of Epilepsy	6 mo-15y Mean 8.5y	8.1-15.1y Mean 11.6 y
Age at diagnosis	12.89y	15.88y
Positive Interictal EEG	2/14 (14.28%)	16/116 (13.79%)
VEEG positive	0/4 (0%)	2/39 (5.12%)
Nuclear scans positive(Interictal)	0/1(0%)	16/16 (100%)
MRI	Normal in 14/16 (87.5%)	-

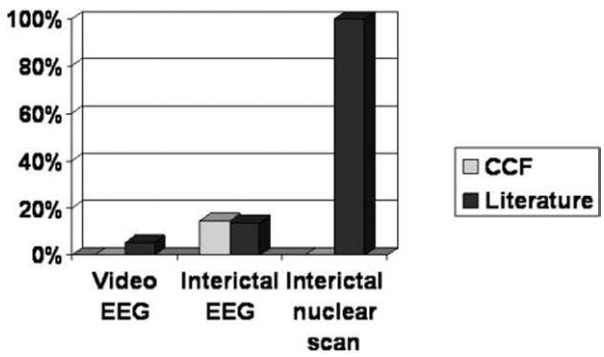

FIG. 1 (175).

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Cerebellar inhibition by transcranial magnetic stimulation in primary dystonia

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Objective: We used transcranial magnetic stimulation (TMS) to test the hypothesis that dystonic patients had an altered function of cerebello-cortical pathway.

Background: Recent evidences indicate a role of cerebellar structural and functional abnormalities in the pathophysiology of dystonia.

Methods: We enrolled 10 patients with primary dystonia and 15 controls with similar age and sex distribution. TMS was performed with two figure of eight flat coils. One coil was placed over primary motor cortex, a second one over contralateral cerebellum delivered a conditioning cerebellar stimulus (CCS). Two intensities were used for conditioning stimulus: 80% and 90% of resting motor threshold (RMT). Five different (3, 5, 7, 9, 15 ms) inter-stimulus intervals (ISIs), between cerebellar and cortical stimuli, were tested. Amplitudes of motor evoked potential (MEP) were analyzed.

Results: CCS at 80% of RMT did not statistically change MEP amplitudes. CCS at 90% of RMT significantly reduced MEP amplitude at 3, 5 and 7 ms ISIs in control subjects but not in dystonic patients. Analysis confirmed a difference between controls and patients at 3 and 5 ms. No difference was found when comparing the two hemispheres of the same patient and the different types of dystonia.

Conclusions: Our results suggest that an abnormal cerebello-cortical function is present in primary dystonic patients. Further studies are required to determine the exact site of dysfunction along the cerebello-cortical pathway and to confirm its presence in different phenotypes of primary dystonia.

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Zolpidem therapy in dystonia

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Objective: To invesitegate the effect of zolpidem for multi-type dystonia symptoms.

Background: Zolpidem is an imidazopyridine agonist that is selective for benzodiazepine type1 binding site on $GABA_A$ receptors that contain $\alpha 1$ subunits. It has been reported that this drug improves motor symptoms in Parkinson's disease and dystonia that is medically refractory. A few case reports were found that zolpidem therapy for dystonia, and detailed studies were not performed. The objective of this study was to invesitegate the effect of zolpidem for multi-type dystonia symptoms.

Methods: 29 patients with dystonia (4 generalized, 8 Meige syndorome, 5 cervical dystonia, 2 blepharospasm, 8 limbs dystonia, 1 spastic dysphonia, 1 tangue dystonia) were treated with zolpidem between 2007 and 2009. The dose of zolpidem was 11.2 ± 5.12mg (mean$\pm$SD). We evaluated their symptom using Burke-Fahn-Marsden dystonia rating scale (BFMDRS) before and after treatment. "Remarkable improvement" was defined as more than 40% improvement by BFMDRS, "Mild improvement" as a less than 40% improvement, but they showed subjective improvement, "No improvement" as a no objective and subjective improvement.

Results: "Remarkable improvement" were 2 patients, "Mild improvement" were 10 patients, and "No improvement" were 17 patients. 8 patients with limbs dystonia included 2"Remarkable Improvement" and 3 "Mild improvement". 5 patients with cervical dystonia showed no response.

Conclusions: Zolpidem may be more effective for limbs dystonia than cervical dystonia.

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A neurophysiological study of patients with complex regional pain syndrome type I and fixed posture of the hand

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Objective: To demonstrate that patients with Complex Regional Pain Syndrome (CRPS) type I, who have developed a fixed posture of the hand, do not show abnormalities of motor cortex plasticity, which is the neurophysiological hallmark of organic dystonia.

Background: CRPS type I is a painful disorder typically following minor injury which may be associated with development of movement disorders such as fixed dystonia. Controversy surround the issue whether movement disorders in CRPS I have a psychogenic origin.

Methods: Methods: Ten patients affected by CRPS type I (1 man, 9 women, age=55.5±9.3 years, disease's duration of 1.1±0.6 years) were enrolled for this study and matched with ten healthy subjects (1 man, 9 women, age=49.8±4.5 years). Patients satisfied the IASP criteria for CRPS I and were tested in both hands. We evaluated by transcranial magnetic stimulation (TMS): intracortical inhibition (ICI) and facilitation (ICF) and sensori-motor integration through short-latency (SAI) afferent inhibition. Synaptic plasticity through paired associative stimulation (PAS) with assessment of topographical specificity was tested by recording from abductor pollicis brevis (APB) and first dorsal interosseous (FDI) muscles.

Results: The study of synaptic plasticity of the motor cortex, did not disclose any difference between patients and controls. ICI and SAI were significantly reduced and ICF was increased in the affected arm of CRPS I patients compared to normal subjects.

Conclusions: Patients with CRPS I and a fixed posture of the hand show a normality of motor cortex plasticity, as we recently reported in psychogenic dystonia. Similarly to patients with psychogenic dystonia, the reduced inhibitory tone of the motor cortex controlateral to the limb affected by CRPS I is probably related to the maintenance of a fixed posture from the patients. On the other side, we found a altered sensory-motor integration possibly determined, at central level, from a continuous nociceptive input that modifies sensitive-motor inputs interactions.

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Jaw-opening oromandibular dystonia secondary to Wilson's disease. A preliminary report of 5 cases after use of botulinum toxin type A

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Objective: The aim of this study was to evaluate effects of botulinum toxin type a (BTX-A) injections in the treatment of jaw-opening oromandibular dystonia secondary to Wilson's disease (WD).

Background: WD is an autosomal recessive inherited disease of cupper metabolism, and it is presented with hepatic, psychiatric and neurological symptoms. In general, treatment improve most of neurological symptoms, however, dystonic forms, particularly, oromandibular dystonia, with jaw-opening, are more resistant to the treatment.

Methods: This study included 5 patients (four men and 1 women, with mean age of 27,2) with a previous confirmed diagnosis of WD with neurological involvement (with 8,6 years of follow-up) and associated with jaw-opening oromandibular dystonia. Botulinum toxin type A (Botox) was injected respecting the following protocol: 35 units for each lateral pterygoid muscle (intra-oral injection guided by electromyography); 30 units for the submentalis complex (total amount of BTX-A=100 Units). Following 3 weeks of the first application, patients were re-evaluated and after 3 months using the subitem Mouth of the Burke-Fahn-Marsden Scale (BFMS=0-8 points).

Results: Jaw-opening oromandibular dystonia was partially reduced after use o BTX-A. BFMS ranged from mean value of 5,6 points (pré-BTX-A) to 4,2 points (post-BTX-A). Most common side-effect was transient dysphagia (40% of cases).

Conclusions: There was a partially improvement of jaw-opening oromandibular dystonia, after use of BTX-A in this preliminary study with five patients with WD.

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Dystonia induced by peripheral trauma: Organic or psychogenic?

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Objective: Two illustrations of the challenges in deciding whether hand cramps secondary to peripheral trauma are organic or psychogenic.

Background: Dystonia is defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures. A cause-and-effect relationship between brain injury and subsequent movement disorder is well established, but a link with peripheral trauma remains more controversial.

Results: Patients: Case 1: a 16-year-old right-handed girl developed an abnormal posture of the right hand one week after a fall. The symptoms got steadily worse and a fixed posture (flexion and subluxation of the third and fourth right fingers, flexion and aduction of the right thumb and flexion of the right wrist) soon developed with complete loss of function of the hand. After four subsequent applications of botulinum toxin type A she was able to move her thumb and to a lesser degree her second and third fingers. She required a three-step surgical approach due to subluxations over 17 months. The patient achieved a stable moderate improvement following hand surgery (Video) Case 2: a 35 year old man with a history of affective disorder and work difficulties developed pain and clumsiness in the right hand. He underwent decompression surgery for an electrophysiologically confirmed carpal tunnel syndrome. Three months later he developed an intermittent contortion of the hand which waxed and waned in severity but gradually worsened The neurological examination was normal except for a fixed hyperextended right hand. (Video)

Conclusions: Our first patient fulfilled Jankovic's criteria for the diagnosis of organic dystonia induced by peripheral trauma, However recovery after local surgical intervention would be most unusual in organic dystonia. The other patient had features which would support a psychogenic origin according to Fahn's criteria. including a fluctuating course, incongruous fixed posture following carpal tunnel surgery and a background of severe psychological problems and the nonattendance to subsequent evaluations. Both cases presented diagnostic and management challenges with different opinions on causation expressed by many experts.

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Botulinotherapy of stomatological movement disorders

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Objective: To evaluate movement disorders of lower face in practice of stomatology and treat them with botulinum toxin.

Background: Failure of stomatological treatment (especially in orthodonty and orthopedy) may be due to insufficient diagnosis of cranial dystonia, bruxism and other chewing dyskinesias. Pretreatment with botulinum toxin may be effective for prevention of chewing muscles' hypertonus after stomatology.

Methods: 150 stomatological patients (m-50, f-100, mean age - 42 years) with various complaints (crash of ceramics, paradontitis, dental abrasion, tension in lower face, etc.) were examined by neurologist - specialist in movement disorders. Special stomatological EMG of chewing and occlusion was performed.

Results: High incidence (50%) of dystonia signs was find out (mild cranial dystonia, cranio-cervical, accompanied with writer's

cramp), 35 % of bruxism and 15 % - different chewing parafunctions. Palpation and EMG revealed muscles involved (temporalis, masseter, both pterygoideus). Botulinum toxin (Botox and Lantox, ratio 1:1) was injected in all involved muscles in different proportions according to the type of occlusion (orthognatic, frontal or distal), total dosage was 100 ME of both products. As the result stomatological treatment was succesfull.

Conclusions: Patients with stomatological failures have to be examined for dystonia and other dyskinesias. EMG and Botulinotherapy have to be widely introduced in everyday practice of stomatology. Multidisciplinary approach is necessary for modern stomatological practice.

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Linking DYT1 and DYT6 dystonia on the molecular level: Repression of *DYT1* gene expression by the transcription factor activity of THAP1 (DYT6)

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Objective: To gain insights into the molecular mechanisms explaining the phenotypic overlap of DYT1 and DYT6 dystonia, we characterized the role of THAP1 in transcriptional regulation of *DYT1*.

Background: The pathophysiology of dystonia is not well understood. Mutations in two genes have been associated with monogenic forms of primary (isolated) dystonia: i) mutations in TorsinA cause DYT1 dystonia; ii) mutations in the *THAP1* gene lead to DYT6 dystonia. The THAP1 protein may be involved in transcriptional regulation and belongs to a family of sequence-specific DNA-binding factors.

Methods: We performed chromatin immunoprecipitation (ChIP) to test for binding of THAP1 to the predicted *DYT1* promoter. Further, we used luciferase reporter gene assays to define the core promoter of *DYT1* and to test the effect of wild-type and several DYT6-causing mutations in *THAP1* on the expression of *DYT1*. Different missense mutations in *THAP1* expression constructs were generated by site-directed *in-vitro* mutagenesis. To verify the results *in vivo*, we measured expression of *DYT1* in fibroblast cell cultures from *THAP1* mutation carriers using quantitative PCR.

Results: ChIP analysis revealed that THAP1 specifically binds within the *DYT1* promoter region. The most critical region to regulate *DYT1* expression was narrowed down to a stretch of approximately 200 bps upstream of exon 1. Co-transfection with full-length wild-type THAP1 strongly repressed the *DYT1* promoter activity compared to cells transfected with empty vector. Furthermore, functional analysis of mutant THAP1 proteins revealed that substitutions of specific amino acids within the THAP domain significantly reduced THAP1 repression of *DYT1*. This was also confirmed in fibroblasts from *THAP1* mutation carriers who showed a robust, about two-fold increase in *DYT1* expression compared to controls.

Conclusions: Our data clearly demonstrate that THAP1 represses the activity of the *DYT1* promoter, linking the molecular pathways underlying DYT1 and DYT6 dystonia. The function of THAP1 in regulation of gene expression establishes transcriptional dysregulation as a cause of dystonia. Identification of additional target genes will further elucidate the pathophysiology of dystonia.

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Onset of dystonia and environmental factors in familial and sporadic primary late onset of dystonia

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Objective: To compare the distribution of relevant clinical features (age of dystonia onset, gender and tendency to spread) and of certain environmental risk/protective factors in familial and sporadic patients with primary late-onset dystonia.

Background: The etiology of primary late-onset dystonia is unknown. Genetic inheritance may explain the etiology of familial late-onset primary dystonia, the role of genes is less clear in sporadic cases for whom a genetic contribution has been suspected but never proved. A limited number of controlled studies suggested a contribution of environmental factors but it remains unclear whether environmental factors differently concur to familial and sporadic cases. If familial and sporadic cases have different etiology or a different burden of shared genetic/environmental factors, then different clinical features and differences in the distribution of certain environmental risk factors may be expected between the two groups.

Methods: First-degree relatives (n. 801) of 234 probands with primary late-onset dystonia were screened for familial aggregation of dystonia by a validated two-step procedure yielding 95% sensitivity and 100% specificity. Information on demographic/clinical features and environmental factors (eye disease and coffee drinking) was collected by a structured interview.

Results: Our procedure yielded a diagnosis of dystonia in 55 relatives from 50 families. The rate of family history of dystonia in our series was therefore 21% (50/234). Probands who had affected relatives and those who did not were comparable for gender distribution, age of dystonia onset, tendency to spread and frequency of eye disease and coffee drinking, even after stratifying for cranial and extracranial dystonia.

Conclusions: The lack of differences in age of dystonia onset and in the distribution of certain environmental risk factors suggests that familial and sporadic primary late-onset dystonia have similar etiology and probably the same burden of shared genetic/environmental factors. This piece of information has implication for designing the best strategy aiming at the identification of the etiologic basis of primary late-onset dystonia.

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The D216H (rs1801968) polymorphism in the DYT1 gene: A potential susceptibility factor for familial dystonia in Argentinean cases

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Objective: To evaluate the role of the D216H variant in the DYT1 gene as a susceptibility factor for dystonia in familial cases in an Argentine population.

Background: Generalized torsion dystonia is often associated with a deletion of three nucleotides c.904_906delGAG (GAGdel) in the DYT1 gene. Interestingly, in vitro studies have shown that the H216 variant of this gene induces the formation of cytoplasmic inclusion bodies, similar to those observed in cells expressing the GAGdel (Kock et al 2006). Moreover, a preliminary study in a German population conducted by Brüggemann et al. (2009), identified the H216 variant of this gene as a potential risk factor for developing familial dystonia in noncarriers of the GAGdel.

Methods: Subjects: we included 19 cases with primary focal, segmental or generalized dystonia, and 200 unrelated Argentinean subjects. Family history was regarded as positive when at least one first degree or a second degree relative have dystonia based on a family history interview and clinical examination. Genetic Analysis: genotyping of D216H and GAGdel was performed by a high resolution DNA melting curve analysis using SYTO 9 intercalation dye on the Corbett Research Rotor-Gene 6000 (QIAGEN Rotor-Gene Q).

Results: We detected a significantly higher frequency of the H216 variant in familial dystonia cases (42%) without the GAGdel, compared to controls (20%). The phenotypes included generalized, segmental and focal dystonia, and one case of Tourette syndrome.

Conclusions: Our findings are in concordance with those previously reported in a German population, who identified the H216 vari-

ant as a risk factor for the development of dystonia. Interestingly, in our population, this polymorphism was associated with a wide spectrum of dystonic phenotypes, including cervical dystonia and writer's cramp. Further epidemiologic and neuropathological studies are needed to confirm the role of H216 in the complex pathogenesis of primary dystonia.

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Prevalence of focal task-specific dystonia among professional musicians in a community-based study from Argentina

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Objective: To estimate the prevalence of focal task-specific dystonia (FTSD) among professional musicians in a community-based study from Argentina.

Background: FTSD is an unusual disorder characterized by muscular incoordination or loss of voluntary motor control restricted to specific motor acts. Performing music at a professional level requires extensive training and constitutes a risk factor for the development of FTSD. The estimated prevalence is 0.5-15 % of professional musicians. The diagnosis of dystonia in musicians constitutes a significant challenge, particularly concerning medical, professional and economic consequences.

Methods: Professional musicians from different orchestras of Buenos Aires were invited to complete a confidential an anonymous self-assessment questionnaire. We developed a questionnaire including demographic, epidemiological and clinical data and specific questions for dystonia in musicians. Individuals were assumed to have suggestive symptoms of FTSD if they responded affirmatively to part A and B of question 8 and negatively to question 9. Only those questionnaires that had no missing data were considered for analysis. Statistical analysis was performed using G-Stat software, version 2.0. $P<0.05$ was considered significant.

Results: 190 questionnaires were distributed, 65 individuals (44 men) composed the study sample, with a mean age of 44.01 years. $\pm$13,83. Suggestive symptoms of FTSD were detected in 11 (16.92%) individuals, with a higher prevalence in string players (7/11). European ancestries were identified in 72.23 %. One case reported a positive family history and 2 cases sensory tricks.A longer practice time and a longer period playing musical instruments were reported by musicians with probable FTSD but it failed to reach significance.

Conclusions: This study constitutes the first attempt to estimate the prevalence of FTSD among Argentinean musicians. Although the lack of clinical evaluation constituted a limitation of our study, the estimated prevalence in this population appears to be higher than other international series. Nevertheless, these results should be interpreted with caution, according to the different settings and the variations in case ascertainment and diagnostic criteria.

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The radiological signs of cervical dystonia

J.A. Porter, M.B. Kitts (Winston Salem, North Carolina, USA)

Objective: To define diagnostic features of Cervical Dystonia on X-Ray or Cross sectional imaging.

Background: The majority of patients with neck pain and dystonia are seen by primary care physicians, who have a poor understanding of the condition. Not uncommonly an X-Ray or scan is ordered.The standard Radiology and NeuroRadiology texts and Journals do not reference or describe cervical dystonia, and therefore there is no literature on possible findings in the condition. Therefore it is not listed as a differential diagnosis, in the report. As result an opportunity is lost for early identification of these patientsThe majority of patients with neck pain and dystonia are seen by primary care physicians, who have a poor understanding of the condition.

Methods: A series of 16 Cervical Dystonia patients, identified by a Movement Disorders Neurologist, were reviewed with reference to findings on Imaging. Except when formal interpretation had been dictated by a neurologist, no features were mentioned, and Cervical Dystonia was not present in the differential diagnosis. Informed Consent was obtained for image review.

Results: Findings included objective torsion on AP views, (50%), obliteration of the normal Cervical curve, (40%), and hypertrophy of the extra-axial muscles (86%) A group of patients without dystonia, having examinations for other reasons, had images studied in a similar fashion and incidence of peripheral muscle asymetry were low (under 10%) Representative multiple examples will be presented.

Conclusions: Cervical Dystonia is a disorder not only underdiagnosed by primary care physicians, Knowledge of its presentation and Clinical signs is rare amongst Orthopaedic surgeons and even Spine Specialists It appears there are in particular features on the extra axial component of a CT or MRI study, which are overlooked, as their significance has not been described, in the Radiological literature. An opportunity for early diagnosis, treatment and even avoidance of surgery is thus lost.

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Craniocervical dystonia as the presenting symptom in multiple sclerosis

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Objective: To report a patient with probable multiple sclerosis (MS) presenting with craniocervical dystonia.

Background: Dystonia is an uncommon feature of MS, and rare as the presentation of MS. Such an unusual presentation poses a diagnostic dilemma. However, we should consider MS in the differential diagnosis of secondary dystonia in the appropriate clinical setting.

Methods: We report a 43 year-old man with sudden onset of cervical dystonia, jaw opening dystonia and blepharospasm. Talking, chewing and stress exacerbated his symptoms, which abated during sleep. He had no exposure to dopamine receptor blocking agents or history of birth injury. He was otherwise healthy. A paternal aunt had MS.

Results: Work up for infectious, connective tissue, vasculitic, endocrine and metabolic causes (including copper studies) was negative or normal. Brain MRI (performed three months after onset) revealed multiple non enhancing periventricular and corpus callosum lesions suggestive of MS. Additional lesions were seen in the right thalamus, right internal capsule, right midbrain, left substantia nigra and cervical cord. There were CSF, but not serum, oligoclonal bands. He has not had a repeat MRI for financial reasons. His dystonia improved moderately from benztropine, diazepam and botulinum toxin injections.

Conclusions: There are a few reports in the literature of dystonia, typically hemidystonia, as the initial presentation of MS. To our knowledge, there is only one report of a patient with MS presenting with craniocervical dystonia. In this respect, our patient is exceptional. Both had unilateral lesions in the genu of the internal capsule. Various different topographies have been associated with dyskinesia in MS including internal capsule, thalamus and upper brainstem, as in our case. We believe that this is an extremely rare clinical isolated syndrome suggestive of MS.

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Cervical dystonia supported by imaging procedures – new method of examination for laterocollis – first results

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Objective: A frequent reason for insufficient effects of botulinum toxin on cervical dystonia is that injections are placed into the wrong muscles. In a large study (80 patients with cervical dystonia, and 50 patients without cervical dystonia) we proved the importance of

imaging procedures for the detection of dystonic muscles. Evaluating the muscles of both sides via computed tomography seems to be problematic for laterocollis, as muscle cross-sections can only be compared with images of the same level.

Methods: The cervical muscles of 40 patients with laterocollis were examined via computed tomography. Subsequently, we attempted a mathematical "straightening" of the cervical spine in the CT scanner. In 20 patients the scan was repeated after a period of 3 months.

Results: In none of the patients with laterocollis it was possible to compare both sides of the cervical muscles (figure 1). After the mathematical "straightening" of the neck, we were able to compare the muscle cross-sections of all our patients (figure 2). During this process we noticed that both muscle diameter and form of the muscle cross-section can be evaluated. In the controls we observed that botulinum toxin treatment will reduce the diameter of muscles, and return to their physiological form.

Conclusions: In case of insufficient effects of botulinum toxin, computed tomography can be recommended for the comparison of muscles of both sides. In patients with laterocollis it is impossible to compare both sides at the same level by CT. Additional mathematical "straightening" will be beneficial for the comparison of form and diameter of muscles in cross-sections of both sides.

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Spinocerebellar ataxia type 8 (SCA8) presenting as dystonia

D.E. Riley (Cleveland, Ohio, USA)

Objective: To report a case of SCA8 presenting as dystonia.

Background: SCA8 is an autosomal dominant disorder characterized by adult-onset slowly progressive ataxia, often in association with corticospinal tract signs. Dystonia is not a known manifestation of SCA8.

Methods: Case report with MRI findings and genetic sequencing.

Results: A 16-year-old right-handed girl developed "big and sloppy" handwriting, holding a pen at an "unusual" angle. Two years later, she had trouble using scissors with the right hand. At age 19 she developed head shaking, and later turning of her head toward the right with simultaneous tilt to the left. She also noted while carrying a beverage cup that her right wrist would involuntarily extend. She took to using her left hand to write or apply makeup. She had intermittent dysphonia, described as "hoarseness". She had had long-standing, though not lifelong, slow speech. Family history was negative. On exam at age 21, she had tonic rightward head rotation with left tilt. There was dystonic posturing of the right arm, mainly wrist and finger flexion. Other findings included slightly scanning slow speech, hypermetric saccades, lower limb hyperreflexia and a spastic catch at the knees. There was no limb ataxia, and she was able to walk in tandem fashion without difficulty. Plantar responses were flexor. MRI showed normal basal ganglia but severe cerebellar aplasia/atrophy. A spinocerebellar ataxia genetic profile detected a large CTA/CTG expansion in the ATXN8OS gene of 288 repeats (normal 15-50), consistent with spinocerebellar ataxia type 8.

Conclusions: SCA8 has not previously been associated with dystonia. Presented here is a young woman with a SCA8 expansion mutation who not only exhibited dystonia, but for whom dystonia was the dominant clinical feature. This was accompanied by only mild cerebellar dysfunction, despite radiologic evidence of severe cerebellar aplasia/atrophy. SCA8 has been associated with false positive genetic testing, especially in the setting of MSA. This poses difficulty in establishing a causal relationship with a previously unassociated clinical manifestation. In this case, however, the clinical cerebellar findings (albeit all mild), the severe cerebellar aplasia/atrophy and the massive gene expansion beyond the known asymptomatic range (maximum 250 repeats) all argue that the genetic defect was not an incidental finding.

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Dystonia secundary to Parry Romberg syndrome: Unresponsive to deep brain stimulation. Case report

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Objective: To present a case of Dystonia secundary to Parry Romberg Syndrome Unresponsive to Pallidal deep brain stimulation.

Background: We present a woman of 44 years old with Parry Romberg Syndrome that began at 9 years old in right side body. The patient was show in 2006 dystonia in left side body with more intensity at arm and coreic movement at this place. We utilized levodopa therapy in her tratment with response 30 per cent of symptoms. After 1 year of levodopa therapy we utilized pallidal deep brain stimulation.

Methods: We studied to patient with levodopa therapy and follow the symptoms during one year. The patient was not present secundary effects of treatment and ameliored her quality of life. After presentation at ethical comitte of our institution we decided to utilice right pallidal deep brains stimulation.

Results: The dystonic symptoms changed after surgery; the intensive coreo-dystonic symtoms of left arm to desapair but to began with torticolis to right and fixed dystonic symptoms of left leg.

Conclusions: The quality of life of our patient worse with right pallidal deep brain stimulation because she can not walk at any electrical possibilities of pallidal stimulation. We consider that this unresponsive case to DBS is secundary to atrophy and fibrosis in this kind of patients.

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Jaw clenching in anti-Ri-autoantibody-associated paraneoplastic syndrome

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Objective: To report a case with atypical dystonic phenotype caused by anti-Ri-autoantibody associated brainstem encephalitis.

Background: Brainstem is a major site of autoimmunity in anti-Ri antibody-associated paraneoplastic syndrome. Horizontal gaze palsy, opsoclonus-myoclonus and ataxia are known as typical clinical features. Although reported rarely, oromandibular dystonia may associate with this syndrome.

Methods: Case presentation.

Results: A 55 year-old woman has been complaining of weight loss, gait disturbance, diplopia and difficulty of jaw opening for two years. On neurological examination, she had bilateral complete horizontal gaze palsy and marked limitation of downward gaze without opsoclonus-myoclonus. She also had dysarthria, ataxia, bilateral dysmetria, hyperreflexia and extensor plantar reflex on the right side, reflex jaw clenching upon any attempt for either active or passive jaw opening. Electrophysiologic evaluation for jaw-clenching revealed simultaneous contraction of lateral pyterigoid, massetter and temporalis muscles of both sides on jaw-opening. Moreover, synchronized contraction of orbicularis oculi and frontalis muscles were also present during eye-opening. Magnetic resonance imaging of the brain demonstrated a hyperintense lesion in pontine tegmentum that was not enhanced with gadolinium. Serum and cerebrospinal fluid (CSF) studies showed a high titer of anti-Ri antibodies. Other paraneoplastic markers were negative and other CSF examination was unremarkable. Patient was evaluated primarily for breast and gynecological cancers. The mammography disclosed presence of a mass measuring 3.5X5.5 cm in the left breast. A modified radical mastectomy was done. The pathology was compatible with ductal carcinoma. Intravenous immunoglobulin treatment was administered. Adriamycin and cyclophosphamide chemotherapy regimen was started. She has been followed for 2 months. On follow-up, a mild clinical improvement was observed especially in jaw opening.

Conclusions: Neurological deficits and imaging findings of anti-Ri-antibody associated paraneoplastic syndrome are clearly related to brainstem involvement. Atypical motor phenotype caused by reflex dystonic contractions of antagonist muscles also suggest participation of segmental brainstem neuronal networks.

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Long-latency transcortical stretch reflexes in childhood hypertonic dystonia

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Objective: To evaluate the hypothesis that dystonic hypertonia in children is mediated by transcortical stretch reflexes.

Background: Hypertonia in dystonia has traditionally been attributed to the effect of co-contracting muscles generating strong opposing forces about a single joint. However, simulation of musculoskeletal biomechanics suggests that co-contraction is unable to produce hypertonia. Therefore we performed a series of pilot experiments to test whether elevated stretch reflexes could be responsible for childhood hypertonic dystonia.

Methods: 1. Angle, angular velocity, and EMG were measured in the biceps and triceps of 8 children with hypertonic dystonia during passive motion of the elbow. 2. Reflex onset latency was measured in 10 children with hypertonic dystonia. 3. Responses to perturbations during voluntary movement were measured in 10 children with hypertonic dystonia. 4. Single-pulse subthreshold TMS was applied over M1 at 12, 32, 42, or 52msec following rapid passive extension of the elbow in control subjects.

Results: 1. Position- or velocity-dependent EMG responses were found in the biceps and triceps of all children with hypertonic dystonia [van Doornik and Sanger, Movement Disorders 24(7):965, 2009]. 2. The onset of abnormal elevation in stretch reflexes in the biceps occurred most often during the long-latency reflex interval between 50 and 80msec following stretch. 3. Perturbations during active movement resulted in reflex increase in activity in the stretched muscle and decrease in activity in the shortened muscle at a latency of 50-80msec after stretch. 4. Transcranial magnetic stimulation produced a greater than 3-fold increase in the stretch reflex response in 10% of trials in healthy children.

Conclusions: Taken together, the first three results support the involvement of long-latency stretch reflexes in childhood hypertonic dystonia. The fourth result suggests that nonspecific activation of motor cortex can increase long-latency stretch responses. Therefore we conjecture that involuntary and nonspecific activation of motor cortex may be one mechanism for abnormal elevation of long-latency reflexes that could lead to hypertonic dystonia.

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Spatial discrimination threshold abnormalities are not seen in a pilot study of *DYT6* dystonia gene mutation carriers

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Objective: To determine whether sensory integration as measured by spatial discrimination thresholds (SDTs) is abnormal in *DYT6* dystonia (THAP1) gene mutation carriers.

Background: SDT abnormalities, consistent with altered sensory processing, have been identified in idiopathic brachial and cervical dystonia (CD) but not in *DYT1* dystonia. *DYT6* shares features with both *DYT1* and cervical dystonia and whether *DYT6* carriers would show abnormalities on SDT is unknown.

Methods: Subjects included 9 *DYT6* mutation carriers (mean age: 39.5 years), two of whom were manifesting carriers (MC), 15 *DYT1* mutation carriers (mean age: 43.8 years, including 7 MC), 7 with CD (mean age: 47.6 years) and 33 controls (mean age: 37.3 years). Subjects with neurologic abnormalities other than dystonia, palmar callouses, or extended use of vibrating tools were excluded. The SDT was tested using the standardized grating orientation task which uses plastic JVP (Johnson-van Boven-Philips) domes (Stoelting Co, IL) applied to the fingertips. Grating widths were 0.75 - 4.5 mm, and these where applied starting with the largest (either 4.5 mm for subjects age 45 or older or 2.5 mm for the rest), and then proceeding with narrower ones until 60% of the answers for a given grating width were correct. The SDT for each hand was calculated by linear interpolation of the 75% level of accuracy. The medians (the final SDTs) were compared to that of controls using Mann-Whitney tests.

Results: SDTs for CD (1.49), *DYT1* (1.49), and *DYT6* (1.38) did not significantly differ from controls (1.73).

Conclusions: Our data suggest that carrying the *DYT6* gene is not highly associated with spatial abnormalities as detected by SDT. However, our pilot study included a small number of affected *DYT6* carriers, and it is possible that SDT abnormalities are only present in those manifesting a phenotype of dystonia and are not a marker of genotype; we cannot exclude this possibility with our sample size. In contrast to other studies, we did not find that SDT was abnormal in CD subjects. This may also be a reflection of sample size, although it is supportive of the recent work demonstrating that temporal discrimination threshold testing may be superior to SDT in detecting higher sensory abnormalities in dystonia gene carriers.

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The syndrome of childhood-onset arm tremor followed by later development of cervical dystonia is a distinct dystonia subtype

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Objective: To delineate clinical characteristics of primary cervical dystonia (CD) patients with action tremor in the arms.

Background: Action tremor affecting the arms is common in adult CD patients. Its classification and nosologic categorisation has long been a matter of debate, in partic. whether it represents a subtype of essential tremor or a manifestation of dystonia. Some neurophysiological studies suggest that there are different subtypes of action tremor in CD patients but whether this holds true in a clinical setting is unclear.

Methods: We interviewed, clinically examined and videotaped 57 CD patients presenting to our botulinum toxin clinic using a standardized clinical questionnaire and a number of validated scales. Clinical diagnosis was made by consensus of the on site clinician (A.M.) and an independent reviewer of the video tapes (A.S.). Based on the ADL and the onset age of arm tremor, CD patients were divided into three subgroups. Group 1 (n=22, 39%) with CD without symptomatic arm tremor (ADL<25), gr. 2 (n=24, 42%) with CD and sympt. arm tremor (ADL>25) that had developed simultaneously with, later, or less than 5 yrs before onset of CD; gr. 3 (n=11, 19%) with CD and sympt. arm tremor (ADL>25) that had developed more than 5 yrs before CD onset. Testing for DYT 1 and DYT 6 mutations was performed in 35 patients.

Results: There was a preponderance of men in gr. 3 (male/female ratio 9:2), and of women in gr. 1 (7:15) and 2 (7:17). A positive family history was more common in gr. 3 (pos./neg./unkn.; 5:5:1) than in gr. 1 (3:19:0) or 2 (6:13:5). Median onset of arm tremor was much earlier (12 yrs; range 4-40) in gr. 3 than in gr. 2 (54 yrs; range 40-64). CD onset was also earlier in gr. 3 (40, range 7-60) than in gr. 1 (45, rage 26-76) and 2 (51, range 30-75) but overlap betw. groups was considerable. Facial dystonia or laryngeal dystonia was present in 9/22 patients in gr. 1, 10/24 patients in gr. 2 but in none of the patients in gr. 3. Dystonia severity and characteristics of arm tremor (e.g. position-dependence) did not differ betw. gr. 2 and 3. No mutations in DYT 1 or DYT 6 genes were found.

Conclusions: Childhood-onset arm tremor with later development of CD is a distinct dystonia subtype that can be distinguished by arm tremor onset age and spread of symptoms.

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Paroxysmal dystonia related to neuromyelitis optica

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Objective: To report the first patients with paroxysmal dystonia secondary to neuromyelitis optica (NMO).

Background: NMO is a severe autoimmune disease of the CNS which clinical spectrum ranges from unilateral isolated optic neuritis to extensive myelitis with bilateral optic neuritis. Dystonia is characterized by sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures. It can be continual or paroxysmal and focal, segmental, multifocal, generalized or hemidystonic according to the bodily distribution. Concerning its etiology, secondary dystonia can originate from lesions on the basal ganglia, upper cervical cord or peripheral nervous system.

Methods: Four non-consecutive in-patients were admitted in our Department to treat a relapse in their primary disease between 2008-2009. All patients fulfill the NMO diagnostic criteria according to Wingerchuk et al., 2006. The dystonia was characterized according to Ad Hoc Committee of the Scientific Advisory Board of the Dystonia Medical Research Foundation, 1984.

Results: Four female patients with NMO diagnosis were admitted in our Hospital with an acute attack of cervical or cervico-dorsal myelitis. The clinical details of each patient are seen in the Table.

TABLE (196). *Patients details*

Patient	Age (years)	Disease duration (years)	Neurological examination	Dystonia distribution	MRI (site of the acute lesions)
1	65	37	tetraparesis, bilateral amaurosis	Four limbs	Cervical
2	35	8	paraparesis, bilateral amaurosis	Left upper limb, lower limbs	Cervical
3	51	1	paraplegia, left optic neuritis	Lower limbs	Thoracic
4	34	2	paraparesis	Four limbs	Cervical and thoracic

During treatment either with IV methyl-prednisolone or immunoglobulin, all of them presented with generalized paroxysmal kinesio or non-kinesiogenic dystonia. Carbamazepine 300–900 mg/day (mean dose 600 mg/day) was then introduced with marked improvement of the abnormal movement in all four patients.

Conclusions: To our knowledge this is the first description in the literature of paroxysmal dystonia in the course of NMO. It should be emphasized that the abnormal movements in all four patients appeared during treatment of the bout and while the NMO symptoms were waning.

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Identifying genetic risk factors of musician's dystonia

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Objective: To perform a genome-wide association study (GWAS) in musician's dystonia (MD).

Background: MD, a type of focal task-specific dystonia (FTSD), presents with painless muscular incoordination of extensively trained movements when a musician is playing his instrument. The frequency of MD is estimated at about 1-2% among professional musicians; it is highly disabling and in many cases terminates performance careers. While the pathophysiology remains largely elusive, clinical genetic studies of MD with a positive family history of dystonia in up to 25% of patients suggest a hereditary component. However, no genetic cause of MD has been identified yet.

Methods: We collected and clinically characterized 350 patients with MD at the Hanover Institute of Music Physiology and Musicians' Medicine, Hanover, Germany. Based on history and a detailed neurological examination, all were classified as having primary dystonia. Of these, 193 patients were included in a genome-wide association study (GWAS) using the Affymetrix 6.0 SNP gene chip. As controls, we used a population-based cohort of 984 healthy individuals from Northern Germany (Popgen) previously genotyped on the same platform. Statistical analysis was performed after detailed quality control using the Cochran Armitage Trend Test.

Results: Genotype frequencies of 177 MD patients passed the quality control and were compared to those of the controls. Genotypes were analyzed at 558,280 *single nucleotide polymorphisms* (SNPs). Inspection of all signal intensity plots for markers with $p<10^{-5}$ revealed 30 associated SNPs. Several of these SNPs clustered in the same chromosomal region suggesting biological relevance. Among the 30 SNPs of interest, nine showed evidence for a genome-wide association with p-values between $9x10^{-9}$ and $2x10^{-15}$.

Conclusions: We identified several SNPs/chromosomal regions that show a significant association with MD in a GWAS with a relatively small patient cohort. This may be explained by clinical and ethnic homogeneity within this group of patients and by the lack of negative selection for genes predisposing to this disorder. A replication study in additional MD patients and patients with other types of FTSD is currently underway.

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Modulatory effects of 5Hz rTMS over the primary somatosensory cortex in focal dystonia – an fMRI-TMS study

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Objective: To assess modulatory effects of 5Hz rTMS when applied over the primary somatosensory cortex in patients with focal dystonia.

Background: Dystonia is associated with impaired somatosensory ability. The electrophysiological method of repetitive transcranial magnetic stimulation (rTMS) can be used for non-invasive stimulation of the human cortex and can alter cortical excitability and associated behaviour. Among others, rTMS can alter/improve somatosensory discrimation abilities, as shown in healthy controls.

Methods: We applied 5Hz-rTMS over the left primary somatosensory cortex (S1) in 5 patients with right-sided writer's dystonia and 5 controls. We studied rTMS effects on tactile discrimination accuracy and concomitant rTMS-induced changes in hemodynamic activity measured by functional magnetic resonance imaging (fMRI).

Results: Prior to rTMS, patients performed worse on the discrimination task than controls even though fMRI showed greater task-related activation bilaterally in the basal ganglia (BG). In controls, rTMS led to improved discrimination; fMRI revealed this was associated with increased activity of the stimulated S1, bilateral premotor cortex and BG. In dystonia patients, rTMS had no effect on discrimination; fMRI showed similar cortical effects to controls except for no effects in BG.

Conclusions: Improved discrimination after rTMS in controls is linked to enhanced activation of S1 and BG. Failure of rTMS to increase BG activation in dystonia may be associated with the lack of effect on sensory discrimination in this group and may reflect impaired processing in BG-S1 connections. Alternatively, the increased BG activation seen in the baseline state without rTMS may reflect a compensatory strategy that saturates a BG contribution to this task.

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The blink reflex recovery cycle distinguishes patients with benign essential blepharospasm from patients with presumed psychogenic blepharospasm

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Objective: To test if the blink reflex recovery cycle differs between patients with presumed psychogenic blepharospasm (PB) and patients with benign essential blepharospasm (BEB).

Background: PB is often difficult to distinguish clinically from BEB. The blink reflex recovery cycle measures the excitability of human brainstem interneurons and is abnormal in BEB. We hypothesize that patients with presumed PB would have a normal blink reflex recovery cycle.

Methods: We investigated the R2 blink reflex recovery cycle at interstimulus intervals (ISI) of 0.2, 0.3, 0.5, 1, and 3 seconds in 10 patients with BEB (9 females, 1 male; mean age 67 (±6) years), 9 patients with presumed PB (6 females, 3 males; mean age 55 (±6) years), and 9 healthy controls (6 females, 3 males; mean age 60 (±8) years). To test individual patients, the R2 indices were calculated as average of the recovery values at ISIs of 0.2, 0.3 and 0.5 second (the upper limit of normal was defined as mean (control group) + 2SD). All patients had spasm of the orbicularis oculi (OO) muscles.

Results: The R2 recovery cycle was significantly disinhibited in patients with BEB, whereas patients with presumed PB did not differ from controls on a group level. The R2 index was abnormal in 9/10 patients with BEB, and in none of the PB patients. Age at onset was earlier in PB (mean 47.3years) compared to the BEB group (mean 55.2years), without reaching statistical significance. Atypical features in the PB group were sudden onset, precipitating events, immediate (seconds to minutes) or lacking response to botulinum toxin injections, remissions, continuing asymmetry of symptoms, paroxysmal attacks, unusual sensory tricks, distractibility and psychiatric co-morbidity.

Conclusions: A normal blink reflex recovery cycle indicates normal brainstem interneuron excitability and may thus provide a useful objective tool in differentiating true BEB from atypical (presumed psychogenic) cases.

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Comparative study of the variability of Tsui scale in patients with cervical dystonia in the resting position and on action

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Objective: Evaluate the clinical characteristics of involuntary cervical movements in cervical dystonia patients during rest and action (walking) using the Tsui scale.

Background: It is well known that some actions and postures may elicit or exacerbate involuntary movements in cervical dystonia. Besides, when walking, patients may present a change in the pattern of muscle activation or amplitude/duration of involuntary movements. We aimed at evaluating a set of patients before treatment with BnT in the resting position and walking to verify whether there were differences in amplitude and duration of involuntary movements according to a time-honored clinical scale, so to demonstrate that a complete evaluation of cervical dystonia patients must include examination of the patient while performing some action, such as walking.

Methods: We prospectively evaluated 20 patients with cervical dystonia seen at the Neurology Clinic of the Hospital of Clinics of Sao Paulo from november 2009 to december 2009 for treatment with botulinum toxin (BnT). The patients were examined before BnT shooting, after at least three months of the lastest toxin treatment. We performed the Tsui scale on each patient in the resting position while seated and walking in a room. Each patient was evaluated by one of the examiners.

TABLE (199). *Variability of Tsui values between examination in the resting position and action*

Patient number	Resting Tsui	Action Tsui
1	10	12
2	2	2
3	10	10
4	10	10
5	23	25
6	1	4
7	14	18
8	4	10
9	6	8
10	8	8
11	12	12
12	19	23
13	14	20
14	6	8
15	2	4
16	6	2
17	7	7
18	7	4
19	14	18
20	6	8

Results: Twelve patients (60%) were female. Ages varied from 34 to 80 years (57,5 ±14,88). The duration of dystonia varied from 1 to 39 years (11,68±10,45). The time of treatment varied from 5 to 202 months (84,6±70,81). Eleven patients presented torticollis either isolated or combined with other movements. The remaning patients presented other types of movements. The resting Tsui scale varied from 1 to 23 (9,05±5,68). The action Tsui varied from 2 to 25 (10,65±6,81). The difference between action and resting Tsui in a same patient varied from - 4 to 6 (1,6±2,58) (Table). Six patients presented no change in Tsui figures. Two patients presented improvement of their movements when walking.

Conclusions: Patients with cervical dystonia presented worsening of their clinical picture when walking. Walking must be included in the clinical examination of cervical dystonia patients.

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A novel exon deletion mutation of the epsilon-sarcoglycan gene in a Chinese family with myoclonus-dystonia syndrome associated with epilepsy

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Objective: To identify the genetic feature in a Chinese family with Myoclonus dystonia syndrome (MDS).

Background: MDS is an autosomal-dominant movement disorder characterized by involuntary jerks with dystonic movements and postures. Epilepsy rarely occurs in MDS. Mutations in the epsilon-sarcoglycan (*SGCE)* gene have been found to be a major causative gene of MDS.

Methods: We have screened for *SGCE* and *DYT1* mutations in a Chinese family with MDS associated with epilepsy. DNA from peripheral blood cells and amplified all exons and exon-intron junctions of the *DYT1* and *SGCE* genes by PCR. Mutations of the *DYT1* and *SGCE* gene were analyzed by direct sequencing. Additionally, multiplex ligation-dependent probe amplification (MLPA) assay targeting the *SGCE* gene to evaluate large exon deletion or duplicate mutation were performed if patients with negative point mutation.

Results: Five members over three generations were affected. The index case and his older sister presented with a typical MDS phenotype. The father of the index presented with generalized tonic clonic seizure and was controlled by anti-epileptic medicine. The grandfather (dead) was reported to have oromandibular involuntary movement after 40 years old. The niece of the index had mild myoclonus at the age of 20. No point mutation was detected in *DYT1* and *SGCE*

gene by direct sequencing. However, a novel exons deletion (6-8) mutation was found in the index and the niece of the index.

Conclusions: Our result supports the fact that myoclonus dystonia is a clinical and genetic heterogeneous disease. MPLA should be performed in routine deletion analysis of *SGCE* in point mutation-negative MDS patients.

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The results of botulinum toxin treatment for cervical dystonia

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Objective: to study efficacy of Botulinum toxin type A for patients with cervical dystonia.

Background: Cervical dystonia is a priority movement syndrome. It is characterized by a forced head position, a permanent pathological posture, spasm, a clonic component or tremor or a combination of these symptoms with pain. Botulinum toxin injections into tense muscles are the option for cervical dystonia treatment during more than 15 years in Russia. This method gives a considerable improvement for most patients.

Methods: 39 patients with cervical dystonia were treated with Botulinum toxin type A (500 Units Dysport®) at the state regional clinical diagnostic center. There were 15 (38,5%) men, 24 (61,5%) women. The average age was 38,8 years (from 22 to 74). The average disease duration was 8,2 years. There is predominance of rotatory torticollis - 22 (56,4%). We also have registered laterocollis in 8 (20,5%) patients, retrocollis- 2 (5,1%) and anterocollis -3 (7,7%). 4 (10,3%) patients have complex forms of cervical dystonia. Severity, disability and pain in these patients were assessed with Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) before and after the treatment.

Results: We have chosen the muscles which were responsible for forming cervical dystonia and pain: torticollis- m. Splenius capitis, m. Semispinalis capitis, m. Trapezius on the ipsilateral side and contralateral m. Sternocleidomastoideus; laterocollis - m. Sternocleidomastoideus, m. Trapezius and m. Splenius capitis on the ipsilateral side; retrocollis - m. Splenius capitis, m. Semispinalis capitis, m. Trapezius–on both sides, anterocollis- m. Sternocleidomastoideus on both sides. The period between repeat injections varied from 3,5 to 8 months. The patients got these injections from 1 to 3 times for a year in average. The total ball (TWSTRS) was 35,2±1,59 before the treatment and 18,2±0,89 ($p<0,05$) over 1 month after the treatment.

Conclusions: The analysis of the results of the treatment let us make a conclusion about the efficacy of the Botulinum toxin therapy and consider it as the first choice for cervical dystonia.

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Hemidystonia and contralateral hemiballism following acute encephalitis by influenza a H1N1 virus and Mycoplasma pneumoniae: A case report

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Objective: To report a case of a patient with an unusual movement disorder following acute encephalitis by Influenza A H1N1 virus and Mycoplasma.

Background: Encephalitis can represent a complication of both Influenza virus and Mycoplasma infections especially on the pediatric population. Although uncommon, these encephalitides are associated with significant morbidity and mortality. There are few reports of influenza A H1N1 viral encephalitis associated with seizures and altered mental status, but with complete recovery after appropriate antiviral therapy. The presence of abnormal involuntary movements as manifestation of these infections is rare with Mycoplasma and has been never described with Influenza A H1N1 virus. We will present a pediatric patient with encephalitis followed by an unusual movement disorder, who was found to be infected with both Influenza H1N1 virus and Mycoplasma.

Methods: Single case report.

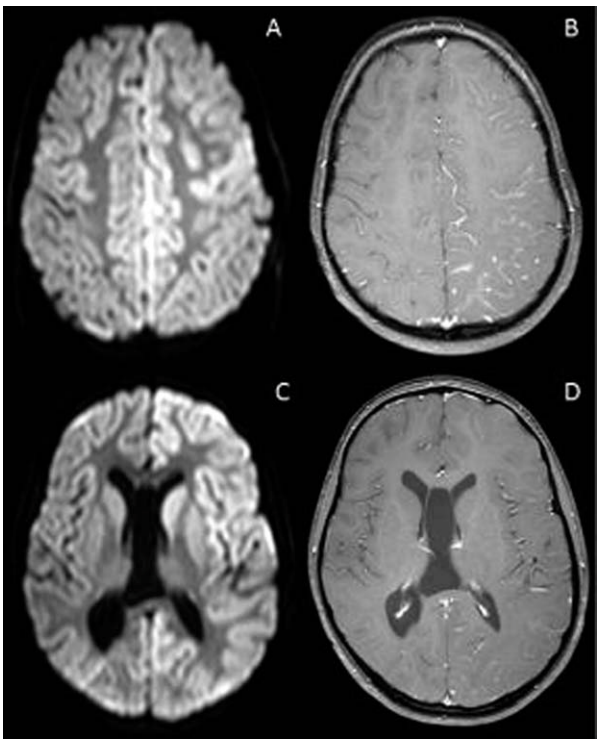

FIG. 1 (202). MRI brain from Oct 2009: Pannels A and C show T2W FLAIR sequence. Pannels B and D show T1W post gadolinium sequence. The images show diffuse high T2W-FLAIR signal on the gray-white matter junction of the left fronto-parieto-occipital lobe and both striatums (left more than right) consisting with edema. In addition, there is gyral enhancing on the left fronto-parieto-occipital cortical region.

Results: A 7 years old girl with history of seizure disorder secondary to perinatal hypoglycemia, was admitted to a local hospital with high fever and status epilepticus. After being comatose for few days the patient woke up with severe altered mental status and a combination of right hemydystonia and left hemiballismus. Extensive work up showed a normal CSF, an abnormal MRI of the brain, the presence of Influenza A H1N1 virus detected by nasopharyngeal PCR, and elevated IgM titers for Mycoplasma pneumoniae. The patient was diagnosed with encephalitis secondary to both Influenza A H1N1 virus and Mycoplasma. She was treated with broad spectrum antibiotics, high dose steroids, IVIg, antivirals (oseltamivir phosphate) and plasmapheresis with a modest improvement on the symptoms. Tetrabenezine was used obtaining some decrease in the dystonia and hemiballismus.

Conclusions: To our knowledge, this is the first report of severe encephalitis secondary to Influenza A H1N1 virus. In addition, this is the first report of a patient with encephalitis presenting with this unusual combination of hemydystonia and contralateral hemiballismus. Influenza A H1N1 virus has to be recognized as a agent capable of producing severe encephalitis specially when associated with other pathogens. Abnormal involuntary movements must be kept in mind as possible presentation of encephalitis associated with Influenza H1N1 virus or Mycoplasma.

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Evaluation of the dose conversion ratio between Dysport® and Botox® in clinical practice

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Objective: To evaluate the conversion ratio between Dysport and Botox.

Background: The potency of botulinum toxin type A (BoNT-A) preparations is expressed in mouse units (MU), but due to differences in the assays used these units are not equivalent. The equivalence ratio between the two BoNT-A preparations Dysport and Botox is a matter of ongoing debate. Ratios ranging from 11:1 to 2:1 can be found in the literature.

Methods: In our movement disorder clinic, after switching from Dysport to Botox for economic reasons, we retrospectively evaluated the conversion factor. Based on values published in the literature patients were switched from Dysport to Botox using a ratio of 4:1. The individual dose was then adjusted according to efficacy and side effects. One year after switching we evaluated for each patient the mean dose of Dysport prior to switching and the mean dose of Botox after the switch and calculated the ratio.We included patients with cervical dystonia (CD), hemifacial spasm (HSP) and blepharospasm (BSP) who had received treatment with Dysport for at least one year prior to switching and were treated at least another year with Botox after switch in a comparable manner.

Results: A total of 120 patients with a mean age of 61 years were included. There were 55 men and 65 women. 56 patients (46.6%) suffered from CD, 38 patients (31.7%) from BSP and 26 patients (21.7%) from HSP. The conversion ratios (n=120) ranged from 1.84 : 1 to 6.61 : 1 (Dysport to Botox). 48.3% of patients fell into the Dysport-to-Botox ratio group of 4 to 5; 26.6% of patients lay between 3 and 4; 17.5% fell into the group between 2 and 3, and 5.8% lay between 5 and 6. Only 1 patient (0.8%) each had a ratio lower than 2 : 1 and higher than 6 : 1.The overall median ratio for the whole group was 4 : 1.

Conclusions: The wide range of conversion ratios in our retrospective study indicates that a universally applicable dose-conversion factor between Dysport and Botox does not exist. Rather, it has to be established for each individual patient. Our results suggest that, when switching between Dysport and Botox, a ratio of 4:1 (Dysport to Botox) might initially be employed. When using a dilution of Dysport in 2.5 ml saline and Botox in 2 ml saline, one can adopt the amount in ml 1 : 1. This minimizes the risk of confusion or miscalculation, and thereby contributes to patient safety.

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Rapid-onset dystonia-parkinsonism: Case report

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Objective: We report the case of an apparently sporadic RDP with a novel mutation in ATP1A3.

Background: Rapid-onset dystonia-parkinsonism (RDP) is a rare autosomal dominant movement disorder with variable penetrance associated with different mutations in the Na/K-ATPase alpha 3 subunit gene (ATP1A3). RDP is characterized by the abrupt onset (hours–weeks) of dystonia and parkinsonism, followed by moderate or no progression over weeks and little or no improvement thereafter, despite treatment with levodopa. RDP has been described in a small number of families.

Methods: A 32-year old woman was referred to us 2 years ago with abrupt onset of severe speech and swallowing difficulties, global motor slowness, and gait disturbances due to right foot dystonic movements. These signs had developed over several hours with minimal progression in the following week, when she reached a plateau and remained stable ever since. The symptoms occurred 3 days after her second childbirth (first childbirth passed regularly). Twenty-four hours before the onset of the disease, an episode of mild, athetoid right hand movements occurred.

Results: The neurological examination revealed a moderately expressionless face, severe dysarthria, dysphagia, drooling, and orolingual dystonia with sardonic grin. She was also bradykinetic (arms/legs) with right foot dystonia, primarily present during walking. The MMSE score was 30/30. Treatment trials with levodopa/benserazide, amantadine and baclofen were unsuccessful. Laboratory (including cerebrospinal fluid examination and work-up for Wilson's disease), neurophysiological, and MRI examinations were normal. Molecular analysis was done as previously described and a heterozygous missense mutation in exon 15 of ATP1A3 was found. Her parents (mother aged 54; father aged 57) were found clinically unaffected, but refused to participate in genetic testing.

Conclusions: Therefore, we could not determine if the mutation was de novo; instead we tested 95 Serbian controls and this mutation was not found in any of these. Transcranial brain parenchymal sonography was conducted as previously described and revealed bilateral hyperechogenicity of the substantia nigra. This finding was unchanged after 12 months. Visual inspection and semiquantitative analysis of SPECT showed normal and symmetric uptake in both striata.

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Case report: Focal dystonia associated with cerebellar stroke

J. Tapia-Nunez, Z. Peng-Chen, P. Sotomayor-Duran, P. Chana-Cuevas (Santiago, RM, Chile)

Objective: Isolated lesions of the cerebellum and its pathways have been associated with focal dystonia. We present a case of focal dystonia secondary to ipsilateral cerebellar stroke.

Background: Case description: An hypertensive woman of 70 years old, was hospitalized on December 2005 because of headache, dizziness and ataxia of left arm. Brain CT scan without contrast showed left ischemic cerebellar infarction. Laboratory and neurovascular study were normal. The patient was discharged with mild residual ataxia and left hemibody dysmetria. One month after, she started to develop athetotic movements of left hand with dystonic component of phalanges, involving mainly pinky and thumb. She was treated with Risperidone, Clonazepam Trihexyphenidyl with no significant response. Brain MRI 2007: Showed previous left cerebellar infarction and vascular microangiopathy.

Conclusions: Comment: The clinical case described the presence of focal dystonia associated with ipsilateral cerebellar infarction, supporting recents reported cases of focal dystonia associated with cerebellar injury. The pathophysiological cause could be the interruption of the complex system of pathways connecting the cerebellum with the thalamus and basal ganglia, with possible participation of olivo-pontine fibers.

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A 17-year experience of botulinum toxin A in cervical dystonia

F. Vivancos, I. Ybot, E. D-Tejedor (Madrid, Spain)

Objective: To expose our experience data with botulinum toxin type A (BTA) for treatment of cervical dystonia (CD) at a specialized office out-patient population in LPUH.

Background: CD is the most common form of adult-onset focal dystonia, and BTA has become the first-line treatment for this condition.

Methods: We conducted a retrospective review of CD patients medical histories, all treated with Dysport®, from 1992 to 2009 in the Neurology department (Movement Disorders Unit) of the LPUH. We finally obtained a full data sample of 37 patients.

Results: Sex ratio: F 62%/M 38%. 60% of cases were idiopathic, 46% of all of them with more than 10y duration of CD. The main component for head deviation was rotational (46%) and laterocollis (43%). On average, patients were treated for 7y (r,range 1 to 17y) and received 15,9 injection cycles (median=14,5; r 1 to 40); the mean(m) dose was 487 units, r[320-650]. The most frequently injected muscles were trapezius, sternocleidomastoideus and splenius capitis, always under EMG guide to verify muscle hyperactivity. 97% patients are still responders (clinical examination);70,2% of them are also taking oral medication, to prevent immunological arrest of efficacy using higher doses. 7 patients experienced dysphagia during Dysport® treatment (r from 2 to 12 years). None led to stop the therapy.

Conclusions: These data confirm the efficacy and safety of Dysport® in CD over an extended period of up to 17y in CD. The EMG guide let us select and act on the specific affected muscles, ensuring a good and prolonged response with low doses of BTA.

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Efficacy and safety of iron chelating agent deferiprone in patients with pantothenate kinase-associated neurodegeneration (PKAN)

G. Zorzi, L. Chiapparini, A. Solari, A. Piga, F. Longo, E. Bertini, B. Garavaglia, F. Zibordi, D. Aquino, N. Nardocci (Milano, Italy)

Objective: To assess the efficacy of iron chelating agent Deferiprone in PKAN patients i) by measuring iron concentration in the globus pallidus on MRI ii) by clinical assessment using the Burke-Fahn and Marsden Dystonia Rating Scales (BFMDRS) and health-related quality of life scales (SF-36 and CHQ-PF50) after six months therapy.

Background: PKAN is an autosomal recessive disorder due to defect in pantothenate kinase 2 gene (PANK2) and is associated with brain iron accumulation which is neurotoxic. Currently no cure is available. Deferiprone is an iron chelating agent effective in promoting iron excretion and preventing the progression of iron accumulation. It has been shown to improve clinical symptoms in patients with Friedereich ataxia and other neurological disorders.

Methods: Deferiprone was orally administered (25 mg/kg/day) to 9 PKAN patients (3M/6F, age range:10-38) for six months. To detect iron deposition in both globus pallidus, T2* relaxometry (and calculated R2* maps) was performed with a 1.5T MR before and after treatment. R2* values were compared using a paired two-tailed t-test. Clinical assessment and evaluation of dystonia was scheduled every two months; evaluation of health-related quality of life before and after treatment. Blood cell count was performed weekly, complete haematological assessment was performed every two months.

Results: Deferiprone was overall well tolerated. One patient dropped out for neurotropenia There was a significative reduction of iron content in globus pallidus after treatment ($p=0.046$). There was no change in the scores obtained at the BFMDRS and SF-36 and CHQ-PF50 scales.

Conclusions: Our data demonstrate the effect of Deferiprone in reducing brain iron accumulation without concomitant clinical amelioration. Future trials in PKAN are warranted to clarify the rationale of using chelating agents in this and similar disorders.

POSTER SESSION 1
MONDAY, JUNE 14, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 14:00-15:30

EDUCATION IN MOVEMENT DISORDERS

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Hypersecretory effect (transient autonomic dysfunction) during DBS programming

M.V. Alvarez, P.M. Grogan, M. Rodriguez (Lackland AFB, San Antonio, Texas, USA)

Objective: To report two patients with transient autonomic dysfunction while undergoing deep brain stimulator (DBS) programming.

Background: Remarkable clinical improvement in a variety of movement disorders has been achieved with DBS implantation since the mid-1980's. An additional benefit to this therapy is the low incidence of side effects. When experienced, typical side effects include diplopia, paresthesias in the contralateral body, dystonic muscle contractions, vertigo, nausea, dysarthria, and mood alterations. Transient autonomic dysfunction, including hyperhydrosis and sialorhea, occurring during DBS adjustment programming has been rarely reported. We present two patients with hypersecretory effect during STB-DBS programming.

Methods: Report of two cases.

Results: Case 1 – a 45 year old man with a history of Parkinson's disease (PD) for 5 years underwent bilateral subthalamic nucleus-DBS (STN-DBS) implantation for his symptoms. He experienced no significant side effects following implantation. During subsequent STN-DBS programming, however, he noted profuse sweating about his head and neck without change in vital statistics. He denied any discomfort or pain. Case 2 - a 48 year old man with an essential tremor (ET) for 20 years underwent bilateral STN-DBS implantation. He experienced no side effects following implantation. While undergoing STN-DBS programming, however, he noted profuse salivation without change in vital statistics. He denied any discomfort or pain. In both patients, STN-DBS adjustments were immediately halted once symptoms developed. After changing stimulation parameters (i.e. voltage, frequency, pulse width, electrode polarity, and electrode combination), their symptoms resolved completely and did not recur.

Conclusions: Although rare, transient autonomic dysfunction can occur in patients during DBS adjustments. The most likely explanation for its development is activation of efferent sympathetic pathways to the brainstem. Fortunately, these side effects are temporary and easily corrected by adjusting stimulation parameters.

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Large amplitude exercise ('ThinkBIG') improves motor dysfunction in Parkinson's disease patients

M.V. Alvarez, P.M. Grogan, M. Rodriguez (Lackland AFB, San Antonio, Texas, USA)

Objective: To report the beneficial effects of a large amplitude exercise program in improving motor function in patients with Parkinson's disease (PD).

Background: The motor dysfunction associated with PD, specifically tremor, rigidity, bradykinesia, and gait instability, creates substantial disability in afflicted patients. Exercise has been shown to improve motor dysfunction in PD, and may even confer disease-modifying, or "neuroprotective", benefits. While various forms of exercise have been evaluated in PD, no particular form has demonstrated clear superiority compared to others.

Methods: Case series: 20 pts, age 55-85 (mean 71), 1F:19M participated in our ThinkBIG program. Patients were objectively assessed utilizing UPDRS (global quantitative measure of PD symptoms; higher score α higher disability) and Tinetti (standardized evaluation of mobility & stability; lower score α higher disability, 0-28) scales at baseline, and follow up at 4 and 8 weeks after. All patients remained on their baseline PD medications.

Results: All patients completed the study. Baseline scores: UPDRS III ranged from 12-64 (mean 30.3), Tinetti ranged from 10-26 (mean 20.3). 4-week follow up scores: UPDRS 3-53 (mean 20.4; 33% improvement), Tinetti 14-28 (mean 24.2; 19% improvement). 8-week follow up scores: UPDRS 2-45 (mean 15.1; 50% improvement), Tinetti 16-28 (mean 25.6; 26% improvement).

Conclusions: Large amplitude movement exercise results in substantial improvements in motor function of PD patients. Although longer follow will be required, given the sustained benefits over an 8-week period, large amplitude exercise may confer disease-modifying benefits in patients with PD and not just symptomatic benefit.

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Nintendo Wii[r]: The role of a youthful game for an aging disease

M.V. Alvarez, P.M. Grogan, M. Rodriguez (Lackland AFB, San Antonio, Texas, USA)

Objective: To report the beneficial effects of incorporating Nintendo Wii® game activity into an exercise program for improving motor function in patients with Parkinson's disease (PD).

Background: The motor dysfunction associated with PD, specifically tremor, rigidity, bradykinesia, and gait instability, creates substantial disability in afflicted patients. Exercise has been shown to improve motor dysfunction in PD, and may even confer disease-modifying, or "neuroprotective", benefits. While various forms of exercise activities have been evaluated in PD, no particular form has demonstrated clear superiority compared to others.

Methods: Case series: 20 pts, age 55-85 (mean 71), 1F:19M participated in the program. All had successfully completed an 8-week program employing large-amplitude exercise (ThinkBIG). Patients were objectively assessed utilizing UPDRS (global quantitative measure of PD symptoms; higher score α higher disability) and Tinetti (standardized evaluation of mobility & stability; lower score α higher disability, 0-28) scales at baseline, and follow up 4 weeks after Nintendo Wii® activities began. All patients remained on their baseline PD medications.

Results: All patients completed the study. Baseline scores: UPDRS III ranged from 2-45 (mean 15.1), Tinetti ranged from 16-28 (mean 25.6). 4-week follow-up scores: UPDRS 2-40 (mean 12.6; 17% improvement), Tinetti 20-28 (mean 26.8; 5% improvement). All patients reported Wii® exercise as fun-filled and rewarding, and subjectively noted improved energy levels, improved parkinsonian symptoms, and reduced depressive symptoms. No adverse event was reported. The combined benefits of both ThinkBIG and Nintendo Wii® 12-week exercise program resulted in a 58% improvement in mean UPDRS III scores and a 32% improvement in mean Tinetti scores.

Conclusions: Incorporating Nintendo Wii® game system activities into exercise programs for PD patients results in further improvement in motor function.

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Can hyposmia recover with treatment of Parkinson's disease?

M.V. Alvarez, P.M. Grogan (Lackland AFB, San Antonio, Texas, USA)

Objective: To report a patient with Parksinon's disease (PD) who noted improved olfactory sensation, as measured by the University of Pennsylvania Smell Identification Test (UPSIT), following Rasagiline initiation.

Background: Hyposmia is a common, non-motor clinical symptom of PD that can present up to 10 years before typical motor symptoms develop. Currently, there are no treatments for this disorder, but a phase IV clinical trial assessing potential benefit with Rasagiline treatment is underway.

Methods: Case report.

Results: A 71 year old man with PD diagnosed in 2006 with relatively mild motor dysfunction reported a prominent loss of olfactory sensation for 'as long as he could remember'. He had never tried any medications for PD management. His examination was pertinent for a mild rest tremor and diffuse bradykinesia; his UPDRS III score was 20. He opted for a trial of Rasagiline after his motor complaints became more prominent. His baseline olfactory sensation was quantified using UPSIT prior to Rasagiline initiation as part of routine clinical screening; his score (13/40) indicated severe hyposmia for age. Five months later, he was retested with UPSIT and his score had improved by 4 points to 17, though subjectively he reported no difference with his sense of smell. He denied any unwanted effect from rasagiline.

Conclusions: The effects of the non-motor symptoms of PD can be as deleterious to a patient's quality of life as the motor symptoms. Although the motor symptoms of PD have several available successful treatments to offer patients, there is unfortunately nothing currently to offer as treatment for hyposmia and some other non-motor complaints. We are hopeful our patient's improvement represents a trend toward continued improvement in olfactory sensation along with other motor symptoms of PD, and that the results of the phase IV trial of Rasagiline produce similar recovery of function in other PD patients.

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Withdrawn by Author

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Development of a health professional's webpage on the society website

C.B. Moskowitz, M. Graziano (Esch-sur-Alzette, Luxembourg)

Objective: To build within the Society an international multidisciplinary interactive virtual group of professionals in counseling, nursing, rehabilitation and genetics, who enrich and broaden the scope of care, management and research initiatives in movement disorders.

Background: From its inception, the Society has openly welcomed members and encouraged participants who are not physicians (Bylaws, 1985; Strategic Plan, 2006). Barriers to full membership and fuller participation are assumed to be geographic, financial, leadership and program issues. Sessions and posters by non-physcian faculty have increased in recent years. The executive committee is more pro-active. The internet is now a robust educational tool beyond facilitating communication. The confluence of these factors has reduced barriers to full Society participation.

Methods: Three health professionals, invited by the executive committee to design a webpage in the MDS website, met in Paris to formulate goals and objectives. In 5 months, others with special interest and/or expertise in movement disorders were invited via e-mail and telephone to join as leaders, write role delineations and/or suggest other educational resources. EHDN and PSG researchers forwarded an e-mailed invitation to their colleagues to logon to the website, learn about the Society and the new group. The Society's project management tool will allow more professionals to work collaboratively on multidisciplinary projects in cross-training and improving care.

Results: Seven representative icons are linked to role descriptions for speech, language and swallowing therapy, occupational therapy, physical therapy, nursing, genetics, dietetics/nutrition, and clinical psychologists. One icon is linked to the purpose and evolving nature of the group. A new resource section highlights educational links. The 2010 needs survey will document demographics, culture of learning and unmet educational needs of respondents. Outreach efforts before webpage launch identified over 100 interested professionals.

Conclusions: In 6 months we have documented a need to aggregate movement disorder practitioners world-wide across disciplines in order to cross-train (one discipline learning from another), to meet unique educational needs, to increase access to their colleagues and ultimately to improve the breadth and quality of patient and family care.

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Development of educational standards for U.S. nurse DBS programmers

S.L. Heath, C. Whitney, T. Pretto, S.V. Grube, J. Simpson, G. Vernon, R. Greenberg, H. Watson, R.A. Hillman, S. Gillespie (San Francisco, California, USA)

Objective: 1. Establish educational standards for U.S. nurses to become proficient DBS programmers. 2. Describe the required clinical experience to become proficient programming patients with DBS.

Background: Traditionally, in many countries only physicians program deep brain stimulation (DBS) devices in movement disorders patients. However, in many U.S. academic and private practice settings, in collaboration with physicians, nurses are primarily responsible for DBS programming. Many are experienced neuroscience

nurses and work in advanced practice roles, such as nurse practitioners and clinical nurse specialists. They gained their DBS programming expertise through a combination of education, mentorship, and on-the-job training. As the number of people with DBS increases, so does the need for neuroscience nurses who are competent to program implanted devices. A pathway for novice programmers to become proficient in DBS programming does not exist. Therefore, establishing educational standards for DBS nurse programmers is needed.

Methods: The chair of the Movement Disorders Special Focus Group (MDSFG) of the American Association of Neuroscience Nurses (AANN) convened a focus group of a total of 12 experienced nurse DBS programmers from across the U.S. The group reviewed the DBS literature, consulted select State Boards of Nursing, and conferred with AANN's Board of Directors and their practice guidelines liaison for approval of the standards. The group, led by the chair of the MDSFG, met six times via conference call and communicated regularly via email until consensus was reached.

Results: The focus group submitted their recommendations to the leadership of AANN for posting on the national website. This recommendation includes an algorithm that guides the educational and clinical training of neuroscience nurses in the Movement Disorders field who want to become proficient as DBS nurse programmers.

Conclusions: Providing quality care to those with deep brain stimulators requires a team of expert clinicians knowledgeable about DBS. An important member of this team is the nurse programmer. Education and training for nurses performing DBS should be structured according to professional standards of practice.

POSTER SESSION 1

MONDAY, JUNE 14, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 14:00-15:30

EPIDEMIOLOGY

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Under-representation of ethnic minorities in movement disorder clinics in the United Kingdom

B. Williams, L. Brown, M. Hagger, N. Bajaj (Nottingham, United Kingdom)

Objective: Disparity in use of secondary care health services across ethnic groupings is an important issue and is unlikely to be unique to neurological disease. We have investigated the proportion of ethnic minority patients compared to white patients with Parkinson's disease (PD) presenting to a Movement Disorder Service in Derby, a Midlands city with a high proportion of ethnic minority persons.

Background: PD is found in all ethnic groups, however there is debate to whether prevalence rates are equivalent. Early studies suggested lower prevalence in Asian populations with more recent studies suggesting equal prevalence rates across many ethnic groups.

Methods: The computer database of the Derbyshire Movement Disorder Service was interrogated to ascertain the proportion of ethnic minority patients as compared to white patients in City PCT regions; these figures were then compared with the demographic distribution of ethnic minority individuals across this geographical region with figures from the 2007 Office for National Statistics Database. Whole group analysis was done and then sub-group analysis for the most at risk population (aged 60/65 and over). Ethnicity was categorised by the 16 groups used for National Statistics.

Results: Compared to the total population of Derby City, under representation of Indian, Pakistani, Bangladeshi and Black Caribbean populations was found amongst PD patients in the movement disorder clinic. Under representation of South Asians was significant on grouped data ($p=0.011$), although non-significant on age banded (60/65) data ($p=0.99$). Black Caribbean under-representation was seen on both whole group and sub-group analyses. The age profile of the South Asian populations was found to be skewed, with a significantly lower proportion of their population aged 60/65 and above ($p=0.0001$) than all other groups in Derby.

Conclusions: Under-representation of ethnic minority groups in the movement disorder clinics in Derbyshire appears to have mixed causation. The young age of the South Asian population in Derby City may explain their apparent under representation in the Movement Disorder Clinic although under-representation of the Black Caribbean population appears to be a genuine finding.

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Prevalence of apathy and depression in patients in the early stage of Parkinson's disease: The ANIMO study

J. Benito-Leon, E. Cubo, C. Coronell (Madrid, Spain)

Objective: To assess the prevalence and clinical correlates of apathy and depression in a large representative Spanish sample of Parkinson's disease (PD) patients in the early stage.

Background: Depression and apathy are a major handicap in PD. Little information exists on the prevalence of these conditions in the early stage of PD. Our aim was to assess the prevalence and clinical correlates of apathy and depression in a large representative Spanish sample of PD patients in the early stage.

Methods: We studied a sample of PD patients, with a disease duration $\leq$2.0 years, recruited from a Spanish cross-sectional survey (the ANIMO study), measuring health-related quality of life (HRQOL) by the EuroQoL-5D and apathy by the Lille apathy rating scale (LARS). Depression was diagnosed according to DSM-IV-TR criteria. The Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn & Yahr (HY) staging were performed on the same day.

Results: 705 PD patients (60% males, 40% females) with a mean age of 69.0$\pm$10.9 years, motor UPDRS of 20.7$\pm$11.5, and a median HY stage of 1.5 were included. Apathy (LARS $\geq$ -21) was diagnosed in 257 (36.5%) of PD patients and any type of depression (minor and major depression) in 313 (44.4%). Both depression (rho=-0.290, $p<0.001$) and apathy (rho=0.287, $p<0.001$) were associated with poorer HRQOL scores. Multiple regression analyses confirmed that apathy and depression were independent predictors of low HRQOL.

Conclusions: In this well-defined early PD group, apathy and depression were common in PD patients in the early stages of the disease. These conditions may impact negatively on PD patients' HRQOL, even at the beginning of the disease.

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Parkinson's disease registry in Thailand: An 18-month update

R. Bhidayasiri, N. Wannachai, S. Limpabandhu, T. Asawawichienchinda, L. Kaewwilai, R. Decahastin, K. Phanthumchinda (Bangkok, Thailand)

Objective: The goal is to generate a confidential database containing basic information about individual cases of PD in various regions of Thailand. Chulalongkorn Comprehensive Movement Disorders centre (www.chula-parkinsons.org) as a representation of the Thai

Red Cross society and the Ministry of Public Health of Thailand implement this work.

Background: Little is known about the epidemiology of PD in Thailand. Therefore, a nationwide PD registry in Thailand is established in 2008 to determine the number of PD patients (pts) and to identify the trends of PD rates in Thailand.

Methods: Project staff will be contacting physicians, healthcare facilities as well as directly promoting the campaign to Thai residents through different sources of media, including public radio, television and newspaper. Based on the interest expressed by disease advocates, a means of PD pts who voluntarily register their own clinical information (age at onset, disease duration, symptoms, social stigmata) will be created.

Results: The project commenced in July 2008 and will last three yrs. As of January 2010, a total of 21,593 (32.7% of target PD population) pts voluntarily registered and 6198 pts completed the 7-item questionnaire containing basic clinical information. There were 3157 males (50.9%) and 3041 females. 2587 (41.7%) patients were > 70 yrs old and 362 pts (5.8%) represent a young-onset PD. 4295 pts (69.3%) had tremor as their initial symptom, followed by bradykinesia (55.3%). In contrast, 3929 pts (63.4%) reported bradykinesia as their major troublesome symptom. 39.8% of pts reported symptoms of motor fluctuations with wearing-off being the most common (92.6%). 5010 pts (80.8%) take levodopa while only 25.1% and 20.4% of pts utilize anticholinergics and dopamine agonist respectively. 68.8% of pts denied history of smoking.

Conclusions: Due to the complexity of the project, the registry will be developed in several stages. 18 mths after the launch of the project, a total of 21,593 pts have been recruited and a nationwide database using state-of-the-art procedures and technology.

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Body weight in Parkinson's disease: A systematic review and meta-analysis

M.A. van der Marck, H.C. Dicke, Z.H.A. Kentin, G.F. Borm, B.R. Bloem, S. Overeem, M. Munneke (Nijmegen, Netherlands)

Objective: A systematic review of the literature with meta-analysis was performed to evaluate body weight in patients with Parkinson's disease (PD).

Background: A low Body Mass Index (BMI, kg/m^2) is associated with adverse health outcomes. Repeatedly, suggestions have been made that PD patients have a lower body weight compared to healthy controls. However, studies were not consistent and differences were not always significant. The aim of the present study was to critically examine the available evidence on body weight in PD and to quantify this using a meta-analysis.

Methods: A systematic literature search was performed in MEDLINE, EMBASE, Cinahl and Scopus. Studies were eligible when (a) included patients were diagnosed with idiopathic Parkinson's disease, (b) BMI data were presented in the study, (c) body weight was measured by a professional, and (d) PD patients were compared to a healthy control group. Moreover, articles had to be published in English and had to be available as full paper. BMI values were extracted from studies for meta-analysis. When available, data on disease severity (Hoehn and Yahr stage (H&Y)) were extracted for random effects model.

Results: A total of 13 studies were included in the meta-analysis. PD patients had a significantly lower BMI than controls (difference -1.3, 95% CI -1.9 - -0.8; Figure 1). A higher disease severity was associated with a lower BMI. Two studies reported BMI levels, and found a low body weight (BMI<20) in 20% and 19% (male) and 35% (female).

Conclusions: Patients with PD have a lower BMI compared to controls. The data suggest that disease severity influences body weight. It is important to monitor weight as part of the treatment of PD, since low body mass index and weight loss can lead to adverse health outcomes.

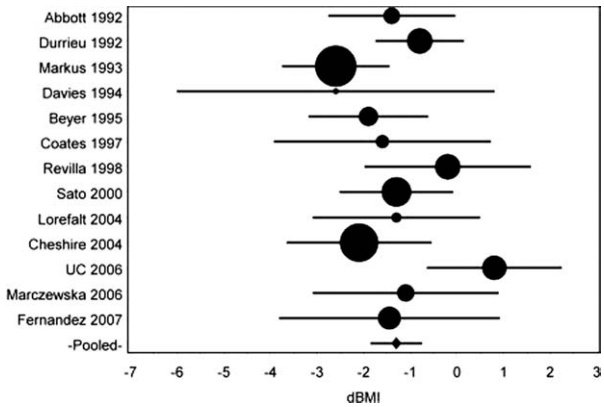

FIG. 1 (218).

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Screening Questionnaires for Symptomatic Parkinson's disease: A Systematic Review

N. Dahodwala, A. Abrams, A. Siderowf, M. Baumgarten, J. Karlawish (Philadelphia, Pennsylvania, USA)

Objective: To review the medical literature on screening for Parkinson's disease (PD) and to compare the validity of the screening questionnaires used.

Background: PD is a common, treatable condition that often remains undiagnosed, even when typical clinical signs are present. Better community-based detection of symptomatic cases of PD would improve the quality of life for individuals with PD through the appropriate initiation of treatment. More accurate case ascertainment would also facilitate the conduct of research studies of PD prevalence.

Methods: Online databases PubMed and EMBASE were systematically searched for English-language articles from January 1980 to December 2009. In each database, a "Parkinson(s) disease" or "parkinsonism" term was combined with a screening term ("screening instrument," "screening questionnaire," "screen" and "prevalence survey") and a validity term ("validation," "sensitivity," and "specificity"). Included studies reported the psychometric properties of at least one PD or parkinsonism screening questionnaire that assessed self-reported symptoms.

Results: Twenty-six studies met the inclusion criteria. Eleven different screening questionnaires were identified. The two most commonly tested questionnaires were a 9-item screen of parkinsonian symptoms and a combined 15-item screen of neurological symptoms with 7 simple physical tasks. Sensitivity estimates ranged from 48-100% and specificity estimates ranged from 22-100%. Greater accuracy was seen when a questionnaire was administered by trained interviewers or physicians and in the detection of previously diagnosed moderate to severe PD. Specificity was maximized when the screen included assessment of physical tasks such as tone and gait by a non-medical interviewer.

Conclusions: Screening questionnaires can detect both diagnosed and undiagnosed symptomatic PD. In addition to the specific questionnaire items, the accuracy of the screening questionnaires was greater when detecting moderate to severe PD. However, these questionnaires have not demonstrated sufficient efficacy in the detection of early or mild parkinsonism. Thus, the choice of an appropriate PD

screening questionnaire will depend upon the purpose of the screen and the resources available.

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Vascular and hypoxaemic risk factors for amyotrophic lateral sclerosis: A prospective cohort analysis with a case-control study

C. Moreau, V. Brunaud-Danel, J. Dallongeville, A. Duhamel, A.C. Wiart, L. Laurier-Grymonprez, T. Perez, C. Monaca, L. Defebvre, A. Destée, D. Devos (Lille, France)

Objective: To assess the prevalence and prognostic value of vascular and hypoxaemic risk factors in amyotrophic lateral sclerosis (ALS).

Background: ALS is a degenerative disease that attacks the motoneurons. Given the latter's high oxygen consumption, hypoxia-responsive angiogenic factors have been implicated in the physiopathology of ALS.

Methods: We included all confirmed ALS patients from the Nord-Pas de Calais region of France (prospectively and regularly monitored in our centre) having died between 2006 and 2008. Vascular and hypoxic risk factors were assessed at diagnosis and regularly during the disease progression. Patients lacking detailed medical records were excluded. Risk factors at diagnosis were compared with those in a case-controlled population. Prognostic factors for survival were assessed by using bootstrap resampling.

Results: The mean±SD age of the 102 confirmed ALS patients included in the study was 63±12 years and the mean post-diagnosis survival time was 31±16 months. The statistically significant risk factors for ALS were hypertension (56% of patients vs. 41% of stratified, age- and sex-matched controls (n=400)) and current smoking (27% vs. 15%). There were non-significant trends for obesity (p=0.05) and overweight (p=0.06). At diagnosis, the main prognostic factors for survival were age, current smoking, low vital capacity and elevated morning plasma bicarbonate on waking (reflecting nocturnal hypoventilation).

Conclusions: Our results strongly support the hypothesis whereby vascular and hypoxic risk factors are involved in ALS. We suggest that the pathogenesis of ALS involves a reduction in neural vascular perfusion (hypertension) and deregulation of the hypoxia response. Hypoxaemic factors greatly influence survival. Rigorous antihypertensive therapy, smoking cessation and (as soon as nocturnal hypoventilation is evidenced) non-invasive ventilation should be implemented.

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Environmental factors and Parkinson's disease: A case-control study in Belgrade, Serbia

E. Dzoljic, H. Vlajinac, S. Sipetic, J. Marinkovic, J. Maksimovic, V. Kostic (Belgrade, Serbia)

Objective: A case-control study was performed in Belgrade in order to investigate the association between Parkinson's disease (PD) and some environmental factors.

Background: Environmental toxins, in particular, pesticides have been implicated as risk factors in Parkinson's disease.

Methods: During the period 2001-2005, 110 new PD patients/cases and 220 hospital controls,chosen among patients with degenerative joint disease and some diseases of the digestive tract, were interviewed. Cases and controls were matched by sex, age (+/- 2 years) and place of residence (urban/rural).

Results: According to multivariate conditional logistic regression analysis PD was positively asssociated with exposure to insecticides (Odds Ratio – OR 3.22, 95% confidence interval – 95%CI 1.32-7.87), dyes (OR 25.33, 95%CI 2.89-222.0) and naphtha and its derivates (OR 9.53, 95%CI 1.04-86.96), and with gardening (OR 5.51, 95%CI 3.04-10.01), well water drinking (OR 2.62, 95%CI 1.40-4.90) and springhead's water drinking (OR 2.19, 95%CI 1.15-4.16). Negative association was found for service sector working (OR 0.15, 95%CI 0.04-0.59). The results obtained did not changed after adjustment for smoking.

Conclusions: The findings of the present study support the role of environmental factors in the occurance of PD.

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Stressful life events preceding Parkinson's disease

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Objective: to investigate possible relationship between stressful life events and Parkinson's disease (PD).

Background: Stressful life events have been implicated as risk factors in Parkinson's disease.

Methods: We conducted a case-control study in Belgrade, Serbia. During the period 2001-2005 the group of 110 consecutive newly diagnosed Parkinson's disease cases was compared with the control group comprising 220 subjects chosen among patients with degenerative joint disease and some diseases of the digestive tract. Cases and controls were matched by sex, age (+/- 2 years) and place of residence (urban/rural).

Results: According to conditional multivariate logistic regression analysis, Parkinson's disease was significantly related to retirement (Odds ratio – OR=18.73, 95% confidence interval – 95% CI: 1.99, 175.4), birth of child (OR=66.22, 95% CI: 8.30, 526.3) and bombardment (OR=5.66, 95% CI: 2.38, 13.48). Association with death of close friend was at the borderline of statistical significance (OR=11.30, 95% CI: 0.94, 135.1). The average number of stressful life events was significantly greater in cases than controls ($p<0.001$), and the risk increased with the number of stressful events ($p<0.001$).

Conclusions: The results of the present study support the hypothesis that stress can play a role in the development of Parkinson's disease.

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Is the advice given to Parkinson's disease patients in vitamin and nutrition stores accurate and reliable?

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Objective: To determine what advice is given to Parkinson's disease patients who ask about supplements in vitamin/nutrition stores.

Background: Complementary and alternative medicines have become popular alternatives to "conventional" treatments for many different diseases in the United States. It is estimated that over 60% of individuals will try an alternative medicine, and for Parkinson's disease patients studies suggest that over 40% may pursue this route. One of the more common complementary therapies in Parkinson's disease is the use of vitamins and supplements.

Methods: A survey of eight nutrition and vitamin stores was conducted. The selection of stores was at random and included small shops and national chains. The salespeople were asked what would be recommended for a newly diagnosed 66 year old male who was otherwise healthy. If asked about symptoms, the patient was said to have some "shaking and stiffness." If the questioner was asked about medications, he was to feign ignorance about which prescription medicines the patient was on and was only to indicate a multi-vitamin and a B-complex vitamin.

Results: Recommendations from the salespeople were quite varied. In 6/8 stores, the salesperson looked up Parkinson's disease in a nutrition book to determine the best agent. Only 1/8 mentioned that nothing was available. None specifically recommended talking to a

doctor prior to buying any of the supplements, although one recommended having a pharmacist review medicines to see if there would be any interactions between prescription medicines and the supplements. Nearly all (7/8) recommended Coenzyme Q10, although the dosages and reasons for the recommendation were quite varied.

Conclusions: The recommendations by nutrition and vitamin store proprietors are diverse and unreliable. Although most individuals did not feel confident about making a recommendation without first checking a reference guide, there was very little hesitancy about giving a recommendation after reviewing the book without mention of interactions with medications or physician oversight. It is important for the physician to address supplement issues with the patient proactively since the information may otherwise come from questionable sources.

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Using drug purchase data to estimate the occurrence of Parkinson's disease in Israel, 1998-2008

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Objective: To estimate yearly prevalence, incidence and trends of Parkinson's disease (PD) in Israel over the past decade.

Background: The high occurrence of mutations in *LRRK2* and *GBA* genes among Ashkenazi Jewish PD patients raises the question whether PD occurrence in Israel is higher than expected in Western countries. Health Maintenance Organization (HMO) data of drug purchases are comprehensive and accurate, and may be a reliable source for estimating the actual prevalence and incidence of PD in Israel.

Methods: PD cases were identified from the 1998-2008 drug-purchase data of the second largest HMO in Israel, covering 1.8 million members, ~25% of Israel's population. We developed a case definition algorithm based on different profiles of drug types, age at first purchase, purchase density, and follow-up time; and defined the certainty level of a subject being a PD patient as: definite, probable or possible.

Results: Of 7,134 subjects (52% men) who met our algorithm criteria for PD, 56% were defined as definite cases, 11% as probable and 33% as possible PD patients. Overall, mean age at first purchase was 69 (SD 13) years. The prevalence of PD between 2000 and 2007 increased from 170 to 256 per 100,000. Age- and gender-specific prevalence rates were higher in older people, and among men. Prevalence rates per 100,000 in 2005 for ages 50+, 60+ and 70+ were 1,083, 2,013 and 3,482, with men/women ratios 1.17, 1.23, 1.30, respectively. An annual incidence of 30 per 100,000 was stable over the past decade. Similar to the prevalence, incidence rates increased with age, more predominantly in men. Incidence rates per 100,000 in 2005 for ages 50+, 60+ and 70+ were 156, 300 and 568, with men/women ratios 1.27, 1.33, 1.42, respectively.

Conclusions: The findings demonstrate that among Israeli PD patients, age at first purchase of PD-related drugs was ~10 years older than age of motor symptoms onset reported in all Israel academic medical centers. This may be due to overrepresentation of younger PD patients in tertiary centers. The substantial increase in PD prevalence in Israel over the past decade, which might indicate increased survival of patients, is of major impact on health and social services.

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Are patients being referred *before treatment* with suspected parkinsonism? A survey of 17 UK centres

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Objective: To assess if national guidance advising patients are referred untreated to a movement disorder specialist is being followed.

Background: The 2006 NICE guidance on Parkinson's disease recommends that people should be referred quickly and untreated to a specialist with expertise in the differential diagnosis of this condition (National Institute of Health and Clinical Excellence (NICE) 2006, CG035). Assessment by a specialist neurologist or geriatrician, without prior dopaminergic treatment, confers better diagnostic accuracy (Schrag, Ben-Schlomo, Quinn, Journal of Neurol Neurosurg Psychiatry 2002; 73: 529-534), with implications for prognosis and management.

Methods: Data was collected by participants on the 15th BGS Parkinson's Academy. We collected data from 17 secondary care centres across the UK (up to 20 patients per site). All referrals from the community were considered if the referrer requested an opinion on tremor, parkinsonian features or movement disorder. Patients were excluded if the referral was made within secondary care, if patients had an established diagnosis of a parkinsonian syndrome made by a movement disorder specialist or if no adequate drug history was available.

Results: Data was collected on 325 patients. 6.8% of patients referred to a movement disorder specialist were on dopaminergic therapy - 4.6% (15/325) were on recently initiated dopaminergic therapy and a further 7 had long-standing levodopa prescriptions. Of the treated patients, all were taking levodopa and 3 were also taking other dopaminergic treatment. The duration of treatment, where it could be ascertained, varied from 3 weeks to 10 years.

Conclusions: The majority of referrals were made on untreated patients with fewer than 7% on treatment when first seen. Further promotion of the NICE guidelines in primary care would appear to be appropriate and since 1.9% were on long term dopaminergic therapy in the community without formal diagnosis there would also appear to be a place for prescription review in primary care. However, we were encouraged that most referrals were being made appropriately as suggested by NICE guidance.

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Pain in Taiwanese patients with Parkinson's disease – characteristics, severity and the correlation with depression and quality of life

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Objective: To evaluate the characteristics of pain and its effects on life of quality in Taiwanese patients with Parkinson's disease (PD), we conducted this clinical study in a large center of Movement disorders in Taipei based on a cross section survey.

Background: Pain has been recognized as a non-motor symptoms of PD and several documents reported that prevalence of pain is as high as 68~85% in European countries. Some authors also postulated that central pain may also be noted in up to 10% PD patients and depression may coexist with pain.

Methods: We used questionnaires including Brief Pain Inventory, Taiwanese Depression Scale and WHOQoL-Bref to evaluate the prevalence of pain and its related events in PD patients who visited "Centre of parkinsonism and Movement Disorders" at the National Taiwan University Hospital. A comprehensive neurological examination and face to face interview with the questionnaires were performed in a cross section survey.

Results: Overall, within 360 patients of PD (mean age:60±11.2, Female:172, duration of illness:5.6, H/Y stage: 2.0), 98 subjects (27%) complained about pain as initial or cardinal symptoms. Among them, there was a significant female predominance ($p=0.004$). The mean severity of worst pain was 5.2±2.1 in rating scale from 0-10. The severity of pain was negatively correlated with QoL in physiological and psychological domain ($p=0.007$, either), but not with depression scale ($p=0.184$). Pain-affected events indicated that most severe in mood and work, but least in relationship with other peoples

($p<0.001$). The QoL (physiological, psychological, environmental and social domains) between two groups with or without pain was no different, but depression scale was significantly higher in pain group ($p=0.03$).

Conclusions: Our data suggest that the prevalence of pain in our PD patients is approximately 27% and with a female predominance. The severity of pain is moderate and negatively correlates with both physiological and psychological domains of life of quality.

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A retrospective study about characteristics of Wilson's disease at tertiary care institute of North India

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Objective: To study the clinical profiles, laboratory findings, brain imaging of Wilson's disease and response to treatments.

Background: Wilson's disease is an autosomal recessive systemic disorder of copper metabolism due to a defect of copper transport by hepatic lysosomes with secondary pathology resulting from copper overload in liver, brain, kidney and skeletal system.

Methods: Cases of Wilson's disease were taken from hospital records from 2004 December to 2009 December. Total 32 cases were diagnosed. Study was carried out to see clinical characteristics, presence of K-F ring, laboratory parameters, biochemical levels and brain imaging.

Results: Total 32 cases were diagnosed of Wilson's disease. 22 were male and 10 were female. 28 cases were of less than 15 years of age and 4 were adults. Youngest patient was of 6.5 years of age and oldest patient was of 32 years of age at diagnosis. The mean duration of disease before diagnosis was 6 months in children (<15 yrs) and 2 years in adult (>15 years). In children dystonia was most commonest presentation (90%), parkinsonism (82.5%), both were in 73.4% and tremor in 60% and in adults parkinsonism was commonest presentation (75%), dystonia (50%) and tremor were present in 50% of adult patient. Sialorrhoea was present in 60% of children and 25% of adult patients. Unclear voice were present in 80% of cases. Dysphagia was present in 44% of children and 25% of adult patients. KF ring was absent in 3 children. CT brain was performed in all the cases, most common abnormality observed is bilateral symmetrical hyperlucency of basal ganglia in 13 (40.6%). MRI brain performed in 24 cases. 4 had normal MRI brain. Abnormality were observed in 20 cases, most common was hyperintensities of basal ganglia (62.5%), thalamus in 45% and brainstem in 31.5%. 4 patients were only on zinc and 28 were on both zinc and D-penicillamine. Out of 28 cases 10 has left D-penicillamine (2 due to adverse effects and 8 due to unaffordability). All has excellent response to treatment except one child.

Conclusions: Wilson's disease was more common in children. Dystonia, parkinsonism, tremor, sialorrhoea and unclear voice were commonest features. KF ring were present in 91% of cases. Bilateral symmetrical hyperintensities of basal ganglia was commonest MRI abnormality. Zinc is safest to start. Wilson's disease has excellent response to D-penicillamine.

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Hyperechogenicity of the substantia nigra is associated with an increased risk to develop Parkinson's disease: A 37 months longitudinal multi-centre study of 1847 elderly free of PD at baseline

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Objective: The aim of this study was to investigate the predictive value of hyperechogenic substantia nigra (SN+) as marker for an increased risk for Parkinson's disease (PD) in healthy elderly subjects.

Background: Recent studies using transcranial ultrasound (TCS) indicate a high prevalence SN+ among patients with PD.

Methods: In a prospective three-centre longitudinal study 1847 subjects >50 years, free of PD at baseline were investigated and re-examined after an average of 37 months. The following baseline characteristics were analysed: echo status of midbrain on TCS, the Unified Parkinson's Disease Rating Scale (UPDRS part III) and olfactory function tested with Sniffin' Sticks. The predictive value (relative risk (RR) with 95% confidence interval (95%-CI)) and positive predictive value (PPV) of developing PD was calculated.

Results: Compared to baseline, 11 subjects had converted to PD at follow-up. In subjects with SN+ at baseline the RR was 17.37 (95%-CI:3.71-81.34) for incident PD. In contrast subjects with hyposmia at baseline had a RR of 3.94 (95%-CI: 1.12-13.89). The highest risk ratio for PD was observed in subjects with both SN+ echostatus and hyposmia plus baseline scores of ≥ 3 on the UPDRS motor section (RR=48.39, 95%-CI, 11.82-198.11). This combination of markers showed also the highest PPV for the development of PD in the observed time span (PPV of 25%).

Conclusions: This is the first study, demonstrating an increased risk for PD in elderly subjects with SN+. Our findings suggest that this brain echo feature is a relevant risk marker for PD. Longer follow-up of this cohort is needed to verify this finding and also to define predictive values of combinations of further putative risk markers to identify subjects for future interventional trials aiming to delay the conversion to PD.

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Eye movement abnormalities found in patients with parkinsonism within three months after the first visit

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Objective: To investigate eye movements in patients with newly diagnosed parkinsonism.

Background: Eye movement abnormalities have been described in Parkinson's disease (PD), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP). These investigations have been made in patients with established diseases, usually several years into the disease. The possibilities of using eye movement analysis in the

TABLE 1 (229).

	Vertical saccades			Horizontal saccades			Smooth pursuit 20°
	Latency ms	Velocity °/s	Precision	Latency ms	Velocity °/s	Precision	Gain
Diagnosis (n)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Definite PD (96)	315 (74.3)	218b (44.2)	79.6a,b (18.8)	316 (79.4)	382 (74.9)	86.1c (22.7)	0.686a (0.185)
Probable PD (25)	347b (80.1)	188a (47.3)	83.4 (39.3)	347a (68.8)	361 (79.5)	84.0a (21.1)	0.616 (0.203)
PSP (6)	419 (181)	118b,e (84.3)	51.4b,f (29.1)	332 (77.3)	247 (96.7)	73.4 (15.5)	0.450 (0.163)
MSA (13)	310 (71.6)	191 (45.1)	71.8d (17.6)	322 (108)	335 (65.3)	78.9d (29.0)	0.515a,d (0.135)
Unclassifiable (6)	390 (102)	219 (106)	90.8 (56.7)	443b (130)	370 (130)	82.6 (44.9)	0.530 (0.141)
Controls (37)	293b (61.0)	234a,e (44.2)	84.7a,d,f (6.09)	286a,b (71.7)	387 (62.5)	87.8 a,c,d (9.16)	0.749 d (0.167)

a, d, f) $p=0.015$ (Mann-Whitney U-test, exact) b, e) $p=0.030$ (Mann-Whitney U-test, exact) c) $p=0.045$ (Mann-Whitney U-test, exact).

differential diagnostic procedure have been discussed. The difficulties in the differential diagnostics are greatest early in the course of the disease and it is of importance to analyze the eye movements also very early.

Methods: During the years 2004 through 2008 we included all new patients presenting with parkinsonism (n=177) in our catchment area (142,000 inhabitants), in a population-based incidence cohort study. The eye movements were examined in 37 healthy controls and in 146 patients within three months after the first visit before the initiation of any treatment. The clinical diagnosis was set at a 12-month follow-up visit and established clinical diagnostic criteria were used.

Results: See Table 1 for details.

Conclusions: There were several significant eye movement abnormalities in patients with parkinsonism investigated within three months of their first visit, not only in PSP, where disturbance of eye motor control is a prerequisite for making the diagnosis, but also among the PD and MSA patients. There were no statistically significant differences between patients with MSA or PSP, probably due to the few cases in each group. We will follow these patients for at least five years and repeat the eye motor examinations during the course of the disease.

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Withdrawn by Author

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Comorbid conditions in patients with Parkinson's disease: A US claims database analysis

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Objective: To conduct a cohort study in a large population using insurance claims to examine the rates of selected co-morbidities in PD patients, and the relative rates of these comorbidities in an age-and-gender matched sample of individuals free from PD.

Background: Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting approximately 4.1 million people worldwide. The mean age at symptom onset is in the 6th decade and therefore the majority of affected subjects are at increased risk for geriatric comorbidities. Very little information is currently available on the epidemiology of such comorbidities in patients with PD.

Methods: A retrospective cohort study design was utilized to investigate the geriatric comorbidities in the MarketScan® Research databases. This is a HIPAA-compliant, fully integrated patient-level database containing information from over 29 million patients. The PD cohort (n=45,649) included patients with at least 2 diagnoses of PD (ICD-9 332.0). The 1:1 age-and-gender matched control cohort included only subjects with no diagnostic code for PD.

Results: Using a combination of coding algorithms we identified the baseline prevalence (during 6 months before index), period prevalence and incidence of pre-selected comorbidities including diabetes mellitus, hyperuricemia/gout, cardiovascular, pulmonary and liver diseases. The period prevalence rates in the 12 months post-index of pre-selected comorbidities were consistently higher in the PD group than in the age- and gender-matched reference group.

Conclusions: Comorbid conditions are prevalent in the PD populations. Better understanding of comorbid conditions in PD may improve personalized treatment approaches.

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Gastrointestinal disorders in patients with Parkinson's disease: A double-edged sword

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Objective: To investigate the clinical and health economic impacts of gastrointestinal disorders (GID) in patients with Parkinson's disease (PD).

Background: A majority of patients with PD eventually develop GID, which can impair the onset of symptom relief by PD drugs. There was a need to better understand the rate and consequences of GID amongst patients diagnosed with PD.

Methods: A two years matched retrospective cohort study was performed in a registered Pharmetrics® datacut, a US claims database containing records on demographics, diagnoses, procedures, provider, prescriptions and claims that span from 2000 to 2008. Patients with at least two prior diagnoses of Parkinson's disease, with continuous prescriptions of levodopa or dopamine agonists between 1 Sept 2005 and 1 September 2006 were selected. Patients with and without GID were matched by age, gender, comorbidities, and treatment regime. Their respective emerging health outcomes were followed-up for two years. Outcomes were defined on the basis of a literature review and included neuropsychiatric, motor, urogenital disturbances, healthcare utilization and related costs.

Results: In the datacut, GID incidence among patients with PD increased over time to stabilize at 75% at 92 months. 485 patients with PD and GID were matched to 485 controls with PD but without GID. GID was associated with significantly higher rates of neuropsychiatric and motor disorders, including psychosexual dysfunction (RR=8, p=0.05), anxiety (RR=1.61, p<0.01), depression (RR=1.28, p=0.03), ataxia (RR=1.24, p=0.03), pain (RR=1.28, p<0.01), movement disorders (RR=1.39, p<0.01), urinary incontinence (RR=1.43, p=0.02), and risk of fall (RR=1.44, p=0.04). ER admissions (ratio=1.42, p<0.01), number of concurrent drugs (ratio=1.06, p=0.04) and PD and non-PD healthcare costs (ratios=1.13 and 1.12, p<0.01 respectively) increased during the observation period in the GID patients.

Conclusions: Our data suggest that the prevalence of GID in patients with PD is high and increases over time. GID have a substantial deleterious effect on major PD-related clinical and societal outcomes. Non oral formulations of PD drugs (apomorphine or L-dopa pumps or rotigotine) may offer a good opportunity to bypass gastrointestinal tract, and accordingly maximize patient response to treatment.

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Parkinsonian syndromes among the community-dwelling elderly: High prevalence of vascular parkinsonism in southern Brazil

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Objective: To evaluate the prevalence of Parkinson's disease (PD) and other parkinsonian syndromes among community-dwelling elderly living in Southern Brazil.

Background: Brazil is a continental country and only one punctual community-based study has evaluated the prevalence of parkinsonian syndromes among the Brazilian elderly (Barbosa et al, 2006). No such a study has been conducted in Southern Brazil.

Methods: Four hundred and fifty elderly people living in two communities (Estancia Velha and Charqueadas) of Brazilian Southernmost state were invited to participate in the study. Of those, 434 (96.4%) subjects agreed to participate in the evaluation. Individuals were evaluated by two movement disorder neurologists. Parkinsonian syndromes were classified into Parkinson's disease (PD), Drug-induced parkinsonism (DrP), Vascular parkinsonism (VaP), and Atypical parkinsonism (AP) causes.

Results: Mean age was 70.2 (± 6.2) years and 282 (65.0%) were female. A total of 42 (9.9%) subjects were found to have a parkinsonian syndrome. Of those, 13 (3.0%) were diagnosed as PD, 16 (3.7%) as DrP, 10 (2.3%) as VaP, and 3 (0.7%) as AP. There were no significant gender differences in these prevalences. Nine (64.4%) of PD cases were newly diagnosed. Of note, prevalence of hypertension (84.6%) and clinically manifested stroke (10.1%) were higher,

as compared with reports from most regions of the world for this age-group.

Conclusions: Prevalence of parkinsonian syndromes in Southern Brazil was higher than reported in most international studies. This finding was specially associated with the elevated prevalence of VaP, what is in accord with the high frequency of clinically manifested stroke in this population. Conversely, the prevalence of PD and DrP was similar to previously reported internationally. References: Barbosa MT, Caramelli P, Maia DP et al. Parkinsonism and Parkinson's disease in the elderly: a community-based survey in Brazil (the Bambuí study). Mov Disord. 2006 Jun;21(6):800-8.

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Clinical and demographic features of Parkinson's disease patients attending to a referral center in Mexico City

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Objective: To describe the clinical and demographic features of PD patients attending a national referral center in Mexico City.

Background: Parkinson's disease (PD) is the one of the most frequent movement disorders worldwide. Incidence and prevalence of PD in Mexico is unknown. Referral centers are known to be vulnerable to referral bias which may make comparisons with other series difficult.

Methods: We carried out a cross-sectional study. A total of 402 patients were evaluated at the Movement Disorder Clinic from July 2007 to July 2009. From this, 226 had a diagnosis of PD by the United Kingdom Parkinson's Disease Society brain bank criteria but only 212 patients had complete data for the analysis. Demographic characteristics as well Hoehn-Yahr stage, treatment, levodopa equivalent dose and non motor symptoms were registered.

Results: Demographic and clinical data is shown in Table 1.

TABLE 1 (234). *Main features of the PD population*

	Mean ± Standard Deviation
212 patients	93 women/119 men
Age (years)	63.1 ± 11.4
Age at diagnosis (years)	56.9 ± 11.8
Disease duration (years)	6.6 ± 5.2
Hoehn-Yahr	2.4 ± 0.7

74% of the patients had tremor as the initial motor manifestation. 58.4% had a right-sided onset. 47% had a mild disease (HY 1 a 2), 46% moderate (HY 2.5 a 3) and only 7% had a severe disease. Non motor symptoms were present in 95% of the sample with constipation, urinary urgency and depression as the more prevalent. 70% (n=148) of the patients were on a levodopa preparation (55% were on monotherapy). About 57% of the patients received a dopaminergic agonist (23% as montherapy), 11% were on MAO inhibitors and only 5% were on COMT inhibitors. Mean dose of medications is shown in table 2 and treatment choice by age group in figure 1.

At the first visit to the clinic almost 25% of the patients were treated with an anticholinergic. Motor fluctuations and dyskinesia data was only available for 59 patients with 51% presenting fluctuations and dyskinesia in 21%. 23% of the sample was also receiving antidepressants.

Conclusions: Although we expected a referral bias in our simple the mean age of our PD patients is similar to other international population-based studies while age at diagnosis is discretely lower. Antiparkinsonian treatment with dopaminergic agonists was low in comparison with international reports and may be due to the fact that our population usually lacks social security. Non motor symtpoms were present in 95% of the patients with depressive symtpoms being more frequent than in other populations.

TABLE 2 (234). *Mean dose of antiparkisonian medications*

Medication	Mean dose ± SD (mg/d)	Range
Levodopa (n=148)	605 ± 325.6	1525 (100–1625)
Pramipexol (n=110)	1.5 ± 1.1	4.25 (0.75–5)
Amantadine (n=29)	244 ± 75	300 (100 - 400)
Biperiden (n=52)	3.4 ± 2	7 (1–8)
Entacapone (n=11)	445.5 ± 258.3	600 (200–800)
Rasagiline (n=14)/ Selegiline (n=13)	1 / 7 ± 3.5	1 / 9 (1–10)
LEDD	615.1 ± 404.6	1900.5 (45–1945)

SD: Standard deviation. LEDD: Levodopa equivalent daily dose.

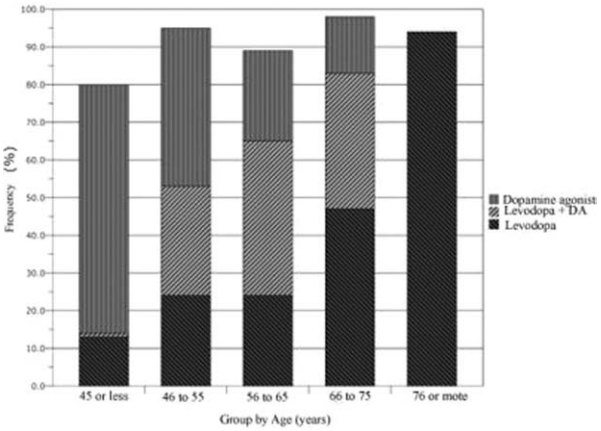

FIG. 1 (234).

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The Birmingham, UK joint motor disorder clinic: A descriptive study

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Objective: To describe (1) types of patients referred to the clinic, (2) diagnoses made, (3) patient management, and (4) patient follow-up.

Background: A unique clinic is run in Birmingham, UK for patients with concomitant motor and psychiatric disorders. A neurologist and a neuropsychiatrist evaluate patients jointly, and share their management.

Methods: Data was available for 260 clinic appointments, which, after removal of duplicate entries for patients who attended more than one appointment, resulted in a list of 123 individual patients. Medical notes were requested and, where unavailable, electronic clinical letters were sought. Two authors (LS and NT) collected data individually and, where clarification was required, both authors performed data collection and a consensus was reached. Data was entered onto Microsoft Excel, and data analysis was performed using SPSS.

Results: Of the 123 patients identified, 61% were male (mean age at referral 49.5 years). Neurologists referred over 50% of

patients, and psychiatrists 27%. Approximately half of all patients referred had a previous psychiatric history; depression was most common. Parkinson's disease-related problems made up over a third of referrals (mainly psychosis and depression), and this group had a higher mean age at referral (62.5 years). Conditions related to Parkinson's disease accounted for 36% of diagnoses, and functional motor disorders 22%. The clinic made interventions (predominantly pharmacological at 53.6%) in approximately two-thirds of patients. Non-pharmacological therapies accounted for 10% of management decisions. A quarter of patients were discharged after one appointment, a third of whom were diagnosed with functional motor disorder. Sixteen per cent were discharged at a later date. The largest proportion of patients was still under follow up at the time of data collection.

Conclusions: Two groups of patients were heavily represented in this clinic: patients with Parkinson's disease and those with functional motor disorders. Overall, the clinic has a higher prevalence of previous psychiatric illness than one would expect in the general population. Interventions were made in approximately two-thirds of cases, with pharmacological strategies being the most common.

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Chronic low back pain and lumbar deformities are increased in patients with Parkinson's disease

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Objective: The present study aimed in the quantification of lower back pain in parkinsonian patients and its morphological correlates in lumbar X-ray.

Background: Parkinson's disease (PD) with a manifestation age around 65 years and an prevalence of 200/100.000 is a common disabling condition of the elderly. Parkinsonian patients are often more troubled by chronic low back pain (LBP) then people in the same age. Besides muscular imbalance by the movement disorder itself skeletal and joint deformities are causes of pain.

Methods: 100 patients with PD were inquired about back pain through self-questionaires (Oswestry Low Back Pain Disability Questionnaire, VAS back pain and VAS leg pain) during their follow up in the neurological clinic. Patients with reported pain underwent x-ray of the lumbar spine in two planes and flexion-extension views if necessary for treatment.

Results: Chronic LBP was reported by 82 of 100 PD patients. Between patients with and without LBP no significant differences were found regarding demographics and PD scores (H&Y stage, disease duration, UPDRS III motor score, daily dopamine equivalent dosages). In PD patients with LBP the Oswestry mean score was 31.46 (range 0-74). VAS mean scores were 46mm for back pain and 33mm for leg pain. Pain qualities were described as generally pain in 63 patients, pricking in 10 patients, tingling in 11 patients, burning in 6 patients and other pain in 3 patients. The pain duration was on average 134.04 month (range 0.75-600 month). Lumbar x-rays of 44 patients with LBP were analized. Those revealed osteochondrosis in 32 (76.2%), scoliosis in 24 (54.5%), spondylolisthesis with instabilities in 9 (20.5%) cases.

Conclusions: Chronic LBP and degenerative lumbar spine deformities are much more common in patients with Parkinson's disease compared to the population. This problem might be related to the disease specific muscular imbalances by rigidity and dystonic symptoms. Regarding that spine surgery in PD patients is more often related with complications further knowledge about musculoskeletal conditions in individual patients is of crucial importance for optimized conservative and operative treatment in Parkinson's disease.

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The long latencies of ALS, parkinsonism and dementia on Guam

J.C. Steele (Tamuning, Guam, Guam)

Objective: To define the latencies of ALS/PDC.

Background: Until 1960, native Chamorros of Guam and migrants of other ethnicity were prone to a familial proteinopathy which accumulated tau, alpha-synuclein, ubiquitin and TDP-43 (McGeer) and that was expressed by phenotypes of classical ALS, parkinsonism including PD, PSP and CBD, and dementia of Alzheimer and frontotemporal type (Steele). It is termed the ALS/parkinsonism-dementia complex (ALS/PDC) and is known locally as *lytico-bodig*. During the past 50 years ago, the phenotypes of ALS/PDC have steadily declined and the age in onset has increased. In 2009, ALS which was 100 times more common than elsewhere in 1953 is now rare, parkinsonism is much less frequent, and dementia is the only phenotype which remains prevalent in late life.

Methods: We have learned about the latencies of the different phenotypes of ALS/PDC by studying them in migrants from and to Guam.

Results: Many Chamorros who were asymptomatic when they left Guam to live abroad before 1960 subsequently developed neurological symptoms many years later. The intervals were different and longer for parkinsonism than ALS, and longest for dementia. Majoor-Krakauer has reported that US servicemen residing on Guam for only 1 to 2 months at the end of WW II developed ALS 35 years later, and pathologists Hirano and Perl have identified resident Caucasians coming to Guam in 1952 and 1956 who developed fulminant ALS with NFD 41and 39 years later. After 1947, Filipinos came as construction workers to rebuild Guam and many remained as residents. Garruto has confirmed pathologically verified ALS with NFD and PDC in them after long latencies that are similar to those of Chamorros. The longest interval so far recorded is in a 17 year old Filipino immigrant to Guam in 1947 whose symptoms of parkinsonism and Richardson's syndrome did not begin until 55 years later when he was 72 years of age. His certain diagnosis of ALS/PDC is confirmed by neuropathologist Dickson.

Conclusions: Our observations explain the manner and reasons for the orderly decline of ALS/PDC by the latency of its phenotypes, after ending of its cause on Guam in the 1950s. Although, the etiology of ALS/PDC is still not identified, its long latency is similar to such chronic infections as postencephalitic parkinsonism, SSPE and prion disease, and suggests a similar pathogenesis.

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The Slovakia assisted living study: Prevalence, recognition and treatment of dementia, parkinsonism and depression in the assisted living population of Slovakia

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Objective: To obtain a direct estimate of the prevalence of dementia, parkinsonism and depression among residents of assisted living in Slovakia and their rates of recognition and treatment.

Background: Cognitive decline, parkinsonism and depression are frequent accompaniment of ageing. Prevalence of these disorders rises together with age. Among residents of assisted living facilities there is presumption of higher occurrence of these disorders.

Methods: 866 people living in assisted living facilities (mean age 77,7 years) were examined in order to review the occurrence of cognitive deficit, depression, parkinsonism and other monitored diseases. Patients were evaluated by neurologists professionally focused on neurodegenerative disorders and dementias. Cognitive functions were evaluated by means of MMSE and depression was evaluated by means of GDS (Geriatric depression scale).

Results: Out of the total there were 113 residents (13%) with parkinsonism. This number includes 61 "probable" and 52 "possible"

cases. 83 of parkinsonian patients (73,5%) suffered from dementia, 59% of these patients suffered from depression. The most frequent cause of parkinsonism was Parkinson's disease, followed by Vascular parkinsonism, Lewy body disease, Drug induced parkinsonism, Frontotemporal dementia with parkinsonism and Fahr disease. Only half of these patients were admitted in the assisted living facility with the diagnosis of parkinsonism. Only 31% of patients were treated with antiparkinsonics, only 2,65% of parkinsonian patients with dementia were treated with AChE inhibitors and only 18% of parkinsonian patients with depression were treated with antidepressants.

Conclusions: By means of this review we were monitoring three major neuropsychiatric problems that affect people living in assisted living facilities – cognitive deficit, depression and parkinsonism. All these three entities were significantly under-diagnosed and under-treated in assisted living facilities setting. This finding emphasizes the need for accurate detection and treatment of mentioned disorders also in assisted living facilities and nursing homes.

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Prevalence of parkinsonism in a health maintenance organization from Buenos Aires City

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Objective: The goal of this study is to assess the prevalence of the different parkinsonisms in a health maintenance organization (HMO) from Buenos Aires City, Argentina.

Background: Parkinson's disease (PD) is the most frequent parkinsonism (Ps). Little is known concerning the prevalence of other Ps in South America.

Methods: The population were all members of the "Plan de Salud, Hospital Italiano de Buenos Aires", a large prepaid health medical organization in Buenos Aires City. Regular surveillance of the HMO's computer-based medical record system for Ps or related disorders and the computerized pharmacy system to identify persons that had received antiparkinsonian drugs was conducted by movement disorders specialists. Patients were divided in 6 categories using international criteria for each Ps: PD; Secondary parkinsonism (SP): pharmacological, vascular; multiple system atrophy (MSA); Progressive Supranuclear Palsy (PSP); Cortico Basal Degeneration (CBD); Lewy Body Disease (LBD); and Indeterminate (Ind)for patients who were not able to classify. Prevalence was calculated with 95% confidence interval for eacht Ps at 31/12/2008 and expressed in cases per 100,000 affiliates.

Results: From a total of 148,301 members older than 18 years, 627 Ps were identified, with a median of 80.7 years. Sixty per cent (375) were female. Estimated prevalences per 100,000 affiliates for each groups were: PD 236,94 (IC95% 209–264,88); SP 84,39 (IC95% 67,38–101,4); MSA 3,24 (IC95% 0–7,22); PSP 5,68 (IC95% 0,67–10,68); CBD 2,43 (IC95% 0–5,98); LBD 72,22 (IC95% 56,42–88,01) and Ind 103,86 (IC95% 85,08–122,64).

Conclusions: Coincidently with the literature PD was the most frequent Ps and atypical Ps (PSP, MSA) were within expected values. We observed a high prevalence of Ind probably related with the methodology used for case detection.

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Involuntary movement in Bickerstaff brainstem encephalitis

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Objective: To clarify characteristics and frequencies of involuntary movement in Bickerstaff brainstem encephalitis (BBE).

Background: BBE is characterized by progressive, relatively symmetric external ophthalmoplegia and ataxia by 4 weeks and disturbance of consciousness. Although parkinsonism was described in Case 1 of the original report by Bickerstaff and Cloake (1951), there have been few case reports of involuntary movement in BBE.

Methods: Serum samples of patients were referred for anti-ganglioside antibody testing from hospitals throughout Japan. Medical records were reviewed of patients for a diagnosis of BBE who had acute ophthalmoplegia, ataxia and impaired consciousness. We examined detailed clinical profiles and laboratory findings of the BBE patients who showed involuntary movement during the illness.

Results: Among 134 patients who fulfilled the BBE criteria, five (4%) showed involuntary movement. Three patients had parkinsonism (tremor and rigidity). These patients developed parkinsonism on days 8, 8 and 30 and disappeared with course on days 11, 21 and 44. Two patients developed ballism on days 5 and 30, and disappeared with course on days 8 and 60. Serum IgG anti-GQ1b antibodies were positive in all the five patients. In one of the patients with ballism, T_1-weighted MRI showed high intensity abnormalities in the globus pallidus. Brain MRI of another four patients was normal. Electroencephalogram showed β waves in two patients, θ waves in two and normal in one.

Conclusions: Four percent of the BBE patients presented parkinsonism and ballism during the illness course, supporting CNS involvement in BBE. Recognition of the existence of such patients may be helpful for the diagnosis and treatment of BBE.

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Combining data from healthcare databases in Europe: A study of dopamine agonists

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Objective: To demonstrate the value of combining data from multiple databases to address urgent safety issues, such as the risk of cardiac valve fibrosis with dopamine agonist use.

Background: To explore the association between rare exposures and outcomes, a single automated database may not provide sufficient sample size and heterogeneity of exposure needed for comparative pharmacoepidemiologic drug safety research.

Methods: Cohorts of new users of either 1) DAs or 2) levodopa, and 3) database, gender and age-matched controls from general population were identified from THIN-UK, Italian HSD-THALES, Dutch-IPCI GP databases, and Dutch-PHARMO record linkage system between 1996 and 2007. After database-specific extractions using common data model, a unique output dataset was created.

Results: During the study period, cohorts identified were: 1) DA users for PD (N=10,790) or hyperprolactinemia (N=8,386), 2) levodopa (N=14,669), and 3) controls (N=29,311). Statistically significant differences on DA use were observed among Countries. Overall, cabergoline was the most frequently used DA (43%), irrespective of indication of use, with highest use in Italy (47%) and lowest use in UK (22%). Non-ergot DAs had the highest use in UK (35%) and NL (25%) and lowest use in Italy (18%).

Conclusions: Combining data from multiple databases increases study size and heterogeneity of exposure, which can facilitate drug comparisons.

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The emerging role of spinocerebellar ataxia 17 in a Canadian movement disorders clinic

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Objective: To determine the importance of routine testing for Spinocerebellar Ataxia (SCA) 17 and to outline the first two cases in the Southern Alberta Movement Disorders Clinic (SAMDC).

Background: SCAs are a heterogenous group of autosomal dominant (AD) ataxias. In the SAMDC, longitudinal follow up of patients

since 1998 has shown that SCA3 is the most common AD ataxia (24%, 5 families) followed by SCA2 (14%, 3 families), and SCA6 (10%, 2 families). No etiology was found in 38% based on data collected prior to availability of testing for SCA17. SCA17 testing is now available but not included in our standard SCA panel.

Methods: Two patients with positive genetic testing for SCA17 were reviewed and the prevalence of SCA17 determined. Banked DNA samples were tested in other patients with AD history of SCA for SCA17.

Results: Patient #1, female, presented at age 40 with a 5 year history of progressive gait disturbance, prominent cerebellar findings and hyperreflexia. Worsening gait, spasticity, urinary incontinence, and dementia resulted in significant care requirements by age 50. Of 3 sisters, one had similar symptoms. Patient #2, female, presented at age 26 with depression, 2 years of progressive gait difficulty, and visual hallucinations. Initial exam showed bradykinesia, ataxia, and hyperreflexia. Progression resulted in home placement by age 32. Her mother had similar symptoms. SCA17 testing was positive in both patients 10 and 7 years after presentation with 53 and 55 repeats, respectively. Both families had initially been included in the 38% of AD ataxias without a known genetic etiology.

Conclusions: Of the AD SCAs, SCA17 appears to have a significant prevalence of 10% in our region, as high as SCA6. We recommend genetic testing for SCA17 be included in the routine panel of AD SCAs.

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Attributable risk of passive community metal exposure on urban incident Parkinson's disease: A GIS study of medicare beneficiaries

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Objective: To determine the association between neighborhood release of copper, lead, and manganese and urban PD incidence using Medicare claims data and Environmental Protection Agency metal release data.

Background: Many studies have focused on rural, agricultural risk factors and risk of PD; little is known about PD risk factors for those living in urban areas. Copper, manganese, and lead are established neurotoxins associated lewy body component formation *in vitro*, clinical parkinsonism, and possibly PD. A recent study suggests that PD among Medicare beneficiaries is non-randomly distributed, with clustering of cases in regions that contain metal emitting facilities (A W Willis et al., *Neuroepidemiology,* 2010).

Methods: We conducted a retrospective cross-sectional study of 29 million U.S. Medicare beneficiaries aged 65 and older in the year 2003. PD incidence in urban areas was determined using beneficiaries who had lived in the same county since at least 1995. Cumulative onsite release of copper, manganese and lead from the EPA Toxic Release Inventory from 1988-1998 was used to create exposure categories of "no" reported release (<100lbs per year) or "high" reported release (>75th percentile) for each metal. We compared PD incidence between urban counties with high reported release of each metal to urban counties with no reported release of all three metals.

Results: Over 17,000 urban incident PD cases were identified by ICD-9 code. Age, race, and sex standardized PD incidence (new cases per 100,000) in counties with no copper, lead or manganese output was 320.17 (95%CI: 278.06-367.55). Incidence was greatest in urban counties with high manganese release, 560.50 (95%CI: 414.64-730.04), followed by urban counties with high copper release, 487.84 (95%CI: 446.16-533.58). Urban counties with lead release had a slightly greater incidence 328.69 (95%CI: 279.04-384.51). Among urban dwelling people with PD, the etiologic attributable risk percent was 41.38% (95%CI: 33.85%-48.04%) for copper and 44.56% (95%CI: 33.55%-53.75%) for manganese.

FIG. 1 (243). Age, race and sex standardized prevalence (per 100,000) of Parkinson Disease among Medicare beneficiaries in the United States (year=2003).

FIG. 2 (243). Location of TRI reporting copper, manganese and lead facilities, 1988–1998.

Conclusions: PD incidence among Medicare beneficiaries is greater in urban areas with high industrial release of copper and manganese. Environmental exposure to metals may account for an important fraction of PD cases in urban areas.

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Malignancy frequency analysis in a Parkinson's disease patients sample

I. Ybot, F. Vivancos, A. Tallon, E. D-Tejedor (Madrid, Spain)

Objective: To analyze the frequency of malignant neoplasms (MN) in an out-patients sample of Parkinson's disease (PD) cases attended at a PD office in LPUH.

Background: It's been described a low MN incidence and prevalence in PD patients (PDpt). Some genetic mutations may influence inversely in both pathologies, promoting the degeneration of cells, and avoiding uncontrolled cell proliferation mechanisms at the same time.

Methods: Performing a detailed randomized review of 126 medical histories of PDpt diagnosed from 1971 to 2009, according to The UK Brain Bank Criteria, and telephone interviews, we obtained a definitive full data sample of 107 cases. All patients consented for reviewing and anonymous publication of medical data. We analyzed: sex, birth date, age at the moment of inclusion (iA), age at PD symptoms onset (PDA), time of evolution (Et), age at diagnose of MN(MNA), MN type (smoking or non smoking-related, melanoma); smoking, alcoholic use and physical activity to sweat (PA); weigh (W,Kg), height (H,meters), body mass index (BMI); PD

treatment (L-Dopa, or not), and familiar history of PD and malignancies.

Results: Population analysis: 55,1% (n=59) men, 44,9% (n=48) women; iA: 35y-91y, mean (m) 68,23y; PDA range (y): [19-83] (m=58,68; SD=12,6); Et: 0-43y (m=9,55). 63,6% (n=68) had never smoked; 26,2% (n=28) were ex smokers (9,3%, n=10, <20 cigarettes/day; 16,8%, n=18, >=20cig/day); 9,3% (n=10) were active smokers (4,7%, n=5, <20cig/day; 4, 7%, n=5, >=20cig/day). 70,1% (n=75) never drunk alcohol; 19,6% (n=21) presented daily alcohol intake; 6,5% (n=7) drunk 1-6 days/week (d/w); 3,7% (n=4) did it occasionally. 61,7% (n=66) performed no usual sweating PA; 20,6% (n=22) did it 3 or more d/w; 13,1% (n=14) did it once/twice a week; and 4,7% (n=5) did it occasionally. BMI:99,1% (n=106)>=30 Kg/m2 and 0,9% (n=1) was 26-29. MN frequency: 84,1% were never diagnosed of MN (n=90), whereas 15,9% (n=17) were; 6,5% (n=7) of these latter, were smoking-related MN; and 9,3% (n=10) weren't. There was no melanoma case. 92 subjects received L-Dopa treatment and 15,2% (n=14) presented MN, in contrast to 20% (n=3) of 15 patients who didn't received this treatment.

Conclusions: Our data confirm a decreased prevalence of MN in PDpt. There's no melanoma in our sample,according to previous studies that reject L-Dopa relation with this MN, but against those ones that do establish it. Our results must be compared in healthy people to analyze the RR of MN in our PDpt.

POSTER SESSION 1
MONDAY, JUNE 14, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 14:00-15:30

GENE THERAPIES AND CELL-BASED THERAPIES

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Transgenic porcine xenografts: A model of brain immune response in parkinsonian primates

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Objective: To study survival, functional differentiation and local immunological modulation of transgenic embryonic pig xenografts in the brain of parkinsonian macaques.

Background: Neural grafting of embryonic mesencephalic neurons in Parkinson's disease (PD) has shown biochemical and clinical recovery post-surgery but limited long-term survival of the graft probably due to disease-related toxicity, potential immunological rejection and neuroinflammation. To test such hypothesis, we developed a model of xenotransplantation in PD primates implanted with embryonic neuronal tissue from either wild type or transgenic pigs expressing CTLA4-Ig, an immunosuppressive molecule that confers resistance to T lymphocyte-mediated rejection in the brain.

Methods: 6 *macaca fascicularis* were injected with 0.25mg/kg MPTP until the appearance of PD symptoms. Ethovision analysis of videotapes was used to determine the total distance moved in cm. PD animals were unilaterally injected with CTLA4+ pig embryos (e28) into the left putamen and kept under peripheral immunosuppression. All animals underwent magnetic resonance imaging and positron emission tomography scans with ^{18}F-radiolabelled L-DOPA before and after MPTP intoxication and 6 months after grafting. 3 brains were recovered for histology.

Results: Behavioural analysis shows a recovery of spontaneous locomotor activity in PD grafted animals at 6 months. Imaging PET data shows a unilateral increase in L-DOPA signal on the grafted hemisphere. Histology of 3 subjects reveals a large porcine graft composed of dopaminergic, serotoninergic and gabaergic differentiated neuronal cells and various glial components.

Conclusions: Preliminary histology and ongoing behavioural characterization suggest survival and differentiation of CTLA4+ porcine embryonic grafts in the striatum of immunosuppressed PD primates as shown by positive PET scans of the grafted striatum and graft-induced alleviation of disease symptoms.

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Derivation of dopaminergic neurons from human embryonic stem cells and IPS cells in animal-free conditions ready to use them in a treatment of Parkinson's disease

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Objective: Our main objective is to generate highly pure midbrain dopaminergic neurons from induced pluripotent (IPS) cells and human embryonic stem cells (hESC) in adherent and animal-free conditions to use them in a treatment of Parkinson's disease (PD).

Background: HESC and IPS cells provide unique models to study early events in human development. The hESC- and IPS- derived neural cells can potentially be used to replace or restore different tissues including neuronal that have been damaged by disease or injury. We have recently reported a highly efficient method to generate functional regional specific neurons in adherent conditions from hESCs. In this study the cells of two different pluripotent lines were converted to neural rosettes using adherent and animal-free conditions.

Methods: The hESC or IPS cells were exposed to chemically defined medium that contains insulin, transsferrin, sodium selenite and animal-free supporting matrix. Exposing the progenitor cells in a form of rosettes to ascorbic acid and BDNF we obtained functional midbrain dopaminergic neurons suitable for use in a treatment of animal models of PD.

Results: The gene and protein expression profile of obtained IPS- and hESC- derived dopaminergic neurons was confirmed by RT-PCR and immunocitochemistry. These cells express markers characteristic for dopamine neurons: Lmx1a, Aldh1a1, TH, TrkB, and have similar expression levels of DA and DOPAC. The functional characteristics of dopaminergic neuronal precursors were confirmed by patch clamp analysis and HPLC. These findings suggest that our differentiation protocol has the capacity to generate electrophysiologically active dopamine neurons under in vitro conditions without embryoid body formation, co-culture with stromal cells and without presence of mesodermal or endodermal cell lineages.

Conclusions: The results reported here provide a very simple and efficient protocol that can serve as an experimental tool to study factors and processes involved in human neural development under defined in vitro conditions. This is important for the studies of developmental biology and will be critical for the future success of cell replacement therapy in PD patients.

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Evidence of motor recovery after retinal pigment epithelial (RPE) cells implantation in the rat model of Parkinson's disease (PD)

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Objective: To assess the therapeutic potential of RPE cells for treating PD.

Background: Striatal transplantation of dopamine or DOPA (dihydroxyphenylalanine) producing cells is a promising approach in treating PD. RPE lines the inner layer of retina and play vital role in visual function of the eye. These cells produce DOPA as a precursor to their characteristic pigment melanin and hence can be used in the cell transplantation strategies of PD management. We used RPE cells passively attached to gelatin microcarriers for transplantation in the rat model of PD and observed recovery in motor function by performing Rotarod test.

Methods: Eyes for RPE isolation were obtained from the National Eye Bank, AIIMS, New Delhi. RPE cells were isolated by the mechanical method i.e. by gently scrapping the RPE layer after removing anterior of the eye. RPE cells were grown and maintained contamination free for up to 5 passages. Dry microcarriers (Cytodex 3, Sigma) were hydrated and autoclaved. RPE cells and microcarriers were gradually mixed in aliquots and incubated for 24 hr at 37oC in CO2 incubator. Approximately 5000 cells (attached to microcarriers) were stereotactically implanted in the 6-OHDA (6-hydroxydopamine) lesioned rat model of PD using coordinates: for lesion, AP= −5.3mm, L=2.5mm, DV=7.7mm; for transplantation, AP=1.5mm, L=2.3mm, DV=5.0mm, according to atlas by Paxinos. A total of 16 rats were lesioned with 6-OHDA and divided into two groups with 8 rats per group; Group 1 with no transplantation and Group 2 with RPE transplantation. Rotarod testing was done 4 times: post lesion (PL), week 4 post transplantation (PT), week 8 PT and on week 12 PT. Rats were allowed to sit on the rotating rod (speed set at 10 rotations/min) and the fall time was recorded. The same was done 3 times per day for 3 consecutive days. For the comparison and statistical analysis, only the 3rd day readings were used.

Results: Average duration (in seconds) on rotarod on day 3 by both groups was: Group 1- PL=112s, 4th W=93s, 8th W=132s, 12th W=131s; Group 2- PL=116s, PT4=168s, PT8=200s, PT12=220s.

Conclusions: Group 2 showed significant improvement in the rotarod performance as compared to the control group thereby supporting the therapeutic role of these cells.

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Investigation of optimal transduction targets in the nigrostriatal system for pleiotrophin gene therapy in a parkinsonian rodent model

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Objective: To determine the optimal pleiotrophin (PTN) transduction site(s) within the nigrostriatal system for maximal neuroprotective and neurorestorative effects.

Background: Our laboratory has shown that the trophic factor PTN is vital for development, maintenance, and repair of the nigrostriatal dopamine system. We have demonstrated that striatal overexpression of PTN that recapitulates peak developmental levels provides significant neuroprotection for tyrosine hydroxylase immunoreactive (THir) neurons in the substantia nigra (SN), significantly increases striatal THir neurite density, and can reverse functional deficits in forepaw use. PTN functions like glial cell-line derived neurotrophic factor (GDNF) in the nigrostriatal system, and GDNF gene transfer has been shown to achieve optimal functional restoration when trophic factor overexpression occurs simultaneously in both the SN and striatum (Kirik et al., 2000).

Methods: Rats were unilaterally injected in the striatum, SN, or both with recombinant adeno-associated virus serotype 2/1 (rAAV2/1) expressing PTN and green fluorescent protein (GFP) or GFP alone. Four weeks post vector injection all rats received unilateral intrastriatal injections of 6-hydroxydopamine (6-OHDA). Rats were tested for forelimb asymmetry prior to vector injection, immediately before and 4 weeks post-lesion. Stereological analyses of transduction volume, SN THir neuron survival, and striatal THir neurite density are ongoing.

Results: Our results suggest that striatal PTN overexpression produced by PTN gene transfer can provide neuroprotection and promote functional recovery in the nigrostriatal system. Optimal PTN transduction sites are to be determined.

Conclusions: The current study will deduce if nigral, striatal, or transduction of both structures will be optimal for neuroprotection and functional restoration. Optimal surgical PTN transduction parameters are essential for development and use of PTN gene transfer as an effective therapeutic strategy for Parkinson's disease.

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A phase I clinical trial on the safety and efficacy of ProSavin® a dopamine replacement gene therapy for Parkinson's disease (PD): An interim report

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Objective: To evaluate the safety, tolerability and efficacy on motor impairment of a new dopamine replacement gene therapy (ProSavin®) in patients with Parkinson's disease (PD).

Background: Oral dopaminergic treatments have remained the primary standard of care for PD. Although highly efficacious in the early stages of disease, their discontinuous intake is associated with debilitating long term side effects. We have developed a lentiviral vector (ProSavin®) derived from the equine infectious anaemia virus expressing the three key dopamine biosynthetic enzymes (tyrosine hydroxylase, aromatic L-amino acid decarboxylase and GTP cyclohydrolase-1). ProSavin was previously demonstrated to mediate dopamine production and cause behavioural correction in the rat model (Azzouz et al., 2002) and in a severe MPTP-lesioned non human primate model (Jarraya et al., 2009).

Methods: We conducted a phase I open label clinical trial in six patients with PD assessing ProSavin in two doses (group 1, 1X, n=3, 12 months post-surgery follow-up ; group 2, 2X, n=3, 6 months post-surgery follow-up). The primary endpoints are : (1) the number and severity of any adverse events associated with ProSavin administration, including the incidence of dyskinesias, and (2) the patients' responses to ProSavin administration by assessment using, the UPDRS Part III, six months following surgery.

Results: No serious adverse events were observed throughout the study, specifically there were no OFF state dyskinesias, no immune response to ProSavin and no surgical serious adverse events. All patients decreased their OFF L-dopa UPDRS III score. The highest motor improvement observed was up to 52.9% at 6 months (mean improvements of 28% and 33.5% in groups 1 and 2 respectively).

Conclusions: Our data demonstrates the safety of ProSavin and encourgaging signs of efficacy. A double-blind, placebo-controlled (sham surgery) trial of ProSavin in PD is highly warranted to demonstrate the degree of any thereupeutic benefit and to rule out any placebo effect.

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Enriching the environment for haematopoietic stem cell transplantation in MPTP-treated primates

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Objective: To determine the viability and potential of CD133s in a GDNF-enriched environment to repair, replace, or regenerate the loss of DA in the striatum of bilaterally MPTP-treated parkinsonian-like primates.

Background: Previous findings from our laboratory indicate that human umbilical cord blood (hUCB), particularly the fraction of CD133 stem cells, yields significant behavioral and histological improvements over human embryonic stem cells in a rodent model of Parkinson's disease (PD). In comparison to hESCs, hUCBs are a heterogeneous population rich in haematopoietic stem and progenitor cells, lack ethical implications, can be collected easily and noninvasively, and are more immune immature than other adult stem cells. One concern about hUCB cells is their propensity to migrate out of the transplant site. The present study examined the effects of striatal CD133 transplantation with and without pretreatment with striatal glial cell line-derived neurotrophic factor (GDNF) transfection.

Methods: Cynomolgus monkeys (n=10) were lesioned with both a right intracarotid and systemic injection of MPTP. The monkeys were symptomatically stable for over a year before transfected with GDNF (n=5) or needle sham lesioned (n=5) one month prior to transplantion with CD133 stem cells (n=10) into the right putamen. Timed arm-reach tasks and Clinical rating scores on/off L-dopa were performed weekly and before sacrifice. One monkey from each group was sacrificed at one month after transplantation and the remainder at four months. The brains, livers, spleens, bone marrow, lymph nodes and peripheral blood were taken from all primates for immunohistochemistry. Tissue sections were stained for tyrosine hydroxylase (TH), dopamine transporter (DAT), neuronal nuclei (NeuN), CD133 human nuclei (CD133), or double-labeled for DAT and CD133 for cell counts.

Results: All subjects demonstrated improvement in both behavioral assessments. The greatest statistically significant improvement was ipsilateral to the graft. The most fundamental finding thus far is that, when transplanted into a GDNF-enriched striatum, more CD133 stem cells remain at the injection site.

Conclusions: Our data suggest that combining transfection with a neurotrophic factor prior to transplantation with hUCB cells may enhance the retention, dopamine (DA) phenotype and restorative properties of the cells at the graft site.

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Therapeutic microinjection of autologous adult human neural stem cells and differentiated neurons for Parkinson's disease: Five-year post-operative outcome

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Objective: Neural stem cell-derived neurons offer new cellular therapeutic alternatives for diseases of the central nervous system. Selective neural repair can be particularly valuable in progressive degenerative diseases with discrete cell loss, like Parkinson's disease.

Background: Some benefits were previously demonstrated following transplantation of fetal embryonic tissue. This approach, however, carries inherent risks of immunological reactions, infectious transmission, and intractable dyskinesias, in addition to serious ethical concerns.

Methods: Cortical and subcortical tissue samples were obtained during neurosurgical procedures. Neural stem cells were isolated and expanded in vitro for several months. Safety, differentiation and functional studies were performed during the expansion phases. Nine months after harvesting, autologous cell suspensions containing differentiated dopaminergic and GABAergic neurons were microinjected unilaterally in a patient with advanced Parkinson's disease. 18F-dopa PET studies and neurological evaluations were performed serially (pre/post-operatively).

Results: Over the next 36 months, the overall Unified Parkinson's Disease Rating Scale (UPDRS) improved by 81% while "on" medication and 83% while "off" medication. At five-years post-operatively, clinical motor scores returned to baseline. At three and twelve months post-operatively, 18F-dopa PET studies showed a 55.6% and 33.2% increase in dopamine uptake in the implanted left putamen.

Conclusions: Adult neural stem cells derived from a patient's cerebral tissue can become a source of differentiated neurons, useful for grafting in the treatment of Parkinson's disease. The combined GABAergic and dopaminergic cells produced a long lasting motor improvement. This approach has the potential to make neural stem cell therapy acceptable and available to a large number of patients.

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Grafted serotonin neurons aggravate L-DOPA induced dyskinesia: In vivo evidence by microdialysis and [18F]fallypride PET imaging

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Objective: To provide direct in vivo evidence that development of L-DOPA induced dyskinesias in grafted parkinsonian rats is due to uncontrolled release of dopamine (DA) from serotonin (5HT) terminals in the striatum.

Background: Conventional DAergic VM transplants contain a variable numbers of 5HT neurons due to boundaries used for tissue dissection. 5HT neurons are able to convert L-DOPA to DA and store in vesicles. In the absence of sufficient DAergic innervation, release of DA from 5HT neurons might be uncontrolled which could worsen dyskinesia. 5HT1A/1B agonists can effectively block occurrence of dyskinesia both in parkinsonian and in grafted rats.

Methods: DA denervation was induced in SD rats by injection of 6-OHDA into the MFB. 4 weeks after lesioning, all animals received daily 6 mg/kg L-DOPA (+10 mg/kg benserazide) over 4 weeks to induce stable dyskinesia. Animals were divided into 3 groups to receive either 5HT or DA-rich cells deposited into the striatum, while a third group was kept as control. 8 and 12 weeks after grafting, abnormal involuntary movements (AIMS) were evaluated after L-DOPA challenge. Brain extracellular levels of DA and 5HT were measured by microdialysis. DA receptor occupancy was measured by PET. Rats were then perfused for postmortem analysis.

Results: In contrast to slight increase in control dyskinetic and 5HT-rich grafted animals, AIMS scores significantly decreased in the DA-rich grafted group. Microdialysis experiments showed that the KCl-induced DA release capacity significantly increased after L-DOPA administration in animals grafted with 5HT-rich cells. Micro-PET under baseline conditions showed that (1)following 6-OHDA lesioning binding potential for [18F]Fallypride was increased, (2)5HT-rich grafts did not correct this abnormality and (3)DA-rich grafts were functionally effective. PET imaging after L-DOPA administration is ongoing.

Conclusions: In line with the literature there were a good survival of DA-rich cell transplants and they were functionally effective. On the contrary, L-DOPA induced dyskinesia were increased in the 5HT-rich transplant group. Microdialysis data showed that 5HT cell transplants use L-DOPA as a source of DA which could be released from stores by KCl induced depolarization.

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Restore neurotrophin signaling to enhance functional restoration following neural stem cell transplantation in Parkinson's disease

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Objective: In the present study restoration of neurotrophin signaling was attempted through co-transplantation of Neural stem cells (NSCs) and Olfactory Ensheathing Cells (OECs) using rat model of PD and the molecular events involved therein were explored.

Background: NSCs have given a new avenue to cell replacement therapy of Parkinson's disease (PD), the efficacy of which could be enhanced by increasing their post transplantation survival and integration with the host tissue. Several factors could influence this and irregularities in neurotrophin signaling could be one of them, as impaired neurotrophin levels and suppressed neurotrophin signaling

has recently been reported in Parkinson's disease and this could be targeted to enhance functional restoration. OECs are specialized glia and have been reported to impart long term neurotrophin support to transplanted NSCs following co-transplantation.

Methods: Rat model of PD was prepared through unilateral stereotaxic injections of 6-OHDA (8 μg/2μl in 0.2% L-ascorbate saline) in the right medial forebrain bundle following coordinates (in mm with respect to bregma): anterior posterior (AP)=4.4, lateral (L)=1.2, ventral (V)=7.8 followed by intrastriatal transplantation of NSCs pre differentiated to dopaminergic neurons, alone or together with OECs. For transplantation, NSCs (express nestin, PSA-NCAM) and OECs (express p75NTR) obtained from ED13 rat fetuses and adult olfactory bulb respectively were cultured and used.

Results: Four weeks post transplantation the animals assessed for modulation in neurotrophin signaling, exhibited a significantly restored PI3K/Akt signaling in co-transplanted animals as evident from enhanced levels of p-Akt and its downstream effectors p-GSK and p-CREB, which correlates well with survival of grafted NSCs, restored TH expression and neurobehavioral restoration compared to 6-OHDA lesioned or NSCs alone transplantation.

Conclusions: The results suggest that modulation in PI3K /Akt pathway could be targeted for better functional restoration following NSCs transplantation in PD.

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Vascular endothelial growth factor-B186 improves motor behavior in vivo in a rat model of Parkinson's disease

X. Yue, T. Falk, S. Zhang, S.J. Sherman (Tucson, Arizona, USA)

Objective: To investigate whether Vascular Endothelial Growth Factor-B (VEGF-B186) has a neuroprotective effect in a unilateral 6-hydroxydopamine (6-OHDA) rat in vivo model of Parkinson's disease (PD).

Background: The treatment of PD using neurotrophhic factors has shown preclinical promise, but so far successful translation into clinical trials has proven difficult. This could be due to problems with the delivery systems or the choice of an appropriate growth factor. We have previously proved that VEGF-B is up-regulated after rotenone treatment and exogenous VEGF-B167 is neuroprotective in a rotenone in vitro model of PD. This indicated that VEGF-B, a trophic factor distinct from the glial-derived neurotrophic factor (GDNF) family of trophic factors, is activated by neurodegenerative challenges to the midbrain.

Methods: (1) We added exogenous VEGF-B186 (5ng/ml), the more diffusible isoform of VEGF-B, to rat midbrain cultures on day 6. The cultures were fixed on day 11 and dopaminergic cell number was analyzed by tyrosine hydroxylase immunocytochemical staining. (2) Intra-striatal infusion of VEGF-B186 (3μg/4μl) or vehicle (PBS, 4μl) prior to a 6-OHDA lesion (20μg/rat, 6 hours) were performed in 12 adult SD rats (6 rats/group). Amphetamine (5mg/kg, i.p.) induced ipsilateral rotation and cylinder test were observed at 2 weeks post lesion. The experiment is ongoing.

Results: (1) VEGF-B186 (5ng/ml) has a neurotrophic effect comparable to the effect of VEGF-B167 in the midbrain cultures ($p<0.05$, n=9 culture dishes/group, two tailed t test). (2) We have preliminary evidence that intra-striatal infusion of VEGF-B186 6 hours prior to the 6-OHDA lesion improves behavioral measures indicating a neuroprotective effect. VEGF-B186 reduced amphetamine mediated ipsilateral rotation significantly, as compared to vehicle-injected controls, at 2 weeks after the 6-OHDA administration ($p<0.05$; n=6/group; two tailed t test). The cylinder test evaluating forepaw preference showed a trend of overcoming the lesion-induced right forepaw preference in VEGF-B186 treated animals (n=6/group) after treatment although no statistical difference was observed.

Conclusions: Our preliminary data suggest that VEGF-B could be a new candidate trophic factor for the treatment of PD.

POSTER SESSION 1
MONDAY, JUNE 14, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 14:00-15:30

HUNTINGTON'S DISEASE

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Postural control in Huntington's disease–cross sectional results from the TRACK-HD study

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Objective: To investigate postural stability with 1) eyes closed (EC) 2) eyes open (EO) in controls, premanifest (preHD) and early manifest Huntington's disease (HD) gene-carriers and to investigate correlations to clinical scores, disease burden and volumetric brain measures.

Background: Impaired postural stability is a well known feature of HD. A retropulsion test as well as gait parameters are included in the standard clinical assessment battery, the Unified Huntington's Disease Rating Scale (UHDRS). Objective measures of related functional disabilities are of interest as outcome measures in clinical trials.

Methods: 115 controls, 115 premanifest and 111 (110 EC) manifest HD subjects stood in a designated position on a force plate. Three trials were registered in each condition (EO and EC). Linear models of center of mass mobility (distance, surface, and velocity) were calculated and correlated to UHDRS, disease burden, and volumetric brain measures.

Results: All groups were distinguished from each other in both conditions. The differentiation of preHD vs. controls reached higher p-values in the EO condition. Volumetric brain measures (except whole brain volume), disease burden, and clinical scores of disease severity were correlated to all measures for the combined gene-positive group and the early HD group. Motor score correlations were also found in the premanifest group. Using voxel-based morphometry postural instability was correlated with reduced grey matter (caudate, occipital lobe and cerebellum) and white matter (corpus callosum, internal, and external capsule).

Conclusions: Static stabilometry using a force plate may serve as an outcome measure for motor dysfunction in HD and preHD with higher effect sizes in manifest disease. Longitudinal performance will be assessed in follow-up visits of TRACK-HD. Acknowledgment: TRACK-HD is supported by the CHDI/High Q Foundation, a not for profit organization dedicated to finding treatments for HD.

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Evaluating methods to enrich clinical trial populations in individuals at-risk for Huntington's disease: The prospective Huntington's disease observational at-risk study (PHAROS)

K.M. Biglan, S. Eberly, D. Oakes, E. Kayson, J. Warner, A.B. Young, I. Shoulson, HSG PHAROS Investigators (Rochester, New York, USA)

Objective: To determine the preferred methods for enriching clinical trial populations in individuals at-risk for Huntington's disease (HD).

Background: Future trials in individuals at-risk for HD aimed at delaying the onset of disease will require large sample sizes and long duration of follow up. Enriching clinical trial cohorts for those individuals closest to onset or those more likely to exhibit measurable abnormalities may improve trial efficiencies.

Methods: PHAROS (*Arch Neurol* 2006; 63:991) investigators unaware of gene status assessed all domains of the Unified Huntington's disease Rating Scale (UHDRS) in participants at-risk for HD. Data were analyzed by CAG expanded (≥37) versus non-expanded (<37). A repeated measures analysis of the UHDRS by dichotomous (≥ or<0.15) 5-year probability of estimated onset (Langbehn formula), quartiles of pathological burden scores (age x [CAG–35.5]) (*Ann Neurol* 1997;41:689) and quartiles of age at enrollment were performed.

Results: Individuals near to onset showed worse motor, behavioral and cognitive measures than non-expanded individuals. Individuals far from onset were indistinguishable from non-expanded on motor and cognitive measures but were similar to near to onset on behavioral measures. Individuals in the highest quartile of disease burden were worse on motor, cognitive and functional measures than the lower quartiles and non-expanded. There was no clear relationship between quartiles of disease burden and behavioral measures. The two highest age quartiles at enrollment (>40) performed worse on motor scores relative to non-expanded while the lower two quartiles (≤40) performed similarly to the non-expanded group.

Conclusions: Probability of estimated onset, pathologic burden scores, and age may all be useful methods for enriching clinical trial populations in individuals at-risk for HD. Pathologic burden score may be the most useful method as it is more precise than age, taking CAG repeat length into account; and unlike estimated onset can be used to follow individuals after disease onset. In addition, it is an estimate of the degree of pathologic involvement at the time measured and makes no prediction about future disease course.

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Longitudinal analysis of intermediate CAGn repeat length expansion in the prospective Huntington's disease at-risk observational study (PHAROS)

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Objective: To evaluate the clinical phenotype of individuals at-risk for Huntington's disease (HD) with intermediate CAGn repeat expansions.

Background: Recent reports suggest that some individuals with intermediate CAGn repeat expansions in the huntingtin gene may develop manifest HD (*Mov Disord* 2007;22:127). It remains unclear, however, how to counsel individuals with intermediate repeat length expansions regarding their risk for disease.

Methods: PHAROS (*Arch Neurol* 2006; 63:991) investigators unaware of gene status assessed all domains of the Unified Huntington's disease Rating Scale (UHDRS) in participants at-risk for HD. Data were analyzed by CAG expanded (≥37), intermediate (27-36), and non-expanded (≤26). Subjects missing CAG data (n=4) and those with a motor diagnosis of HD (rated ≥99% diagnostic confidence) at baseline (n=14) were excluded. A repeated measures analysis adjusted for age and gender measured select motor, cognitive, behavioral and functional measures of the UHDRS over time.

Results: Of a total of 983 participants were analyzed, 51 (5.1%) had an intermediate repeat expansion, 345 (35.1%) were expanded, and 587 (59.7%) were non-expanded. The mean (SD) duration of follow up was 5.6 (2.7) years with a maximum follow up of 10 years. Participants with intermediate repeat length expansions behaved like non-expanded individuals for UHDRS motor, cognitive and functional measures but behaved like expanded individuals (worse) on UHDRS behavioral measures.

Conclusions: Individuals in a cohort at-risk for HD with intermediate CAGn expansions (27-36) behave similarly over time to those without expansion, but have worse behavioral symptoms similar to expanded individuals. This suggests that shorter expansions than traditionally deemed pathologic may influence the behavioral phenotype in HD and may increase the risk of future disease onset. Because of the relative rarity of intermediate repeat expansions, confirmation in larger cohorts over longer periods of time will be necessary to determine the effect of intermediate expansions on clinical phenotypes.

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Intergenerational variability of Huntington's disease (HD) with intermediate CAG repeat lengths: A case report

N.L. Chan, Y. Bordelon, W. Grody, S. Perlman (Los Angeles, California, USA)

Objective: To explore the intergenerational variability in clinical presentation and age of onset of HD patients with intermediate CAG repeat lengths in the "gray zone."

Background: It is well known that the age of HD onset is roughly inversely proportional to the length of the expanded CAG trinucleotide repeat in the huntingtin gene. Yet CAG repeat length accounts for only 50-70% of age of onset variability and the remainder of variation in both onset and clinical phenotype may be accounted for by other modifying genes and/or environmental factors. Additionally, intermediate repeat lengths in the gray zone, between 36-39 repeats, are associated with reduced penetrance. Expression of disease in patients carrying such repeat lengths is quite variable and not well documented.

Methods: We conducted a chart review on a father and daughter who have genetically confirmed HD repeat lengths in the gray zone.

Results: The patient is a 46 year old woman with genetically confirmed HD with 38/17 CAG repeats. She first developed mild orobuccolingual and proximal upper extremity chorea at age 44. The chorea progressed slowly over the past two years to involve her entire face, trunk and upper extremities. She has also developed mild gait difficulty with poor balance, an ataxic dysarthria, dysphagia and depression. She otherwise remains cognitively intact and independent. She came to medical attention only after her father was recently diagnosed with HD at age 67. His gene testing revealed 37/17 CAG repeats and his clinical course is dominated by recent cognitive dysfunction and gait instability, without chorea.

Conclusions: We present an intriguing case of significant intergenerational variation in both age of onset and clinical presentation in a daughter and father with CAG repeats in the gray zone in the huntingtin gene differing by only one trinucleotide repeat. This further supports the role of additional modifying genes and/or environmental factors in the development of HD, especially in patients with reduced penetrance alleles. Further investigation into these modifying factors are thus warranted and have important implications in both prognosis and genetic testing.

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Cognition and brain metabolism of preclinical mutation carriers of Huntington's disease: A follow-up study

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Objective: To explore cognitive performance and glucose metabolism in the brain of preclinical mutation carriers of Huntington's disease over a two year period. This study is part of an ongoing follow-up project on the development of a reliable biomarker of neuronal dysfunction in preclinical Huntington's disease.

Background: Carriers of the Huntington's disease (HD) mutation who do not yet suffer from motor symptoms are considered preclinical mutation carriers (PMCs). HD not only leads to progressive loss of motor functions but also causes cognitive, behavioural and emotional changes, eventually leading to dementia. However, it is unclear

which of these domains is most informative in marking an individual's transition from healthy functioning to clinical HD. Brain pathology is thought to occur firstly and most severely in the striatum, but changes in other brain regions will also arise, resulting in widespread brain atrophy. It has not yet been clarified which specific pathological processes in the brain may be responsible for the diversity in cognitive dysfunction of PMCs. Given the interconnections between basal ganglia and cortical areas, we expect cognitive function to be affected early in the disease process.

Methods: 22 PMCs and 13 controls underwent neuropsychological assessment, neurological examination and ^{18}F-fluorodeoxyglucose (FDG). All measures were repeated after two years.

Results: Cross sectional analyses of our data already showed that all but one PMC had normal cognitive performance at baseline and follow up. However, metabolic abnormalities appeared in roughly half of them, with the putamen being affected most often. Psychomotor tasks correlated significantly with putamen metabolism. Possible changes over time in metabolic function are now being analysed.

Conclusions: Metabolic changes can already be shown in PMC who do not yet present with motor or cognitive signs of HD. Putamen metabolic activity correlates with psychomotor performance of PMC. The two year period may be too short to capture significant change over time. A further follow-up will be planned to evaluate cognitive function and brain activity 9 years after baseline.

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Are gait and step initiation parameters early markers of Huntington's disease in presymptomatic mutation carriers?

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Objective: To quantify gait and gait initiation in presymptomatic Huntington's disease (HD) subjects.

Background: Presymptomatic mutation carriers (PMC) present early gait disturbances. Gait initiation combines preparation and execution of the first step. Interaction between motor and cognitive aspects of preparation and execution of movement can be studied using a paradigm of gait initiation with and without external cueing.

Methods: 17 PMC were recorded and compared to a group of 25 healthy controls (HC) for gait initiation and 57 HC for gait. They had to walk at their preferred speed and to initiate gait with and without an external beep.

Results: PMC demonstrated decreased walking speed, cadence, reduced stride length and increased stride-to-stride variability. Only this latter parameter seemed accurate to differentiate PMC from HC with appropriate sensitivity (0.81) and specificity (0.87). PMC demonstrated decreased 1st step duration compared with HC in both conditions. PMC also presented shorter amplitude of the postural adjustments in PMC compared with HC. These impairments were more pronounced in the self-triggered condition. No strong correlation between locomotion and motor, neuropsychological or psychiatric assessments were observed in PMC.

Conclusions: [We confirm early impairment of gait in PMC. Preparation and execution of the 1st step are impaired in PMC particularly in self-triggered condition. Temporal parameters of step execution (duration), but also spatial parameters of postural adjustments preceding 1st step (backward shift of the centre of pressure) could be considered as early markers of the disease. However, only few parameters (stride-to-stride variability, 1st step time in self-triggered condition) could be used as a diagnostic tools to differentiate PMC from HC.

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Impact of caffeine intake on Huntington's disease (HD) course

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Objective: To determine whether in HD, the age at onset (AAO) (primary endpoint) and the rates of functional, motor and cognitive decline (secondary endpoints) are influenced by caffeine intake.

Background: Currently, HD progression cannot be prevented by any neuroprotective treatment despite major advances in the understanding of its pathogenesis. The relationship between the AAO and the length of the CAG repeat expansion accounts for nearly 60% of the variance whereas the 40% remaining would be due to other genetic and environmental factors. Caffeine is a non-selective A2 adenosine (A2A) receptors antagonist which are selectively localised on striatal medium-sized neurons expressing enkephalin and dopaminergic D2 receptors, known to be the most vulnerable ones in the HD.

Methods: 62 HD patients were included from 8 Huntington French Speaking Network sites over a six-month period. Information about caffeine consumption was collected with one validated self-questionnaire. All patients were evaluated twice a year (at least 1 year between 2 assessments) using the Unified Huntington's Disease Rating Scale. Factors influencing AAO were examined using a stepwise regression analysis.

Results: The comparable rates of functional decline and demographic characteristics with other published studies suggest that our limited population was representative of HD patients. The mean daily caffeine intake from all sources for the period of the last 10 years was 226 mg/day. We found a significant correlation between AAO and caffeine intake (R^2=0,041, p=0,016), so high caffeine intake was associated with earlier AAO. However, we failed to demonstrate a relation between caffeine intake and the rate of functional, motor and cognitive decline.

Conclusions: Our findings could have a great therapeutic impact because they suggest that caffeine could be the first environmental modifier of AAO in HD. Consequently, the modulation of A2A receptors may represent new therapeutic approaches of HD.

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Two case reports of "almost homozygous" alleles in patients afflicted with Huntington's disease with divergent clinical manifestations

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Objective: Objective: To present 2 separate case reports of patients who each possessed two "almost homozygous alleles" of different CAG repeat expansions (each patient had copies of both full and Intermediate penetrance). Both patients developed different severity of clinical manifestations of Huntington's disease (HD) at different ages.

Background: Background: Huntington's disease is a genetically dominantly transmitted disease caused by a defect in the CAG repeat sequence greater than 35 triplets. Repeat size inversely correlates with age of onset. A separate category of HD alleles termed the "intermediate alleles" consists of patients that posses between 27 and 38 repeat CAG sequences. The intermediate alleles are not known to cause HD, yet have the potential to mutate into the disease range. To our knowledge, no prior case of an affected individual with a homozygous genetic composition of 2 very different CAG repeat sequences (full penetrence and Intermediate) has gone on to develop HD. We present 2 different patients each with homozygous alleles of varying penetrance who developed HD at different ages. What makes this scenario even more distinct are the several aspects of genetic testing from the two cases that may lead to various ethical dilemmas?

Methods: Methods: Two patients; age 39, -with a full penetrance allele (49) and an intermediate allele (30), and a second patient, age 69 with a reduced penetrance allele (38) and an intermediate allele

(28) are presented. Clinical histories, videotaped examination, and family pedigrees were obtained.

Results: Results: Genetic testing revealed in patient one alleles of 49 and 30 repeat sequences and in patient two, alleles of 38 and 28 repeat sequences. Both are unusually rare combinations of penetrance in patients who both developed HD. Family pedigrees of both patients and videotapes of each patient's clinical symptoms will be provided.

Conclusions: Conclusion: Two patients with varying degrees of CAG repeat sequences, both "almost homozygous" that developed divergent clinical manifestations of HD. These results also raise certain ethical dilemmas in regards to genetic testing of offspring and other family members.

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[^{123}I]-FP-CIT/SPECT for evaluating dopamine presynaptic terminal involvement in Huntington's disease: A pilot study

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Objective: To evaluate the usefulness of SPECT in assessing damage to the pre-synaptic dopaminergic system in Huntington's disease (HD) using [^{123}I]-FP-CIT (DaTSCAN), a selective radioligand with regulatory approval as the diagnostic test for investigating functional dopaminergic neuron loss in the striatum in Parkinson's disease.

Background: Dopaminergic neurotransmission appears to be important in the pathophysiology of HD symptoms. Post-mortem studies have demonstrated severe reductions in dopaminergic post-synaptic receptors (predominantly subtypes D1 and D2) in the striatum, confirming post-synaptic nigrostriatal dopamine system damage. However, the existence of pre-synaptic dopamine neuron dysfunction is subject to debate.

Methods: We studied twelve symptomatic HD patients using DaTSCAN/SPECT imaging. [^{123}I]-FP-CIT caudate and putamen uptake levels were qualitatively and semi-quantitatively analyzed to assess pre-synaptic damage in the striatal dopamine system. Possible correlations were analyzed between HD severity on the Unified Huntington's Disease Rating Scale (UHDRS), duration of clinical symptoms, and [^{123}I]-FP-CIT/SPECT striatal uptake.

Results: DaTSCAN/SPECT qualitative analysis showed reduced striatal uptake in eight patients. Semi-quantitative analysis revealed a significant reduction in four. Of these four, uptake reduction was at putamen level in all, and also at caudate level in one. Although we observed no linear correlation between HD severity and reduced striatal [^{123}I]-FP-CIT uptake, the patients with the worst UHDRS scores had more severe reductions in radioligand uptake.

Conclusions: This is the first study to use in vivo [^{123}I]-FP-CIT/SPECT imaging to confirm prior descriptions using PET of a pre-synaptic dopaminergic system defect in HD. Our results suggest that [^{123}I]-FP-CIT/SPECT may be useful in evaluating dopaminergic neurotransmission integrity in HD.

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Sleep and sleepiness in Huntington's disease (HD): Effects on patient and caregiver quality of life

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Objective: To better understand the association of sleep difficulties and daytime sleepiness in patients with Huntington's disease, their effect on quality of life, and their effect on the sleep and quality of life of their caregivers.

Background: HD is thought to affect nighttime sleep and may cause daytime sleepiness. These disturbances may also affect the sleep of caregivers, and may adversely affect quality of life of patients and caregivers.

Methods: 48 patients with Huntington's disease and 40 of their caregivers were interviewed during a routine clinic visit. HD subjects were administered surveys including Epworth Sleepiness Scale (ESS) and Pittsburg Sleep Quality Index (PSQI). They rated daytime sleepiness and sleep quality using Visual Analog Scales. HD subjects' demographic information, UHDRS score, disease duration, and CAG repeat number were recorded. Caregivers were administered the caregiver burden scale and rated their own sleep quality and daytime sleepiness using Visual Analog Scales. Descriptive statistics and Spearman rank correlation coefficients (r_S) were used to analyze the data.

Results: 20 male and 28 female HD subjects and their caregivers participated in the study. The mean age of patients was 51 (SD 13.1) years, the mean UDHRS was 35.72 (SD 13.86), and the mean disease duration was 4.40 (SD 3.84) years. Medications included SSRI in 24, benzodiazepines in 18, anticonvulsant non-benzodiazepine in 3, chloral hydrate in 4, neuroleptics in 12, other non sleep medications in 26, and other sleep medications in 3 subjects. 25% of subjects had excessive daytime sleepiness (ESS >10) and all had poor quality sleep (PSQI>5). There was a significant association between poor sleep quality and daytime sleepiness in HD subjects ($r_S=0.32$, $p=0.03$). Caregivers of subjects with more severe disease had worse sleep at night (r_S 0.41, $p=0.01$). Caregivers who have difficulty sleeping at night were more sleepy during the day (r_S 0.51, $p=0.00$) and had higher caregiver burden (r_S 0.36, $p=0.03$).

Conclusions: Sleep disorders are frequently reported by HD subjects and their caregivers. Poor sleep quality in caregivers adversely affects caregiver burden. Additional study is required to determine whether adequate treatment of sleep disorders in HD lessens daytime sleepiness of patients and their caregivers, and the burden of caregiving.

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Pioglitazone ameliorates behavioral, biochemical and cellular alterations in quinolinic acid induced neurotoxicity: Possible role of peroxisome proliferator activated receptor-ϒ (PPARϒ) in Huntington's disease

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Objective: The present study was designed to evaluate the neuroprotective potential of pioglitazone in attenuating behavioral, biochemical and cellular alterations in Quinolinic acid induced neurotoxicity.

Background: Peroxisome proliferator activated receptor-ϒ (PPARϒ) is a member of the PPAR family of transcription factors and proposed to play an important role in neuroinflammatory conditions such as PD, HD, stroke etc. Emerging evidences indicates that PPARϒ activators attenuate neuroinflammatory cascades in various neurodegenerative complications such as PD, stroke etc.

Methods: Quinolinic acid (QA) was administered unilaterally in rat brain striatum. Pioglitazone (10, 20, 40 mg/kg, p.o.) was administered for 21 days in QA-treated animals. During 21 days protocol, behavioral parameters (body weight, locomotor activity, balance beam walk performance) were assessed on day 1, 7, 14 and 21. On day 21, biochemical parameters (oxidative stress, mitochondrial function, tumor necrosis factor- α levels) were estimated and striatal lesion volume measurements were done.

Results: Intrastriatal administration of QA significantly altered body weight and motor function (locomotor activity and beam walk performance) as compared to sham treated group. Further, intrastriatal QA treatment significantly caused oxidative damage (increased lipid peroxidation, nitrite concentration and decreased endogenous antioxidant enzymes), mitochondrial enzyme complex (I, II & IV) activities and TNF-α level as compared to sham treated animals. Pioglitazone treatment significantly improved body weight and motor function (locomotor activity and balance beam walk performance), oxidative defence (attenuate lipid peroxidation, nitrite concentration and restored endogenous antioxidant enzyme) and mitochondrial

enzyme complex levels as compared to QA treated group. Further, pioglitazone treatment significantly attenuated the striatal lesion volume in QA treated animals, suggesting a role for the PPARϒ pathway in QA induced neurotoxicity.

Conclusions: Altogether, this evidence indicates that PPARϒ activation by pioglitazone attenuates behavioral, biochemical and cellular alterations in QA-treated animals and this could be an important therapeutic avenue to ameliorate the HD like symptoms.

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Nigrostriatal function in Huntington's disease: Evidence from a SPECT study

L. Kiferle, E. Unti, D. Volterrani, C. Rossi, D. Frosini, G. Manca, V. Nicoletti, U. Bonuccelli, R. Ceravolo (Pisa, Italy)

Objective: To evaluate (1) the integrity of nigrostriatal projections and (2) whether the dopamine transporter (DAT) levels are correlated with clinical and neuropsychiatric features in a group of Huntington's disease patients.

Background: Controversy exists over whether there is loss of nigrostriatal terminals in HD. Postmortem studies of HD substantia nigra reported conflicting results, varying from minimal neuronal loss to 40%. The few imaging studies evidenced a reduction of striatal DAT uptake and vescicular monoamine transporter type-2 in HD. No correlation with clinical data has been investigated yet.

Methods: 7 HD patients and 7 controls age-matched underwent SPECT scans with ^{123}I-FP-CIT, a tracer that selectively binds to DAT, following an adequate drug wash-out. The association between clinical aspects (age of onset, duration and severity of disease, number of triplets, severity of involuntary movements and bradikynesia), neuropsychological assessment (verbal and visuospatial memory, attentive, executive and abstractive capacities), neuropsychiatric features (NPI) and striatal DAT uptake (ROI approach analysis) was explored.

Results: Striatal ($p<0,05$), caudate ($p<0,05$), putaminal ($p<0,01$)uptake was significantly lower in patients with respect to controls. No correlation between striatal uptake and clinical or neuropsychological features was found. Patients with prevalent neuropsychiatric symptoms at disease onset showed a lower striatal uptake in comparison with patients with prevalent cognitive and motor onset.

Conclusions: Reduced striatal DAT binding suggests nigrostriatal pathology in HD, that could be related to substantia nigra degeneration. The absence of any correlation with age of onset, disease duration and severity as well as number of triplets could suggest that nigrostriatal pathology occurs early in the course of the disease. The lack of any correlation between clinical and neuropsychological features with striatal DAT uptake might suggest that motor and cognitive aspects in HD are not related to nigrostriatal degeneration. The finding of a different striatal pattern in HD with a behavioural onset needs to be explored in a larger cohort.

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The iron content in brains in Huntington's disease

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Objective: It has been hypothesized that changes of iron content in the brain may be involved in the pathogenesis of Huntington's disease (HD). In our previous study we found a significant shortening of T2 relaxation time (T2) in the pallidum (GP) ($P<0.00001$) and an increase of T2 in the frontal white matter (FWM) ($P<0.05$) of HD patients compared to controls. The aim of our study was to detect whether the deposits of iron change during the disease progression.

Methods: To ascertain the hypothesis, we re-investigated 12 HD right-handed patients from previous study within the mean interval 3.6 (SD 0.5) years. Twelve healthy control subjects for comparison of fractional anisotropy (FA) were scanned using the same MR protocol.

Results: We found a significant decrease of T2 relaxation time in the left GP ($P<0.01$) and a significant increase of T2 relaxation time in the FWM on both sides ($P<0.01$) in HD patiens compared to their first MR examination. We found a significant decrease of FA in the FWM in HD patients compared to the control group (left $P<0.001$; right $P<0.04$).

Conclusions: These results suggest an additional increase in the iron concentration in the left GP. Progressive iron accumulation may be caused by higher oxidative stress in the dominant hemisphere. It could not be explained by the atrophy of the GP because marked asymetric pallidal degeneration in HD was not observed. Previous studies also failed to reveal physiological age-related iron increase in the GP after 25 years of age. We suppose that the increase of T2 in the white matter may be related to the further desorganisation of the FWM tracts due to the possible defect in axonal transport, suggested in a number of neurodegenerative diseases.

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Valproate increases the survival in a transgenic mouse model of Huntington's disease

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Objective: Huntington's disease is a devastating neurodegenerative disorders. The pathophysiological processes involve excitotoxicity, reduced gene transcription due to the decreased level of histone acetylation and accompanied by the loss of gamma-aminobutyric acidergic (GABAergic) medium-sized spiny neurons in the striatum. Thus, the antiepileptic drug valproate, which has GABAergic, antiexcitotoxic and histone deacetylase inhibitor effects, might exert a beneficial neuroprotective effect in this disorder.

Methods: We have tested the effect of valproate on survival in the N171-82Q transgenic mouse model of HD, following its intraperitoneal administration in a daily dose of 100 mg/kg and studied the motor performance in open field test.

Results: Valproate significantly prolonged the survival of the transgenic mice and significantly ameliorated their diminished spontaneous locomotor activity, without exerting any noteworthy side-effect on their behaviour.

Conclusions: The beneficial effect of valproate can be explained by its complex pharmacological activity including histone deacetylase inhibitor effect. The poor designed previously clinical trials indicated no clinical benefit in Huntington's disease, it is worth considering a new trial design with higher dose and sufficient number of participating patients.

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Effect of MK-801 against intra-striatal quinolinic acid induced Huntington's like behavioral, oxidative stress and cellular alterations in rats

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Objective: In the present study, first the dose of quinolinic acid that mimics the symptoms of HD was standardized and then the neuroprotective effect of MK-801 (noncompetitive NMDAr antagonist) was evaluated against intrastriatal quinolinic acid induced behavioral, oxidative stress and cellular alterations in rats.

Background: Huntington's disease (HD) is a common neurodegenerative disorder characterized by motor disturbances, subcortical dementia and psychiatric problem. Pathogenesis of HD revolves so far around excitatory amino acids as the primary cause of neuronal loss. However, number of recent reports suggests the involvement of excitotoxicity and oxidative damage.

Methods: A single unilateral (ipsilateral striatum) injections of quinolinic acid (100, 200 and 300 nM) were made in to striatum. Animals were tested for motor functions using actophotometer and

rotarod apparatus followed by various biochemical estimations (Lipid peroxidation, redox ratio, nitrite level, catalase, super oxide dismutase) and mitochondrial enzyme complex I to IV) were assessed.

Results: Quinolinic acid (300 nM) significantly reduced the body weight and caused motor in-coordination and produced oxidative damage in the cortex and striatum as indicated by raised lipid peroxidation, nitrite concentration, depletion of superoxide dismutase, catalase and different glutathione levels. Beside, quinolinic acid (300 nM) significantly altered the mitochondrial enzymes complex levels and caused histopathological alterations in the striatum. MK-801(0.02, 0.04, 0.08 mg/kg, ip) treatment significantly improved body weight, behavioral alterations (locomotor activity and rotarod performance) and attenuated oxidative damage and mitochondrial enzymes complex dysfunction. Besides, MK-801 treatment significantly reversed histopathological alterations in striatum.

Conclusions: The results suggest the antioxidant and neuroprotective action of MK-801 against the quinolinic acid induced Huntington's like behavioral, oxidative stress and cellular alterations in rats.

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Using the Mattis Dementia Rating Scale (DRS) to track cognitive change in Huntington's disease (HD)

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Objective: To assess change over time on the Mattis Dementia Rating Scale (DRS) in Huntington's disease (HD).

Background: Cognitive outcome measures are needed for clinical trials of disease-modifying and symptomatic therapies in HD. The Mattis DRS is an easily administered scale for dementia that may be sensitive to executive dysfunction. It was recently used as a primary outcome measure in a 24-week study of a cholinesterase inhibitor in another subcortical dementia, Parkinson's disease (Dujardin et al, 2006). Little is known, however, about longitudinal change on this measure in HD.

Methods: We used a mixed effects model to analyze DRS scores obtained during five years of follow-up of 137 subjects with HD.

Results: Mean follow-up time was 2.8 (1.2 SD) years. Mean age of the subjects was 45.8 (11.5 SD) years and mean number of CAG repeats was 45.2 (4.5 SD). Mean rate of decline on the DRS was 3.2 (3.5 SD) points/year for the whole group, but 3.9 (2.7 SD) points/year for those with baseline MMSE <26. Using the DRS for cognitive trials in HD, the sample size required to detect a clinically significant 50% slowing of decline in subjects with baseline MMSE <26 would be 106 patients/arm (alpha=0.05, power=90%).

Conclusions: The Mattis DRS declines significantly over time in an unselected HD population. Because of its sensitivity to executive dysfunction and ease of administration, the Mattis DRS may be a useful outcome measure for assessing effects of a therapeutic agent for cognition in HD.

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Efficacy and safety of the dopaminergic stabilizer pridopidine (ACR16) in patients with Huntington's disease

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Objective: To study the effects of the dopaminergic stabilizer pridopidine (ACR16) on symptoms and function in Huntington's disease (HD).

Background: The clinical phenotype of HD includes motor symptoms, behavioral disturbances and cognitive decline. Patients with HD are often treated with medications for which evidence of efficacy is lacking. Pridopidine is a dopaminergic stabilizer, a novel class of drugs that act at dopamine-2 receptors and display state-dependent behavioral effects. Pridopidine has psychomotor stabilizing properties in animal models with relevance to HD and has not been shown to induce bradykinesia. We hypothesized that pridopidine would reduce the phenotypic expression of HD and performed a randomized, double-blind, placebo-controlled trial.

Methods: Patients with HD received pridopidine (50 mg/day, N=28), or placebo (N=30) during a four weeks trial. The primary outcome measure was the change from baseline in weighted cognitive score, assessed by cognitive tests (Symbol Digit Modalities, Verbal fluency and Stroop tests). Secondary outcome measures included changes in the Unified Huntington's Disease Rating Scale, Hospital Anxiety and Depression Scale, Leeds Sleep Evaluation Questionnaire, Reitan Trail Making Test A and Clinical Global Impression of Change. Safety assessments were also performed.

Results: There was no significant difference between pridopidine and placebo in the change from baseline of the weighted cognitive score. However, secondary measures such as affective symptoms showed trends towards improvement and there was significant improvement in voluntary motor symptoms compared with placebo ($P<0.05$). Pridopidine was well tolerated, with a safety profile similar to placebo.

Conclusions: Pridopidine may improve voluntary motor dysfunction in HD without negatively affecting involuntary movement. Larger longer-term trials are warranted.

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Therapeutic indications and prescription habits in Huntington's disease: Results from the REGISTRY observational study

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Objective: This study aims to characterize the distribution of the more frequent therapeutic indications and corresponding pharmacological choices in Huntington's disease (HD), assessing its variability in several european countries.

Background: The recommendations for the treatment of HD are mainly dependent on expert opinion. An evidence-based treatment in HD is flawed by a lack of proven efficacy for most of the pharmacological interventions presently used.

Methods: Demographic, phenotypical and medication data were collected from the participants (asymptomatic mutation carriers and individuals with symptomatic HD) of the REGISTRY study between 2004 to 2007. Indications were identified and translated into English homogeneously. We calculated the frequency of therapeutic indications and corresponding prescribed drugs for the total cohort and for each country. The project was approved by the Scientific and Bioethics Advisory Committee of the EHDN.

Results: 1569 participants from 13 european countries were included. Female: 53.7%. Mean age±SD: 49.6±12.1. Mean age of disease onset±SD: 42.3±11.6. 369 different therapeutic indications were found in a total of 5049 entries. Depression (734 or 48.78% patients), and chorea/dyskinesia (675 or 43.3% patients) were the most frequent indications in 12/13 countries. Further, in 9/13 countries these were the two most frequent indications. Psychosis, insomnia and irritability were the second most frequent indications in Denmark, Portugal and United Kingdom, respectively. Overall, the most frequent used drugs for the indication depression were citalopram (n=180, 24.5%) and paroxetine (n=159, 21.7%). For chorea/dyskinesia the most frequent options were tiapride (n=197, 21.9%) and tetrabenazine (n=163, 18.1%). For both indications, the relative frequency of each of these drugs varied significantly between countries.

Conclusions: Across Europe, depression and chorea/dyskinesia are the most frequent indications for treatment in HD. The list of clinical problems for which therapeutic interventions were identified evidences the variability of prescription habits in Europe as well as the need to address relevant symptoms of HD as apathy, irritability and cognitive impairment that currently are not prioritized by clinicians.

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Assessing patients' access to tetrabenazine (xenazine) after FDA approval

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Objective: To assess patient satisfaction with regard to current accessibility of the drug as compared to prior utilization through IND, granted to JJ in 1979.

Background: In 2008, the monoamine depleting drug tetrabenazine (Xenazine) was approved by the FDA for the treatment of the chorea associated with Huntington's disease (HD). The drug is now available as an orphan therapy through specialty pharmacies.

Methods: A self-administered questionnaire was constructed to assess patients' experiences, costs, and attitudes related to perceived efficacy and tolerability of tetrabenazine prescribed for the treatment of a variety of hyperkinetic movement disorders. A mail survey was then conducted using as study population all patients currently enrolled in the tetrabenazine treatment program at the Baylor College of Medicine Parkinson's Disease Center and Movement Disorders Clinic (PDCMDC).

Results: The questionnaire was mailed to 265 patients and 240 (90.6%) completed the survey. The respondents included 76 (31.7%) patients with Tourette's syndrome, 87 (36.2%) with tardive dyskinesia, and 42 (17.5%) with HD. Tetrabenazine use for more than 5 years was reported by 95 (39.6%) respondents. Prior to taking tetrabenazine, 220 (91.7%) patients indicated their symptoms made them moderately to severely ill. Of the 235 (97.9%) patients currently taking tetrabenazine, mean daily dose of 54.95±23.91 mg. Some side effects were reported by 135 (56.2%) patients and included drowsiness (29.2%), slowness of movement (14.6%), restlessness (5.4%) and depression or mood change (12.5%). Before FDA approval, 192 (80%) patients purchased the drug from the PDCMDC. With the current Specialty Pharmacy Program, 156 (65%) patients were initially approved for coverage by their insurance carrier; most of the other claims were successfully appealed. Before FDA approval 137 (57.1%) of patients were paying $200-$300 per bottle, but since the FDA approval 200 (83.3%) have less than $100 out-of-pocket cost. Of the responders, 219 (91.2%) patients stated that they were satisfied or very satisfied with their response to tetrabenazine and 205 (85.4%) with the Specialty Pharmacy Program.

Conclusions: Our survey indicates a high level of satisfaction among patients prescribed tetrabenazine for their hyperkinetic movement disorder with cost-effective access to the drug via a specialty pharmacy system.

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Estimation of prevalence and molecular characteristics among Huntington's disease patients of Argentina

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Objective: To estimate the prevalence and characterize the genetic profiles of Huntington's disease (HD) from a cohort of patients in Argentina.

Background: HD is a neurodegenerative disorder caused by the abnormal expansion of CAG repeats, it prevalence rate in Western Europe and United State is 5 to 10 cases per 100,000 people. Although in South America certain populations from Venezuela and Peru represent exceptional communities, there is no information regarding the prevalence of HD in Argentina. Several authors have shown a positive correlation between CAG repeat sizes on normal chromosomes with the frequency of HD; in fact, populations with lower prevalence of HD showed a low CAG size on normal chromosomes.

Methods: We analyzed the genetic characteristics and the CAG repeats in HD gene among 33 noninstitutionalized HD patients and 90 individuals from normal populations of Argentina. The size of CAG repeats was determined in both alleles of patients and controls. These results were compared with worldwide populations. Informed consent was obtained and the study was approved by the institutional boards. Statistical calculations were made using G-Stat 2.0. $P<0.05$ was significant.

Results: The sample included 18 females and 15 males with HD. The mean age of onset was 36.8±14.87 years. Two subjects showed infantile onset. Expanded CAG repeat was inversely associated with age at onset (r: -0.56 for Pearson correlation coefficient, r^2: 31.87%, $p<0.001$). Mean of expanded and unexpanded CAG repeats were 45.33 and 18.73 respectively in HD, whereas in normal individuals this number was 17.82 repeats. Less than 15% of the pooled normal alleles were in the >20 repeats range; intermediate alleles were not found. The CAG size in normal individuals has been found to be intermediate between Western (mean=18.4) and Chinese (16.4) or African (16.2) populations.

Conclusions: In this Argentinean cohort the estimated prevalence of HD is expected to be lower than in Western European populations. Although Western European ancestry has been reported in 80% of the Argentinean population, additional geographical or environmental factors might contribute to the variation of prevalence rates in different populations.

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Decreased levels of serotonin receptors in the basal ganglia of a murine Huntington's disease model

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Objective: To study changes in serotonergic transmission in the R6/2 mouse model of HD.

Background: The 5-HT1B receptor is particularly enriched in human basal ganglia. Few and contradicting results about the role of disrupted serotonin receptors exist in the literature about HD.

Methods: The R6/2 HD model was used. Binding studies with CP93129, iodocyanopindolol and RTI-55 were performed as well as in situ hybridisation for the 5-HT1B in the striatum.

Results: We found reduced 5-HT1B mRNA in the striatum and reduced 5-HT1B binding in the GPi and SNr and GTPgS binding in its projections to the GPe. Binding to RTI-55 was also reduced to both DAT in the striatum and SERT in the GPe.

Conclusions: These results are of interest since, in animal models of other movement disorders, a new role of serotonin in the pathogenesis of dyskinesias has recently emerged. In the future we would like to study how disrupted serotonin function in other brain regions contribute to both cognitive decline and mood disorders which are present in HD. There is a decrease in dopamine receptors and a relative excess of dopamine in HD. Since dopamine has been postulated to be neurotoxic in HD, it is reasonable to inhibit dopaminergic transmission in terms of symptomatic treatment, one possible way would be by blocking the 5-HT autoreceptors in the striatum. In the present study we found a down regulation of 5-HT1B receptors in the striatum. Furthermore, using the R6/2 mice model of HD we reproduced the findings in human tissue from HD individuals as published by Castro et al. Reduced expression of 5-HT1B autoreceptors may inhibit dopaminergic transmission indirectly. This could be either a compensatory mechanism or just may reflect neuronal loss in the striatum as part of general HD pathology.

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Lack of interaction between acidic nuclear phosphoprotein 32 family member E (ANP32e), protein phosphatase 2A (PP2A) and amino-terminal fragments of mutant huntingtin (Htt) in human neuritic striatal aggregates

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Objective: To evaluate the potential interaction between Anp32e, Htt and PP2A in human striatal tissue and test its relevance in the pathogenesis of Huntington's disease (HD).

Background: Several observations suggest a role for the disruption of axonal transport in the pathogenesis of HD. Huntingtin is a

positive regulatory factor for vesicular transport whose function is lost in cell models of disease.We have identified Anp32e and described its role as an inhibitor of PP2A. We also confirmed that Anp32e regulates PP2A activity in dendrite vesicle trafficking and endocytosis. This protein phosphatase plays an essential role in many aspects of cellular physiology involved in the pathogenesis of HD, including the regulation of vesicle transport directionality.

Methods: Aptamers: We developed monoclonal and polyclonal oligonucleotide based synthesized antibodies (DNA aptamers) against Htt, PP2A and ANP32e, following previously described techniques. Immunohistochemistry and confocal microscopy: Coronal microtome sections of paraffin-embedded human frontal cortex and caudoputaminal junction from four controls and grade 4 adult-onset HD cases were processed for specific aptamer's staining. Control samples were made by preincubation of the aptamers with an excess of blocking peptide. Staining was examined using a confocal laser scanning microscopy.

Results: An amino-terminal fragment of huntingtin was found to interact with Anp32e and PP2A in vesicles and synapses of normal striatal neurons. In human HD-affected striatal neurons, ANP32e and PP2A are reduced and showed no interaction with huntingtin in abnormal neuritic aggregates.

Conclusions: Our findings suggest that the lack of interaction between ANP32e, PP2A and an amino terminal fragment of huntingtin plays a role in the pathogenesis of HD. The loss of the functional association between these proteins could trigger the selective striatal neuropathology of HD through impairment in axonal transport.

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Clinical features of Huntington's disease in 241 Chinese patients

X.-Y. Guo, S.-S. Zhang, B. Zhao, R. Huang, H.-F. Shang (Chengdu, China)

Objective: To thoroughly explore the clinical characteristics of Huntington's disease (HD) in China.

Background: The clinical characteristics of HD in China are unclear.

Methods: A computer-based online search of China National Knowledge Infrastructure was performed to review case reports concerning HD published between 1980 and 2008; the clinical characteristics were analyzed.

Results: A total of 80 studies involving 241 patients (141 males and 100 females) were collected, 82.0% of which were from provinces of North China. In addition, 97.9% of the cases had a family history of HD, and paternal inheritance (64.6%) was greater than maternal inheritance (35.4%). Moreover, onset age was significantly less than from maternal inheritance. The mean onset age of HD was 5.2±11.5 years, mean age of death was 45.6±13.5 years, and the mean course of disease from onset to death was 11.6±5.6 years. Onset characterized by involuntary movement accounted for 69.9%, including 66.4% in the entire body, 16.4% in the upper limbs, and 14.7% in the head and face. Psychiatric symptoms accounted for 26.5%, and disturbed intelligence accounted for 3.0%. In addition, 38.7% of patients were complicated by dysarthria, dysphagia, and cough after drinking. A total of 70.1% displayed brain atrophy and lateral ventriculomegaly on CT or MRI. A total of 88.9% of patients scored <23 in the Mini-Mental State Examination (MMSE). Of the reported patients, only 22 underwent *IT15* gene testing with positive results.

Conclusions: Huntington's disease is more frequently detected in males than females, and the majority has a family history. The disease has high incidence in Northern China, in particular with paternal inheritance. In addition, the disease often struck middle-aged people, and the time of onset in paternal inheritance was earlier than maternal inheritance. There were no significant differences in age of onset between males and females, and the course of disease was not related to paternal or maternal inheritance. The symptoms of onset included involuntary movement, complicated by psychiatric symptoms, and rarely cognitive impairment. In addition, involuntary movement of the pharynx was commonly observed in patients. Genetic detection has been the gold standard for clinical diagnosis of HD, and more attention should be paid to this detection method.

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Molecular diagnosis of Huntington's disease in Peruvian population

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Objective: The aim of our study was to establish the clinical and genetic features, in the largest series of Peruvian HD cases reported in the literature.

Background: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder, characterized by involuntary movements, emotional disturbances and cognitive deficits, caused by a CAG unstable repeat expansion on chromosome 4p16.3.

Methods: We perform molecular diagnosis with the PCR technique, to analyse DNA of 227 patients from the blood samples register at Instituto Nacional de Ciencias Neurologicas, in order to confirm the clinical diagnosis of HD made by a neurologist in patients until 2008. Informed consent was obtained from all patients.

Results: Molecular analyses were available in 227 cases, 58 families were identified with 131 symptomatic carriers. The range of expanded alleles varies between 36 to 59 repeats, the mean CAG repeat in normal allele was 16.95 (sd±3.91), intermediately allele 37.62 (sd±1.16) and the HD causing allele 43.96 (sd±5.95).We found 95 cases with parental inheritance, with predominance with paternal transmission (53.7%). Motor component predominated as the initial symptom (46.6%).We found a significant inverse correlation between age of onset of symptoms and the length of the CAG triplet repeats ($r=-0.628$, $P<0.01$). Also, 9 patients were diagnosed with Juvenile onset with a range between 37–90 repeats, and 9 patients with Late onset with a range between 36–42 repeats.

Conclusions: The molecular analyses were similar to those reported in other population.

POSTER SESSION 2
TUESDAY, JUNE 15, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

PARKINSON'S DISEASE: BEHAVIORAL DISORDER

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Impulsive control disorders in Parkinson's disease

M.R. Arce, N.S. Garretto, T. Arakaki, M.S. Mancuso, V.E. Diaz Aragunde, L. Abaroa (Buenos Aires, Argentina)

Objective: We evaluated the presence of impulsive control disorders (ICD) in patients (p) with Parkinson's disease (PD).

Background: There is increasing recognition that several abnormal behaviors including pathological gambling, compulsive buying and eating, punding and hypersexuality are present in p with dopaminergic treatment.

Methods: So far we have evaluated 203 p with PD. Data were collected by semistructured interview asking about eating, gambling, compulsive buying, hypersexuality and punding. The antiparkinsonian treatment at the moment of ICD and the management of the compulsive behaviors were analized.

Results: Two hundred three p, 107 male (52.7%), age 65±9.72 y/o, duration of PD: 6.92 years, HY stage I: 19.3%, II: 64%, III:16.7%. Fifty one over 203 p (25.1%) showed ICD and 25 of them were males. More than one ICD was observed in 37% of p. Compulsive eating was the most frequent disorder (25p), followed by punding in 16 p, compulsive buying and hypersexuality in 12 p and gambling in 11p. Dopaminergic agonists were taken in 33/51p: combined with levodopa in 27 and 6 as monotherapy. Levodopa was taken alone by the remaining 18 p. There were no differences in age, duration of PD, dopaminergic agonists and levodopa dosis between ICD vs non ICD p. Only 17% of p with ICD needed specific treatment. Quetiapine was used in 2 of them, dopaminergic agonists and levodopa were reduced in 3 and 2 p respectively, pramipexole was discontinued in 1 p and switched to piribedil in 2 p. Three p attend self-help groups and others receive family supervision. In most cases, ICD symptoms were not refferred spontaneously by p. These adverse effects could be mostly unknown considered to be too mild to consult a physician about them.

Conclusions: At the moment ICD is probably underdiagnosed. Early recognition could permit adequate management, thereby avoiding the familiar, financial and professional consequences of this type of behavior disorders.

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Is alexithymia a non-motor symptom of Parkinson's disease?

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Objective: We aimed to investigate the occurrence of alexithymia in PD and whether it is primarily linked to the disease process or secondarily to psychopathology in PD.

Background: The relationship between Parkinson's disease (PD) and alexithymia has received little attention. Only one study showed that alexithymia, and in particular difficulties in describing and communicating emotions, may be a relevant feature in PD and it is often associated with depression, the most common psychiatric disorder in patients with PD. However, studies comparing the frequency of alexithymia in PD patients compared to controls are lacking.

Methods: One hundred controls and 100 PD patients (16 naïve-PD and 84 treated-PD) underwent a clinical and psychopathological evaluation. Alexithymia was assessed with the Toronto Alexithymia Scale twenty item (TAS-20). The severity of depressive symptoms was measured with Beck Depression Inventory and Hamilton Depression Rating Scale. A structural psychiatric interview was used to diagnose major and minor depression. Logistic regression analyses with 95% confidence intervals (CI) were used to assess the associations between alexithymia and PD.

Results: The occurrence of alexithymia was double in PD patients than controls, and increased with increasing depression severity. However, alexithymia was also associated with PD independently from depression; after adjustment for sociodemographic factors, antidepressant use, and Beck Depression Inventory score, PD patients had an almost fourfold higher risk of having alexithymia (OR=3.9, 95% CI=1.5-10.0), and 24 times increased odds of having high scores on the TAS-20 items assessing difficulties in identifying emotions than controls (OR=23.7, 95% CI=10.1-55.6). Treated-PD exhibited more alexithymic characteristics than naïve-PD and controls. However, also naïve-PD patients had higher alexithymia scores than controls.

Conclusions: Ours findings suggest that alexithymia is a non depression-dependent phenomenon in PD patients, which may be associated with the PD disease process. Alexithymia is an important non-motor symptom of PD that should be considered in the diagnosis and management of patients with PD.

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Prevalence of dopamine-related behaviour disorders in parkinsonian patients treated with continuous subcutaneous infusion of apomorphine

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Objective: To assess the prevalence of dopamine replacement therapy (DRT)-related behaviour disorders in patients with Parkinson's disease (PD) treated with continuous subcutaneous infusion of apomorphine.

Background: Some patients with PD develop DRT-related compulsions including Dopamine Dysregulation Syndrome (DDS), punding, and Impulse Control Disorders (ICDs). Pulsatile administration of DRT is believed to be one of the mechanisms underlying these behaviour disorders.

Methods: For this multicenter observational study all PD patients with an apomorphine pump implanted for at least 3 months examined at the outpatients clinic or in the ward over a 3-month period were included. The assessment included UPDRS scoring, DDS diagnostic criteria, Evans punding scale, MIDI impulsivity scale.

Results: 35 consecutive patients from 5 centres were included (mean age: 65.4±12 years; disease duration: 13.1±3.8 years). The mean duration of apomorphine administration was 1.7±1.4 years; mean infusion duration: 14.4±4.5 hours; mean daily dose : 73±43 mg. 10 patients were allowed rescue doses (mean number: 2.5±1 per day; mean dose : 3.9±1 per bolus). The mean total daily levodopa equivalent dose (LED) was 1576±702 mg. 7 patients (20%) tended to increase their DRT intake, 8 (23%) had binge eating, 6 (17%) were compulsive buyers, 5 (14%) were pathological gamblers and 2 (6%) had hypersexuality. There were no addictions to other substances such as tobacco or alcohol. 17 patients (49%) engaged daily in hobbyism for more than 2 hours (mean 3.9±1.7 hours).

Conclusions: We found a high prevalence of punding in PD patients receiving continuous subcutaneous apomorphine. However, the prevalence other behaviour disorders such as ICD and DDS is comparable to that seen in advanced PD patients not on apomorphine.

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Parkinson's disease psychosis (PDP): An under-diagnosed condition in spite of its prevalence and impact

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Objective: To survey the diagnosis of PDP.

Background: Parkinson's disease psychosis (PDP) is a prevalent neuropsychiatric manifestation affecting up to 40% of PD patients. PDP has no appropriate or FDA approved treatment and is a major contributor to caregiver burden and patient institutionalization. However, the disorder is not commonly recognized, and, as we report here, is also under-diagnosed.

Methods: 205 neurologists and 100 psychiatrists were asked to estimate the number of patients in their practice diagnosed with PDP; then were asked to refer to 3 recent PD patient charts and provide their diagnosis and symptoms. A total of 915 charts of PD patients were reviewed with varying degrees of progression.

Results: Physicians estimated that only 18% of their PD patients were diagnosed with psychotic symptoms. Among these cases, the diagnostic term of PDP was used only 36% of the time. Moreover, after chart review of those patient designated as undiagnosed, 14% were found to be experiencing moderate/severe psychotic symptoms.

Conclusions: "PDP", as a diagnostic term, is not widely adopted. Only 36% of PD patients with psychotic symptoms are diagnosed with the term "PDP". In this study, 14% of PD patients experiencing moderate/severe psychotic symptoms were not diagnosed. This suggests psychosis may be under-diagnosed in the PD population. This

study emphasizes the need to increase the awareness and diagnosis of PDP amongst patients, caregivers and physicians through efficient communication/education programs and the development of improved screening/diagnostic tools.

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The relationship between mood and motor phenotype in Parkinson's disease (PD)

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Objective: To explore the relationship between depression, anxiety and motor subtype using data gathered as part of a prospective study of mood state in Parkinson's disease (PROMS-PD).

Background: Previous studies have suggested that depressed mood may be more common in subjects with a postural instability gait difficulty (PIGD) form of PD. Few studies have explored the association between anxiety and motor features.

Methods: Information on depression, anxiety and related symptoms was obtained in 513 PD patients in the "ON" state using the modified Geriatric Mental State (GMS). Self-reported depressive and anxiety symptoms were also assessed using the Hospital Anxiety and Depression Scale (HADS). Motor subtype was determined from the UPDRS parts II and III and information collected for motor complications.

Results: Mean HADS score in the PIGD subgroup was elevated compared with the two other groups for depression (mean estimated differences PIGD vs. tremor dominant=1.15; 95% confidence interval, CI, 0.15–2.15; PIGD vs. indeterminate=1.54, 95% CI 0.04–3.05) and for total score compared with the indeterminate group (mean estimated difference=3.41, 95% CI 0.47-6.4). Distribution of motor phenotype was compared against a mood-related classification, derived from latent class analysis of binary symptom variables from GMS items. Motor phenotypes were not evenly distributed across four groups derived from a latent class analysis of binary symptom variables from GMS items, with relative over-representation of the PIGD subgroup and under-representation of the tremor subgroup in a group with high probability of depressive symptoms relative to the cohort as a whole and other mood phenotypes. Compared with psychologically healthy patients, patients with a high probability of anxiety, with or without depression, showed a higher frequency of motor complications, with the exception of freezing.

Conclusions: We identified a "double-dissociation" between two motor phenotypic factors and mood disturbance: one (PIGD subtype) related to depression in the absence of prominent anxiety and the other (motor fluctuations) related to anxiety, with or without depression. Our findings suggest heterogeneity of mood phenotype in relation to motor features and have potential pathophysiological and therapeutic implications.

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Facial emotion recognition in Parkinson's disease

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Objective: The aim of this study was to investigate differences in recognition of facial emotion expressions in a large sample of PD patients under stable dopaminergic therapy compared to a group of well-matched HC subjects. We also investigated the relationship between facial emotion recognition performances and individual cognitive domains.

Background: Parkinson's disease (PD) patients frequently experience non-motor symptoms such as impaired facial emotion recognition. Contradictory results have been reported in recent studies aimed at investigating one of these non-motor symptoms, that is, impaired facial emotion recognition.

Methods: Seventy PD patients and 70 healthy controls (HC) were submitted to a clinical, neuropsychological and psychopathological evaluation. Facial emotion recognition performance was assessed using Penn Emotion Recognition Test (PERT).

Results: PD patients were impaired in recognizing low- and high-intensity facial emotions of disgust. This effect was selective, because their global ability to recognize emotions was intact. Both PD and HC recognized high-intensity emotions better than low-intensity emotions, except for disgust, which was recognized better at low-intensity. In PD patients, both overall facial emotion recognition and selective disgust recognition performances were related to deficits in many neuropsychological domains such as verbal and visuospatial memory, attention, praxis, executive functions and verbal fluency.

Conclusions: The present study confirms the presence of a selective deficit for disgust recognition in PD independent from stimulus intensity. Disgust facial expression recognition is easier for low-intensity than for high-intensity faces, regardless of which group the subject's belonged to (PD or HC) and, thus, could be the expression of a physiological process. Finally, our findings support those of a relationship between cognitive deficits and impaired recognition of facial emotion of disgust. The ability to recognize emotions should be considered a complex cognitive process. It requires the integrity of several functions, suggesting that the structural or functional derangement of discrete neural pathways involved in these cognitive functions may make it difficult to recognize emotions expressed by others.

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Improvement of punding behavior after bilateral subthalamic stimulation

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Objective: To evaluate the therapeutic effect of subthalamic stimulation (STN-DBS) on punding in patients with Parkinson's disease (PD).

Background: Punding is a stereotypic motor behavior, in which there is an intense fascination with repetitive, excessive and purposeless activitiesincluding less complex acts (e.g. shuffling papers, reordering bricks, or sorting handbags), or more complex acts, such as hobbyism (gardening, painting), writing, or excessive computer use. Punding behaviors are often related to an individual's previous occupation or interests. The prevalence ranges from 1,5% to 14%. Punding in PD is related to the dopaminergic treatment since it is reversible after dose reduction.

Methods: 89 consecutive PD patients were assessed for STN-DBS. They were evaluated for cognitive status and carefully screened for behavioral disorders using the scale for hyper- and hypodopaminergic behaviour in PD (Ardouin et al, 2009). Punding was present in 7 patients (2,2%) and, to date, 2 of them underwent STN-DBS.

Results: Case1: This 50 year old taxi driver developed PD in 2002. He was initially treated with pramipexole and began in the following year to ritually dismantle the central unit of his computer and other electrical equipment, during up to 2 hours perday. After STN-DBS daily levodopa equivalent doses were reduced from 640 mg (L-DOPA 340 mg) to 416 mg (L-DOPA 250 mg) and punding resolved and never reoccurred. Case2: At the age of 45, this very active woman was diagnosed for PD. After 3 years of PD, she developed a complex repetitive behavior of sewing in each free minute, often all night long. Reduction of dopaminergic treatment was not possible due to emerging apathy. At age of 52, she underwent STN-DBS allowing a complete withdrawn of dopaminergic treatment resulting in the disappearance of punding but also worsening apathy.

Conclusions: Similar to other hyperdopaminergic behaviors, punding is improved by STN-DBS and consists in an indication rather than an exclusion criterion for this treatment.

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Risk and learning in impulsive and non-impulsive patients with Parkinson's disease

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Objective: To evalutate decision making and risk behaviour in patients with Parkinson's disease with and without impulsive compulsive behaviour.

Background: Dopamine replacement therapy can lead to impulsive or compulsive behaviours (ICB) such as pathological gambling (PG), hypersexuality, compulsive shopping and binge eating in a minority of patients with Parkinson's disease (PD). Relatively little is known about the interaction between these behavioural changes, medication and cognitive function in Parkinson's disease.

Methods: Twelve patients with idiopathic Parkinson's disease without ICB and 18 PD patients with ICBs were compared against 22 healthy controls. Patients were tested prior to their morning medication (off state) and then retested 1hour after medication (on state). All patients fulfilled the Queen Square Brain Bank criteria for PD and were taking L-dopa. The first task was a forward and backward digit span test to assess working memory. The second task was a learning task in which subjects were required to discern which of two stimuli (a circle and a star) was most often rewarded. After selecting the stimulus they were told whether they have lost money (5 pence) or earned a reward (10 pence). Participants were told to pick the most often rewarded stimulus as many times as possible. The final task was a validated gambling task which was designed to probe the risk aversion of the subjects.

Results: PD patients with ICB showed decreased learning from negative feedback and increased learning from positive feedback off compared to on dopaminergic medication. Their learning profile was the opposite of that found in the PD patients without a diagnosis of ICB. Both patient groups showed increased risk preference on medication relative to controls and the subgroup of ICB patients with pathological gambling were more risk prone than the PD group. Furthermore PD patients with ICB had poorer working memory performance than either controls or PD patients without ICB.

Conclusions: These findings may have therapeutic and clinical implications. The reduction in the overall anti- parkinsonian medication with positive reinforcement of non impulsive behaviour is likely to be more beneficial than aversion therapy in PD patients with impulsive compulsive behaviours.

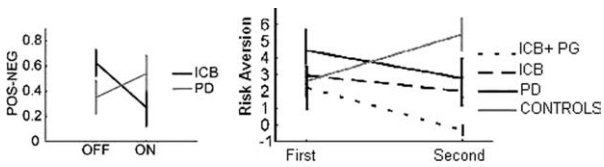

FIG. 1 (286).

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Predictors of impulse control disorders in MMPI-2 in patients suffering from Parkinson's disease: A pilot study

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Objective: To evaluate the specific scales of MMPI 2 questionnaire as detectors and predictors of the impulse control disorders (ICD) in patients with Parkinson's disease (PD).

Background: It is supposed that some characteristics can differentiate the patients in whom dopamine dysregulation syndrome can develop.

Methods: 46 patients suffering from PD (13 with ICD and 33 without ICD) and 56 patients from control group were studied with the Minnesota Multiphasic Personality Inventory MMPI-2. The domains with expected high sensitivity for apparent addictive behaviour were compared between these three groups. The mean disease duration and mean dose of levodopa in PD group were recorded.

Results: There were 46 patients with PD and 56 patients from control group. ICD were identified in 13 patients. The mean age was 64.7 years in ICD group, 63.6 years in PD group without ICD and 58.0 years in control group. The mean disease duration was 11.2 years in ICD group and 5.5 years in PD group without ICD. The mean dose of levodopa was 853.8 mg in ICD group and 501.1 mg in PD group without ICD. Among scales with expected high sensitivity for apparent addictive behaviour were evaluated the scale predicative about self-control insufficient (DISC), social responsibility (Re), alienation self and others (Si3, AAS) and antisocial practises (APS).We found significantly higher scores in Si3 and AAS scales and significant lower score in Re scale in ICD group as compared to other two groups. There were no significant differences in DISC and APS scales.

Conclusions: This is a first comparsion of some personality characteristics concerning to ICD in PD patients. The MMSE-2 might be a good tool for detection and prediction of ICD in Parkinson's disease.

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Clinical characteristics of patients with visual hallucinations (VH) in PD

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Objective: To determine the demographic and clinical variables associated with VH in PD including age, sex, disease duration, dopaminergic medication, sleep disorders (daytime somnolence, nocturnal insomnia and REM sleep behavioural disorder[RBD]), current psychopathology (depression, anxiety and apathy), and presence of cognitive dysfunction including visuoperception.

Background: VH are a common and important non-motor symtpom of PD.

Methods: Physician-administered and self-completed clinimetric scales. 94 participants.

Results: When adjusted for multiple comparisons (Bonferroni correction, significance $p<0.00069$) several clinical variables were significantly different between the VH (N=30) and non-VH groups (N=64): disease duration ($p=0.0001$), treatment duration ($p<0.0001$), motor function (UPDRS part III, $p<0.0001$) and motor complications (UPDRS total part IV, $p<0.0001$), poor sleep in particular excessive daytime somnolence (Pittsburgh Sleep Quality Index [PSQI] daytime subscale, Epworth Sleepiness Scale and SCOPA-sleep-daytime, all $p<0.0001$), RBD ($p=0.0005$), disorders of mood (Hamilton Depression Rating Scale [HDRS] $p=0.0002$, Hospital Anxiety Depression Scale [HADS] total $p<0.0001$, HADS depression $p=0.0004$) and autonomic dysfunction (SCOPA-AUT total, $p<0.0001$). In addition, VH were associated with global cognitive impairment scores (Addenbrooke's Cognitive Examination [ACE] total score, $p=0.0001$ and SCOPA-COG total, $p=0.0004$) but in particular frontal cortical dysfunction (Frontal Assessment Battery [FAB] total score, FAB motor series subscore and SCOPA-COG executive subscore, all $p<0.0001$ and FAB inhibitory control subscore, $p=0.0006$). Several tests of visuoperceptive cortical function including Birmingham Object Recognition Battery (BORB) object decision, overlapping images (both $p<0.0001$), minimal feature match ($p=0.0006$) and association match ($p=0.0002$) were associated with VH. In contrast, there was no association of VH with cognitive tests assessing orientation, attention, verbal fluency, constructional visuospatial tasks (the ACE tasks of intersecting pentagons, Neckar cube and clock face) and low-level visual perceptual tasks on BORB.

Conclusions: Disease duration, motor impairment, sleep disorders including RBD, mood, autonomic dysfunction and cognitive factors

including executive function and visuoperceptive cortical processing are associated with VH in PD.

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Ophthalmic pathology and visual hallucinations (VH) in PD

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Objective: To determine the importance of ophthalmic pathology and cortical visual processing in the aetiology of VH in PD.

Background: Impaired visual processing can result from pathophysiological changes inherent to PD such as retinal dysfunction, diminished visual acuity, reduced contrast sensitivity, colour discrimination and motion perception, and impairment of central visual processing pathways or coexisting, particularly age-related, ophthalmic factors such as cataracts, macular degeneration, retinopathy and visual field deficits or environmental considerations such as poor luminance.

Methods: (1) Ophthalmological measures including logarithm of minimal angle of resolution (logMAR) visual acuity testing, Goldmann kinetic perimetry mean peripheral field diameter, descriptive assessment of cataract presence, location and degree of opacity. (2) Testing for visual agnosia, the Birmingham Object Recognition Battery (BORB) (Riddoch and Humphreys, 1993) including low level aspects of visual perception (elemental features such as orientation, length, and object size), higher visual perception (identification of overlapping images, matching objects from usual and unusual viewpoints and identification of objects from minimal features) and stored perceptual knowledge (object decision tasks) and semantic knowledge (associative matching).

Results: The ophthalmic and visuoperceptive variables were compared between patients with VH (N=23) and those without (non-VH) (N=27). None of the ophthalmic parameters including visual acuity, visual fields, overall presence of ophthalmic pathology, cataracts or macular degeneration showed significant difference between the VH and non-VH group. However, several of the visuoperceptive variables (BORB minimal feature match, $p=0.0011$, overlapping images, $p=0.0014$, object decision, $p=0.0026$, association match, $p=0.008$, size match, $p=0.026$ and orientation match, $p=0.022$) were significantly impaired ($p<0.05$) in the group of patients with VH, with minimal feature match and overlapping images scales meeting significance for multiple comparisons (Bonferroni correction, $p<0.0024$).

Conclusions: In terms of visual pathways, our clinical data suggest that it is not ophthalmological pathology or apperceptive visual agnosia, but mainly higher visuoperceptive dysfunction that is most important.

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Testing an aetiological model of visual hallucinations in Parkinson's disease

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Objective: To validate an integrated model of VH in PD.

Background: The exact aetiology of VH in PD is unknown but several factors have been implicated in the aetiopathogenesis in clinical, polysomnographic, functional imaging and histopathological studies. Attempts have been made to formulate an integrated model based on an imbalance of external and internal inputs (Diederich *et al*., 2005, Diederich *et al*., 2009). This includes (a) central dopaminergic overactivity (b) impaired visual processing, (c) impaired regulation of brainstem sleep-wake cycle and dreaming, including REM sleep behavioural disorder (RBD) and (d) cognitive impairment.

Methods: (1) Application of physician-administered and self-completed clinimetric scales. (2) Binary logistic regression analysis was performed to assess the effect of different clinimetric variables on the main dichotomous outcome measure (presence or absence of VH).

Results: In order to validate the *a priori* hypothesis of an integrated model of VH in PD including dysexecutive cognitive impairment, RBD and abnormal visual processing the variables (1) Frontal Assessment Battery [FAB] score, (2) presence of RBD (3) statistically significant Birmingham Object Recognition Battery (BORB) subscales (object decision, minimal feature match, association match, overlapping images), (4) dopaminergic medication (Levodopa Equivalent Units) and (5) disease duration (an important confounding variable) were included in a multiple regression model. Disease duration ($p=0.016$), RBD ($p=0.021$), BORB object decision ($p=0.010$) and BORB association match ($p=0.022$) were all independently predictive variables in this multivariate analysis of VH in PD. When all variables (excluding collinear variables) that were significantly associated with VH in the univariate analyses were added to the regression analysis, the four independent determinants of VH in PD were RBD ($p=0.042$), autonomic function (SCOPA-AUT) ($p=0.002$), FAB ($p=0.054$) and BORB object decision ($p=0.018$), overall predicting the presence of VH in 65% of patients.

Conclusions: Our data suggest that impaired visual processing, alteration of brainstem sleep-wake cycle and dreaming, including RBD and frontal cognitive impairment are important in the aetiopathogenesis of VH in PD. Dopaminergic medication was not a statistically significant predictive variable in this analysis.

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Reckless driving associated with dopamine agonist use

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Objective: To describe a case series of patients experiencing episodes of reckless driving associated with dopamine agonist treatment.

Background: Driving safety is a significant concern for patients with Parkinson's disease (PD). Motor symptoms such as bradykinesia and tremor can interfere with safe automobile operation: for instance, patients with postural flexion may be unable to check their blind spot secondary to decreased range of motion. Non-motor symptoms may also affect driving ability, including impaired attention and executive dysfunction. Medications can impair driving ability, via motor fluctuations, dyskinesia, and somnolence. Dopamine agonists (DA) have been implicated in sleep attacks while driving, and may be associated with risky driving decisions.

Methods: Retrospective chart review.

Results: Case #1: 68-year-old man with a 13-year history of PD, with motor fluctuations and dyskinesia. He had been taking 6 mg pramipexole and 1200 mg levodopa daily for 6 months. His work required driving long distances. He admitted to driving after midnight at speeds exceeding 100 mph, with little insight of the risk. Case #2: 69-year-old woman with mild parkinsonism, on 4 mg of extended release ropinirole for three weeks. She reported passing multiple cars on a two-lane highway, around a blind curve. She felt "blank" during the incident, but was highly disturbed afterwards. After stopping ropinirole, she had no more episodes. Case #3: 54-year-old man with PD, on transdermal rotigotine 4 mg for four weeks. He impulsively drove to a convenience store at 3 AM, for food. He drove at high speed into a telephone pole, fracturing his wrist and femur.

Conclusions: DA are associated with impulse control disorders, and may alter how the brain perceives and avoids risk. DA-associated impulse control disorders include pathological gambling and hypersexuality. Reckless driving may be another manifestation of DA-associated impulse control disorders.

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Frequency and type of impulse control disorders occurring in Parkinson's disease patients treated with dopamine agonists in a 2 year retrospective study

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Objective: Determine the ICD frequency in a Parkinson's disease clinic where DA-treated patients were routinely asked about such aberrant behaviors.

Background: Impulse control disorders (ICDs) provoked by a dopamine agonist (DA) often go undetected in clinical series, especially if not specifically inquired.

Methods: We utilized the Mayo Health Science Research database to ascertain all patients seen by Mayo-Rochester Movement Disorders Clinic Staff during two years (11/1/07-10/31/09) while taking a DA for PD; ICDs were routinely ascertained during these clinic visits. We sampled a quarter of the identified patients, reviewing the charts and tabulating outcomes.

Results: Among 577 patients cross-referenced in the computer search for PD and DA therapy, 146 were sampled for chart review, identifying 94 meeting inclusion criteria. New ICDs occurred during those two years in 14 (14.9%) (12 male) and were pathologic in 6 cases. Hypersexuality (7), gambling (3), excessive spending (2), eating (2), compulsive hobbying (2), excessive alcohol intake (1) were identified. Most ICD cases were concurrently taking carbidopa/levodopa (71.4%), and all but two (85.6%) were taking therapeutic DA doses. DA was tolerated (6), reduced (6), or stopped (2) with 9 eventually stopping it. Reducing or ceasing DA led to resolution of behavior.

Conclusions: Dopamine agonist therapy for PD carries a substantial risk of impulse control disorders (14.9%), with hypersexuality and gambling most common. Risk factors include male sex, concurrent carbidopa/levodopa therapy and DA doses in the therapeutic range, although ICDs may occur on subtherapeutic agonist doses.

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External cueing improves temporal characteristics of motor imagery in patients with Parkinson's disease

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Objective: To evaluate the effect of external cues on motor imagery (MI) of upper limb movements in patients with Parkinson's disease.

Background: MI has recently gained attention as a promising rehabilitation method for neurological patients. In patients with PD, however, MI ability has been questioned, because MI was shown to be performed more slowly, especially on the most-affected side. These findings limit the implementation and potential benefits of MI practice in PD rehabilitation. Since external cueing is known to largely improve physical performance in PD, we investigated whether it can facilitate MI in a similar way.

Methods: 14 non-demented patients (MMSE $\geq$24) in early and mid stages of the disease (H&Y 1-3), who were "on" medication, and 14 age-matched controls, physically executed and performed visual MI of two tasks: 1) a cyclical goal-directed aiming task at a fixed speed (0.5Hz), performed as accurately as possible, and 2) the Box and Block Test, performed at maximum speed. These tasks were carried out in the presence and absence of visual cues. Visual analogue scales were used to assess imagery vividness, and mental chronometry and eye-movement recording to objectively evaluate the temporal characteristics of MI in comparison to physical execution.

Results: Repeated measures ANOVA's on the Box and Block Test showed that visual cues significantly improved the participants' imagery vividness ($p<0.05$) and led to less variability in imagery duration over trials ($p<0.01$). PD patients were slower than controls during both MI and execution ($p<0.05$), but the presence of cues significantly reduced their MI duration, leading to greater similarity in the timing of motor imagery and physical execution ($p<0.01$). This was confirmed by the increase in eye-movement frequency and velocity in the aiming task ($p<0.05$), indicating faster MI in the presence of cues.

Conclusions: The provision of visual cues improves the vividness and temporal structure of MI in patients with PD. Since cueing can be used to diminish PD patients' bradykinesia during imagery, we hypothesize that it can enhance the efficacy of MI practice in PD rehabilitation.

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Evolution of hyperdopaminergic behaviors in PD patients treated with dopamine agonists

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Objective: To describe evolution of impulse control disorders (ICD) induced by dopamine agonist (DA) treatment in Parkinson's disease (PD).

Background: ICDs have been reported in PD patients treated by DA but factors associated with clinical improvement remain to be determined.

Methods: Clinical outcome of ICD and treatment history were obtained retrospectively in 25 PD patients with ICDs defined according to the criteria proposed by Ardouin et al. (Rev Neurol, 2009).

Results: The cohort consisted of 19 men and 6 women with a mean age of 52$\pm$9,8 years including 13 cases of pathological gambling, 8 cases of hypersexuality, 9 cases of compulsive shopping and 10 cases of compulsive eating. More than one ICD was observed in 11 patients. ICDs occured with pramipexole (11), bromocriptine (4), pergolide (6), ropinirole (2) and piribidil (5). No specific pattern of ICD was found to be associated to a given DA. Gambling and hypersexuality were more frequent among men, compulsive shopping and compulsive eating were more prevalent among women. Two patients improved 1.5 months after deep brain stimulation and consecutive reduction of DA. Among the other patients, 9 improved whereas 14 had ongoing ICDs. When present, improvement occured within 5.4$\pm$4.5 months after adjustment of DA dose. Improved patients had an earlier PD-onset (43$\pm$9 years vs 50$\pm$9 years; p=0,05) and a younger age at ICD-onset (48$\pm$8 years vs 56$\pm$10 years; p=0,04). 8/17 men improved (47%) compared to only 1/6 women (16%). There was no difference in terms of disease duration or severity, treatment duration, cognition or mood between groups. Initial dose of L-dopa, DA and total L-dopa equivalent doses (LED) were similar between the groups at baseline. In the improved group, reduction of DA doses was higher (347$\pm$161 mg vs 190$\pm$171 mg; p=0,017) and compensatory increase of L-dopa was higher (338$\pm$194 mg vs 25$\pm$318 mg; p=0,015) while total LED remained stable in both groups.

Conclusions: Reduction of DA is a major factor for ICD-improvement in PD while a compensatory increase of L-dopa may not worsen ICDs. Younger age at onset of PD and ICD and male gender may be indicative for an improvement.

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ADX48621, a novel mGlu5 negative allosteric modulator alleviates L-DOPA-induced chorea and dystonia in the MPTP-lesioned macaque model of Parkinson's disease

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Objective: To investigate the anti-dyskinetic effects of ADX48621 in the MPTP-lesioned macaque model of Parkinson's disease.

Background: Previous studies have indicated that blockade of the mGlu5 receptor has the potential to reduce L-DOPA-induced dyskinesia in both rodent and primate models of Parkinson's disease. The current study investigated the potential of ADX48621, a novel negative allosteric modulator (NAM) of the mGlu5 receptor, to alleviate L-DOPA-induced chorea and dystonia in the MPTP-lesioned non-human primate model of Parkinson's disease.

Methods: Eight macaque monkeys (*Macaca mulatta*) were rendered parkinsonian by administration of MPTP. L-DOPA-induced dyskinesia was induced by treatment with L-DOPA for 4-5 months. All animals displayed marked L-DOPA-induced dyskinesia when

challenged with a dose of L-DOPA sufficient to fully reverse parkinsonian symptoms. Each animal displayed an idiosyncratic combination of choreic and dystonic symptoms. Animals were dosed with placebo, 3, 10 or 30 mg/kg ADX48621 30 min before the L-DOPA administration. The effect on dyskinesia and efficacy of L-DOPA was assessed for 4 hours post L-DOPA dose.

Results: In the first 2 hours post L-DOPA ADX48621 dose dependently inhibited, to an equal extent, the chorea and the dystonia components of dyskinesia. A trend was seen at 10 mg/kg with statistical significance at 30 mg/kg ($p<0.01$ for chorea, $p<0.05$ for dystonia). This dose, virtually abolished chorea and dystonia over the 4 hour course of the experiment without any effect on the anti-parkinsonian action of L-DOPA as determined by disability scores. The effective plasma concentration of ADX48621 was approximately 1000 ng/mL.

Conclusions: These data suggest that ADX48621 has utility to reduce L-DOPA-induced dyskinesia in Parkinson's disease patients. In addition, the effect on dystonia opens the possibility that this compound could treat other forms of this condition.

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Increased risk of developing depression for patients with Parkinson's disease (PD): A retrospective cohort study

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Objective: The aim of the present study was to assess the risk of depression over time in patients with PD compared with those without PD by adjustment for the potential confounding influence of general risk factors for depression.

Background: The general risk factors for depression include female sex, higher age, personal or family history of depression, and comorbid somatic diseases. Depression frequently accompanies or preceding PD and may have a negative impact on activities of daily living, cognitive performance, and quality of life. The temporal or causal relationship between PD and depression still remains unclear and needs further large population study.

Methods: A retrospective cohort design was used based on the National Health Insurance reimbursement database in Taiwan. Patients diagnosed with PD at or after the age of 40 and who were diagnosed in the period from 2000 to 2003 (N=1806), were compared with age-matched controls from non-PD group (N=7165). Both groups were followed-up until diagnosis of depression or censored by December 31, 2007. Hazard ratios (HR) and 95% CI were calculated using Cox proportional hazards models adjusted for age, sex, socioeconomic status and comorbidity. Subgroups based on age and sex at diagnosis of PD were evaluated separately.

Results: The demographic data showed the PD patients were poorer, and slightly more unemployed and living in the southern area of Taiwan. They were also more likely to have Diabetes mellitus, hypertension and hyperlipidemia. The crude HR (95% CI) for PD vs non-PD subjects was 3.35 (2.62 to 4.27) and increased to 5.08 (3.94 to 6.54) in multivariable analysis. The sex- and age-stratification analysis for the risk of depression in association with PD showed greater risk for women and increased with age. Compared with men of non-PD, women with PD had a HR of 7.35 (5.13 to 10.5).

Conclusions: Our data stress the importance of being aware of depression in PD patients, especially in elderly woman and support the tight association between PD and subsequent depression.

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Anti-parkinsonian effects of ADX48621 a mGluR5 negative allosteric modulator, in the rat haloperidol induced catalepsy model

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TABLE (297). *Mean catalepsy times 90 min after haloperidol administration rats*

Treatment	Catalepsy time (sec) Mean (± SEM)	% change from vehicle	Plasma concentration (ng/ml)
Vehicle	69.1 ± 7.7	-	-
ADX48621 1mg/kg N=10	56.0 ± 3.7	-19	54.4 ± 10.2
ADX48621 3mg/kg N=10	39.7 ± 3.7	-43	328 ± 25.5
ADX48621 10mg/kg N=10	32.8 ± 4.8**	-53	1723 ± 218
ADX48621 30mg/kg N=10	24.2 ± 2.6***	-65	3617 ± 384
MTEP 30mg/kg N=10	31.4 ± 4.8**	-55	-

**$p<0.01$, ***$p<0.001$.

Objective: To evaluate the potential for anti-parkinsonian effect and dose response of ADX48621, a negative allosteric modulator (NAM) of metabotropic glutamate receptor 5 (mGluR5).

Background: Loss of striatal dopaminergic control leads to excessive glutmatergic activity within basal ganglia and dyskinesia. Furthemore, excess glutamate release onto the substantia nigra appears to play a role in nigral degeneration. Inhibitors of mGluR5 have been shown to reduce dyskinesia induced by l-dopa administration and to have a protective effect on dopaminergic neurons in animal models of Parkinson's disease (PD). Hence mGluR5 inhibitors have potential for treatment of PD.

Methods: Male Sprague-Dawley rats were injected with haloperidol (1 mg/kg, i.p.) 30 minutes prior to oral administration of vehicle, ADX48621 (1, 3, 10 and 30 mg/kg) or MTEP (30 mg/kg), a mGluR5 NAM positive control. N=10 animals per treatment group. Catalepsy was assessed 60 minutes after the drug administration (ie 90 min post haloperidol) using a grid test. Rats were placed on a vertical wire grid with the head pointing toward the ceiling and all paws gripping the grid. Latency to movement of both forepaws to relocate the body was measured with a maximum latency "cut-off" time of 120-seconds. Plasma was collected at the end of the experiment, 70 mins post dose of study treatment, to measure ADX48621 concentration.

Results: Mean (SEM) catalepsy time with vehicle was 69 (±7.7) secs. Compared to vehicle, ADX48621 decreased catalepsy time, dose dependently, by 19% 43%, 53%, and 65% at 1, 3, 10 and 30 mg/kg, respectively. There was a trend to efficacy at 3mg/kg with statistical significance at 10 ($p<0.01$) and 30 mg/kg ($p<0.001$). MTEP decreased catalepsy time by 55% ($p<0.01$). The minimal effective dose (MED) was 10 mg/kg with a corresponding plasma concentration of 1723 ng/ml.

Conclusions: ADX48621 demonstrated anti-parkinsonian-like properties in this rodent model with a minimal effective dose of 10 mg/kg suggesting that the compound may have utility in the treatment of Parkinson's disease.

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Prevalence of dopamine dysregulation syndrome in Parkinson's disease patients–candidates for deep brain stimulation

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Objective: To estimate the prevalence of Dopamine Dysregulation Syndrome (DDS) among Parkinson's disease (PD) patients who are potential candidates for deep brain stimulation (DBS) surgery.

Background: DDS is a neuropsychological disorder in patients with PD associated with compulsive misuse of and addiction to dopamine replacement therapy (DRT) resulting in behavioral disturbances affecting social and occupational functioning. Management is difficult. Prognosis is poor with tendency to relapse. DDS has been reported in approximately 4% of all PD patients. Clinical observations and reports in literature suggest that the prevalence might be

TABLE (298). *Diagnostic criteria for Dopamine Dysregulation syndrome*

a	Parkinson's disease with documented levodopa responsiveness
b	Need for increasing doses of DRT in excess of those normally required to relieve Parkinsonian symptoms and signs
c	Pattern of pathological use: expressed need for increased DRT in the presence of excessive and significant dyskinesias
d	Impairment in social or occupational functioning
c	Development of hypomanic, manic, or cyclothymic affective syndrome in relation to DRT
	Development of a withdrawal state characterized by dysphoria, depression, irritability, and anxiety on reducing the DRT
	Duration of disturbance of at least 6 months

Table adapted from Giovannoni et al, JNNP. 2000;69(4):566-7.

much higher in the subgroup of patients who are potential candidates for DBS surgery.

Methods: We performed a retrospective chart review of all patients referred to our center for consideration of DBS for PD between years 2006 and 2008. All charts included reports of evaluation by a movement disorders neurologist, detailed neuropsychological and, if applicable, psychiatric assessment. Patients were considered to have DDS if they satisfied previously published diagnostic criteria.

Results: 75 patients with PD were evaluated for potential DBS during this time. 13 were excluded because of incomplete documentation. Of the remaining 62 patients, 9 (14.5 %) met diagnostic criteria for DDS.

Conclusions: Our results suggest that the prevalence of DDS among patients considered for DBS surgery may be up to 3.5 times higher than in PD population in general. Possible reasons for the increased prevalence are that DBS candidates have more advanced disease, have been on DRT for a longer period and taking higher doses, and have motor fluctuations and dyskinesias. These may represent risk factors for developing DDS, in addition to younger age and premorbid high "risk-taking" personality. Subthalamic nucleus (STN) DBS can potentially provide long-lasting improvement of this disabling and difficult to treat condition. DDS should be recognized and STN DBS should be considered earlier in these patients in order to break the pathological reward anticipation cycle. Patient's behavior should be observed closely with additional care from psychiatrist and psychologist.

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Impulsive stealing in Parkinson's disease (PD): The first case associated with dopaminergic medication

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Objective: To describe a case of impulsive stealing associated with dopaminergic medication in a patient with PD.

Background: The DSM IV describes the essential feature of impulse control disorders (ICD) as "the failure to resist an impulse ... to perform an act that is harmful...", kleptomania is listed among the ICDs. Impulsive and compulsive symptoms occur in 10-14% of PD patients on dopaminergic medication and include pathological gambling, hypersexuality, compulsive shopping, compulsive eating, punding and dopamine dysregulation syndrome. We found only one case report of impulsive stealing in a PD patient after STN DBS (Sensi et al., 2004).

Methods: The 58 year old female patient was diagnosed with PD in 2005 and treated with pramipexole 2.25mg od. Levodopa/carbidopa was added in 2006 and rasagiline 1mg in January 2008. Levodopa CR was increased by 100mg od in July 2008, in October 2008 her daily medication was levodopa CR 600mg, pramipexole 2.25mg and rasagiline 1mg. She had long-standing symptoms of depression, anxiety, obsessive compulsive personality traits and skin-picking. These traits were not interfering with function. There was no history of theft or other ICDs prior to PD.

Results: In early 2008 she developed compulsive shopping and accrued a credit card debt of max Cdn$17,000 which she hid from her family and prevented retirement. The skin picking escalated resulting in near constant picking and a non-healing skin lesion. She occasionally gambled without being a pathological gambler but just prior to the theft used rent money to gamble. In October 2008 she suddenly developed an irresistible urge to steal a pack of photo album pages ($6) while in a store. She had not planned the act and felt this was completely out of character resulting in strong feelings of guilt. Her pramipexole was reduced to 1.5mg od, no further incidences of stealing occurred.

Conclusions: To the best of our knowledge this is the first description of a case of impulsive stealing in PD associated with dopaminergic medication. Whether her behaviour would have been repetitive as necessary for a diagnosis of kleptomania will remain unknown as her agonist dose was reduced. Impulsive stealing should be considered in the spectrum of ICDs associated with dopaminergic medication, especially in patients with other ICDs and pre-existing compulsive traits.

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Pramipexole induces a conditioned place preference in parkinsonian-like rats

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Objective: To determine if pramipexole has rewarding properties in parkinsonian-like rats and/or sham controls.

Background: Pramipexole is a dopamine (DA) agonist that improves motor deficits in Parkinson's disease (PD). Pramipexole is implicated in impulsive control disorders and a DA dysregulation syndrome in subpopulations of PD patients. As these maladies reflect dysfunction in reward circuits, investigations into the rewarding properties of pramipexole, particularly in PD, are warranted. Conditioned place preference (CPP) indicates if a drug exhibits rewarding properties and if it promotes drug-seeking behavior. The abused psychostimulant, methamphetamine (meth) reliably produces CPP in rats; thus, meth was used as a positive control to verify that PD-like rats can execute CPP. This paradigm was then employed to ascertain the rewarding properties of pramipexole.

Methods: 6OHDA or vehicle was bilaterally injected into the dorsolateral striatum. A forelimb adjusting step task validated lesioned-induced motor deficits. Rats were divided into 5 groups based on lesion type and treatment (sham/saline, sham/meth, sham/pramipexole, 6OHDA/meth, 6OHDA/pramipexole). Three weeks after surgery, the CPP task was initiated. This involved a pretest, followed 2 days later by 8 days of conditioning with alternating days of saline, and +meth (1mg/kg ip); ±pramipexole (2mg/kg ip, a dose that improved step task deficits) or vehicle. The next day, CPP testing was conducted in drug-free rats. Significant CPP was defined as spending more time in the drug-paired compartment during the CPP test *vs* the pretest ($p<0.05$). 6OHDA-induced DA lesions were immunohistochemically verified *post mortem*.

Results: PD-like rats demonstrated persistent stepping deficits that were reversed by pramipexole. PD-like rats and sham controls exhibited similar meth-induced CPP. PD-like rats also exhibited pramipexole-induced CPP. The trend for CPP with pramipexole in controls did not reach significance.

Conclusions: These data reveal that PD-like rats exhibit reward-mediated associative learning. Pramipexole has rewarding properties in PD-like rats and the memory of this reward is sufficient to promote drug-seeking-like behavior upon withdrawal. Pramipexole-induced CPP was not seen in controls, suggesting a possible vulnerability to the rewarding effects of pramipexole in a parkinsonian brain state.

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Long term follow-up of Parkinson patients with impulse control disorders

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Objective: Impulse control disorders (ICDs) are mainly triggered by dopaminergic therapy in Parkinson's disease (PD).

Background: Although we studied a small number of patients the recovery from compulsive behaviors may be associated with the decrease in DA dosage and increase in levodopa. In patients who were on high doses of DA, ICDs could be persistent. Furthermore, majority were given antipsychotic and/or antidepressant drugs.

Methods: Among 33 patients with ICDs, 22 patients (81.8 % men) were followed for a time period. Demographics, dopaminergic therapy and disease severity were compared between two time points (Time 1: time of diagnosis of ICD, Time 2: last visit) and between patients who recovered from ICDs and patients with ongoing ICDs. Types of antipsychotic and antidepressant medication were noted.

Results: Mean follow-up period was 53.7 months. Mean dopamine agonist (DA) dose was significantly lower and levodopa dose was significantly higher at Time 2. Total UPDRS score was significantly increased. ICDs were dissolved in 16 patients (73 %), but persisted in six (27 %). In ICD(+) subgroup, DA doses in Time 1 was found significantly higher than ICD(-) subgroup (3.09 vs 5.26 mg/day, respectively). However, age, PD severity, disease duration and levodopa dosage were similar. Fourteen patients were prescribed atypical antipsychotics and 13 antidepressants.

Conclusions: Although we studied a small number of patients the recovery from compulsive behaviors may be associated with the decrease in DA dosage and increase in levodopa. In patients who were on high doses of DA, ICDs could be persistent. Furthermore, majority were given antipsychotic and/or antidepressant drugs.

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'Walkabout': An unrecognized compulsive behavior in Parkinson's disease

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Objective: To describe five Parkinson's disease (PD) patients with walkabout, a behavior disorder little known in this disease.

Background: Walkabout is defined as excessive, aimless wandering (walking or driving). In PD, it was described originally by Giovannoni et al (2000) as an akathisia and urge to walk of patients during the 'on' phase; often wandering far from home. It is considered a compulsive behavior, and is included in the Section 2 of the Questionnaire for Impulsive-Compulsive Disorders in PD (QUIP), besides punding and hobbyism. Its frequency is of "3% of patients with PD, much less common that other compulsive behaviors, like hobbyism ("15%) or punding ("10%). Dopaminergic agents using for treating PD are probably involved in its physiopathology.

Methods: Semistructured interview to Parkinson's disease patients attending the outpatient Movement Disorders Unit, about abnormal behaviors occurring anytime.

Results: Five patients with advanced PD and motor fluctuations, all males, exhibit aimless wandering of walking great distances, preferably in the early morning and during 'on' state. Two of them, during his walk, gathered useless objects from the street or in the wastebaskets, and take them home. To the questions on the reasons of this behavior, the patients didn't explain, as in akathisia, a physical sensation of restlessness, though they could not explain exactly why they walked so long distances. The exact beginning of the treks was also difficult to know, but in all cases the abnormal behavior appeared after PD onset.

Conclusions: Walkabout can be considered as a compulsive behavior quite specific of PD. In some cases, it can be accompanied of searching of useless objects. For the patient and family, this behavior habitually neither is considered to be abnormal nor relates to the PD, for what a specific interview is important to detect it.

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Parkinson's disease psychosis (PDP): A condition which is undertreated

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Objective: To survey physicians who treat PD and to characterize their treatment of PDP including their use of antipsychotic drugs (APDs) in these patients.

Background: PDP is a difficult condition to treat. Existing APDs commonly interfere with dopaminergic Parkinson's therapies. Additionally, the delicate health status of patients requires a careful approach when considering antipsychotic treatment. This study aims to provide insight about the treatments PD patients receive when diagnosed with psychotic symptoms.

Methods: 305 physicians (205 neurologists and 100 psychiatrists) were asked to review charts of current PD patients with psychotic symptoms and to describe how patients are treated. In total, 380 patient charts were reviewed.

Results: Chart review revealed that 39% of PD patients diagnosed with psychotic symptoms were not receiving APDs. Of those receiving APDs, use was as follows: quetiapine (56%), aripripazole (14%), risperidone (12%), olanzapine (10%), clozapine (4%), ziprazidone (2%) or other (2%).

Conclusions: 39% of PD patients diagnosed with psychotic symptoms are not receiving antipsychotic treatment. Therefore, PDP appears to be significantly undertreated. Among treated patients, atypical APDs were the most frequently used drugs (98%) to treat PDP. Quetiapine was the most frequently prescribed APD (56%), but appeared to be under-dosed to be fully effective for the psychotic symptoms. Physicians reported numerous limitations of currently prescribed antipsychotics, including the loss of motor control, questionable efficacy, and safety concerns, to name a few. This illustrates the need for improved treatment options.

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White matter lesions and depression in patients with Parkinson's disease

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Objective: Approximately 30-40% of patients with Parkinson's disease (PD) have significant depressive symptoms. In previous studies depression in the early-onset PD patients differ from late-onset group of patients and there are suggestions that depression in these two groups may have different etiologies. The severity of hyperintense lesions in the cerebral white matter (WML) correlated with depression particulary in elderly population.

Background: The aim of this study was to investigate whether WML were associated with depression in patients with PD onset above age of 60 by comparing PD patients, with and without depression, and healty age- and sex-matched controls.

Methods: For this study, 62 patients with PD, 31 with depression (PDD) and 31 without (PDND), and 30 control subjects were recruited. MRI scans of patients and controls were rated for WML, blind to diagnosis, using the Scheltens visual rating scale. Other evaluation included a detailed history of vascular risk factors and current medication, disease severity and MMSE test. Depresseion were diagnosed using DSM-IV criteria and scored used Hamilton depression rating scale. Both bivariate and multivariate statistical analyses were carried out.

Results: Compared with PDND group, the PDD group had significantly higer level of WML in the periventricular areas and frontal deep white matter.

Conclusions: Our results suggest that WML with specific localisation may contribute to depression in PD.

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Biomarkers for Parkinson's disease in patients and their first degree relatives

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Objective: To find out if our simple and quick tests for preclinical biomarkers in PD can be used in clinical setting and to establish the prevalence of preclinical biomarkers in PD patients and their siblings.

Background: Apart from 10-15% of PD which is hereditary, the etiology is still unknown. According to the 'dual hit' hypothesis an unknown pathogen penetrates nasal and gastric mucosa, enters the nervous system and progresses towards the cortex of the brain. It is known that the disease begins years before the onset of motor symptoms. Braak (2003) has divided the progression of Parkinson's disease into six stages. The first two stages are a part of preclinical phase in which sleep disorders, loss of ability to smell, autonomic dysfunction and mood disorders may appear. These non-motor symptoms may be a mean to discover PD in its earliest phase. Today we have no reliable screening method for early diagnosis of PD. Such a screening tool will however be of great importance if a successful neuroprotective therapy is developed.

Methods: 33 patients with PD, 48 of their siblings and 31 control subjects participated in the study. Each participant completed University of Pennsylvania Smell Identification Test, Questionnaire of Dysfunction of Autonomic Nervous System, REM Sleep Behavior Disorder Questionnaire and Hospital Anxiety and Depression Scale.

Results: The difference in the results between patients with PD and control group was significant for all biomarkers tested, i.e. smell identification ability, autonomic dysfunction, REM sleep behavior disorder, anxiety and depression. There was however no significant differences between the results of siblings and control subjects.

Conclusions: The study confirmed that patients with PD have significantly more preclinical biomarkers than the general population. The consistency in the results showed that the methods used may become a way to diagnose PD in its preclinical phase. The prevalence of biomarkers in both siblings and control subjects was similar. This might be a consequence of number of participants or less sensitive methods. However a small number of studies and their different results in this area call for a larger and more detailed research.

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Nondysphoric depression in Parkinson's disease and frontotemporal dementia

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Objective: To compare the prevalence of nondysphoric depression (NDD) in Parkinson's disease (PD) and frontotemporal dementia (FTD).

Background: Nondysphoric depression is characterized by ideational and vegetative depressive symptoms with limited endorsement of emotional symptoms (i.e., sadness or anhedonia). This condition has been found to be a risk factor for cognitive decline and mortality but, with the exception of stroke, it's prevalence in neurologic conditions in not known. In the 2-week post-stroke period NDD has a prevalence of 6.6% and is associated with right hemisphere damage suggesting that NDD is a variant of depression with underreported emotional symptoms in association with damage to brain regions subserving emotion processing and experience.

Methods: Consecutive visits to the Instituto de Neurologia Cognitiva (INECO), Buenos Aires, Argentina between years 2005-2009 with confirmed diagnosis and full psychiatric assessment constituted the study sample. Patients (n=37) meeting criteria for early stage PD (Hoehn & Yahr stage I and II) and FTD (n=37) (Clinical Dementia Rating Scale mean=1.1, SD=.75) were prospectively studied with the self-administered Beck Depressive Inventory (BDI-II). Patients met criteria for depression if they had a BDI-II score $\geq$10. Patients met NDD criteria when depressed mood and/or loss of pleasure were not endorsed, and at least one psychological symptom (e.g., thoughts of death, guilt) and two vegetative symptoms (e.g., sleep problems, weight loss) were present.

Results: Groups were comparable in age (PD mean 65.2, SD =10.3, FTD mean 69. 9, SD=8.2; t (72)=1.00, p=.3) and gender (21 men in PD and 23 men in FTD; $\chi 2$=0.22, p=.6). While there were 20 (54%) subjects with DD and 1 (2.7%) meeting NDD criteria among PD patients, 18 (48.6%) met DD and 7 (18.9%) NDD criteria in the FTD group. Therefore a significant difference in NDD prevalence between PD and FTD patients was found (z =3.43, p=0.02). Interestingly 57% of all NDD patients had BDI-II scores of 10 or greater.

Conclusions: While dysphoric depression is common in PD and FTD, nine times more FTD than PD patients have difficulties endorsing sad mood or loss of pleasure when affected by ideational and vegetative symptoms of depression. These patients present with NDD perhaps because endorsement of affective symptoms of depression is reduced by disruption of frontal-limbic circuits subserving emotional awareness. These findings suggest that close attention should be paid to atypical depressive conditions in FTD. The long-term outcome of this nondysphoric variant of depression in FTD warrants further examination in prospective studies.

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Pramipexole-induced risky behavior in a rat model of Parkinson's disease

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Objective: To evaluate the effects of pramipexole (PPX) on risky behavior in a rodent model of Parkinson's disease (PD) using a probability discounting paradigm with intracranial self-stimulation (ICSS) as the positive reinforcer.

Background: A subpopulation of PD patients treated with dopamine (DA) agonists demonstrate impulse control disorders, such as pathological gambling. Preclinical models are needed to better understand the underlying neurobiology of these disorders. Probability discounting assesses impulsivity (ie, risk-taking) in humans and lab rats. In this task, a subject chooses between a small reinforcer that is always delivered and a large reinforcer that is delivered with varying probabilities. Risky behavior is reflected in a preference for the large, uncertain reinforcer.

Methods: 6-OHDA or vehicle was bilaterally injected into the dorsolateral striatum and a stimulating electrode was implanted into the lateral hypothalamus. A forelimb step task validated lesioned-induced motor deficits. Rats were trained in a 6 phase lever pressing protocol to determined large and small reinforcers based on current strength. After a stable baseline of risk-taking behavior was established, a clinically used DA agonist, PPX, was given to a subset of rats ($\pm$2mg/kg ip, 2Xday for 13 days; dose selection based on improvements in step task deficits). Risk-taking was assessed 30min after the morning injection on the first and every third day of treatment. Risk assessments continued after cessation of PPX treatment. DA lesions were immunhistochemically verified *post mortem*.

Results: PD-like rats demonstrated persistent deficits in the step task, yet acquired and performed all phases of the ICSS protocol. PD-like rats and controls had similar risk assessment profiles. PPX promoted risk-taking in PD-like rats (n=8) and controls (n=3); eg, preference for the large reinforcer was enhanced $\sim$40% above baseline at the most uncertain probabilities (ie, 30, 15 and 5%). Tolerance did not develop with repeated treatments. Risk-taking returned to baseline within 2-3 weeks of PPX cessation for nearly all rats tested.

Conclusions: These data reveal that at a dose that improved motor deficits imposed by localized striatal DA deafferentation, PPX increased impulsivity in PD-like rats and in unlesioned controls. This

paradigm allows for investigations of the neurocircuitry underlying PPX-induced risky behavior.

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Impulse control disorders in Parkinson's disease: Results of an epidemiological survey in Tuscany-Italy

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Objective: To assess Impulse control disorders' (ICD) prevalence in a large group of Italian Parkinson's disease (PD) patients.

Background: ICD include pathological gambling (PG), hypersexuality (HS), compulsive shopping (CS) and compulsive eating (CE). Many recent studies have revealed an increased prevalence of ICD in PD pts in association with dopaminergic treatment. Only one study has assessed pathological gambling frequencies in Italian PD pts while there are no evidences for others ICD.

Methods: Minnesota Impulsive Disorders Interview (MIDI) has been telephonically administered to PD pts afferent to two movement disorders units. Only non-demented PD pts, responsive to dopaminergic treatment were enrolled in the study.

Results: 708 PD pts (mean age 72, range 38-82) completed the screening process. Eight pts were drugs naïve, 60 were assuming Ldopa or Ldopa/entacapone therapy, 255 dopamine agonists (DaAgo), 385 a combination therapy. Sixty-four (9.2%) screened positive for an ICD at the time of the calling or after PD diagnosis: the frequencies of PG was 4.3% (N=30), near to HS (N=22; 3.1%). Only 9 pts (1.3%) should be considered for CE while 1 patient showed CB, and 2 described computer addiction. Nine pts (1.4%) screened positive for more than one ICD: usually PG as serious disorder, associated with HS or CE. All pts who screened positive for ICD were assuming DaAgo or combination therapy. Two pts could be classified as having Dopamine Dysregulation Syndrome. Moreover Ldopa alone is not associated with ICD.

Conclusions: Our data are consistent with recent studies suggesting an association between ICD and dopaminergic treatment in PD pts. Particularly PG and HS are the most frequently observed disorders and should be actively investigated in all pts assuming DaAgo or combined therapy. It's important to note that only 20% pts showing an ICD do not emerge during routine clinical evaluation while previous studies reported a 75%, showing an improved diagnostic accuracy.

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Comparative neuropsychological profile of pathological gambling, hypersexuality and compulsive eating in Parkinson's disease

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Objective: To investigate cognitive correlates underpinning pathological gambling (PG), hypersexuality (HS) and compulsive eating (CE) in Parkinson's disease (PD).

Background: The impulse control disorders (ICDs) pathological gambling (PG), hypersexuality (HS) and compulsive eating (CE) are being increasingly identified in Parkinson's disease (PD) patients. PG has been associated with frontal/executive dysfunctions, whereas HS, CE and cognitive dysfunctions have not been investigated in PD.

Methods: Two-hundred PD outpatients were screened for PG, HS and CE. Based on clinical criteria, we identified 13 HS patients, 12 with CE, 14 with PG and 10 with multiple ICDs (mICDs). Fourteen PD patients matched for age, gender, and schooling without ICDs served as controls. Clinical features, and neuropsychiatric and neuropsychological functioning were assessed in the five groups.

Results: Demographic, clinical, neuropsychiatric and neurological aspects did not differ among groups. ICD patients performed significantly worse than controls on the Trail Making Test, part B minus part A, and on the Complex Figure Copying Task, whereas performance did not differ among the four ICD groups. HS and mICD patients performed worse than PG patients and controls on the Stroop Test-interference task. HS, CE and mICD patients performed worse than controls on memory tasks. Verbal memory was lower in HS, CE and mICD than in PG.

Conclusions: ICDs are associated with impaired cognitive function; the severity of impairment decreases in the order ICDs and HS > CE > PG. Our findings support the concept that HS and CE are associated with prefrontal and memory dysfunctions, whereas PG is related to dysfunction of frontal-striatal circuitry.

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Action and object naming in PSP (progressive supranuclear palsy)

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Objective: PSP is a rare brain degeneration disorder. It is also termed as Steele-Richardson-Olszewski syndrome. Slurred speech is one of the symptoms and thus we can check other language impairments. Is it just dysarthia, dysphonia only or any other language impairment?we undertook this research to understand action and object naming in PSP. The major aim of this paper is to identify:- is there any impairment in action and object naming in PSP Is action naming or object naming or both are impaired.

Background: many researches have been conducted in understanding the processing of action and object words in diseases like PSP.there seems to be no literature or work done to understand this processing for Hindi language. the verbs in Hindi are very much different than verbs in other languages like English. we have tried to work by keeping Hindi as the source language.

Methods: 3 PSP, Hindi speaking patients and 2 right handed Hindi speaking healthy participants were included in the study. The patients were provided by Neurology Department, GB Pant Hospital, New Delhi. word generation The generation task involved 54 simple nouns and 30 simple verbs in Hindi. The task of word generation involved a set of black and white line drawings. Picture naming being the most widely used technique to investigate lexical retrieval, was used for this paper Each participant's response was analyzed separately. The study undertook the analysis of the following variables:- Word frequency Response time Error percentage.

Results: the patients took the least time when giving the correct response but took more time while naming associates or while giving wrong answers. The percentage of error in naming depended on the frequency of word. If the word was LF the patients showed more errors w.r.t. HF and MF words. The patients took more time in giving the wrong (completely unrelated answers). The phenomenon is thus almost the same as in the case of object naming The word frequency had no effect on the error percentage for action naming. All patients showed error percentage of more than 50 % (overall) and under each category (of word frequency) Once we compare the action and object naming we find that there is a pattern that should very well be stated. The action naming takes more time in patients than object naming. Moreover the error percentage is higher in action naming w.r.t object naming.

Conclusions: the action naming is more effected than object naming in PSP.

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Does asymmetry of motor symptoms or other factors tell us something about risk of compulsive reward-seeking activities in patients with Parkinson's disease?

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Objective: This study aimed mainly to investigate if the side of symptoms onset may be predictive of subsequent compulsive reward-seeking activities (CRSAs) in patients with Parkinson's disease (PD). Secondly, others factors potentially associated with CRSAs were evaluated.

Background: Asimmetry of the motor impairment of PD has been noted in all three cardinal features of PD. This laterality is seemingly related to asymmetric level of dopamine due to a decrease in the number of dopaminergic neurons in the substantia nigra contralateral to the side onset of PD. Dopaminergic neurons are not only implicated in voluntary movement control but also play a significant role in the brain's reward system and the modulation of behaviours.

Methods: Consecutive PD patients were included in this study. CRSAs as impulse control disorders (ICDs), compulsive creativity (CC) and repetitive behaviours (RPs), such as punding and compulsive singing, were looked for and data were collected by an interview. Clinical assessment included the UPDRS motor score and the Hoehn and Yahr stage.

Results: 319 (163 male and 156 female) patients with a mean age of 72.87 (SD±9.75) years and mean disease duration of 127.44 (SD±70.56) months were included in this analysis. The mean Hoehn and Yahr stage was 2.91 (SD ±0.79). 44 PD patients with CRSAs were detected: 28 with ICDs, 7 with CC and 13 with RBs. Analysis of right- and left-sided onset showed that left-sided symptoms were significantly associated with ICDs ($p<0.006$), whilst RBs were not associated. Besides ICDs were significantly associated with dopamine agonists, male gender, dyskinesias, psychoses and hallucination, whilst RBs with dementia.

Conclusions: Our findings suggest the hypothesis that predominance of left side motor symptoms in PD patients may influence the onset of CRSAs such as ICDs, seemingly reflecting a dysfunction in the right hemisphere. This predominance was not significantly related to RPs, where cognitive impairment represented the most important risk factor. In male patients with predominance of left-sided symptoms and concomitant presence of dyskinesias, psychoses or hallucination, increment of the dopaminergic therapy (mainly dopamine agonists) should be carefully evaluated.

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Behavioral, neuropsychiatric and cognitive disorders in parkinsonian patients with and without motor complications

P. Solla, A. Cannas, C. Serra, L. Lavra, E. Costantino, F. Di Stefano, V. Piras, G. Floris, F. Marrosu, M.G. Marrosu (Monserrato, Cagliari, Italy)

Objective: To identify the presence of behavioral, neuropsychiatric and cognitive disorders in Parkinson's disease (PD) patients and to evaluate their correlations with motor complications (MC).

Background: PD is hampered by long-term treatment induced MC (e.g., dyskinesias and motor fluctuations) and non-MC such as behavioral, neuropsychiatric and cognitive disorders. The factors affecting these MC and non-MC are still largely unknown and their interactions are not yet fully evaluated.

Methods: Consecutive PD patients received a comprehensive structured clinical evaluation including pharmacologic treatment, MC and non-MC. Among the latter, presence of behavioral disorders such as impulse control disorders (ICDs) and repetitive behaviours (RBs), neuropsychiatric symptoms (depression, anxiety, psychoses and hallucination) and dementia was investigated.

Results: 322 patients with a mean age of 72.8 (SD ±9.7) years and mean disease duration of 10.6 (SD ±5.9) years were included in this analysis. Patients with MC had longer disease duration, younger age at onset and higher doses of treatment. Dyskinesias were significantly associated with dementia ($p<0.004$), hallucination ($p<0.001$), RBs ($p<0.013$) and with ICDs such as hypersexuality ($p<0.002$), shopping ($p<0.024$), whilst were not associated with pathological gambling (PG), compulsive eating (CE), depression and anxiety. Dyskinesias were also generally significantly associated with psychoses, but not with delusional jealousy (DJ). Motor fluctuations were significantly associated with dementia ($p<0.007$), hallucination and psychoses ($p<0.002$) whilst were not associated with RBs, ICDs, depression and anxiety.

Conclusions: We found that increased presence of dementia and hallucinations is common in PD patients with MC (both dyskinesias and motor fluctuations), whilst RBs and ICDs such as hypersexuality and shopping are more common only in patients with dyskinesias. Interestingly MC were not associated with PG, CE and DJ. These data suggest the hypothesis of a possible underlying psychopathological predisposition rather a mere pharmacologic effect in PD patients with DJ, whilst open an important issue in patients with PG and CE.

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Effect of visual stimuli with ambiguous localization on motor performance in Parkinson's disease

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Objective: To determine how motor tracking performance in Parkinson's disease (PD) subjects degrades as visual sensory input becomes progressively ambiguous.

Background: Previous work has suggested that the brain carefully weighs the reliability of different stimuli before making a movement. Given that PD patients heavily rely on visual cues, we investigated how PD subjects would react as visual input became less reliable in a manual tracking task.

Methods: We quantified motor performance of 7 PD subjects (mean age=64yrs, Hoehn and Yahr stage 2-3, mean UPDRS score=39) and 4 control (C) subjects (mean age=62yrs) during a visually guided tracking task that required both shoulder and elbow movement. PD subjects were studied off medication (PDOff) and then again 45 minutes following L-dopa administration (PDOn).Subjects stood in front of a large screen and tracked a projected circular target along a Lissajous path with their dominant index finger. In the baseline condition the target and the path followed a smooth trajectory. For the ambiguous conditions, the target "jittered" around the path with three different amplitudes, but subjects were instructed to ignore the jitter and follow the baseline path. Slow and fast speeds were tested. Tracking performance was assessed as the Root Mean Square Error (RMSE) between actual position of their index finger and the baseline curve. We then performed a robust multivariate regression analysis to determine the relative influence of jitter amplitude and speed on RMSE for each of the three groups (CS, PDOff, and PDOn).

Results: PDOff subjects were much more susceptible to jitter amplitude than PDOn subjects ($p=0.0043$) and C subjects ($p=0.021$). PDOff subjects' performance degraded with increasing speed more than PDOn subjects ($p=0.040$). PDOn subjects were unable to improve their tracking performance over subsequent trials.

Conclusions: Our results suggest an impaired ability of PD patients to optimally utilize uncertain visual feedback, of critical importance in PD subjects who may have impaired visual contrast sensitivity from reduced retinal dopamine. Given theoretical studies suggesting a key role of acetylcholine in assessing uncertainty, our results may indicate a non-dopamine responsive impairment. L-dopa may also prevent adaptation to ambiguous stimuli.

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Attentional resource allocation and swallow function in Parkinson's disease

M.S. Troche, J.C. Rosenbek, L.J.P. Altmann, M.S. Okun, C.M. Sapienza (Gainesville, Florida, USA)

Objective: To assess the influence of attentional resource allocation on swallow performance in Parkinson's disease (PD) by testing the effects of a concurrent cognitive and swallowing task on swallow safety (PA score).

Background: The mechanisms controlling swallow safety have long been considered to be mainly reflexive in nature mediated by processes of the swallow CPG in the brainstem. The expectation that

swallowing function might be influenced by cognitive changes is not unfounded as other processes like gait, also mediated via a CPG, have demonstrated dual cognitive-motor task effects. A more comprehensive understanding of the mechanisms influencing and modulating swallow function is important for the development of appropriate interventions for the remediation of swallow impairments.

Methods: Twenty non-demented participants with PD and dysphagia were enrolled. Baseline neuropsychological testing was obtained on all participants. The experimental dual task paradigm included a modified digit forward task while swallowing 10 cc's of thin liquid barium under videofluoroscopy.

Results: Differential effects were found on swallow safety based on baseline scores of cognitive flexibility and attention measures. Participants who were least impaired in cognitive functioning showed no changes in swallow performance in the dual task. Participants who were moderately impaired in measures of cognitive flexibility and attention showed decrements in swallow safety in the dual task condition as compared to the single task. Participants who were most impaired in the domains of cognitive flexibility and attention actually had improvements in swallow safety in the dual task condition. Additionally, decreased swallow timing durations were found overall when comparing single and dual task conditions, but no significant changes were found in measures of airway coordination.

Conclusions: The results of this study support the hypothesis that fronto-limbic top-down drive can influence the swallow plan resulting in changes to swallow performance (in this case, swallow safety). Future studies should focus on further specifying the cognitive mechanisms influencing the swallow plan and focus on use of cognitive therapeutic targets for the management of swallow dysfunction.

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Skin picking in Parkinson's disease: A behavioral side effect of dopaminergic treatment?

W. Tse, T.D. Hälbig (New York City, New York, USA)

Objective: Impulse control disorders (ICDs), as well as repetitive compulsive behaviors are increasingly being recognized in patients with Parkinson's disease (PD), and have been attributed to the use of dopaminergic medications, and in particular to the use of dopamine agonists. We report here a case of a PD patient who developed skin picking behavior while being treated with levodopa and a dopamine agonist, with the behavior resolving upon discontinuation of the dopamine agonist.

Background: Skin picking (SP) is a self-injurious, repetitive behavior which can cause significant tissue damage. It is included as an example of a potential ICD not otherwise specified in the DSM-IV-TR. SP has heretofore not been described, to our knowledge, in PD patients as a potential impulse control disorder.

Methods: This is a case report of a PD patient seen in our Movement Disorders Center.

Results: A 51 year old male had a 10 year history of PD, and was brought to the clinic by his wife who complained that her husband had recently been "picking" at his head. The patient was being treated with levodopa 500 mg/day, entacapone 1000 mg/day and ropinirole 3mg/day.The ropinirole had been added to the patient's regimen to treat wearing-off symptoms. Examination revealed the presence of 5 excoriated lesions on the patient's scalp. Neurologic examination revealed findings consistent with the diagnosis of idiopathic PD. He was tapered off ropinirole, and after two months, the patient reported that he had stopped picking at his scalp.SP has not previously been reported in PD. The fact that the SP resolved upon discontinuation of his dopamine agonist supports the hypothesis that this behavior could represent a behavioral side effect of dopaminergic medication similar to other ICDs. ICDs in PD may be induced in predisposed patients, in particular with those receiving dopamine agonists, probably via excessive stimulation or sensitization of dopamine receptors in mesolimbic structures.

Conclusions: In conclusion, we report a PD patient who developed a new onset SP, in the context of dopamine agonist therapy. Given the potential self-injurious nature of this behavior, physicians should monitor patients for the development of this possible behavioral complication of dopaminergic therapy.

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Response difference to altered auditory feedback in speech in patients with early- vs. late-onset Parkinson's disease

E.Q. Wang, L. Verhagen Metman (Chicago, Illinois, USA)

Objective: To evaluate the hypothesis that the use of altered auditory feedback (AAF) would improve speech intelligibility similarly in patients with early- vs. late-onset PD.

Background: Advanced speech symptoms in Parkinson's disease, such as festinating speech or palilalia and frequent hesitations, are a clinical challenge. This report is a part of a larger study testing the hypothesis that the use of altered auditory feedback (AAF) would improve speech intelligibility in patients with PD and more advanced speech impairment. While the initial results showed improved speech intelligibility in spontaneous speech associated with the use of AAF (Wang, Verhagen Metman, and Bernard, 2008), it was noted that some patients showed more improvement than others. This report is an effort to try to tease out the factors that may influence the outcome measures.

Methods: Using the Systematic Analysis of Language Transcripts (SALT) software (SALT Software V9, LLC., 2009), we analyzed spontaneous speech samples, produced by four older-onset (aged 72.4 SD 6.02 years) vs. four young-onset PD patients (aged 54.2 SD 4.44 years), with and without the use of AAF. The parameters analyzed included mean length of utterance, within utterance pause time, abandoned utterances, number of different word roots, and word per minute (speaking rate). These parameters are thought to reflect the reduction of frequent hesitations and palilalia which in turn demonstrates improved communication efficiency of a speaker.

Results: The results indicated that, regardless the use of AAF, the older-onset patients performed poorer than the young-onset patients in many areas including mean length of utterance, within utterance pause time, abandoned utterances, number of different word roots, and word per minute (speaking rate).

Conclusions: These findings are consistent with the reports that patients with an older age at onset had more rapid progression of PD than those with a younger age at onset in mentation, freezing, and activities of daily living. Possible underlying mechanism for the observed differences in both deterioration of language and speech function and responses to AAF associated with age-onset will be discussed.

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Apathy after STN DBS: Are patients with impulse control disorders at risk?

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Objective: To determine if PD patients with ICDs develop apathy after STN DBS.

Background: STN DBS can induce apathy in PD patients. Some authors suggest that patients with ICDs improve their behavioral disorders after surgery but develop apathy.

Methods: From January 2006 to November 2008, PD patients who were selected for STN DBS were assessed before surgery and were divided into 2 groups: patients without ICDs and patients with at least one ICD and/or DDS. UPDRS, Mattis Dementia Rating Scale, BDI, MIDI, criteria for ICDs and Lille Apathy Rating Scale (LARS) were assessed before and one year after surgery.

Results: Before surgery 27 patients (8 women, 56.4 yo, disease duration: 9 years) were found to have ICDs (pathological gambling:

15, hypersexuality: 14, excessive shopping: 6, DDS: 11), 50 patients (17 women, 63 yo, disease duration:10 years) had no ICDs. The mean LARS score was -24.5 (ICDs group) and -30.1 (non ICDs group)(no apathy). After surgery, the motor improvement was 58% and 65% for the non ICDs and ICDs group respectively. The LEDD decrease was 45% in both groups. The Mattis Dementia Rating Scale remained stable. There was an improvement in BDI scores and no change in LARS scores for ICDs group. 2 patients had a persistent DDS although less severe than before surgery and one patient had an episode of excessive shopping and hypersexuality after reintroduction of dopamine agonist. The non ICDs group developed apathy with a difference in LARS score (-21, range : -36-+25).

Conclusions: This prospective study on 77 PD patients who underwent STN DBS showed that patients with ICDs improve their behavioral disorders but this improvement is not related to the emergence of apathy. However, some patients without ICDs may develop apathy after STN DBS.

POSTER SESSION 2

TUESDAY, JUNE 15, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

PARKINSON'S DISEASE: CLINICAL TRIALS

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Myocardial ^{123}I-MIBG scintigraphy correlates with phenotypes of Parkinson's disease rather than disease severity

K. Araki, H. Shibayama, F. Katada, S. Sato, T. Fukutake (Kamogawa City, Chiba, Japan)

Objective: To optimize the use of myocardial ^{123}I-MIBG scintigraphy (MMS) in evaluation of Parkinson's disease (PD) patients in routine clinical setting.

Background: In Japan, MMS is only available functional imaging study in evaluation of parkinsonian or dementing disorders of central nervous system. Its discriminating power for lewy body disease from other neurodegenerative disease is reported as 80% both for sensitivity & specificity, but it is not fully elucidated for which PD suspected patients it ought to be used in routine clinical practice.

Methods: We retrospectively reviewed the results of MMS performed in PD patients who fulfilled the UK Brain Bank criteria. Cardiac uptake was evaluated by Heart/Mediastinum (H/M) ratio at 20 minutes (early) and 2 or 3 hours (delayed) after radioisotope injection. PD patients were divided into 2 groups; tremor dominant group (T) whose initial symptom is soly tremor and non-tremor or tremor plus group (NT) whose initial symptom is other than tremor or tremor plus other symptoms.

Results: Fifty-seven patients entered study (male 29, female 28), of which 17 comprised T group (age at onset (AO) 66.0±11.5 years, disease durations (DD) 4.64±3.79 years, modified Hoehn & Yahr stage (mHY) 2.35±1.11, levodopa equivalent daily dosage (LEDD) 234±198mg) and 40 comprised NT group (AO 67.6±9.60 years, DD 4.46±3.58 years, mHY 3.04±1.18, LEDD 304±255mg). Statistical difference was positive only for mHY (p=0.0480). H/M ratio was 2.23±0.59 in T and 1.95±0.46 in NT (p=0.0686) in early phase, 1.95±0.77 in T and 1.68±0.49 in NT (p=0.1085) in delayed phase; both considerably lower in NT group though not statistically significant. The linear regression slope for H/M ratio vs DD was -0.226 in T and -0.0997 in NT in early phase, -0.0605 in T and -0.0145 in NT in delayed phase. Namely, H/M ratio with more sensitive to DD in T (the longer duration, the lower uptake ratio) and almost constant in NT at delayed phase.

Conclusions: Above results suggest MMS possibly differentiate T & NT subtype of PD and H/M ratio is not influenced by DD in NT. MMS is thought to be more useful in differentiating non-tremulous parkinsonian disorders than tremulous ones.

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MOTION (safinaMide add-On To dopamine agonist in early Idiopathic ParkinsON's disease) study design: A 24-week, double-blind, placebo-controlled study of the efficacy and safety of safinamide

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Objective: To evaluate the efficacy and safety of safinamide, a first-in-class agent in Parkinson's disease (PD), as add-on therapy to a stable dose of dopamine agonist (DA) in patients with early-stage PD.

Background: To date, no drug has been approved as add-on treatment to dopamine agonists. Safinamide is an α-aminoamide derivative with a dopaminergic and non-dopaminergic mechanism of action. In previous studies, safinamide as add-on therapy to levodopa or DAs has been shown to improve motor symptoms in patients with early- to mid-late-stage PD (Stocchi et al. Neurology 2007; 68 [Suppl 1]: Abst 20.001; Borgohain et al. http://www.movementdisorders.org/congress/congress09/late_breaking_abstracts.pdf). This mechanism of action may provide additional effects on dyskinesia and non-motor symptoms including cognition.

Methods: MOTION is a double-blind, placebo-controlled, parallel-group, randomized, multinational Phase III study of early idiopathic PD patients (<5 years' duration) who are receiving a stable dose of a single DA. Patients will be randomized (1:1:1) to receive 6 months' add-on therapy with safinamide 50 mg/day or 100 mg/day, or placebo.

Results: The primary efficacy outcome is the change from baseline to Week 24 in motor symptom scores (UPDRS Part III). Secondary efficacy outcomes include changes from baseline to Week 24 in activities of daily living (UPDRS Part II) scores, global clinical status, responder rates (≥30% improvement in UPDRS-III scores), cognition, and health-related quality of life. Safety assessments include treatment-emergent adverse events, changes in laboratory safety tests, vital signs, ECG, and ophthalmologic monitoring. Patients completing MOTION may enter an 18-month double-blind extension study.

Conclusions: This study will provide further data on the efficacy and safety of safinamide as add-on to DA for the treatment of patients with PD.

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Controlled study of intermittent theta-burst transcranial magnetic stimulation for the treatment of Parkinson's disease

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Objective: To investigate the safety and efficacy of intermittent Theta-Burst Stimulation (iTBS) in the treatment of motor symptoms in Parkinson's disease (PD).

Background: Progression of PD is characterized by the emergence of motor deficits, which eventually respond less to dopaminergic therapy and pose a therapeutic challenge. Repetitive transcranial magnetic stimulation (rTMS) has shown promising results in improving gait, a major cause of disability, and may provide a therapeutic alternative. ITBS is a novel form of rTMS which may be more potent and safer than conventional rTMS.

Methods: In this randomized, double blind, sham-controlled study, we investigated safety and efficacy of iTBS of the motor and dorsolateral prefrontal cortices in 8 sessions over 2 weeks. Assessment of safety and clinical efficacy over a 1-month period included timed tests of gait and bradykinesia, UPDRS and additional clinical, neuropsychological and -physiological parameters. In addition, safety of iTBS was tested with EMG- and EEG-monitoring during and after stimulation.

Results: We investigated 26 patients with mild to moderate PD: 13 received iTBS and 13 sham stimulation. ITBS increased cortical excitability in the acute phase. We found some beneficial effects on mood, but no improvement or changes in gait, bradykinesia, UPDRS and all other measures. EMG/EEG recorded no pathological increase of cortical excitability or epileptic activity. Few reported discomfort or pain and one experienced tinnitus during stimulation, but there were no other adverse effects.

Conclusions: ITBS of the motor and prefrontal cortices appears safe, induces acute effects, might exert a mood-enhancing effect, but fails to improve clinical performance and functional status in PD. Other techniques with rTMS might be more efficacious, but need to be established in future research.

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AFQ056 treatment of severe levodopa-induced dyskinesias: Proof of concept study

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Objective: To assess the antidyskinetic efficacy, anti-parkinsonian effect, safety and tolerability of AFQ056 in patients with severe levodopa-induced dyskinesias (LIDs).

Background: Severe LIDs in patients with Parkinson's disease (PD) are associated with a high level of disability. As deep brain stimulation is not possible for all patients, there is a great need for other therapies.

Methods: This was a randomized, double-blind, placebo-controlled, 20-day study. Patients were diagnosed with idiopathic PD, on stable dopaminergic therapy, and had severe LIDs ($\geq$18 on the modified Abnormal Involuntary Movement Scale [AIMS]). AFQ056 or placebo was administered twice daily prior to dopaminergic therapy. AFQ056 was titrated during days 1–16 from 25–150 mg bid, or the highest tolerated dose, and then downtitrated. Antidyskinetic effects were assessed using the Lang-Fahn Activities of Daily Living Dyskinesia Scale (LFADLDS), AIMS and Unified PD Rating Scale (UPDRS) part IV 32–33, and antiparkinsonian effects were assessed using the UPDRS part III.

Results: 28 patients (mean age 66 years, 39% women) were randomized to treatment, 14 to AFQ056 and 14 to placebo. Of those on AFQ056, 8 reached the maximum dosage of 150 mg bid. At day 16, AFQ056 showed a significant antidyskinetic effect vs placebo on the AIMS (-9.75 vs -4.84, p=0.032) and UPDRS part IV 32–33 (-2.56 vs -0.98, p=0.001). Non-significant effects of AFQ056 vs placebo were apparent on the LFADLDS (-3.84 vs -2.30, p=0.233) and UPDRS part III (-6.09 vs -2.79, p=0.279). Adverse events were reported by 13 patients on AFQ056 and 11 on placebo, with dizziness and fatigue most common. The majority of these events were of mild or moderate severity. In the AFQ056 group 2 serious adverse events were reported during AFQ056 downtitration (1 psychotic disorder leading to discontinuation, 1 dyskinesia); both were suspected by investigators as related to study drug. In the placebo group 1 patient reported both dyskinesia and PD as serious adverse events.

Conclusions: AFQ056 induced a clinically relevant and statistically significant antidyskinetic effect in patients with severe LIDs. AFQ056 also showed a positive antiparkinsonian effect, and was reasonably safe and well tolerated.

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Memantine improves "off periods" in patients with advanced Parkinson's disease

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Objective: To evaluate if memantine can improve motor symptoms in patients with advanced PD.

Background: Memantine (3,5-dimethil adamantan-1-amine), an uncompetitive antagonist of NMDA glutaminergic receptor, acts like an agonist dopaminergic D2 receptor and has a similar structure to amantadine. It is not known whether it can improve motor symptoms in Parkinson's disease in a similar manner to amantadine.

Methods: We performed a double blind, placebo-controlled, parallel-group, forced-titration study of memantine on demented and non-demented PD patients at the University of Florida Movement Disorders Center. Patients were evaluated at baseline, using the Unified Parkinson's Disease Rating Scale (UPDRS) and a dyskinesia diary. Subjects were initiated on memantine at 5mg (or corresponding placebo) per day, and the dose was increased weekly to a goal of 20 mg daily. The final outcome was to evaluate the motor activity using the UPDRS scale at baseline and changes in dyskinesia diary after the intake of memantine during the time of the study.

Results: 28 patients with were recruited for the study, 14 were assigned to memantine and 14 to placebo. No significant difference in baseline characteristics or in UPDRS was noted between the two groups. After 12 weeks, no significant differences were noted between the memantine and placebo groups in the UPDRS, however there was a small but significant improvement in off time in the active group compared to placebo (-0,18 vs 1,31 hours; P=0,046) observed in the dyskinesia diary.

Conclusions: The subjects in the memantine group experienced a small but significant reduction in off time without report major adverse events. Larger studies will be needed to confirm our initial findings.

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Rationale and design of the IMPACT study: A cluster controlled trial to evaluate cost-effectiveness of multidisciplinary care in Parkinson's disease

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Objective: To evaluate the (cost)effectiveness of multidisciplinary care in Parkinson's disease (PD).

Background: PD is a complex disorder, with both motor and non-motor symptoms. Treatment by a multidisciplinary team might be superior to 'monodisciplinary' care, but this assumption is mainly based on theoretical arguments and expert opinion. The IMPACT study is designed to evaluate the clinical effectiveness and health care costs of multidisciplinary treatment in PD.

Methods: We designed a cluster controlled trial, comparing multidisciplinary care (in the region of Nijmegen) with usual care (in a geographically separate region). Multidisciplinary care included an individually tailored 3-day assessment by a multidisciplinary team of specifically trained health professionals in the Parkinson Center Nijmegen (ParC), a tertiary referral center for PD. Following this assessment, patients received individually tailored therapeutic recommendations. These recommendations included referrals to specifically trained health professionals, who work in the community (ParkinsonNet). Inclusion criteria were idiopathic PD, Hoehn and Yahr stage $\leq$4, age 20-80 years, living independently in the community, no severe co-morbidity and no dementia. Patients were excluded when they already had received a multidisciplinary screening in ParC. Primary outcome measures are the PDQL (a Parkinson-specific quality of life scale) and ALDS (a generic disability rating scale, validated

for PD). Secondary outcomes include costs, disease severity (UPDRS part III and IV), and falls. We also measure the effect on caregivers. The primary outcome was assessed at baseline and at 2, 4, 6 and 8 months. Thus far, we have included 301 patients (150 in the intervention arm).

Conclusions: The study will clarify whether multidisciplinary care is (cost)effective compared to usual care.

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Effect of safinamide on depressive symptoms in patients with mid-late stage Parkinson's disease

R. Borgohain, N.A. Mehta, O.A. Bajenaru, R. Quatrale, V. Lucini, R. Anand, the Study 016 investigators (Hyderabad, India)

Objective: The efficacy of safinamide (50 and 100 mg/day) as add-on therapy to stable levodopa was assessed in a 24-week Phase III trial in patients with mid-late Parkinson's disease (PD) and motor fluctuations (Study 016). Depressive symptoms were also evaluated.

Background: Depression is common in PD patients, but there are currently no treatments that improve both motor and depressive symptoms.

Methods: Study 016 methods were described previously (Borgohain et al, MDS 2009, http://www.movementdisorders.org/congress/congress09/late_breaking_abstracts.pdf). Depressive symptoms were evaluated using the physician-rated GRID-Hamilton Depression Rating Scale (HAM-D). Patients with baseline HAM-D >17 were excluded from the study. Post-hoc analyses: patient-rated 'emotional wellbeing' subscale of the PD Questionnaire (PDQ-39); HAM-D items; change in HAM-D total score according to baseline score (<10 and ≥10) and antidepressant use. Least squares (LS) mean change (baseline to Week 24) between active treatment and placebo was compared.

Results: Safinamide 50 (n=223) and 100 mg/day (n=224) significantly improved ON time without increasing troublesome dyskinesia vs placebo (n=222). LS mean change was significantly greater for safinamide 100 mg/day (not 50 mg/day) vs placebo for HAM-D total score (-1.0 vs -0.3; p=0.018) and PDQ-39 emotional wellbeing score (-5.0 vs -1.5; p=0.009). Changes in HAM-D item scores for early insomnia (p=0.040), work and activities (p=0.029), and somatic anxiety (p=0.006) were significantly greater for safinamide 100 mg/day (not 50 mg/day) vs placebo; depressed mood and loss of appetite were of borderline significance (p<0.06). Most patients (>80%) had a baseline HAM-D total score <10 and >90% were not taking antidepressants. In both subgroups, LS mean change in score at Week 24 was significantly greater for safinamide 100 mg (but not 50 mg/day) vs placebo (-0.4 vs 0.3 [p=0.018] and -0.9 vs -0.4 [p=0.044], respectively). Between-group differences for the other subgroups (HAM-D ≥10 and antidepressant use) were not significant.

Conclusions: In non-depressed PD patients with levodopa-induced motor fluctuations, safinamide 100 mg/day significantly improved both motor symptoms and depressive symptoms rated by physicians and patients.

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Effect of subthalamic nuclei deep brain stimulation on pain in Parkinson's disease: A clinical and neuroimaging study

E. Dellapina, F. Ory-Magne, L. Calvière, W. Regragi, P. Payoux, C. Brefel-Courbon (Toulouse, France)

Objective: To compare the effect of subthalamic nucleus (STN) deep brain stimulation (DBS) (1) on subjective pain threshold, (2) on pain-induced cerebral activity using Positron Emission Tomography (PET) scan in Parkinson's disease (PD) patients with and without neuropathic pain.

Background: DBS of the STN improves motor function in PD. It could also modify pain perception which is altered in PD (Brefel-Courbon et al., 2005; Gerdelat-Mas et al., 2007) because several structures of basal ganglia are both involved in motor and pain process.

Methods: This double-blind, randomized, prospective, cross-over, controlled (DBS OFF and DBS ON conditions) study assessed the effect of STN-DBS on subjective pain threshold (using thermal stimulations, thermotest) and cerebral activity using H215O PET during experimental nociceptive stimulations in 16 PD patients (8 with and 8 without neuropathic pain) in OFF dopaminergic medication.

Results: DBS significantly raised subjective pain threshold (42.6±3.9 in DBS OFF condition and 43.5±3.6 in DBS ON; p=0.03) in 16 patients. This effect was also significantly found in each group of PD patients. PD patients with neuropathic pain had significant lowered pain thresholds compared with those of pain-free patients. STN-DBS decreased pain-induced cerebral activity especially in thalamus and prefrontal cortex (p≤0.05; k≥50).

Conclusions: This study has shown that STN-DBS modified pain perception raising pain threshold and reducing cerebral activity in nociceptive areas in PD patients.

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Pardoprunox adjunctive to L-dopa for treating motor symptoms in advanced PD: Results from a randomized, double-blind, placebo-controlled study

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Objective: To confirm the efficacy and safety of pardoprunox as an adjunct to L-dopa in patients with advanced Parkinson's disease (PD).

Background: The dual mechanism of action of pardoprunox, a partial D_2/D_3 agonist and full 5-HT_{1A} agonist, may provide unique benefits in managing motor symptoms in advanced PD. This study was designed to confirm the benefit of pardoprunox documented in earlier exploratory trials.

Methods: Multicenter, randomized, double-blind, placebo-controlled, parallel group study, with pardoprunox as an adjunct to L-dopa in advanced PD. 295 subjects (pardoprunox 150, placebo 145) were randomized. After 4-7 weeks of titration and two weeks stabilization the subjects entered a maintenance phase of 12 weeks on 12-42mg/day pardoprunox or placebo. The primary efficacy variable was the change from baseline to the endpoint in the mean total daily OFF-time from home diaries. Secondary efficacy variables included the change from baseline in: ON-time without troublesome dyskinesia, ON-time with troublesome dyskinesia; UPDRS sub-scores (i.e., part 2+3; dyskinesia items 32+33, 34) and Clinical Global Impression. Safety assessments were also included.

Results: Pardoprunox treatment resulted in a statistically significant improvement in the primary efficacy variable (OFF time) (-1.62 hversus -0.92h with placebo), at the end-point (p=0.02). This benefit was statistically significant as early as from the 3rd week of titration and was maintained until the end point. This was supported by secondary efficacy parameters (ON time without troublesome dyskinesia +1.47h and +0.80h, total UPDRS -7.9 and -3.0 for pardoprunox and placebo groups respectively). A high drop-out rates due to adverse events (AEs) (37% in pardoprunox versus 12% in placebo) and AE frequency (placebo adjusted: nausea 22%; dizziness 22% and somnolence 18%) suggested that the dose range selected was too high, and/or titration was too rapid.

Conclusions: Pardoprunox showed significant efficacy in the studied dose range but this benefit was associated with significantly reduced tolerability that may be due to an inappropriately high dose or a too rapid titration scheme.

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A multi-center, placebo-controlled, double-blind trial to examine the safety and efficacy of pimavanserin in the treatment of psychosis in Parkinson's disease

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Objective: An international study was conducted to demonstrate the antipsychotic efficacy of pimavanserin, a 5-HT_{2A} inverse agonist, in subjects with Parkinson's disease psychosis (PDP).

Background: Previous studies suggest that because of its specificity for the 5-HT_{2A} receptor and lack of D2 and H1 receptor binding, pimavanserin may provide antipsychotic benefit with an acceptable tolerability and safety profile.

Methods: In this outpatient study, 298 non-demented PD patients with moderate to severe psychotic symptoms were randomized into three treatment arms: placebo, 10 mg or 40 mg pimavanserin (1:1:1 ratio). Study drug was administered orally once-daily for 6 weeks with evaluations on Days 1, 8, 15, 29, and 42. Patients were on stable PD medication through the study period. The primary efficacy endpoint was the change from Baseline to Day 42 on the Hallucinations and Delusions score of the Scale for Assessment of Positive Symptoms (SAPS). Secondary endpoints were the UPDRS and CGI Scale. Exploratory measures included assessments of caregiver burden and sleep.

Results: All arms showed marked improvements in mean SAPS scores: 5.9 points–placebo, 5.8 points–10 mg pimavanserin, and 6.7 points–40 mg pimavanserin. Neither of the active arms showed a statistically significant separation from placebo at Day 42. The high placebo response may have limited the ability to detect treatment effects. Although significance was not achieved at all time points, the 40 mg pimavanserin arm consistently demonstrated signals of efficacy across a number of measures, including the SAPS, CGI-I, SCOPA nighttime sleep measure and caregiver burden scale. Pimavanserin met the key secondary endpoint of motoric tolerability as measured using the UPDRS. Pimavanserin was safe and well tolerated, with the frequency of adverse events generally similar in the pimavanserin and placebo arms.

Conclusions: These data warrant further investigation of 40 mg pimavanserin for PDP.

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Global motor training with rythmical auditory cues improve and maintain balance control in Parkinson's disease (PD) patients

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Objective: To evaluate the efficiency of a global motor training connected to rythmical auditory cues not associated to specific movements on balance control and verify the follow up.

Background: Balance and mobility impairments restrict functional independence in PD. Despite studies showing that sensorial integration deficiency causes difficulties to perform balance reactions on time, spreading to the difficulty of posture maintenance. The literature emphasizes trainings to improve balance and little is known in relation to the use of external auditory to the training itself.

Methods: Assessments were carried out by a blinded examiner in the balance of 30 PD patients average mean age of 67.91 years (DV=6,51), at stages 2 to 3 of H&Y, before and after 10 training sessions, and after 4 and 30 weeks the end of training sessions. The subjects were assessment through BERG test (BT) e Postural Stress Test (PST), also carried out an assessment of independence to the AVDs and motor performance through UPDRS. After a previous assessment, patients were divided in 3 groups for order of arrival. One of the groups (RC), carried out a motor program to balance, associated to rythmical auditory cues. The directions of the training were self-perception, motor performance, attention, and the training program consisted on 5 weeks with 45 minutes duration, divided in 05 minutes warm-up, 30 minutes main part, 10 minutes cool down. The other group carried out the same program without cues (MT) and the last one no training (CG). During the study there weren't changes on patient's usual medicine. The subjects were reassessment after 4 and 30 weeks without the program training.

Results: After a motor training RC group it was found significant improvement of balance in relation to MT group in an average BERG score ($p<0,01$), PST ($p<0,01$), so significant improvement in the score of session II of UPDRS ($p<0,01$) and session III ($p<0,01$). The follow up show the improvement was maintained in 4 weeks in both groups and the after 30 weeks the interventions there were a decrease in balance responses.

Conclusions: Rythmical auditory cues provide significant improvement to the antecipatory and compensatory balance responses in PD. The exigency from the training was fundamental to the improvement and maintains balance responses.

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Effect of rotigotine on control of early morning motor function in Parkinson's disease: RECOVER study

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Objective: To assess the effects of 24-hour transdermal delivery of rotigotine on early morning motor function in subjects with idiopathic Parkinson's disease (PD).

Background: Rotigotine is a non-ergoline dopamine receptor agonist used to treat the symptoms of idiopathic PD.

Methods: This was a multicenter, multinational, double-blind, placebo-controlled, parallel-group trial (NCT00474058) (partly presented at the XVIII WFN World Congress on Parkinson's Disease and Related Disorders; Miami Beach, FL, USA; December 2009). Subjects with idiopathic PD and unsatisfactory early morning motor control were randomized 2:1 to receive rotigotine (2-16 mg/24h) (n=190) or placebo (n=97). Treatment was titrated to optimal dose over 1 to 8 weeks and maintained at that dose for a further 4 weeks. Subjects were hospitalized for 2 nights before assessment at baseline and again at end of maintenance. Early morning motor function was assessed using the mean change in Unified Parkinson's Disease Rating Scale (UPDRS) Part III (Motor Examination) score from baseline to end of maintenance (Full Analysis Set [FAS], last observation carried forward) (primary endpoint). Mean changes in UPDRS Part II (Activities of Daily Living) and Part II+III scores from baseline to end of treatment (FAS, observed cases) were additional endpoints. Responder rates were also assessed; responders were defined as subjects with a) $\geq$20% and b) $\geq$30% improvements in UPDRS Part III score from baseline to end of maintenance.

Results: The rotigotine group showed greater improvement than the placebo group in UPDRS Part III scores at end of maintenance ($p=0.0002$), and in UPDRS Part II scores ($p=0.0005$) and Part II+III scores ($p<0.0001$) at end of treatment (Table). UPDRS Part III responder rates were higher with rotigotine than placebo ($\geq$20% improvement: rotigotine 52%, placebo 33%; $\geq$30% improvement: rotigotine 38%, placebo 19%).

TABLE (329).

UPDRS	Mean (SD) baseline score		Mean (SD) change		Least squares mean (95% CI) treatment difference
	Placebo (n=89)	Rotigotine (n=178)	Placebo (n=89)	Rotigotine (n=178)	
Part III	31.8 (13.6)	29.7 (12.4)	-3.9 (7.3)	-7.0 (7.6)	-3.55 (-5.37, -1.73)
Part II	13.5 (6.3)	12.7 (5.6)	-1.3 (3.4)	-2.6 (3.6)	-1.49 (-2.32, -0.65)
Part II+III	45.2 (18.9)	42.4 (16.9)	-5.2 (9.1)	-9.6 (9.6)	-4.95 (-7.25, -2.65)

Conclusions: In this study, once-daily rotigotine treatment is associated with significant benefits in control of early morning motor function in subjects with idiopathic PD.

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Effect of the exercise program on postural stability in Parkinson's disease

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Objective: To find the effect of long-term chronic exercise program on postural stability in Parkinson's disease (PD).

Background: Postural instability is a major clinical problem in the course of Parkinson's disease (PD), but there have not been proven methods to enhance postural stability.

Methods: PD patients undergoing exercise program were assessed by computerized posturography and were compared with those without regular exercise. Eighteen PD patients (7 men and 11 women, age 65.2±8.8 years, Hoehn and Yahr stage 2.5-3) who participated in exercise program were recruited to exercise group. Exercise programs consisted of Tai Chi, dancing, walking and elastic band exercise and were performed 3 times/week for over 12 months. Sex and age-matched 14 PD patients (5 men and 9 women, age 62.9±8.0 years) without regular exercise constituted control group. All the patients were measured for sensory and voluntary motor control of balance by computerized posturography.

Results: Exercise group showed better performance in reaction time and directional control of stability compared to control group. These findings were more prominent in akinetic-rigid dominant patients (8 patients in each group) and not observed in tremor dominant patients. There was no difference in sensory organization tests and rhythmic weight shift tests between two groups. In overall, age was correlated with dysfunction of sensory organization ($r>0.5$), and performance of akinetic-rigid dominant patients was not different from that of tremor dominant patients.

Conclusions: The authors found that long-term exercise program was helpful for the postural stability in PD. The PD patients with akinetic-rigid dominant type are strongly recommended to undergo long-term exercise.

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Homocysteine-lowering or antioxidant therapy for bone loss in Parkinson's disease

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Objective: To investigate whether homocysteine (Hcy)-lowering therapy or an antioxidant prevented bone loss in Parkinson's disease (PD) patients taking levodopa.

Background: Low bone mineral density (BMD) has been reported in PD patients. Levodopa, an essential drug for PD patients, increases serum Hcy concentrations. Hyperhomocysteinemia has been associated both with low BMD and high fracture risk.

Methods: Forty-two PD patients with low BMD taking levodopa were randomly assigned to Hcy-lowering therapy (5 mg folate and 1500 μg vitamin B_{12} daily), α-lipoic acid (α-LA) therapy (1200 mg daily), or control groups. Primary outcomes were BMD changes from baseline to 12 months. Secondary outcomes were changes in Hcy level, and C-telopeptide (CTX) levels at 12 months. Forty-one patients completed the study.

Results: Hcy-lowering therapy resulted in significantly greater BMD changes at the lumbar spine (4.4%), total femur (2.8%), and femur shaft (2.8%) than control ($P=0.005$ to 0.023). BMD changes in the α–LA therapy group were similar to those of the control group, but changes at the trochanter (4.6%) were significantly greater in the α–LA therapy group than in the control group after adjustment for body mass index changes. Hcy concentrations decreased to 35.2±13.4 % in the Hcy-lowering therapy group, but increased in other groups. Serum CTX levels at 12 months tended to be lower in the Hcy-lowering group (0.442±0.024 ng/ml) than control group (0.628±0.039 ng/ml) ($P=0.159$).

Conclusions: This small trial suggests that Hcy-lowering therapy may prevent bone loss in PD patients taking levodopa.

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Baseline measurement and demographics of patients with Parkinson's disease referred for physiotherapy: A retrospective study

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Objective: The objective of this study sought to report the demographics and baseline measurement of patients with Parkinson's disease attending physiotherapy department at Tan Tock Seng Hospital from 2004-2009.

Background: There is no physiotherapy baseline measurement data for patients with Parkinson's disease available in Singapore.

Methods: A retrospective correlation design was used to look at the demographics and baseline physiotherapy assessment of gait, balance and posture of 108 patients with Parkinson's disease attending physiotherapy at Tan Tock Seng from 2004-2009. Demographics data including number of years diagnosed with Parkinson's disease, mobility status upon assessment and history of falls were reported. Physcial findings of the patients including postural assessment, postural instability assessment using Marsden test, timed 10 metere walk test and timed up and go test were analyzed and reported in this study.

Results: The mean disease duration was 5 years±SD 2.5 when they are referred to physiotherapy. The mean value for timed up and go was 14.9 seconds±12.9SD. The mean timed 10 meter walk is 16.5 seconds±37 SD. The incidence of fall history among the subjects is 50%. There is significant finding ($P<0.05$) in the correlation of the value of timed up and go between the fallers and non-fallers.

Conclusions: This is the first baseline physiotherapy measurement and demographics of patients with Parkinson's disease established in Singapore. However, the result is based on a small sample size due to exclusion of incomplete data. Therefore, further randomized controlled trial with a larger sample size is needed to evaluate the effectiveness of physiotherapy management in Parkinson's disease in Singapore.

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Repetitive transcranial magnetic stimulation using the H-coil for Parkinson's disease

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Objective: To test the efficacy and safety of the H-coil as a treatment for PD.

Background: Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method for brain stimulation, being experimentally assessed for various neuropsychiatric disorders including Parkinson's disease (PD).As the standard coils used for rTMS are presumed to induce stimulation of the superficial cortical layers alone, a new coil, termed the Hesed Coil (H-coil), was developed, allowing more direct stimulation of deeper neuronal pathways.

Methods: Two sequential studies were conducted: 1. A double blind, sham-controlled study of high frequency (excitatory) stimulation over the motor as well as prefrontal cortex. 2. An open pilot study of low frequency (inhibitory) stimulation over the motor cortex along with high frequency stimulation over the prefrontal cortex. In both studies the patients received a course of 12 treatment sessions within one month. Outcome measures, collected on days 1,10,30,60

and 90 included: Unified PD rating scale (UPDRS), Clinical Global Impression of severity and of change scales, pegboard test, foot and finger tapping tests, timed Up & Go test (TUG), as well as several measures of depression and neuropsychological functioning.

Results: 20 PD patients were randomized to the double-blind study, which showed a trend for improvement in UPDRS score in the active treatment group. There was no difference between the groups in other motor scores which slightly improved in both groups. Ten patients participated in the open study, where a significant improvement of several motor measures at day 30 was evident including: TUG, pegboard, hand and foot tapping. A trend for improvement was evident in the UPDRS. The treatment effect disappeared at day 60. In both studies rTMS did not affect depression or cognitive measures and the treatment was well tolerated.

Conclusions: In the small double blind study high frequency rTMs with the H-coil failed to achieve beneficial effects on motor measures of PD while in an open study, low frequency stimulation caused a short-term improvement of some motor measures. Further studies are warranted to define optimal brain areas and stimulation parameters in order to achieve a substantial beneficial effect in PD.

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Nocturnal symptoms response in patients with advanced Parkinson's disease treated with ropinirole prolonged release or placebo

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Objective: To examine the effect of adjunctive ropinirole prolonged release in patients with advanced Parkinson's disease (PD) not optimally controlled with L-dopa on the proportion of responders on the Parkinson's Disease Sleep Scale (PDSS) after 24 weeks of treatment.

Background: The PDSS is a tool that specifically assesses nocturnal symptoms in patients with PD. Total PDSS scores can range from 0 to 150 (0=most severe, 150=patient is free from all symptoms). A cutoff score to define patients with significant nocturnal symptoms has been prespecified at 100: a baseline PDSS total score of $\leq$100 indicates significant nocturnal symptoms and a score of $>$100 indicates mild nocturnal symptoms.

Methods: Patients were randomized to treatment with ropinirole prolonged release (2–24 mg/day, titrated to optimum therapeutic dose) or placebo as adjunct therapy to L-dopa for 24 weeks. Nocturnal symptoms were assessed using the PDSS. The proportion of patients with PDSS total scores $\leq$100 and $>$100 at baseline and Week 24 last observation carried forward (LOCF) was analyzed *post hoc*. Responders were defined as those moving from having significant nocturnal symptoms (PDSS$\leq$100) at baseline, to having only mild nocturnal symptoms (PDSS$>$100) at Week 24 LOCF.

Results: At baseline, 182/387 (47%) of patients had a PDSS total score $\leq$100: of these 93 (51%) received ropinirole prolonged release and 89 (49%) received placebo. Of those patients with baseline PDSS score $\leq$100, 33/89 (37%) receiving ropinirole prolonged release and 14/83 (17%) receiving placebo were classified as responders. The unadjusted odds ratio for responding with ropinirole prolonged release relative to placebo was 2.90 (95% confidence interval: 1.42, 5.95, p=0.004). In patients with only mild nocturnal symptoms at baseline (PDSS$>$100) a similar proportion of patients' PDSS scores fell to $\leq$100 at Week 24 LOCF, regardless of treatment group (20/102 [20%] ropinirole prolonged release; 21/95 [22%] placebo).

Conclusions: In patients with advanced PD not optimally controlled with L-dopa and with significant nocturnal symptoms at baseline, treatment with ropinirole prolonged release provides almost three-fold greater odds of a positive PDSS response compared with placebo.

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Improvements in awake time spent "on" throughout the day in patients with advanced Parkinson's disease treated with adjunctive ropinirole prolonged release

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Objective: To explore the effects of adjunctive ropinirole prolonged release on "on" time throughout the daytime and during the morning, afternoon, and evening in patients with advanced Parkinson's disease (PD) not optimally controlled with L-dopa.

Background: Initial analyses of the EASE-PD Adjunct Study (101468/169; Pahwa *et al. Neurology* 2007;68:1108–15) showed a significant treatment benefit for once-daily ropinirole prolonged release over placebo in mean change from baseline in awake time spent "on" over a 24-hour period.

Methods: Patients were randomized to adjunctive ropinirole prolonged release (2–24 mg/day) or placebo for 24 weeks. During two 24-hour periods before each study visit, patients used a diary to record whether they were awake or asleep and, if awake, whether "on" or "off" for each 0.5-hour period. Changes from baseline in "on" time while awake during different periods of the day (morning: 8 am–1 pm; afternoon: 1–6 pm; evening: 6–10 pm; daytime: 8 am–10 pm) to Week 24 last observation carried forward were analyzed *post hoc*.

Results: Diary data were unavailable for 24/391 patients (11 ropinirole prolonged release, 13 placebo). Adjusted (country and baseline "on" time) mean (SE) changes from baseline in "on" time while awake in the daytime were 1.48 (0.293) hours for patients receiving ropinirole prolonged release and 0.02 (0.298) hours for those receiving placebo (p<0.0001). Patients receiving ropinirole prolonged release experienced significant improvements in mean "on" time compared with patients receiving placebo during each segment of the day: 0.62 (0.122) *versus* 0.02 (0.125) hours (p<0.0001) during the morning, 0.47 (0.124) *versus* 0.05 (0.127) hours (p=0.0007) in the afternoon, and 0.36 (0.108) *versus* –0.08 (0.110) hours (p<0.0001) during the evening, respectively.

Conclusions: Patients receiving ropinirole prolonged release experienced significant improvements in "on" time in all segments of the day compared with placebo. These data confirm that once-daily treatment with ropinirole prolonged release is capable of providing symptomatic benefits throughout the day in patients with PD not adequately controlled with L-dopa. Data submitted to AAN 2010.

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Clinical prospective controlled trial to determine the rasagiline efficacy in the symptomatic improvement of Parkinson's disease in patients under 50 years

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Objective: To determine (1)epidemiological characteristics and (2)clinical efficacy of Rasagiline in levodopa-treated patients under 50 years with PD.

Background: Selective MAO-B inhibitors reduce the breakdown of dopamine in the brain, thus enhancing levels of endogenous dopamine being produced by surviving dopamine being produced by surviving dopaminergic neurons. So far there are no studies of clinical improvement of Rasagiline in patients with Parkinson's disease under 50 years in Latin America.

Methods: We conducted an open administration of Rasagiline (1 mg per day) to twenty patients of both genders with Parkinson's disease and optimized treatment with other anti-PD medications (Levodopa and other agonist) at Movement Disorders Unit Neurology Department 3th level assistance "Unidad Médica de alta Especialidad Hospital de Especialidades Bernardo Sepúlveda Centro Médico Nacional Siglo XXI Instituto Mexicano del Seguro Social" from March 1st

TABLE (336). *RESULTS*

MOUTH	0	1	3	6	p value
UPDRS	43.05± 19.53 SD	40.9± 20.52	42.68± 18.77	41.47± 18.96	p 0.026
OFF TIME (minutes)	96± 33.06 SD	78.25± 43.07	120± 33.05	54.09± 29.13	p 0.001
DURATION OF DYSKINESIA (minutes)	105± 61.23 SD	85.83± 75.64	54.07± 27.65	60.0± 32.07	p 0.028
SCHWAB AND ENGLAND SCALE (SE)	79± 12.9 SD	-	-	83.68± 10.11	p 0.008
LEVODOPA (mg/day)	767.83± 345.35 SD	-	-	375± 176.77	p 0.005

to August 31st 2008. Changes of motor performance, behavior, activities of daily living and complications of therapy were evaluated with UPDRS (Unified Parkinson's Disease Rating Scale) at 0, 1, 3 and 6 months of treatment. Schwab and England's Activities of Daily Living scale (SE) and total levodopa doses were evaluated at 0 and 6 months of treatment. Scales were applied by the same Neurologist. Secondary end points, were improvement of dyskinesias and ON periods and Reduction of carbidopa/levodopa (CD/LD) doses.

Results: The mean age was 46 (SD 7.65), 11 (55%) male, mean period of disease 7.6 years (SD 4.23), the mean of Hoehn and Yahr staging was 2,6 (SD 0.83). The mean reduction in CD/LD was 422.48 mg.(p 0.005). The mean reduction of UPDRS was 1.57 (p 0.026). OFF time period decreased 41.91 minutes (p 0.0001). Dyskinesias mean duration decreased 45 minutes (p 0.028). Mean reduction of Schwab and England's Activities of Daily Living scale was 4.68 (p 0.008). (TABLE 1).

Conclusions: Our data suggests that (1) EP is more frequent in males under 50 (2) Effects of rasagiline improves UPDRS and Schwab and England's scale (3) a significative reduction of clinical fluctuations was observed with levodopa reduction and rasagiline administration.

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Correlation study between nigrostriatal denervation and pain in Parkinson's disease

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Objective: To study the correlation between nigrostriatal denervation and (1) subjective pain threshold, (2) clinical pain and (3) neuropathic pain in Parkinson's disease (PD) patients.

Background: Previous studies (Brefel-Courbon et al., 2005; Gerdelat-Mas et al., 2007) have reported lowered pain thresholds and abnormal activations of nociceptive areas in PD patients reflecting central modification of pain processing. In PD, pain could be related to dopaminergic dysfunction or other monoamine deficit like norepinephrine and serotonine.

Methods: Subjective pain threshold assessment (thermal stimulations; thermotest) and motor examination (UPDRSIII motor scale) were performed in OFF condition (after dopamine withdrawal of 12 hours). We assessed clinical pain with Visual Analogic Scale, SF-McGill pain questionnaire, Brief Pain inventory and neuropathic pain using DN4 and the Neuropathic Pain Symptoms Inventory. Each patient had a SPECT imaging with FP-CIT which binds dopamine transporters. We made statistical correlations between FP-CIT binding ratio and subjective pain threshold and clinical pain scores, using UPDRSIII score as covariable in a generalized linear model.

Results: 14 patients were included with a mean age of 63.4±7.6 years, a mean duration of PD of 7.8±5.0 years, and a mean motor score of 23.1±4.5. Statistical analyses did not reveal any significant correlation between dopaminergic denervation and subjective pain threshold (p=0.16). Moreover, we did not found any significant correlations between dopaminergic denervation and clinical pain scores.

Conclusions: These results suggest that pain perception abnormalities and clinical pain in PD are not directly related with dopaminergic dysfunction. This is consistent with our previous results showing that apomorphine, a dopamine agonist, did not modify pain thresholds (submitted). Our hypothesis is that other monoamine systems (as noradrenergic system known to be involved in pain processing and altered in PD) could play a role in pain in PD patients.

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The investigation of the effect of exercises on static and dynamic balance using balance master in Parkinson's disease

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Objective: The purpose of this study is to assess the effect of exercises in the Parkinson's disease patients using balance master.

Background: Balance Master provides objective assessment and retraining of the sensory and voluntary motor control of balance with visual biofeedback on either a stable or unstable support surface and in a stable or dynamic visual environment.

Methods: Seventeen Parkinson's disease patients, 11 males (%64.7), and 6 females (%64.7), mean age 65.76±8.10; with the same disability participated in this study. Exercises were given suitably according to disability levels. Exercises including posture, balance and coorination were performed by physioterapist's supervision three days a week lasting 45- 60 minutes for twelve weeks. Balanced master was used in assessing static and dynamic balance parameters in the assessments of the patients' balance.Balance master tests consisted of the modified clinical test for sensory interaction on balance (mCTSIB), unilateral stance, limits of stability, rhythmic weight shift, tandem walk, step/quick turn and sit to stand. The measurements were assessed before and after twelve-week exercises program.

Results: In the unilateral balance on the right leg, significant difference was found ($p<0.05$) in the parameters of movement velocity, directional control, endpoint excursion and maximum excursion of limit of stability.

Conclusions: The exercise program, according to our balance master test results about dynamic balance, was found effective more than static balance.

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Methylphenidate for the treatment of gait impairment in Parkinson's disease: A randomized, double-blind, placebo-controlled cross-over trial

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Objective: To evaluate the efficacy of MPD for the treatment of gait impairment in PD.

Background: There is paucity of available therapies for gait impairment in Parkinson's disease (PD). Open-label studies have shown improved gait after treatment with methylphenidate (MPD).

Methods: Twenty-seven subjects with PD and moderate gait disturbance were enrolled into a 6-month placebo-controlled, double-blind study. Subjects were randomly assigned to MPD (maximum, 1 mg/kg divided in three doses, up to 80 mg/day) or placebo for 12 weeks and crossed over after a 3-week washout. The primary outcome measure was change in a gait composite score (stride length + velocity) between groups at 4 and 12 weeks. Secondary outcome measures included changes in motor function, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS), Freezing Of Gait Questionaire (FOGQ), number of freezing episodes per gait diary, and measures of depression, sleepiness, and quality of life. Three-factor repeated-measures analysis of variance (ANOVA) was used to measure changes between groups (MPD, placebo) accounting

for state (off/on), study visit (4 weeks, 12 weeks), and their interactions.

Results: Seventeen patients completed the trial. There was no significant treatment or time effect for any of the variables. Treatment effect was not modified by state or study visit. Although there was a trend for reduced frequency of freezing and shuffling per diary, and 10 of 19 patients requested MPD for ongoing post-study management, the gait composite score, FOGQ, and UPDRS scores worsened in the MPD group compared to placebo. There was a marginal improvement in measures of depression.

Conclusions: MPD tended to worsen gait and measures of motor function, sleepiness, and quality of life. This study provides Class I evidence on the lack of benefit of MPD for PD-associated gait impairment. **Clinical trial registration: NCT00526630.**

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The Parkinson's progression markers initiative: A prospective biomarkers study

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Objective: In 2010, MJFF will launch a large clinical study enrolling 400 PD subjects and 200 healthy controls with the objective to collect clinical, imaging, and biologic data to develop biomarkers of Parkinson's disease progression.

Background: Parkinson's disease (PD) interventional trials rely predominantly on clinical outcomes that often vary within subjects and are not consistent across subjects. Reliable and well-validated biomarkers to monitor PD progression would dramatically improve patient care and accelerate research into both PD etiology and therapeutics. During the past two decades much progress has been made in identifying and assessing PD biomarkers, but as yet, no fully validated biomarker for PD is currently available. Given the recent advances in molecular genetics, neurobiology, imaging technology and radiochemistry that have provided new tools that may be useful for PD biomarkers, and the recognition that the lack of PD progression biomarkers has created a roadblock for further studies of disease modifying therapies, there is increasing consensus that a major initiative to develop PD progression biomarkers is both necessary and feasible.

Methods: The data will be collected over 3-5 years and will include motor and non-motor clinical data, dopamine scans, and biologic fluid (blood, urine, cerebral spinal fluid) collection. Clinical and imaging data will be made available to the PD research community; researchers will be able to apply for access to the stored biologic samples. A portion of collected samples will be used to verify promising biologic analytes.

Results: Since this initiative is launching in 2010 there are currently no results to report.

Conclusions: This initiative will create a consortium of academic centers, government agencies and PD foundations, and pharmaceutical and biotech companies to collectively design, implement and fund a comprehensive program to develop markers of PD progression.

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Predictors of initial adverse events in subjects receiving intermittent apomorphine injections

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Objective: To determine predictors of adverse events associated with apomorphine injects.

Background: Apomorphine injections result in dramatic and rapid improvement in Parkinson's disease motor symptoms. The effect in fluctuating Parkinson's disease is of short duration but similar to that seen with levodopa. Still, concerns about side effects, especially hypotension and nausea, have curtailed apomorphine use. To our knowledge no data exists that can predict who might actually experience these side effects in order to better select patients for this potentially beneficial treatment.

Methods: We prospectively collected detailed adverse event data on all subjects receiving their initial apomorphine injects at the Baylor College of Medicine Movement Disorders Clinic. Specifically, visual analogue scales on nausea and light headedness, and orthostatic blood pressure measurements were done at baseline, 10, 20, 40, and 60 minutes after injection. Approximately half of subjects took trimethobenzamide for three days prior to injects, as per approved protocol, while half took only a single dose just before injections or none. All patients started with 0.2 mg injections and some subsequently took higher doses if clinically indicated. Patient demographics, treatment histories (total dose, L-dopa equivalent to turn on, current or previous dopamine agonist use, etc.), and previous adverse events to other PD treatments were obtained from chart review.

Results: Data was available on 29 subjects but subjects with RLS (2) or atypical PD (2) were excluded. Age was 59.1 ± 9.8, duration of PD was 12.5 ± 4.6, and 69% were male. The most common AE was yawning (58.6%). Orthostatic hypotension was predicted by a history of hallucinations ($p<0.01$) but not by previous orthostatic hypotension or any other feature. Nausea was less in subjects who previously took dopamine agonists ($p<0.05$) but not otherwise predicted. AE in subjects who took 3 days of trimethobenzamide were similar to those who did not.

Conclusions: Previous histories of nausea or orthostatic hypotension should not specifically exclude patients from trying apomorphine injections. The currently approved three day protocol of trimethobenzamide may not be necessary.

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Eighteen months of intervention with exercise improve functional mobility with maintenance of mental state in people with Parkinson's disease

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Objective: The purpose of this study was to verify the effectiveness of an 18-month exercise program on functional mobility and mental state in people with idiopathic PD.

Background: The compromised mobility and the mental dysfunction are among the consequences of Parkinson's disease (PD). Short-term duration of exercise interventions has been applied to people with PD (Gobbi et al., 2009; Tanaka et al., 2009), but the benefits of long-term exercise programs needs to be unveiled.

Methods: Nineteen participants (Stages I to III of Hoehn & Yahr scale; 67 ± 9 year-old; 10 female) were enrolled in an 18-month intensive exercise program (aerobic capacity, flexibility, strength, motor coordination and balance; 3 times a week, 60-minute session). The intervention comprised three phases: one 6-month and two 4-month periods of training, which were intercalated by one 3-month and one 1-month resting/detraining periods, respectively. Basic functional mobility and mental state were assessed by means of the Timed Up and Go test and Mini-Mental State Examination. The assessments were performed pre and post each one of the training periods.

Results: Total score in UPDRS did not change during the overall intervention period. A repeated measure ANOVA showed a moment effect for functional mobility ($F_{4,72}=2.43$; $p<0.05$). Tests of within-subjects contrasts revealed a cubic pattern among the exercise intervention moments ($F_{1,18}=4.144$; $p<0.05$). Regarding the mental state, the same statistical analysis did not showed any change ($F_{4,72}=0.808$; $p > 0.05$).

Conclusions: These results allowed us to conclude that long-term intensive exercise program can improve functional mobility and may

help to maintain mental state, which may reduce the high risk for dementia in people with PD. Based on that, physical activity should be recommended as a component of PD patient's lifestyle. **Acknowledgements:** CNPq, FAPESP, CAPES. GOBBI et al. Exercise programs improve mobility and balance in people with Parkinson's disease. **Parkinsonism Relat Disord**, 15:49-52, 2009. TANAKA et al. Benefits of physical exercise on executive functions in older people with Parkinson's disease. **Brain Cognition**, 69:435-441, 2009.

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Impact of nordic walking on motor function, non-motor symptoms, mood and cognition in Parkinson's disease

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Objective: This study was designed to evaluate the effectiveness of Nordic Walking (NW) concerning the improvement of motor function, non-motor symptoms, mood and cognition in PD patients in a well controlled cohort and to assess potential influencing factors.

Background: Numerous studies suggest effectiveness of physical therapy in the improvement of motor function in Parkinson's disease (PD). However, most studies were not well controlled and did not assess symptoms beyond motor function.

Methods: 24 patients with idiopathic akinetic-rigid type PD, stage Hoehn & Yahr 2-2.5 and 24 matched healthy controls were randomized in a cross-over design to participate in a 24 week study including 12 weeks of instructed and individually heart rate controlled NW training (3x/week, 1 hour) and a 12 week control phase without NW training. At baseline, after 12 and after 24 weeks all subjects underwent assessment of motor function using UPDRS-III and BBS in OFF-condition, of non-motor symptoms using the NMSQ, of depressive symptoms by BDI and of cognitive performance by MMSE and PANDA. The PDQ-39 was used to assess quality of life. Daily activity monitoring was performed using pedometers.

Results: Daily activity improved significantly in both groups (both $p<0.001$) during the training phase. There was no statistically significant change of UPDRS motor scores after training in PD patients (29.6±9.4 vs. 27.9±10.9, $p=0.23$), still 50% of the patients showed an improvement of motor function ranging from 5-40%. In none of the other scores statistically significant changes could be observed in any of the groups ($p=0.20$-0.89). Still, also in these scores some subjects profited to a significant degree. Improvement of motor function correlated with shorter disease duration ($p=0.008$) and sustained cognitive function ($p=0.006$). Quality of life improvement was associated with lower prior activity level ($p=0.007$) and improvement of balance ($p=0.03$). Improvement of non-motor symptoms was most evident in patients with shorter disease duration ($p=0.005$).

Conclusions: The degree to which specific motor and non-motor symptoms as well as mood and cognitive symptoms improve in PD seems to be individually very different. Further analyses are underway to define predictors for individual outcome.

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Pramipexole induced peripheral edema

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Objective: To report the clinical features of and to investigate the predisposing factors and eventual outcomes in patients who developed peripheral edema following treatment with pramipexole.

Background: Pramipexole dopamine agonist, effectively treats early and advanced Parkinson.

Methods: Cases related.

Results: Of the 10 patients who where receving pramipexole, had mild severe peripheral edema, which was attributable to the medication. The mean time of onset of peripheral edema after pramipexole teraphy was 12 months. The mean dose at onset of peripheral edema was dose range the 01 mg a 4,5mg. In all cases the peripheral edema rapidly returned the conition seemed to be dose dependent but also idiosyncratic,as we could not identify any predisposing features. It resulted in extensive medical evaluation in some patients was only responsive to diuretic therapy.

Conclusions: Peripheral edema should be included among the potential adverse events associated with pramipexole therapy.

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Argentine tango effects on balance and gait in Parkinson's disease: Individuals with and without freezing of gait and fall history

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Objective: To compare Argentine tango effects on gait, balance and balance confidence in individuals with moderate Parkinson's disease classified according to fall and freezing history.

Background: Argentine Tango may effectively address mobility and gait problems of those with Parkinson's disease (PD). It is unknown if Tango differentially affects motor function of those with Freezing Of Gait (FOG) or fall history.

Methods: We assigned 18 individuals with FOG (mean age: 68.1±8 years, time with PD: 10.3±5 years, Hoehn &Yahr (HY): 2.5±0.4) and 18 individuals without FOG (68.6±7, time with PD: 7.3±4, HY: 2.3±0.4) to a Tango movement class. We also classified these subjects according to fall status: 18 fallers (age: 69.3±7, time with PD: 10.2±5, HY: 2.6±0.4) and 18 non-fallers (mean age: 67±7, time with PD 8.1±5, H&Y: 2.2±0.3). Subjects attended 20 one-hour classes. Fallers had had 2+ falls in the last 6 months. Freezers experienced freezing more than once per week. We evaluated subjects before and after classes with the Unified Parkinson's Disease Rating Scale (UPDRS), Berg Balance Scale (BBS), Activities-specific Balance Confidence scale (ABC), and Timed Up & Go (TUG). Forward and backward gait were evaluated by GAITRite walkway (CIR Systems, Inc.). Two-way repeated measures ANOVAs (group (Freezer v Non-Freezer, or Faller v Non-faller)) x time (Pre, Post) tested for differences ($p=0.05$).

Results: Freezers scored lower on the ABC and BBS ($p<0.01$), had greater stance percent of gait cycle in forward walking, and

TABLE (345). *A comparison of individuals with and without freezing history on measures of gait, balance and balance confidence before and after tango classes*

Measures	Non-freezers (n=18, 6 females) PRE	Non-freezers POST	Freezers (n=18, 3 females) PRE	Freezers POST
BBS^^#	48.9±4	51.8±3	46.6±5	50.8±3
UPDRS	28.4±7	27.8±7	30.9±9	29.2±8
TUG (s)	9.5±3	9.2±2	11.4±7	10.6±6
ABC (out of 100)*	78±21	81±18	67±19	65±23
Forward Velocity (m/s)	1.1±0.2	1.2±0.3	1.1±0.2	1.2±0.2
Forward stance percent*	64.5±2	63.8±2	65.4±2	64.9±2
Forward base of support (m)	0.10±0.03	0.11±0.03	0.10±0.03	0.10±0.03
Forward Step Length (m)^	0.62±0.1	0.65±0.1	0.62±0.1	0.63±0.1
Backward Velocity (m/s)^#	0.60±0.3	0.72±0.3	0.41±0.3	0.64±0.3
Backward stance percent	67.1±4	66.6±3	68.2±4	68.2±5
Backward Step Length (m)#	0.37±0.1	0.39±0.1	0.32±0.1	0.32±0.1
Backward base of support (m)	0.20±0.05	0.20±0.05	0.19±0.06	0.19±0.05

Values are means ± SD, $p < 0.05$. *Main effect of group, **$p < 0.001$, #$p < 0.01$; ^ Main effect of time, ^^ $p < 0.001$.

TABLE (345). *A comparison of individuals with and without fall history on measures of gait, balance and balance confidence before and after tango classes*

Measures	Non-fallers (n=18, 6 females) PRE	Non-fallers POST	Fallers (n=18, 3 females) PRE	Fallers POST
BBS^^*	49.0±4	51.8±3	46.4±4	50.6±3
UPDRS**	26.4±7	24.8±7	33.4±7	32.0±7
TUG(s)*	9.1±3	8.8±3	11.9±7	11.0±6
ABC (out of 100)*	77±22	80±19	67±16	64±22
Forward Velocity (m/s)	1.1±0.2	1.2±0.2	1.1±0.3	1.2±0.2
Forward stance percent	64.5±2	64.4±2	65.4±3	64.6±2
Forward base of support (m)**	0.11±0.03	0.11±0.03	0.09±0.02	0.08±0.02
Forward Step Length (m)	0.63±0.09	0.65±0.03	0.60 ± 0.01	0.62 ± 0.01
Backward Velocity (m/s)^	0.49±0.3	0.68±0.3	0.51±0.4	0.65±0.3
Backward stance percent	68.2±4	68.2±4	67.1±4	66.7±3
Backward Step Length (m)#	0.37±0.1	0.38±0.1	0.32±0.1	0.32±0.1
Backward base of support (m)	0.20±0.05	0.20±0.06	0.18±0.05	0.18±0.04

Values are means ± SD, $p < 0.05$. *Main effect of group, **$p < 0.001$, #$p < 0.01$; ^ Main effect of time, ^^ $p < 0.001$.

walked backward slower. Fallers scored lower on the BBS and ABC, had greater disease severity and time on the TUG, smaller bases of support and lesser backward step length ($p<0.01$). At post-testing Freezers and Non-freezers had greater BBS scores, forward step length, and backward velocity, while Fallers and Non-fallers had greater BBS scores and backward velocity.

Conclusions: Differences were more pronounced between those with and without fall history. Our data show improved balance and backward gait in those with PD, regardless of falling and freezing status. There may be similar potential for gait and balance improvement with tango in those with and without a history of freezing and/or falls.

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A long-term study of levodopa-carbidopa intestinal gel (LCIG) in advanced PD: Rationale and design

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Objective: To assess the long-term safety, tolerability, and efficacy of LCIG in advanced PD.

Background: L-dopa remains the mainstay of PD treatment because of its recognized efficacy. However, management of advanced PD with oral L-dopa is challenging. Fluctuating L-dopa plasma concentration results in pulsatile delivery of dopamine to the synapse and consequent motor fluctuations. Use of oral extended-release L-dopa and combinations with COMT or DDC inhibitors have shown promise but plasma L-dopa fluctuations remain. LCIG is a suspension of LC in an aqueous gel. A portable pump delivers LCIG to the upper intestine where it is rapidly absorbed. L-dopa plasma fluctuation is much reduced as the influence of erratic gastric emptying is avoided by delivery to the upper intestine. A large Phase III trial of LCIG for US registration is ongoing and we describe it here.

Methods: This is an open-label, 12-month study conducted at 100 centers in 15 countries. Eligible patients have L-dopa-responsive PD diagnosed ≥2 years earlier and severe motor fluctuations with "OFF" time of ≥3 hours/day despite optimized therapy with available PD medications. Patients are screened over a 4-week period before entering a 2-14 day nasojejunal (NJ) test period during which LCIG is infused through an NJ tube to evaluate response and adjust dose. Patients responding to LCIG via NJ can proceed to percutaneous endoscopic gastrostomy (PEG) for placement of a permanent intrajejunal tube. Other anti-PD medications are stopped prior to LCIG initiation and may be reintroduced 28 days post-PEG. Patients are hospitalized during the NJ phase and again for the PEG procedure and further dose adjustment (another 2-14 days). Treatment continues for 52 weeks after PEG placement. Safety measures include vital signs, clinical labs, ECGs, adverse events, the MIDI, and the AIMS. "OFF" time, "ON" time with/without troublesome dyskinesia, UPDRS, PDQ-39, and CGI-I will evaluate efficacy.

Results: The trial is ongoing with 137 of the targeted 250 patients enrolled.

Conclusions: New treatment options are needed for patients with advanced PD. This open-label study will provide important long-term safety and efficacy data on LCIG and will be followed by double-blind studies. Supported by Solvay Pharmaceuticals.

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Pharmacokinetic profile of the adenosine A_{2A} receptor antagonist BIIB014 in healthy volunteers

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Objective: To investigate the pharmacokinetic (PK) characteristics of BIIB014 in healthy volunteers.

Background: BIIB014 is a novel, potent and selective, non-xanthine adenosine A_{2A} receptor antagonist currently under clinical development for treatment of idiopathic Parkinson's disease.

Methods: The pharmacokinetic characteristics of BIIB014 (lactose formulation) were evaluated in young healthy male volunteers after single oral doses of 5 to 100 mg (up to 10 subjects per dose level) and after oral doses of 5 to 50 mg once daily for 10 days (6 per dose level). The effect of food on BIIB014 PK was evaluated after single 10 mg doses of BIIB014 (12 subjects).

Results: After single-dose administration, the peak plasma concentration of BIIB014 occurred at 1.5 to 3 hours post–dose. BIIB014 exposure ($AUC_{0-\infty}$ and C_{max}) appeared to increase linearly with dose up to 15 mg, and nonlinearly above 15 mg, with both $AUC_{0-\infty}$ and C_{max} increasing in a less-than-dose-proportional fashion. The mean $t_{1/2}$ was approximately 19 hours. An average of 3% to 9.5% of the dose was recovered in urine unchanged. After repeated once-daily dosing, BIIB014 exposure increased in a near-dose-proportional manner from 5 to 50 mg. Steady-state was achieved by the fifth dose. Food slightly increased the extent of BIIB014 absorption, with 30% increase in C_{max}, and 10% increase in $AUC_{0-\infty}$.

Conclusions: In Phase 1 clinical studies in healthy volunteers, BIIB014 has demonstrated attractive and predictable PK characteristics at doses up to 100 mg/day that justify further clinical development in patients with Parkinson's disease.

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Parkinson's disease (PD) among inuit in Greenland: Risk factors

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Objective: To investigate polychlorinated biphenyls (PCBs), organochlorinated pesticides (OCs), lead (Pb) and mercury (Hg) as possible risk factors for PD in an arctic population. (PCBs and OCs=Persistent Organic Pollutions (POPs)).

Background: The arctic area has for decades been contaminated with POPs resulting in accumulation in the marine animals. Inuit with its high consumption of these therefore bioaccumulate POPs in the adipose tissue including the brain. Pb is from shot used for hunting birds. The prevalence of PD in Inuit is twice that found in the island of Als, Denmark where the population has had a much lower

exposure to pesticides and metals. This is the first study of PD in an arctic population.

Methods: Study design case-control study Plasma from 39 PD (25 males, 14 females) (mean age 68 yr) and 181 controls (92 males, 89 females) (mean age 66 yr) was analysed for 31 PCBs and OCs as well as for Pb and Hg.

Results: POPs/total lipids (μg/kg) were markedly increased in both PD and controls with no difference in the concentrations except for DDE. The mean DDE/total lipids was higher in the PD-cases (2703 μg/kg) than in the controls (1865 μg/kg) ($p=0.023$). For males there were no difference in Pb between cases and controls while female cases had higher values than controls ($p=0.009$). For both males and females the mean values of Pb were lower than 100 μg/L which the american health authorities have defined as a blood lead level of medical concern. There was no difference in Hg between cases and controls, neither among males nor females but the mean values were 19 μg/L-29 μg/L where WHO recommend less than 10-20 μg/L and thr USA authorities <4.4 μg/L. All analysis are adjusted for age and calculated as log tranformed values of the results of the analysis.

Conclusions: A few epidemiological studies indicate a possible connection between exposure to pesticides and PD. The neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which has a chemical structure close to that of Paraquat, a widely used herbicide, can give parkinsonism in humans as well as in animal studies. We find higher DDE values in PD than in controls and in both cases and controls high values of Hg. A reasonable explanation of the high prevalence of PD in Inuit could therefore in many cases be a genetic background with environmental toxins triggering the development of PD. Further studies are in progress.

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The impact of left prefrontal repetitive transcranial magnetic stimulation on depression with Parkinson's disease: A randomized, controlled, double-blinded, single center study

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Objective: To evaluate the effect of repetitive transcranial magnetic stimulation (rTMS) over the dorsolateral prefrontal cortex (DLPFC) on various motor and non-motor features of idiopathic Parkinson's disease (PD).

Background: Based on several open-label and case studies, rTMS seems to have an antidepressive effect on patients with Parkinson's disease. However, this hypothesis requires confirmation by randomized, controlled, double-blinded studies.

Methods: Twenty-two patients with PD were assigned into 2 groups, one receiving real-rTMS (90% of resting motor threshold, 10 Hz, 450 pulses-day for 10 days) over the left DLPFC, and the other group receiving sham-rTMS. An investigator nurse blinded to the treatment performed three video-taped examinations on each patient: before stimulation (baseline), 10 days (short-term) and 30 days after stimulation (long-term effect). MMSE, UPDRS, Hoehn-Yahr, Epworth, visual analogue and Montgomery-Asberg depression rating scales (MADRS), Beck depression inventory (BDI), and trail making and Stroop tests were applied.

Results: In the rTMS treated group, the depression scales significantly improved (MADRS by 4.5 points and BDI by 4 points, $p<0.05$). Meanwhile, the UPDRS-II, UPDRS-III and the Stroop tests also significantly improved (by 3, 3 and 2 points respectively; $p<0.05$). These changes were consistent over the 30 days. However, none of the examined tests changed from the baseline in the sham-treated group.

Conclusions: In our randomized, controlled, double-blinded, single center study, the left DLPFC rTMS demonstrated at least 30 days long effect on depression and motor functions in PD. However, this result should be confirmed by further clinical trials.

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Influence of pramipexole on tremor, affective and cognitive impairment, quality of life in patients with Parkinson's disease (MIRAGE study)

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Objective: To evaluate efficacy of D2/D3 dopamine agonist pramipexole against symptoms are considered relatively resistant to levodopa.

Background: Levodopa remains "gold standard" of Parkinson's disease (PD) therapy, but there are board spectrum of PD features which are relatively or absolutely resistant to levodopa. Ability of dopamine agonists ameliorate these symptoms remain unclear.

Methods: We conducted the open 6-month study of influence of D2/D3 dopamine agonist praMIpexole on tRemor, Affective and coGnitive impairment, quality of lifE in patients with Parkinson's disease (MIRAGE study). Nine eight patients with Parkinson's desease (PD) from 42 to 75 years old (mean 63.2±10.2) have included (20% patients were older 70 years). Hoehn and Yahr stage varied from 1 to 4 (mean 2.5±0.8). Pramipexole was titrated to effective dose (mean dose 2.1 mg/d). 70% patients were on levodopa (mean dose 351.2±279.4 mg). Efficacy was assessed with UPDRS and spiralography (tremor), Montgomery-Asberg Scale (depression), cognitive tests battery, PDQ-8.

Results: To the end of 6 month study decreasing of resting tremor on 54%, postural and kinetic tremor (assessed with UPDRS and spiralography) on accordingly 50% and 15% were noticed. The severity of depressive symptoms was reduced on 56%. Statistically significant decreasing of motor fluctuations and dyskinesias was also found. There were not significant changes in cognitive functioning. PDQ-8 score decreased on 33%. Clinically significant effect with reducing of motor and non-motor symptoms was noticed in 83% patients. The effect was no depended from disease duration, severity of motor deficit, affective and cognitive disturbances. The prevalence of adverse events was low even in patients older 70 years.

Conclusions: We found pramipexole had improved quality of life in PD patients due to attenuation of cardinal motor parkinsonian symptoms as well as symptoms which relatively resistant to levodopa such as postural and kinetic tremor, and depression.

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Long-term treatment of advanced Parkinson's disease with rotigotine

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Objective: Evaluating continued efficacy and safety of adjunctive transdermal rotigotine, a D2/D3 dopaminergic agonist administered for several years of open-label (OL) follow-up in levodopa-treated subjects with advanced Parkinson's disease (PD).

Background: Two placebo-controlled studies showed good outcomes from adjunctive rotigotine 8 and 12 mg/24h (LeWitt et al, *Neurology* 2007) and up to 16 mg/24h (Poewe et al, *Lancet Neurology* 2007). Each study offered enrollment in OL extensions (NCT00594386, NCT00501969).

Methods: Eligible subjects completing placebo-controlled, double-blind trials (SP650, SP515) had their dose de-escalated, then OL adjunctive rotigotine treatment was titrated to 4-16 mg/24h and maintained, with repeated clinical assessments by Unified PD Rating Scale (UPDRS) and surveillance for adverse events (AEs) and abnormalities on vital signs and laboratory testing.

Results: 395 subjects enrolled into the 4-year SP515OL extension; 206 (52%) discontinued, of whom 76 (37%) discontinued because of

AEs and 51 (25%) withdrew consent. While UPDRS Activities of Daily Living (ADL) mean total score improved from double-blind baseline by -4.5 points during OL titration, it then gradually returned over 4 years to baseline values (+0.8 points). During titration, mean UPDRS Motor Score (MS) improved from double-blind baseline by -10.1 points, then gradually declined to -2.8 points of improvement. 258 subjects entered the SP650OL extension; 143 (55%) discontinued by the end of year 6, of whom 68 (48%) discontinued because of AEs and 35 (25%) withdrew consent. The -4.9-point mean ADL score improvement achieved during titration declined to +4.1 points above baseline over 6 years, and the mean MS declined from an initial -11.4-point improvement to baseline values (-0.2 points). Laboratory testing and vital signs revealed no significant trends for safety problems. Treatment-emergent AEs were typical dose-related dopaminergic effects (such as dyskinesias [4-8% per subject-year] and hallucinations [4-8% per subject-year]).

Conclusions: OL experience with advanced PD subjects previously enrolled in 2 randomized placebo-controlled studies with rotigotine showed continued good efficacy and safety outcomes after several years.

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Fipamezole in the treatment of dyskinesia in advanced Parkinson's disease (FJORD study)

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Objective: Anti-dyskinetic efficacy of fipamezole (FIP) (30, 60, 90 mg tid) vs placebo by an L-DOPA-induced dyskinesia rating scale (LIDS) along with assessments of parkinsonism (UPDRS) and safety.

Background: A therapeutic goal for PD patients chronically receiving L-DOPA is dyskinesia control. FIP is a selective alpha-2 adrenergic antagonist that blocks L-DOPA-induced dyskinesias in MPTP-lesioned monkeys. In an initial proof-of-concept study in dyskinetic PD subjects, FIP (60 and 90 mg/day) significantly reduced modified-AIMS scores.

Methods: FJORD was a double-blind, randomized, placebo-controlled, dose-escalating 28-day study in L-DOPA-treated PD patients with dyskinesia, conducted at 25 centers in the US (115 subjects) and 7 in India (64 subjects). Primary endpoint was change from baseline to Day 28 in LIDS (averaged assessments after 1st dose of FIP and at 0, 0.5, and 1 hr after an 'ON' state from L-DOPA dosing). Data underwent repeat-measures analysis of variance and Jonckheere's test (for the dose response) in the intention-to-treat observed-cases population.

Results: There was no statistically significant difference from baseline to endpoint based on the total study population. However, analysis of US and Indian study participants showed inhomogeneity in baseline characteristics (including demographics, L-DOPA dosing, and parkinsonian features). In a further pre-specified subgroup analysis of the US subjects (mean age, PD duration, and dyskinesia duration: 67.5, 12.0 and 5.6 yrs), FIP, 90 mg tid, was effective at reducing dyskinesia (mean LIDS improvement versus placebo at Day 28: 3.7+1.0; p=0.047) and showed dose-responsiveness (p=0.014 for placebo, 30, 60 and 90 mg tid). LIDS reduction correlated with clinical improvement on the CGI scale (p=0.035). The dyskinesia-lessening effect of FIP was not associated with worsening of parkinsonism. FIP exerted a mild blood pressure elevating effect and had an acceptable profile of adverse effects.

Conclusions: The primary outcome showed no significant change in LIDS rating for the total study population. However, the strong evidence of efficacy in the US study subgroup (comprising 65% of the study population) suggested that FIP may be useful to treat dyskinesia in advanced PD without exacerbating parkinsonism.

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Proof-of-concept clinical trial on the use of oral ridaforolimus, an investigational mTOR inhibitor, for enhanced autophagy in Parkinson's disease

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Objective: The initial objective of this study is to first assess the safety and tolerability of ridaforolimus in an open-label design in a small number of subjects (10) with early PD. Then a phase 2, prospective, randomized, parallel-group, double-blinded, placebo-controlled study will be conducted to assess the putative therapeutic potential of ridaforolimus (40 subjects).

Background: There is evidence to suggest that enhancing autophagy through the mammalian target of rapamycin (mTOR)-dependent pathway may remove aggregate proteins and hence help slow the neurodegeneration of Parkinson's disease (PD). The value of autophagy upregulation may be greatest if treatment is started as early in the course of PD as possible, with the aim of preventing or slowing disease progression.

Methods: Subjects with Hoehn and Yahr stage I and II PD and naïve to any antiparkinsonian medication will be divided into two treatment groups or a placebo group for 36 weeks. The main outcome measure will be a change from baseline in the sum of Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III score at week 36, and there will be several secondary outcome measures, including use of the Parkinson's Disease Quality of Life Questionnaire (PDQ-39), the Patient Global Impression (PGI) scale and the Clinician Global Impression (CGI) scale. It is hypothesized that there will be a significant difference in the change in the UPDRS score between baseline and week 36 in the treatment versus the placebo group, and that early treatment with ridaforolimus will provide benefits consistent with a disease-modifying effect.

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Falls prevention for Parksinson's disease residents in supported accommodation as an outcome of staff education

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Objective: People with Parkinson (PWP) in residential facilities are usually elderly, cognitively impaired, physically disabled, and prone to psychosis with a poor quality of life and with a high fall rate and mortality rate.

Background: People with Parkinson (PWP) in residential facilities are usually elderly with extensive impairments. We wanted to determine if the knowledge base of residential facilities staff could be improved with targeted education and whether this improvement would translate into meaningful improvement in residents' care. We wish to focus on this report on the fall rate as one of the benefits of staff education.

Methods: A curriculum was developed and delivered to 118 staff members in 9 facilities. The curriculum focused on rehabilitation strategies, general PD knowledge, medication issues and accessing local specialist services. The 49 residents with PD in the facilities were elderly (81.6 years), had longstanding PD (152.6 months) and required high level care. Measures undertaken at baseline, 1, 3 and 12 months included staff knowledge base, monthly falls diary, and resident/family questionnaire (RFQ). A multilevel mixed effects Poisson regression was used to analyse the falls data.

Results: The staff knowledge scores and RFQ improved significantly ($P<0.01$) after education from baseline and were maintained to 12 months. There were 197 falls in 49 residents at baseline ranging from 0–24 per resident. The fall rate decreased by 9% per month (IRR{95%CI}=0.91{0.89, 0.92} over the year, but most of the improvement took place in the first four months.

Conclusions: These findings suggest that a simple measure which addresses staff knowledge can significantly reduce falls in PWP in care and such an approach needs to be developed further.

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Dance therapy: Effect on gait measures and quality of life in Parkinson's disease patients

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Objective: To evaluate the effectiveness of dance therapy for improving various aspects of QOL and gait in patients with PD.

Background: The use of dance as movement therapy has been emerging in PD and other neurodegenerative disorders, but data to support efficacy are lacking.

Methods: Nine patients with idiopathic PD voluntarily participated in a PD targeted modern dance class. One neurologically normal subject who had taken the class and one neurologically normal subject who had not taken the class were also included for comparison. There were two consecutive series of movement therapy instruction, each consisting of 8 weekly one hour dance classes. At the end of each series, patients self-reported on quality of life via the SF-36 questionnaire, comparing their status at the end to their status at the beginning of the series. Patients also underwent quantitative gait examination using a GAITRite mat (CIR Systems, Havertown, PA, USA). Of the 9 patients tested, 6 patients participated in both sessions. As a steadily progressive decline is expected with PD, therapy was considered successful if patients' quality of life or function was the same or better after the series of dance classes.

Results: On both occasions the majority of patients self-reported being the same or better on all 8 domains of QOL measured by the SF-36 (physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health). Of the 6 patients who had repeated quantitative gait measures, a majority performed the same or better on velocity, cadence, stride length, swing percentage, stance percentage, single support percentage, and double support percentage.

Conclusions: A cross-sectional pilot study of dance as movement therapy in PD shows an objective improvement in gait mobility and a self-report of longitudinal improvement in quality of life. These measures were robust to the expected disease fluctuations due to differences in timing of PD medications. Thus, dance is a promising method of movement therapy for gait control, and a randomized, controlled study is warranted.

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Assessment of sleep duration and nocturnal awakenings with ropinirole prolonged release in patients with advanced Parkinson's disease

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Objective: To explore the effects of ropinirole prolonged release on sleep duration and night-time awakenings in patients with advanced Parkinson's disease (PD).

Background: Once-daily ropinirole prolonged release as an adjunct to L-dopa has been shown to improve symptom control and reduce nocturnal symptoms as measured by the PD Sleep Scale (EASE-PD Adjunct Study 101468/169; Pahwa *et al. Neurology* 2007;68:1108–15).

Methods: Patients were randomized to treatment with adjunctive ropinirole prolonged release (2–24mg/day) or placebo for 24 weeks. Patients recorded on diary cards whether they were awake/asleep and, if awake, whether "on"/"off" for each 0.5-hour period during two 24-hour periods before each study visit. Sleep duration during different periods of the day and the proportion of patients experiencing a decrease from baseline in the number of awakenings/night are reported for Week 24 last observation carried forward (analyzed *post hoc*).

Results: Data were unavailable for 24/391 patients (11 ropinirole prolonged release, 13 placebo). Adjusted (country and baseline sleep time) mean treatment differences in change in sleep duration (hours) for ropinirole prolonged release compared with placebo for night-time (10pm–8am) and daytime (8am–10pm) periods were not significant (NS) (0.16 [95%CI: –0.09, 0.41, $p=0.204$]; –0.05 [95%CI: –0.26, 0.16, $p=0.625$], respectively). Decreases from baseline in awakenings/night were seen in 46/187 (25%) patients receiving ropinirole prolonged release and 32/173 (18%) receiving placebo. The odds ratio for a decrease in awakenings/night with ropinirole prolonged release *vs* placebo was NS (1.43 [95%CI: 0.85, 2.39; $p=0.180$]), possibly as a high proportion of patients in each group (110/187 [59%] ropinirole, 86/173 [50%] placebo) had no awakenings/night at baseline.

Conclusions: No significant treatment differences were observed in change in night-time or daytime sleep duration, or number of awakenings/night. These data suggest that ropinirole prolonged release neither significantly reduces night-time sleep nor significantly increases daytime sleepiness in patients with advanced PD. This latter point is consistent with previous reports from this study of a non-significant difference in change in Epworth Sleepiness Scale total score. Data submitted to AAN 2010.

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Frequent functional measures substantially reduce sample size in clinical trials

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Objective: Our objective was to calculate the number of subjects necessary to estimate the rate of progression for the first end point in the ADAGIO trial with the same accuracy, but using more frequent (daily and weekly) measures of impairment.

Background: Delayed-start has emerged as the preferred clinical trial design for evaluating whether therapies may be disease modifying. This design helps distinguish symptomatic and cumulative benefits of therapy. The rate of disease progression is typically measured as the change in UPDRS score over time, which is a coarse approximation of the slope versus time. The UPDRS is obtained infrequently, due to cost and time constraints. It is unknown how much of a reduction in variability of the estimated rate of progression could be attained with more frequent measurements.

Methods: We used the first end point in the ADAGIO trial as our outcome criteria, which was the rate of change in the UPDRS score between the UPDRS score obtained on the 12th week and that obtained on the 36th week, which comprised the end of the first phase. The placebo arm included 595 subjects. The reported rate of progression was 0.14 ± 0.01 UPDRS points, which corresponds to an estimated test-retest standard deviation of 4.14 points. We modeled the disease progression to vary linearly with time and calculated a 95% confidence interval in the estimated slope for a variety of measurement intervals and numbers of subjects. We assumed the UPDRS had an intra-rater reliability of 0.90.

Results: The 95% confidence interval for 595 subjects with two measurements taken 24 weeks apart was 0.70 points per year. This represented the uncertainty in rate of progression for the placebo group during phase I of the ADAGIO trial. The same confidence interval was obtained with only 302 subjects (49% fewer) with daily measurements and 361 subjects (39% fewer) with weekly measurements.

Conclusions: Frequent assessments during clinical trials evaluating the potential for disease modification may substantially reduce the number of subjects required, and therefore the cost of the trial. This may be impractical with intensive time-consuming clinical instruments like the UPDRS, but may be possible with assessments performed in the home either with objective devices designed to measure functional impairment or video scoring of rating scales.

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A clinical data management system for clinical trials of movement disorders

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Objective: Our objective was to develop a centralized web-based system for managing and monitoring data from multi-center clinical trials focused on movement disorders. The system was required to be easy to use, robust, and HIPAA compliant with secure, role-based access to the data. It had to support automatic uploads, analysis, and visualization of device data from objective measures of functional impairment. It also had to support standard rating scales and blinded video scoring.

Background: Objective measures of functional impairment are currently under development by many research groups. These have the potential to more precisely measure functional impairment than rating scales and may be able to detect small changes, such as a slowing in the rate of disease progression. This may significantly reduce the number subjects required to provide sufficient statistical power for clinical trials, which in turn would substantially reduce the cost. However, objective measures are typically acquired with sensors that produce large binary data sets that cannot easily be handled by current clinical data management systems.

Methods: We have developed a clinical data management system that meets all of these requirements. The system supports electronic entry and blinded video scoring (where applicable) for most of the standard rating scales, including UPDRS, PDQ-39, and the MoCA. It also supports binary data from several devices designed to objectively measure the motor signs of Parkinson's disease. The system supports monitoring of clinical trials including a visualization of data that is pending, has been collected, or is overdue.

Results: The system has been successfully used in 10 studies involving 7 different sites. No data has been lost and reported satisfaction with the system has been high.

Conclusions: We have developed a new clinical data management system at objectivepd.com designed to support clinical trials in movement disorders. The system includes all of the standard features of most data management systems, but also supports functional measures with devices that produce large data sets, provides real-time visualization and tools for data management and problem resolution, and facilitates on-line video scoring. We are developing a variety of touch-screen data entry devices for direct data entry that will obviate the need for managing and transcribing paper forms.

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Safinamide as add-on to levodopa improves motor function without worsening dyskinesia in patients with mid-late Parkinson's disease

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Objective: The efficacy of safinamide (50 and 100 mg/day) as add-on therapy to stable levodopa was assessed in a 24-week Phase III trial in patients with mid-late Parkinson's disease (PD) and motor fluctuations (Study 016).

Background: Add-on therapy in levodopa-treated patients with PD should improve motor function without worsening dyskinesia.

Methods: Study 016 methods were described previously (Borgohain et al, MDS 2009, http://www.movementdisorders.org/congress/congress09/late_breaking_abstracts.pdf). Assessments included diary ratings (ON, OFF, ON with troublesome/minor dyskinesia), United Parkinson's Disease Rating Scale (UPDRS) Parts II (activities of daily living), III (motor) and IV (complications of therapy) total scores, and Dyskinesia Rating Scale (DRS) scores. Post-hoc analyses: subscale scores for UPDRS Part II (freezing when walking, Item 14), Part III (bradykinesia, Items 23-26, 31; rigidity, Item 22; postural instability gait disorder, Items 13-15, 29, 30), and Part IV (dyskinesia, Items 32-34; dyskinesia and dystonia, Items 32-35; individual scores for Items 32-35). The difference in the change from baseline to Week 24 between active treatment and placebo was compared.

Results: Safinamide 50 and 100 mg/day significantly improved ON time without increasing troublesome dyskinesia vs placebo. UPDRS III total and subscale scores also showed that safinamide improved motor function (Table 1). Although dyskinesia as an adverse event was reported more frequently in the safinamide groups (50 mg, 20.6%; 100 mg, 17.9%; placebo, 12.2%), there was no significant between-group differences in UPDRS IV scores for dyskinesia and dystonia or DRS scores. The levodopa dose was to remain stable during the study, but there was a small increase in dose (0.27%) in the placebo group and small decreases in the safinamide 50 and 100 mg/day groups (-1.05% and -2.16%; p=0.016 for safinamide 100 mg/day vs placebo).

TABLE (359). *Least squares mean change in motor function scores (baseline to Week 24)*

Parameter	Placebo (n=222)	Safinamide 50 mg/day (n=223)	Safinamide 100 mg/day (n=224)
UPDRS III (during ON)	-4.4	-6.4 (p=0.008)	-7.2 (p=0.0002)
UPDRS III, bradykinesia	-1.6	-2.6 (p=0.014)	-2.7 (p=0.005)
UPDRS III, rigidity	-1.1	-1.5 (p=0.060)	-1.6 (p=0.017)
UPDRS III, postural instability gait disorder	-0.2	-0.2 (p=0.278)	-0.3 (p=0.006)
UPDRS II, freezing when walking	-0.2	-0.2 (p=0.730)	-0.3 (p=0.040)

Conclusions: In patients with levodopa-induced motor complications, add-on therapy with safinamide improved motor function without worsening dyskinesia.

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An interim analysis of an open-label extension study to examine the long-term safety and tolerability of pimavanserin in the treatment of Parkinson's disease psychosis

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Objective: A multi-center, open-label extension study is being conducted to assess long-term safety and tolerability in patients with Parkinson's disease psychosis (PDP) who have completed 6 weeks of blinded therapy (pimavanserin vs. placebo) in a previous trial and who, in the Investigator's opinion, may benefit from long-term treatment with pimavanserin.

Background: Pimavanserin is a selective 5-HT_{2A} antagonist being developed for the treatment of PDP. Previous short- and long-term studies have shown that pimavanserin is generally safe and well-tolerated in patients with PDP. This study was intended to provide additional long-term safety data in this fragile elderly population.

Methods: Patients receive 40 mg pimavanserin once a day. This interim analysis was performed to assess safety data through 12 months of treatment. Clinical evaluations occurred 2 weeks, 1 and 3 months after starting treatment, and every 3 months thereafter. Adverse event and concomitant medication assessment, administration of clinical rating scales, physical exam, 12-lead ECG and clinical laboratory tests were performed. A total of 284 subjects had enrolled as of 1 January 2010; 189 remained active. This interim analysis reflects all data collected and audited as of 2 November 2009 for 250 of the first 260 subjects enrolled.

Results: At the time of the analysis, the mean duration of treatment among analyzed patients was 5.3 months (range: 1 day - 23 months); 166 remained ongoing. 47 patients had exceeded 6 months and 23 had exceeded 12 months of treatment. Overall, patient exposure is equivalent to 107 patient years. 130 (52%) subjects experienced at least one AE. The majority of AEs were mild to moderate in severity. Hallucination (8%) and Fall (6%) were the most common AEs. 38 (15%) subjects experienced a total of 39 SAEs, of which 9 were considered to be treatment related. 18 patients discontinued due to an AE. There were 3 deaths; none were considered related to study treatment.

Conclusions: Long-term administration of 40 mg pimavanserin QD appears to be safe and well-tolerated in subjects with PDP.

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Virtual reality for gait training in Parkinson's disease

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Objective: To evaluated the feasibility and efficacy of using Virtual Reality (VR) to improve gait and reduce fall risk in patients with Parkinson's disease (PD).

Background: Gait disturbances are common in PD. Traditional gait training approaches are limited in challenging patients and in enhancing everyday function and reducing fall risk. VR delivers a motivating and exciting training that involves both motor and cognitive challenges and allows for real-time modification of task difficulty based on performance. Thus, theoretically, VR could be well suited for gait training and obstacle negotiation in PD.

Methods: 20 patients with PD received 18 training sessions (3 time/week x 6 weeks) consisting of walking on a treadmill with virtual obstacles projected on a wall. Outcome measures included gait and balance measures as well as PD related measures and quality of life.

Results: Mean age was 66.9±6.21 yrs with mean disease duration of 9.75.4 yrs (H&Y 2-3). All patients completed the training with no adverse responses. Comfortable gait speed significantly improved from 1.16±0.23 m/s to 1.26±0.29 m/s (p=0.001), and patients markedly increased the distance they were able to walk in 6 minutes by 65.8 meters (p=0.004). Stride length, gait variability and obstacle negotiation over ground significantly improved and the negative effects of dual task on gait became smaller (effects of serial 3 subtraction) (p=0.03). parkinsonian symptoms (p=0.02) and performance-based measures of dynamic stability (p=0.001) were positively changed. Training effects on gait speed were maintained at least 1 month post training and patients reported fewer falls and near falls after training.

Conclusions: To our knowledge, this is the first time VR has been used for gait training in PD. The results of this study demonstrate the usefulness of VR in training gait and obstacle negotiation in PD, support the idea that the benefits of this intervention transfer to over ground walking and to the home setting, and suggest that implicit motor learning and behavioral modifications were achieved in response to this 6 week intervention trial.

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Investigation of efficacy and safety of transdermal rotigotine in Japanese de-novo Parkinson's disease (PD) patients

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Objective: To investigate superiority of once-a-daily rotigotine administration to placebo and to assess optimal dose in de-novo PD patients

Background: Continuous dopaminergic stimulation with transdermal rotigotine was considered to be efficacious in de-novo PD patients.

Methods: A Japanese phase 2/3 study was conducted in a multi-center, double-blind, randomized, placebo-controlled, parallel two-arm design. Primary endpoint was change in UPDRS Part 2 and 3 total score from baseline to the end of treatment (EOT). Maintenance dose was selected with a range from 4.5 to 36.0 mg/day. The recommended maintenance dose was assessed to investigate individual dose response curve.

Results: 180 patients were randomly assigned to rotigotine or placebo groups. 88 patients in placebo group and 88 patients in rotigotine group were included in the full analysis set. 44/88 patients (50%) received 36.0mg/day in rotigotine group. UPDRS Part 2 and 3 total scores at baseline and EOT in rotigotine and placebo groups were 27.0±11.8/18.6±12.2 and 28.2±12.2/24.2±14.4 respectively. Absolute changes from the baseline were -8.4±9.7 and -4.1±8.2. The difference from placebo was significant (p<0.002). Efficacy was observed dose-dependently up to 27.0 mg/day in patients treated with 31.5 or 36.0 mg/day. The UPDRS Part 2 and 3 total scores became plateau after 27.0 mg/day in the majority of patients, however, further reduction of the score was observed in 6 patients. Major treatment emergent adverse events in rotigotine group were application site reaction, nausea, vomiting and somnolence. These adverse events were mild to moderate and no serious adverse event was observed.

Conclusions: Once-a-daily rotigotine transdermal application improved patients' activity of daily living and motor function in comparison with patients in placebo group. Rotigotine was also well tolerated from 4.5 to 36.0 mg/day in Japanese de-novo PD patients.

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The influence of disease-dominance on turning problems and freezing of gait in patients with Parkinson's disease

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Objective: To explore symptom-dominance as a contributing factor to turning problems and Freezing Of Gait (FOG).

Background: Patients with Parkinson's Disease with Freezing Of Gait (PD+FOG) have a turning problem which is not present in patients without FOG (PD-FOG)[1]. Turning is the most important trigger for FOG.

Methods: Fourteen patients with FOG (PD+FOG) and 14 PD-FOG defined by the NFOGQ, were matched for age, disease severity, duration and amount of disease asymmetry. Data on the side of disease onset, patient perception of symptom-dominant side and UPDRS asymmetry[2]-score were collected. Patients were asked to turn 180° left and right while measured in a 3D-gait laboratory (Vicon). Turn duration, number of steps and amount of FOG-trials were registered for each turn side. For each separate FOG-episode, the side at which FOG started (FOG onset-side) was determined. Spearman correlations were used for data-analyses.

Results: Side of disease onset, perception of symptom-dominant side and UPDRS-asymmetry were well correlated in the PD+FOG group (r>.60, p=0.02) and the PD-FOG group (r>.80, p<0.01). A moderate correlation was found between symptom-dominant side (side of disease onset and perception of dominant side) and the asymmetry in turning parameters (duration and steps) in PD+FOG (r>.60, p<0.05), but not in PD-FOG. FOG-episodes occurred in 7 out of 14 patients with PD+FOG during turning. The turning side with the greatest number of steps was correlated with the side at which FOG occured most frequently (r=.94, p<0.01). A high correlation (r=.79, p=0.03) was found between the perception of symptom-dominant side and the onset-side of FOG. Pearson's chi-square (X^2=4.71, p=0.03) also showed that freezing occurred more frequently in the symptom-dominant side according to patient perceptions.

Conclusions: Although PD+FOG and PD-FOG had comparable disease characteristics and had similar disease asymmetry, only PD+FOG showed a correlation between side of symptom-dominance and asymmetry in turn behavior. Moreover, FOG-initiation occurred more frequently at the symptom-dominant side. Therefore research into turning problems in freezers should distinguish between turning to the symptom-dominant and non-dominant side. 1. Spildooren J et al. Mov Disord 2009; abstract. 2. Foster E et al. Brain & Cogn 2007.

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Efficacy and safety of rotigotine transdermal application in levodopa-treated patients with Parkinson's disease (PD)

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Objective: To evaluate efficacy, safety and recommended maintenance dose of rotigotine as adjunctive therapy to levodopa in Japanese PD patients.

Background: Efficacy and safety of once-a-daily rotigotine dermal administration were demonstrated in Caucasian patients in EU and US, however, Japanese patients were not been assessed.

Methods: A multi-center, double-blind, randomized, placebo-controlled phase 2b study was conducted in PD patients treated with levodopa. In this study, individual maintenance dose was

determined after optimal dose-titration. Patients received rotigotine or matching placebo in maximal 8-week dose-titration and minimal 4-week dose-maintenance periods. Primary endpoint was reduction of UPDRS Part 3 (on-period) scores from baseline to end of treatment (EOT). Secondary endpoint was reduction of off-period duration.

Results: A total of 176 patients (pts) were randomly assigned to rotigotine (86 pts) or placebo (86 pts) groups. UPDRS Part 3 scores at baseline and EOT were 28.1±12.2 and 26.2±10.4 and 18.0±12.9 and 21.8±12.4 in rotigotine and placebo groups respectively. The changes from the baseline were -10.1±9.0 and -4.4±7.4 and the difference between rotigotine and placebo was -5.7±1.3. It was statistically significant ($p<0.001$), and superiority of rotigotine to placebo in UPDRS Part 3 was shown. Duration of off-period in rotigotine group was significantly reduced over placebo group. Rotigotine 9.0-36.0 mg/day was an optimal dose range according to individual dose-response analysis. Rotigotine group showed more frequent adverse events such as application site reaction, somnolence, nausea, vomiting and headache, however, severe adverse events were not observed. Application of rotigotine at doses up to 36.0 mg/day with dose-titration was well tolerated.

Conclusions: The study showed that rotigotine was superior to placebo in reduction in UPDRS Part 3 score (on-period) and off-period duration, and well tolerated at the doses of 9-36 mg/day in adjunctive therapy to levodopa-treated Japanese PD patients.

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Improved fluctuations following retinal fetal cell implantation compared to controls

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Objective: To determine the long term changes in fluctuations in a subset of subjects undergoing bilateral retinal fetal cell transplants compared to sham surgery.

Background: Recently a multi-center sham/placebo controlled trial of implanted retinal fetal cells failed to demonstrate superior "off" motor scores compared to placebo at one year, largely due to a large placebo response. Measures of fluctuations were not carefully assessed.

Methods: We evaluated long term follow-up in 23 subjects (>1/3 of total cohort) at the Baylor College of Medicine who were enrolled in a sham controlled double bind study of bilateral retinal fetal cell transplants for Parkinson's disease. Prior to unblinding, the site PI evaluated clinical global impressions and fluctuations, and presents long term follow-up.

Results: Twelve subjects received implants and 11 were shams. The mean duration of follow-up was 3.7 years. Prior to unblinding, the correct arm (placebo vs. sham) was correctly predicted in 19/23 subjects ($p<0.01$). This was largely based on CGI due to improved fluctuations, which was not a study efficacy point. UPDRS # "fluctuations" was 2.00±0.90 vs 0.92±0.67 favoring the transplant group ($p<0.01$). Dyskinesia duration and duration of a single dose of L-dopa was similar. One year UPDRS "off" motor scores did not improve. Four sham and two implanted subjects have since received STN DBS. Two transplant patients have died of unrelated causes.

Conclusions: Fluctuations improved in subjects receiving bilateral retinal fetal cell transplant compared to controls. UPDRS motor scores may not be the best efficacy point for implantation trials.

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Safety and tolerability profile of the adenosine a_{2A} receptor antagonist BIIB014 in healthy volunteers: Pooled analysis of four phase 1 studies

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Objective: To investigate the safety and tolerability of BIIB014 in healthy volunteers.

Background: BIIB014 is a novel, potent and selective, non-xanthine once-daily adenosine A_{2A} receptor antagonist currently under clinical development for treatment of idiopathic Parkinson's disease.

Methods: In four Phase 1 studies combined, 108 healthy volunteers have received single (5 to 100 mg) or multiple (2.5 to 100 mg) doses of BIIB014. Safety was assessed by the incidence of adverse events (AEs), changes in vital signs, laboratory tests, ECGs, and clinical evaluations.

Results: BIIB014 was found to be well tolerated. The overall incidence of AEs was 60.2% (n=65) in the subjects who received BIIB014. Across all Phase 1 studies combined, treatment-emergent AEs that occurred following BIIB014 dosing with an incidence of >5% were headache (14%); dizziness (10%); insomnia (7%); nausea and catheter site pain (6%). One SAE (moderate abdominal pain), in a BIIB014-dosed subject that led to withdrawal, was assessed as unlikely related to the study treatment. No severe AEs were observed. No obvious pattern in tolerability was observed following administration of single doses of BIIB014 ranging from 5 to 100 mg. In the multiple-dose study, the overall number of AEs reported was higher and in particular gastrointestinal AEs were more frequent in the top dose group (BIIB014 50 mg once daily). There were no remarkable differences in the BIIB014 safety profile in elderly males versus elderly females, or in elderly versus younger healthy volunteers. There were no remarkable changes in ECG, vital sign, or safety laboratory parameters.

Conclusions: In short-term clinical studies in healthy volunteers, BIIB014 has demonstrated a safe and tolerable profile in the absence of typical dopaminergic side effects that justifies further clinical development in patients with PD.

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Safety and tolerability profile of the adenosine A_{2A} receptor antagonist BIIB014 in Parkinson's disease: Pooled analysis of two placebo-controlled 8-week studies

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Objective: To investigate the safety and tolerability of BIIB014 in patients with Parkinson's disease (PD).

Background: BIIB014 is a novel, potent and selective, non-xanthine once-daily adenosine A_{2A} receptor antagonist currently under clinical development for treatment of idiopathic Parkinson's disease.

Methods: In two Phase 2 studies combined, 119 subjects (age ≥30 years) with moderate-to-advanced PD (Hoehn and Yahr score stage II–IV, with motor fluctuations/OFF-time ≥2 hrs per day) or early PD (Hoehn and Yahr 1 to 2.5) were randomized and received treatment with BIIB014 (n=86) or placebo (n=33) for up to 8 weeks. Safety was assessed by the incidence of adverse events (AEs), changes in vital signs, laboratory tests, ECGs, and clinical evaluations.

Results: BIIB014 was found to be well tolerated. The overall incidence of AEs was 41% (n=35) in the BIIB014 groups and 15% (n=5) in the placebo group. No clustering of AEs under a particular organ category was observed. The most commonly reported AEs were insomnia (5%, 0%; BIIB014, placebo, respectively), hypertension (3%, 0%), dizziness (3%, 0%), and urinary tract infection (3%, 0%). The majority of AEs were mild to moderate. Two BIIB014-dosed subjects (2%) discontinued treatment due to either an AE or SAE. There were no treatment discontinuations due to AEs or SAEs among the placebo-dosed patients. There were no dyskinesia-related AE reports in either study. There were no remarkable changes in ECG or safety laboratory parameters.

Conclusions: BIIB014 up to 100 mg once daily was well tolerated in PD patients with motor fluctuations as adjunct treatment and in early patients as monotherapy for up to 8 weeks. Low rates of side effects observed with BIIB014 offer the potential of an improved safety and tolerability profile in comparison to currently available dopamine replacement therapies.

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The adenosine A_{2A} receptor antagonist BIIB014 is effective in improving ON-time in Parkinson's disease (PD) patients with motor fluctuations

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Objective: To assess the efficacy of BIIB014 in moderate-to-advanced PD patients with motor fluctuations treated with L-dopa and adjunctive medications.

Background: BIIB014 is a novel, potent and selective, non-xanthine once-daily adenosine A_{2A} receptor antagonist currently under clinical development for treatment of idiopathic PD.

Methods: In this Phase 2, international, randomized, placebo-controlled, parallel-group study, 63 subjects (age $\geq$30 years, Hoehn and Yahr score stage II–IV, with motor fluctuations/OFF-time $\geq$2 hrs per day) were randomized to treatment with BIIB014 (30 mg or 100 mg; n=44, lactose formulation) or placebo (n=19) for 8 weeks. All patients were on stable doses of anti-parkinsonian medication prior to the study start. Efficacy endpoints included change from baseline in the total number of hours per day spent in the ON and OFF state measured by patient diaries and change from baseline in Unified Parkinson's Disease Rating Scale (UPDRS) scores.

Results: Treatment with BIIB014 100 mg once daily for up to 8 weeks resulted in a statistically significant least squares mean increase in total ON time of 1.28 hours (77 minutes) compared with placebo. Most of the increase in total ON time was without troublesome dyskinesia (1.19 hours, 71 minutes). There was also a reduction over placebo in OFF time of 0.81 hour (49 minutes). BIIB014 30 mg showed positive but weaker (subtherapeutic) effects. Slight improvements in UPDRS activities of daily living (in OFF state), motor, complications of therapy, and total scores also were observed with BIIB014 100 mg.

Conclusions: BIIB014 100 mg once daily significantly increased ON time in PD patients with motor fluctuations. The efficacy of BIIB014 as demonstrated in this study justifies further clinical development of this compound in patients with moderate-to-late stage PD.

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Safety of recombinant human erythropoietin (EPOrh) in Parkinson's disease (PD): A clinical pilot trial

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Objective: The aim of this study was to assess safety and possible secondary effects of human recombinant EPO (EPOrh) in PD.

Background: First line treatment in Parkinson's disease (PD) might benefit from additional neuroprotection in order to reduce or

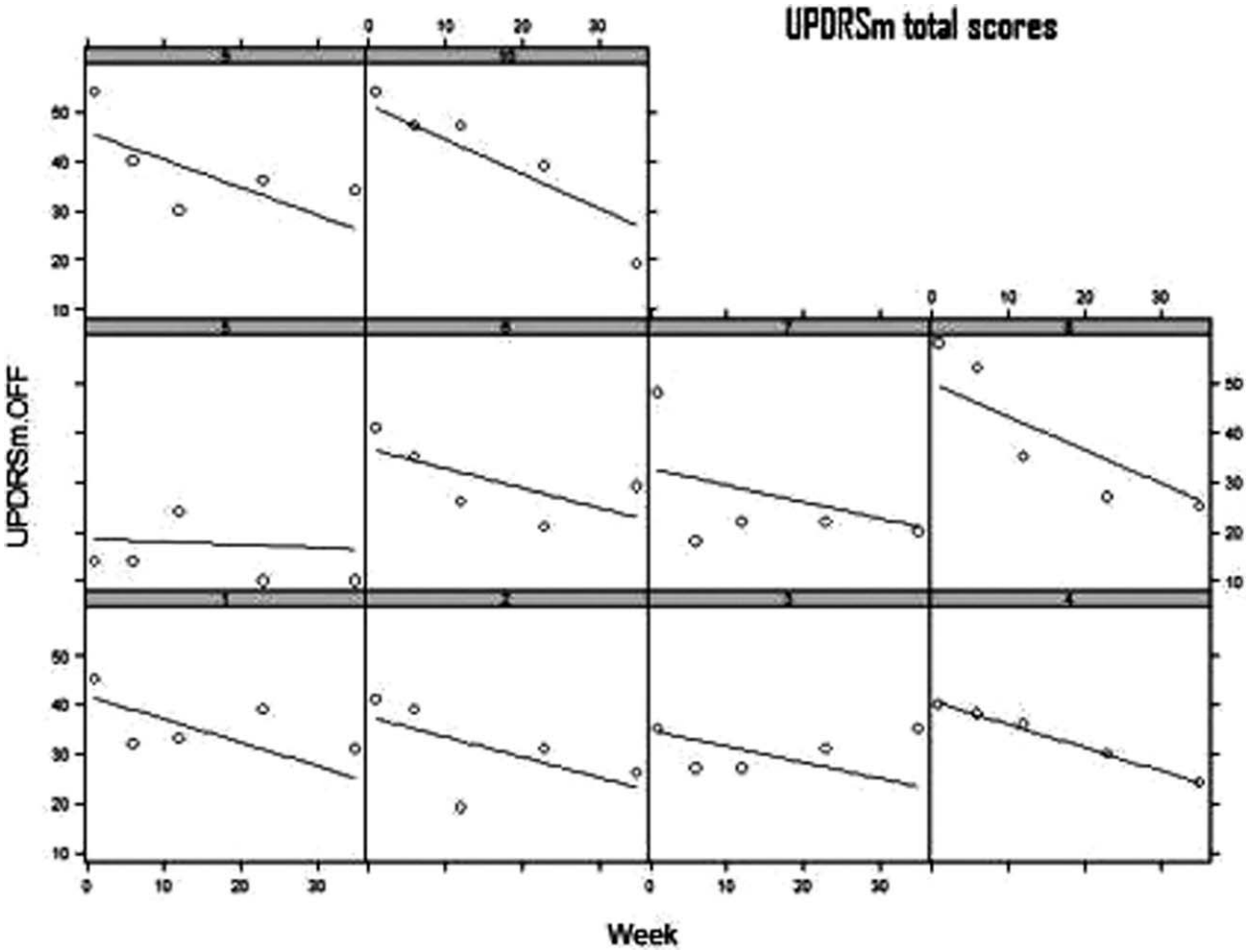

FIG. 1 (369).

slow symptom progression. In this regard Erythropoietin (EPO) has proven efficacy in other neurological disorders but has never been tested in PD.

Methods: In this pilot study, 10 outpatients aged 45–67 years restrited to be in stages I to III on Hoehn and Yahr's PD scale with diagnosis of PD for at least 1 year in accordance with the UK Brain Bank Criteria, received 5 weekly 60 UI/kg subcutaneous injections of EPOrh.

Results: After 35 weeks all patients continued in the study without major adverse events requiring hospitalization. Isolated events during treatment phase were: high blood pressure and a nephritic spasm in two patients with antecedents, numbness in inferior limbs for few days after each injection in other patient and weight increase. Hemoglobin increased significantly up to week 23 but bloodletting was unnecessary. Significant improvement up to week 35was found in the off-medication motor total subscore of the Unified Parkinson's Disease Rating Scale (p:0,0002). The Dementia Rating (p:0,0009) and Hamilton depression (p:0,0129) scales measured at weeks 6 and 12 also showed improvement.

Conclusions: This study supports the safety and potential efficacy of EPOrh as a possible neuroprotective agent for PD, suggesting that further blinded, controlled clinical trials should be carried out. Trial resgistration number: NCT 01010802.

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Sustained efficacy and tolerability of pramipexole extended-release in early Parkinson's disease

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Objective: To assess efficacy and safety of pramipexole extended-release (ER) in early Parkinson's disease (PD) patients, in a 32-week open-label (OL) extension of a 33-week double-blind (DB) trial.

Background: In DB trials, the ER form, taken once daily, has shown efficacy resembling that of the current, immediate-release (IR) form, which must be taken 3 times daily.

Methods: All early PD (H&Y stage 1-3) patients were treated DB with pramipexole IR or ER or placebo for the preceding 33 weeks. IR recipients were switched overnight to ER at the same daily dose and then (in a 6-week transfer phase) titrated to an optimal ER dose administered OL. Throughout the ensuing 26-week maintenance phase, dosage could be adjusted (0.375-4.5 mg/d). Efficacy measures included Unified PD Rating Scale (UPDRS) II+III and Clinical/Patient Global Impression of Improvement (CGI-I/PGI-I) response rates (improvement/no change from OL baseline). Efficacy was analyzed for observed cases censored for L-dopa rescue.

Results: 139 patients had been treated DB with IR and 153 DB with ER. At OL Week 32, the adjusted mean change (SE) from DB baseline in UPDRS II+III score was –9.9 (1.0) for IR-to-ER and –9.5 (1.0) for ER-to-ER, and –0.3 (0.8) and –0.5 (0.8), respectively, from OL baseline. OL CGI-I response rates were 95.2% and 94.0%, respectively, and PGI-I response rates were 89.4% and 88.0%. Final mean (SD) pramipexole dosage was 3.2 (1.3) mg/d for IR-to-ER (no change from OL baseline) and 3.1 (1.3) for ER-to-ER (a decrease of 0.1 from OL baseline). The proportion of patients at highest final dosage (3.75-4.5 mg/d) was 46.0% for IR-to-ER and 47.1% for ER-to-ER. During the OL trial, the frequency of withdrawal due to adverse events was 5.8% (8/139) for IR-to-ER and 5.9% (9/153) for ER-to-ER.

Conclusions: During 32-week OL treatment, pramipexole ER was well tolerated in early PD, and its efficacy was sustained, regardless of formulation in the preceding DB trial. Supported by Boehringer Ingelheim International GmbH.

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Rasagiline in early Parkinson's disease (PD): Additional results from the ADAGIO study

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Objective: To describe unreported data from the ADAGIO study.

Background: The ADAGIO study used a delayed-start study to determine if rasagiline has a disease-modifying effect in PD. Primary analyses demonstrated that early treatment with rasagiline 1 mg/day but not 2mg/day slowed the rate of UPDRS deterioration compared with delayed-start*.

Methods: 1176 untreated early Parkinson's disease (PD) patients were randomized to receive rasagiline 1 or 2 mg/d for 72 weeks (early-start), or placebo for 36 weeks followed by rasagiline 1 or 2 mg/d for 36 weeks (delayed-start). There were no dietary restrictions and certain antidepressants were permitted. The analyses presented here focus on: -UPDRS subscales (mental, activities of daily living [ADL] & motor) analyzed using repeated measures model at weeks 36 (placebo-controlled phase) and 72 weeks (end of active phase) -Need for anti-PD therapy during placebo phase analyzed by logistic regression and time to initiation of anti-PD therapy analyzed by Cox proportional hazards regression -Safety issues including changes in blood pressure (BP), and risk of cheese effect and serotonin syndrome.

Results: Rasagiline 1mg/d significantly improved each of the UPDRS subscales between baseline and week 36 in comparison with placebo ($P<0.01$). Improvement in UPDRS in the early versus the delayed-start group between baseline and week 72 was only significant for the ADL subscale. Rasagiline 2mg/d improved both motor and ADL subscales in change from baseline to week 36 compared with placebo ($p<0.0001$). There was no significant difference between early and delayed groups in UPDRS subscales in change from baseline to week 72. The need for additional anti-PD treatment was ~60% less in the 1 and 2 mg/d groups compared to placebo ($p<0.001$). There were no reports of serotonin syndrome or cheese effect or clinically significant alterations in BP with either dose.

Conclusions: Rasagiline 1 mg/d improved the various UPDRS subscores from baseline, and a significant contribution of ADL was primarily accounted for benefits of early vs. delayed treatment. Both 1 and 2 mg/d doses significantly reduced the need for additional anti-PD therapy versus placebo. No food or drug interactions were observed. *Olanow, Rascol et al, N Engl J Med, 2009.

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Memantine for the treatment of levodopa induced dyskinesias in demented and non-demented patients with Parkinson's disease

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Objective: To investigate if memantine, an NMDA receptor antagonist, can improve levodopa induced dyskinesias (LID) in PD patients with varying degrees of cognitive function.

Background: LID complicates long-term therapy in PD and may be one of the most limiting factors in PD's more advanced stages. Drugs with NMDA receptor antagonism, such as amantadine, have been reported to improve LID. However, side effects limit the usefulness of amantadine in PD, especially among the cognitively-impaired. In this study we investigated if memantine, an NMDA receptor antagonist, can improve LID in PD patients with varying cognitive status.

Methods: We performed a double blind, placebo-controlled, parallel-group, forced-titration study of memantine on PD patients suffering from LID, regardless of their cognitive status, at the UFMDC. At BL, patients were evaluated using the UPDRS, AIMS, MMSE, Global Cognitive Score (GCS, using a computerized cognitive test, Neurotrax), and a 24-hour PD Dyskinesia Diary. Subsequent evaluations at 8 and 12 weeks post-randomization. Subjects were initiated

on memantine at 5mg (or corresponding placebo) per day, and the dose was increased weekly to a goal of 10mg twice daily. No changes in dopaminergic or psychiatric medications were allowed during the study. The primary outcome measure was the improvement in dyskinesias at Week 12 compared to the Baseline.

Results: 28 subjects were randomized in the study, 14 were assigned to the active arm and 14 to the placebo arm. At Baseline, the mean: age was 65.8 years old; PD duration was 13.4 years; time with non-troublesome dyskinesias was 5 hours/day; time with troublesome dyskinesias was 2.1 hours/day; AIMS score was 9.3; UPDRS motor score in the "on" state was 31.3.; MMSE score was 26.8 (SD 4.93) (range 9-24 for those cognitively impaired, mean 19.2, 24-30 for those nonimpaired); and, GCS was 91.7 (SD 14.9). No significant difference in baseline characteristics was noted between subjects randomized to memantine or placebo. No significant difference was noted with regards to side effects between the two treatment arms.

Conclusions: Memantine was well tolerated in PD regardless of cognitive status. However, in this study, memantine did not improve LID.

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Efficacy of amantadine hidrocloride versus bromocriptine in dyskinesias of Parkinson's disease

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Objective: To evaluate the efficacy of amantadine hydrocloride versus bromocriptine in discinesias of Parkinson's disease.

Background: Amantadine hydrochloride is an antagonist of glutamate that can improve discinesias in patients with Parkinson's disease and bromocriptine is an agonist of levodopa that in our country is used frequently in the treatment of discinesias.

Methods: This 18-week, randomized, double-blind study investigated the efficacy of amantadina hydrochloride 300mg daily, versus bromocriptina 15mg daily in levodopa induced discinesias in Parkinson's diseased patients. We utilized the Unified Parkinson's Disease Rating Scale (UPDRS), Abnormal Involuntary Movement Scale (AIMS), Core Assessment Program for Intracerebral Transplantation (CAPIT) for discinesias and Parkinson's Disease Quality-39 (PDQ-39) to evaluate the quality of life. An analysis of variance of repeated measured was utilized.

Results: In the population, amantadina hydrochloride produced a significant improvement in AIMS and CAPIT score compared with bromocriptine, from baseline to week 18. In the evaluations of life quality there were not differences.

Conclusions: Amantadine hydrochloride reduces discinesias and fluctuations in Parkinson's diseased patients compared with bromocriptina without improve the quality of life.

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Quantification of asymmetrical armswing reduction with ultrasound-based 3D gait analysis in early Parkinson's disease

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Objective: Three-dimensional motion analysis is a suitable method to investigate gait disturbances in Parkinson's disease (PD). Aside from conventional spatio-temporal gait characteristics, we aimed to quantify arm swing reduction and side asymmetry of arm movements as an early symptom.

Methods: We investigated limb movements and gait parameters in 40 patients with early PD (mean age: 57,9 ±11 years; HY stages I/II, mean UPDRS III: 12±5) in the drug-off condition compared to 25 age matched controls. Ultrasound-based motion analysis (CMS-HS, Zebris, Isny, Germany) and gait analysis with a force plate integrated treadmill (FDM-T, Zebris, Isny, Germany) were performed during locomotion at four speed levels (2.0-3.5 km/h).

Results: Ante- and retroflexion in the shoulder joint ipsilateral to the clinically most affected body side was significantly reduced in HYI PD patients versus controls ($p<0,001$). Moreover, the side-to-side asymmetry-index of armswing amplitude was higher in PD HYI then in controls ($p<0.001$). The maximum angels of ipsilateral shoulder retroflexion, abduction, adduction as well as elbow extension/ flexion were reduced in PD HYI ($p<0.05$). In PD patients HYII, a reduction of armswing amplitude and arm retroversion as well as elbow flexion/extension was also found on the contralateral body side ($p<0.05$). Spatio-temporal gait parameters showed a prolonged stance along with a shortened swing phase in both PD groups compared with controls ($p<0.05$). At slow speed levels, PD patients in HY stage I also displayed an increased contralateral single-stride-length ($p<0.05$).

Conclusions: The data demonstrate that the pathological arm swing can be quantified by 3D motion analysis in early PD patients. Unilateral hypokinesia is reflected by a reduced range of shoulder and elbow motions. The side-to-side asymmetry of armswing amplitude turned out to be the most suitable screening marker reliably differing between early PD and control subjects. Particularly, a decreased retroversion in the ipsilateral shoulder seems to occur as a very early sign of PD hypokinesia. The altered spatiotemporal gait parameters are most likely compensational to counteract the dysbalance of the body axis due to asymmetrical movements of the upper limbs in early PD patients.

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Exercise as a drug: A delayed start trial on the neuroprotective effects of exercise in Parkinson's disease

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Objective: We utilized a delayed start protocol (as in clinical trials) to evaluate neuroprotective effects of exercise in Parkinson's disease (PD).

Background: Slowing disease progression is a challenge in PD. Currently, no treatment or therapy has been definitively proven to slow disease progression. Additionally, rehabilitation and pharmaceutical trials evaluate interventions differently which does not allow convergence of evidence to guide the treatment of PD. Thus, the current study aims to bridge this gap and evaluate the disease modifying effects of exercise in a similar manner to pharmaceutical interventions.

Methods: 143 individuals participated in exercise trials at the MDRC, 39 had sufficient length of exercise for inclusion in analysis. The EARLY start group (n=20, UPDRS=27.8) completed 24 weeks of Sensory Attention Focused Exercise (PD SAFEx^{TM}). Two delayed groups were evaluated, LATE A (n=9, UPDRS=20.9) was a non-exercising control group for 12 weeks, while LATE B (n=10, UPDRS=20.0) completed a 12 week control exercise program. Following the initial 12 weeks both delayed groups completed 24 weeks of PD SAFEx^{TM}; for exercise description see Sage & Almeida *Mov Disord* 2009. Participants were assessed using the UPDRS (section III) at weeks 0, 12, 24, and 36 (late groups). The delayed start meth-

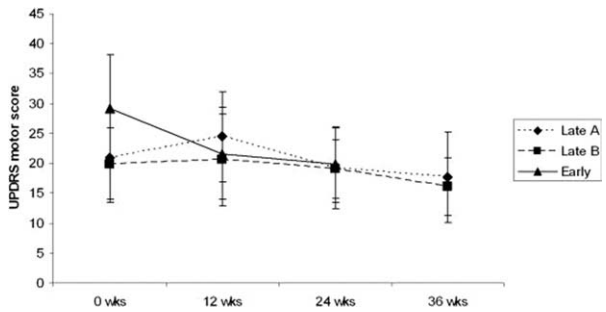

FIG. 1 (375).

odology was adapted from the ADAGIO study (Olanow et al. *Mov Disord 2008)*. The hierarchical endpoints were: (i) greater symptom improvement from weeks 0 to 24 in early group; (ii) greater symptom improvement from baseline to study completion in early group; (iii) similar symptom change over final 12 exercise weeks in all groups.

Results: Over weeks 0 to 24 symptoms significantly improved in the EARLY group relative to the delayed groups ($F(2,35)=6.47$; $p<.01$). Disease severity change from baseline to discharge revealed a trend suggesting the EARLY group had a greater UPDRS improvement then the two delayed groups ($F(2,32)=2.61$; $p<.09$). All groups had similar symptom improvement over the final 12-weeks ($F(2,32)=0.24$; $p<.79$).

Conclusions: These results support a potential disease modifying effect of PD SAFEx™; however, baseline disease severity differences, small sample size and a short time frame need to be considered. Overall, statistical methods from pharmaceutical trials should be encouraged to determine the neuroprotective effects of exercise for PD.

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Pardoprunox in early stage Parkinson's disease: Results from two large studies

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Objective: To assess efficacy and safety of pardoprunox (pdx) as monotherapy in early Parkinson's disease (PD), to establish a dose-response relationship and to compare the effects to pramipexole.

Background: Pardoprunox (pdx), a dopamine D_2 and D_3 receptor partial agonist and full serotonin 5-HT_{1A} receptor agonist was evaluated in two double-blind, placebo controlled studies in patients with early PD. Given the different mechanism of action and the positive results of an earlier proof-of-concept study these two studies were designed as confirmatory trials.

Methods: 802 subjects (n=468 in Rembrandt and n=334 in Vermeer) were randomized to pdx (n=457), placebo (n=229) or pramipexole (n=116). The studies had similar titration of four to seven weeks during which the dose of pdx was titrated to 6 mg/day; 12 mg/day (both fixed doses) or 12–42 mg/day; or pramipexole to 1.5-4.5 mg/day followed by a maintenance period of 24 weeks. The primary efficacy outcome was change in Unified Parkinson's Disease Rating Scale (UPDRS) part 3 from baseline to endpoint. Secondary outcome parameters included UPDRS part 2 and Clinical Global Impression Improvement. Safety assessments were performed throughout the study.

Results: The primary efficacy analysis (UPDRS part 3, LOCF) showed pdx to have a statistically significant benefit versus placebo in both studies (adjusted means: pdx 6 mg/day -6.0 points; 12 mg/day -4.7 points–only tested in Rembrandt study; 12-42mg/day -5.5 points and–4.9 points versus placebo of -2.9 and -2.5 points in Rembrandt and Vermeer study respectively). Pdx showed similar efficacy to pramipexole (UPDRS part 3 scores of -5.7). Secondary parameters supported the results of the primary efficacy outcome. High incidence of AEs (placebo adjusted, most common for pdx were nausea 33%; dizziness 20% and somnolence 29%), combined with the same efficacy across all pardoprunox treatment groups suggests that the dose range was higher than required and the early onset of withdrawal due to AEs suggests that titration was too rapid.

Conclusions: Pardoprunox showed significant efficacy in the investigated dose range similar to pramipexole, however the doses studied were too high and titration too rapid.

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The SEWOP (stalevo in early wearing-off patients) study

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Objective: The aim of this study was to show that Stalevo® (levodopa/carbidopa/entacapone [LCE]) is superior to levodopa/carbidopa (LC) in delaying the need to increase anti-Parkinson's disease (PD) therapy due to inadequately controlled PD symptoms in patients (pts) with early wearing-off.

Background: It is well established that levodopa/dopa decarboxylase inhibitor (DDCI) and entacapone significantly improves symptoms of PD in pts with motor fluctuations.

Methods: The SEWOP study was a 24-month, double-blind, randomized, active-controlled study in PD pts with early wearing-off receiving three daily doses of levodopa/DDCI, who were randomized to LCE or LC four times daily. Primary endpoint was time from initiation of study drug until the pt requires an increase in anti-PD therapy due to inadequately controlled PD symptoms. Secondary endpoints included changes in UPDRS II and III, CGI-C and PDQ-39 scores.

Results: 221 pts with early wearing-off were randomized to LCE (n=115) or LC (n=106). At baseline, mean age, PD duration and levodopa therapy duration were 69.2, 4.0 and 2.9 yrs, respectively. There was a 24% reduction in the rate of endpoints for LCE vs LC (HR=0.76; p=0.166); in the pre-defined subset of pts with advancing PD (H&Y stage $\geq$2.5), there was a 42% reduction in the rate of endpoints for LCE vs LC (HR=0.58; p=0.080). Improvements in UPDRS III scores favored LCE over LC by an average of –0.75 points between Months 1 and 24 (p=0.423). UPDRS Part II and PDQ-39 scores were not significantly different between treatments, but CGI-C scores slightly favored LCE, at Months 6 and 12. LCE was well tolerated.

Conclusions: The SEWOP study indicated a trend toward superiority for LCE over LC for the primary endpoint, in delaying the time from initiation of study drug until the pt requires an increase in anti-PD therapy. In pts with advancing PD, the reduction in the rate of endpoints (42%) may be regarded as clinically meaningful as indicated by CGI-C and UPDRS III scores slightly favoring LCE.

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SETTLE study design: A 24-week, double-blind, placebo-controlled study of the efficacy and safety of safinamide as add-on therapy to levodopa in patients with Parkinson's diseases Add-On Therapy to Levodopa in Patients with Parkinson's disease

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Objective: To evaluate the efficacy and safety of safinamide, a novel agent in Parkinson's disease (PD), as add-on therapy to a stable dose of levodopa in patients with PD and motor fluctuations.

Background: Safinamide is an α-aminoamide derivative with a dual dopaminergic and non-dopaminergic mechanism of action. In previous studies, safinamide as add-on therapy to levodopa or a dopamine agonist has been shown to improve motor symptoms in patients with early- to mid-late-stage PD (Stocchi et al. Neurology 2007; 68 [Suppl 1]: Abst 20.001); Borgohain et al. http://www.movementdisorders.org/congress/congress09/late_breaking_abstracts.pdf). The dual mechanism of action may provide additional effects on dyskinesia and non-motor symptoms including cognition. Here we present data on the methodology of this ongoing study.

Methods: SETTLE is a 24-week, double-blind, placebo-controlled, parallel-group, randomized, multinational Phase III study enrolling patients (30-80 years of age) with idiopathic PD (>5 years' PD duration, Hoehn and Yahr stage I-IV) and motor fluctuations (>1.5 hours OFF time during the day) who are receiving a stable dose of levodopa. Stable doses of a dopamine agonist, anticholinergic and/or amantadine are permitted. After a 4-week levodopa stabilization phase, patients will be randomized (1:1) to receive add-on therapy with safinamide 50-100 mg/day or placebo.

Results: The primary efficacy outcome is the change from baseline to Week 24 in diary-recorded ON time without troublesome dyskinesia. Secondary efficacy outcomes include: UPDRS Parts II (activities of daily living) and III (motor) scores during ON; global clinical impression; cognition; health-related quality of life; Dyskinesia Rating Scale scores. Safety assessments include treatment-emergent adverse events, changes in laboratory safety tests, vital signs, ECG, and ophthalmologic monitoring.

Conclusions: This study will provide further data on the efficacy and safety of safinamide as add-on therapy to levodopa for the treatment of patients with PD.

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Sustained efficacy and tolerability of pramipexole extended-release as adjunctive treatment in advanced Parkinson's disease

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Objective: To assess adjunctive use of pramipexole as an extended-release (ER) formulation in advanced Parkinson's disease (PD), via a 32-week open-label (OL) extension of a ≥18-week double-blind (DB) trial.

Background: The ER form was developed to provide once-daily dosing and more continuous dopaminergic stimulation. In a DB trial in advanced PD, its efficacy resembled that of the current, immediate-release (IR) form, which must be taken 3 times daily.

Methods: All advanced PD (H&Y on-time stage 2-4) patients were treated with levodopa plus DB pramipexole IR or ER or placebo for the preceding ≥18 weeks. IR recipients were switched overnight to ER at the same daily dose and then (in a 6-week transfer phase) titrated to an optimal ER dose, administered OL. Throughout the ensuing 26-week maintenance phase, ER dosage could be adjusted (0.375-4.5 mg/d). Efficacy measures included Unified PD Rating Scale (UPDRS) II+III and Clinical/Patient Global Impression of Improvement (CGI-I/PGI-I) response rates (improvement/no change from OL baseline).

Results: 139 patients had been treated DB with IR and 123 DB with ER. At OL Week 32, the adjusted mean change (SE) from DB baseline in UPDRS II+II score was –14.8 (1.5) for IR-to-ER and –13.3 (1.6) for ER-to-ER, and –2.7 (1.2) and –1.0 (1.2), respectively, from OL baseline. OL CGI-I response rates were 92.0% and 92.2%, respectively, and PGI-I response rates were 91.2% and 88.7%. Final mean (SD) pramipexole dosage was 3.00 (1.4) mg/d for IR-to-ER (an increase of 0.15 from OL baseline) and 2.97 (1.3) for ER-to-ER (an increase of 0.10). The proportion of patients at highest final dosage (3.75-4.5 mg/d) was 45.3% for IR-to-ER and 39.8% for ER-to-ER. During the OL trial, the frequency of withdrawal due to adverse events was 6.5% (9/139) for IR-to-ER and 4.9% (6/123) for ER-to-ER.

Conclusions: During 32-week OL treatment, pramipexole ER was well tolerated in advanced PD, and its efficacy was sustained, regardless of formulation in the preceding DB trial. Supported by Boehringer Ingelheim International GmbH.

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Effects of 4-week compensatory step training on balance and gait performance in patients with Parkinson's disease

C.X. Shen, M.K.Y. Mak (Hong Kong, China)

Objective: To examine the effects of 4-week compensatory step training on balance and gait performance in patients with Parkinson's disease (PD).

Background: The ability to elicit compensatory steps in response to sudden external perturbation plays an important role on preventing falls. However, PD patients were found to exhibit short step length and long reaction time in response to external perturbation. Previous studies have not included the training of stepping strategy in balance enhancement protocols for these patients.

Methods: Thirty-seven PD subjects completed the study. They were randomly allocated into balance group (n=17, mean age: 64.8±7.2; Hoehn and Yahr staging: 2.4±0.5), and control group (n=20, mean age: 63.4±7.4; Hoehn and Yahr staging: 2.4±0.5). In the balance group, subjects were provided with task-specific training to facilitate reaction time and length of compensatory steps during activities with self-induced perturbation and in response to external perturbation. In the control group, subjects received strength training of lower limb muscles with moderate intensity. All subjects underwent 4 weeks of supervised training, with 3 times a week, 70 minutes per session. Outcome measures included limit of stability (LOS) to evaluate the control of body center of mass (CoM) for balance performance, walking speed to reflect walking ability, and Unified Parkinson's Disease Rating Scale-III (UPDRS-III) to measure PD-specific motor impairment. All tests were conducted before and after 4-week training.

Results: Results of 2-way repeated measures ANOVA showed that both balance and control groups had significant improvement in LOS test and walking speed ($p<0.01$). Moreover, the balance group demonstrated more percentage increases in LOS_movement velocity and LOS_maximum excursion of body CoM ($p<0.05$). Only the balance group showed a significant reduction of LOS_reaction time ($p<0.01$). The reduction in UPDRS-III score did not reach a significant level in both groups.

Conclusions: Results of this study suggest that training of compensatory stepping could enhance the control of body CoM during balance activities in patients with PD.

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Weight loss and implementation of clinical trials of multi/antioxidant vitamins and nutritional supplements in Parkinson's disease

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Objective: Factors responsible for weight loss among PD patients and the role of multi/antioxidant vitamins therapy and nutritional supplements.

Background: Parkinson's disease (PD) patients frequently lose weight and are susceptible to malnutrition. The common causes involved in weight loss are considered to be reduced energy intake and/or increased energy expenditure. Supply of multi/antioxidant vitamins and nutritional supplements help to overcome weight loss.

Methods: 90 PD patients (age 59.07±9.07 yrs) satisfying UK PD Brain Bank Clinical Diagnostic Criteria were recruited for the study. Two study groups were designed in which Group A (experimental) consisted of 50 patients (age 58.34±8.294 yrs) who were given multi/antioxidant vitamins along anti-parkinsonian drugs and Group B (control) consisted of 40 patients (age 59.975±9.983 yrs) who were given only anti-parkinsonian drugs. 10 ml of peripheral blood was drawn from all subjects for the baseline level and their follow up was conducted after six months. Biochemical investigations includes: Iron, Total Iron Binding Capacity (TIBC), Total protein, albumin and ascorbic acid estimations. In group A 40 out of 50 patients and in group B 30 out of 40 patients came for follow up after six months. The biochemical investigations were done with the help of commercially available kits and the dietary intake with nutritional supplements were monitered.

Results: In Group A there was a significant increase in the weight of PD patients at the time of follow up (63.25±13.10Kg) when compared with the baseline level (58.37±8.34 Kg). In Group B there was significant reduction in the weight of the PD patients during the same period of follow up (58.53±9.6 Kg) when compared with the baseline (59.70±10.11Kg). Group A revealed the significant increase in the titer of all the multi/antioxidant vitamins supplied. Iron level rose from (15.09±8.78) at base line to (28.49±13.44) at follow up; ascorbic acid from (10.94±0.85) to (12.30±0.56); total protein rose

from (7.06±0.25) as base line to (7.39±0.41) at follow up; albumin from (4.08±0.15) to (4.32±0.35) and TIBC fell from (63.37±33.25) at base line to (56.56±22.94).

Conclusions: PD patients in advanced stage of disease have impaired nutrition status which can be improved by careful attention to their food habits should be made to protect them from weight loss.

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Ropinirole prolonged release may help provide 24-hour symptom control in patients with advanced Parkinson's disease not optimally controlled with L-dopa

F. Stocchi, K. Rolfe, J. Cooper, A. Lipschitz (Rome, Italy)

Objective: To explore the effects of adjunctive ropinirole prolonged release on awake time "on" during the night and early morning, and the probability of being "on" on waking in patients with advanced Parkinson's disease (PD) not optimally controlled with L-dopa.

Background: Ropinirole prolonged release has been shown to increase "on" time over 24 hours and improve nocturnal symptoms as measured by the PD Sleep Scale (EASE-PD Adjunct Study 101468/169; Pahwa *et al*. *Neurology* 2007;68:1108–15).

Methods: Patients were randomized to treatment with ropinirole prolonged release (2–24 mg/day) or placebo for 24 weeks. Patients recorded on diary cards whether they were awake or asleep and, if awake, whether "on" or "off" for each 0.5-hour period during two 24-hour periods before each study visit. Change from baseline in percent of awake time "on" for the overnight (10 pm–8 am) and early morning (5 am–10 am) periods, and the proportion of patients who were "on" on waking on both diary days (patients who were "on" on waking for only one of the two diary days did not qualify) at Week 24 last observation carried forward (LOCF) were analyzed *post hoc*.

Results: Overnight sleep duration was similar between treatment groups. Patients receiving ropinirole prolonged release had a significantly greater increase in the percentage of awake time spent "on" both overnight and during the early morning compared with patients receiving placebo. Mean (SE) changes from baseline (adjusted for country and percent baseline awake time "on") in percent awake time spent "on" for ropinirole prolonged release and placebo, respectively, were 16.6 (3.4) *versus* 3.9 (3.5), $p=0.0002$, for overnight and 16.7 (2.9) *versus* 7.6 (3.0), $p=0.0021$, for early morning. The odds ratio for being "on" on waking was 1.65 (95% CI: 1.05, 2.59), $p=0.029$, in favor of ropinirole prolonged release.

Conclusions: Patients receiving ropinirole prolonged release were more likely to be "on" when awake during the night and early morning, and had higher odds of being "on" on waking, compared with patients receiving placebo. This suggests that adjunctive once-daily ropinirole prolonged release dosed in the morning may help to provide 24-hour symptom control in patients with advanced PD not optimally controlled with L-dopa. Data submitted to AAN 2010.

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Withdrawn by Author

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In young Parkinson's disease patients with dopaminagonist avoid L-Dopa–add a second agonist instead!

M.H. Strothjohann, D. Djundja, G.A. Fuchs (Wolfach, Germany)

Objective: Pulsatile dopaminergic stimulation is known to induce bothersome paroxysmal fluctuations and hyperkinetic movements.

Background: In young Parkinson patients it is mandatory to postpone L-Dopa as long as possible.

Methods: Records of hospitalized young patients with PD with motor and non-motor symptoms who were treated with rotigotine transdermal patch as add on to ongoing dopaminagonist treatment were assessed in a retrospective survey. Six patients were identified, (one female), mean age 50 years (39–56), all H+Y II. Rotigotine was administered according to the needs of the patients; other typical parkinsonian medication (e.g.,Pramipexole, Ropinirole extended release, a-Dihydroergocriptine, Selegeline, Rasagiline) was given and if necessary adjusted according to the needs of the patients' condition. In three patients Pramipexole was administered 3,5 mg (3–4,5), two patients received 16 mg Ropinirole extended release, one patient received 60 mg a-dihydroergocriptine. The items of the third and fourth part of the UPDRS were assessed at admittance and at release.

Results: Patients on average received Rotigotine transdermal patch (mean 7 mg per day, range 4–8 mg). Mean values (ranges in brackets) of UPDRS part III ameliorated from 28,5 (15–49) at admittance (baseline=bl) to 19,2 (8–36) at release (end of monitoring=eom); UPDRS part IV - from 0,7 (0–3) at bl to 0,5 (0 - 3) at eom.

Conclusions: As expected, UPDRS part III (motor activity) scores were improved after adequate treatment according the individually adjusted treatment regimes including rotigotine transdermal patches in all our patients. Improvement may be due to the continuous dopaminergic stimulation which is a consequence of the drug delivery by the rotigotine patch application. Due to the individualized treatment optimization, the regimes of individual treatment differed but the constant dopaminergic drug treatment by rotigotine patch application was common for all patients in this survey. In our survey on six young PD patients, additional treatment with the rotigotine patch improved the items of the UPDRS Part III without introducing L-Dopa. Further controlled investigations are necessary to assess the development of late motor complications to a lesser extend by avoiding L-Dopa.

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Clinical and MRI correlations in Parkinson's disease patients with headache

I.V. Verulashvili (Tbilisi, Georgia)

Objective: The diagnosis of Parkinson's disease (PD) is nearly always based on clinical signs and symptoms. Pain has been recognized as an important feature of PD since the first description of this disease, however there are only few reports focused on this problem.

Background: The aim of this study was: first, to investigate the clinical characteristics of PD patients with headache (PDwH) and secondly, to determine clinical and MRI correlations of PDwH.

Methods: Analysis of the Georgian Study of Health and Aging (557 persons without cognitive impairment at baseline who participated in 2005-2008) enable us to include in this investigation 31 man and 49 women with PD (according to the Unified Parkinson"s Disease Rating Scale). All patients underwent cerebral MRI. Statistical analyses were performed using SPSS 9.0.

Results: From PD 80 patients (the mean age was 68.2)–seventeen (21%) had chronic headache. There were no significant difference in clinical duration of PD in patients with and without headache, as direct correlation between the character of headache and fluctuations in symptoms of PDwH patients. MRI showed basal ganglia hyperintesity in all cases in T1. In PDwH patients MRI angiography revealed aplasia of transverse sinus (4 cases), hypoplasia of straight and transverse sinuses (9 cases) and blood flow in Gallen and Labbe veins (4 cases).

Conclusions: This study suggests a possible relationship between the presence of headache and the pathology of cerebral veins and sinuses in PD patients. In addition such data are of interest for improved care and designing a more adequate provision of treatment resources.

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Open-label extension trial assessing the effects of long-term treatment with rotigotine in subjects with early-stage, idiopathic Parkinson's disease: Results from up to 7 years

R.L. Watts, B. Boroojerdi, J. Jankovic, on Behalf of the SP702 Study Group (Birmingham, Alabama, USA)

Objective: To assess the safety, tolerability, and efficacy of long-term treatment with rotigotine transdermal patch in subjects with idiopathic Parkinson's disease (PD).

Background: Rotigotine is a non-ergoline dopamine receptor agonist used for the treatment of PD.

Methods: Subjects with PD who completed a 6-month, double-blind, placebo-controlled rotigotine study were eligible to enter this open-label, long-term extension. Subjects entered a 4-day dose de-escalation period (concluding at 2 mg/24h or placebo equivalent), followed by a brief titration period (target dose: 2 to 6 mg/24h). Target dose was maintained for the first year, and could be increased up to 16 mg/24h thereafter. Up to 7-year treatment results are reported here. Assessments included treatment-emergent adverse events (AEs) presented as rate per subject-year, laboratory parameters, and change from double-blind baseline UPDRS Part II + III score (last observation carried forward analysis).

Results: Of the 217 subjects who entered the open-label extension, 216 received treatment. More than half of subjects (112 [52%]) received at least 5 years of rotigotine treatment. Mean rotigotine dose at 5 years was 10.0 (SD: 3.6) mg/24h. Over the 7 years, 56 (26%) subjects remained on rotigotine monotherapy and 160 (74%) subjects started levodopa cotherapy. Overall, 24% of subjects discontinued due to AEs. The most frequently reported AEs were somnolence (23% per subject-year), fall (17% per subject-year), and peripheral edema (14% per subject-year). Treatment-emergent application site reactions were reported in 70 (32%) subjects over 7 years (12% per subject-year). There were no clinically relevant changes in laboratory parameters. Mean UPDRS Part II + III scores after 7 years of rotigotine treatment remained within 5 points of subjects' original double-blind baseline scores.

Conclusions: Rotigotine transdermal patch is generally well tolerated by subjects with idiopathic PD for up to 7 years of treatment. There were few AE-related discontinuations.

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Efficacy and safety of long-term and high-dose treatment with ropinirole in Japanese patients with Parkinson's disease

F. Yoshii, Lead-PD Study Group (Isehara, Kanagawa, Japan)

Objective: Efficacy and safety of long-term and high-dose treatment with ropinirole (ROP) (10.5-15 mg/day) were investigated in patients with Parkinson's disease both as adjunct to L-dopa and monotherapy in a multicenter open-label study.

Background: ROP is a non-ergot dopamine agonist, selective for the dopamine D2 receptor family. The clinical usefulness of ROP has been demonstrated in early and advanced Parkinson's disease. However, long-term and high-dose clinical trials with ROP have not been conducted in Japanese patients with Parkinson's disease.

Methods: In patients with Parkinson's disease receiving other dopamine agonists, treatment was switched to ROP and ROP was administered for 1 year, in consideration of a need for dose increase. In patients with adjunct to L-dopa, the mean daily dose of L-dopa was not changed after switching from other dopamine agonist to ROP (318±144mg/day). UPDRS, CGI, off time, and incidence of adverse reactions were evaluated at baseline and 1 year after administration.

Results: A total of 123 patients received ROP (as adjunct to L-dopa: 65 patients, as monotherapy: 58 patients). The mean age was 66 years, and the mean Modified Hoehn and Yahr stage was 2.3. High-dose (10.5 mg/day or higher) ROP was administered to 68 patients (55%), of whom 19 (15%) used 15 mg/day ROP. A total of 93 patients continued 1-year treatment. In these patients, average-doses of ROP were 10.4 mg/day and 10.3mg/day respectively in patients with adjunct to L-dopa and with monotherapy. The UPDRS part II score decreased in both patients with adjunct to L-dopa (from 7.9 to 4.1) and with monotherapy (from 7.7 to 5.4), and the UPDRS part III score decreased from 20.5 to 12.7 in patients with adjunct to L-dopa and from 19.8 to 13.2 in patients with monotherapy. The improvement rate of CGI score (percentage of patients rated as improved or better) was 70% in patients with adjunct to L-dopa and 61% in patients with monotherapy, and it was demonstrated that more patients were likely to improve with an increase in ROP dose. Off-time was tended to decrease after starting ROP. Adverse reactions with an incidence of 5% or higher were somnolence, nausea and hallucination. A detailed analysis is currently ongoing.

Conclusions: It was suggested that long-term and high-dose treatment with ROP was effective in Japanese patients with Parkinson's disease.

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Study about pain in Parkinson's disease

C. Zaharia, V. Tudorica, D. Pirscoveanu (Craiova, Romania)

Objective: The aim of our study was to assess the intensity of pain and the effects of pain on Parkinson's disease (PD) patients behavior.

Background: Pain has been recognized as a non-motor symptom in PD. There is musculoskeletal pain, neuritic or radicular pain, dystonia- associated pain, akathitic discomfort. High levo-dopa levels may also induce pain.

Methods: We comprised in our study 68 patients (28 men and 40 women) with PD stage II to IV Hoehn and Yahr. Our patients were levodopa (L-Dopa) treated (average doses 875 mg/day). We assessed their intensity of pain using 5-Point Verbal Rating Scale (VRS-5), 6- Point Behavioral Rating Scale (BRS-6) and 11-Point Box Scale (BS-11). Most of our patients presented musculoskeletal pain and dystonia-associated pain. We slowly reduced total daily L-Dopa and introduced concomitant dopaminergic treatment (ropinirole modutab 2 to 16 mg/day). The intensity of pain was assessed at the beginning of the study and 6 months later. We used the same scales during our study : VRS-5, BRS-6 and BS-11. The results were analysed by Student Test.

Results: At the beginning of the study, using VRS-5 we obtained the results as follows: 10% of patients no pain, 45% mild pain, 33% discomforting pain, and 12% distressing. Mean BRS-6 score at baseline was 4,1 and mean BS-11 score was 7,8. After 6 months of treatment with L-Dopa + ropinirole modutab, the patients showed a significant improvement at the intensity of pain : 17% of patients no pain, 52% mild pain, and 31% discomforting pain. We did not find distressing patients at the end of the study. We also obtained at endline an improvement of mean BRS-6 scores (2,9) and mean BS-11 scores (4,2).

Conclusions: Our opinion is that using dopaminergic treatment we can improve the intensity of pain in patients with PD. We consider that the study must go on because we need to evaluate much more patients for a relevant conclusion.

POSTER SESSION 2

TUESDAY, JUNE 15, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

PARKINSON'S DISEASE: COGNITION

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Increased reaction time predicts visual learning deficits in Parkinson's disease

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Objective: To investigate whether indexes of motor performance are correlated to explicit learning of visual or motor sequences in early stage Parkinson's disease (PD).

Background: PD is characterized by motor slowness comprising bradyakinesdia and delay in movement initiation. PD impairs not only motor functions but also attentional and learning processes as PD patients learn motor sequences at slower rate than normal controls.

Methods: Subjects were 23 PD patients (Hoehn & Yahr stage I-II) and 13 age-matched normal controls. All subjects performed two tasks. In both, a central point and eight radially-arranged targets were displayed on a screen; targets were highlighted in synchrony with a tone at 1 Hz. The first was a motor task where subjects were required to move as soon as possible to randomly presented targets by minimizing reaction time. The second was a visual learning task where targets were presented in a preset order and subjects were asked to learn the sequence order by attending to the display without moving.

Results: PD patients showed higher reaction (p=0.02) and movement (p=0.008) times, while visual learning was reduced compared to controls (p=0.0009). For PD patients, reaction times, but not movement times, displayed an inverse significant correlation with the scores of visual learning (r=-0.66, p=0.0006). No correlation was found between UPDRS part III scores and motor or learning indices. No significant correlation was found in the normal group between learning indices and both reaction and movement times.

Conclusions: Impairment in non-motor explicit sequence learning correlated with increased reaction time in early PD. Similar mechanisms may mediate declarative explicit aspects of sequence learning and movement preparation: the involvement of fronto-striatal brain network in both may reflect the use of attentional and working memory resources.

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Neuropsychological performance of early onset PD cases with and without *GBA* mutations: The CORE-PD study

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Objective: To compare neuropsychological performance in early onset PD (EOPD) cases with and without glucocerebrosidase (*GBA*) mutations.

Background: Two independent autopsy studies demonstrated an association between *GBA* mutation status and cortical Lewy bodies. It is unknown whether PD cases who are *GBA* carriers have more cognitive impairment than non-carriers.

Methods: Mutations in *PRKN, LRRK2* and *GBA* were assessed in 953 cases with EOPD ascertained based on age at onset (AAO) <50 years. A subset of 109 cases including 11 *GBA* carriers (5 L444P, 6 N370S and 3 carriers of both *GBA* and *PRKN*) and 44 *PRKN* carriers underwent neuropsychological testing. Clinical criteria were used to create 3 cognitive domains: memory, visuospatial and executive functioning from transformed z-scores of individual tests.

Performance in each domain was compared between *GBA* carriers (n=11) and non carriers (n=98) using t-tests. The association between *GBA* mutation status (outcome variable) and each domain was examined using logistic regression, adjusting for covariates.

Results: Mean age, AAO, education, disease duration, and UPDRS-III scores did not differ between *GBA* carriers and non-carriers. Carriers' MMSE performance was similar to non-carriers (28.5 vs. 29.0 p=0.35). *GBA* carriers performed more poorly than non-carriers in the executive (p=0.011) and memory domains (p=0.022), but similarly in visuospatial performance (p=0.375). After adjustment for disease duration, age, education and *PRKN* mutation status, memory (OR=2.4, p=0.033) and executive domains (OR=2.4, p=0.035) were associated with *GBA* mutation status in a logistic model.

TABLE (390).

Cognitive Domain	Neuropsychological tests included
Verbal Memory	California Verbal Learning Test-II (CVLT) Total Recall (trials 1-5)
	CVLT Long Delayed Free Recall
	CVLT Short Delayed Free Recall
	Visual Reproduction I of the Wechsler memory scale
	Visual reproduction II of the Wechsler memory scale
Visuospatial	Benton Visual Retention Test Matching
	Benton Facial Recognition Test
Executive Functioning	Trail Making Test (Part B Time - Part A Time)
	CVLT false positives
	Stroop Color Word Trial
	Controlled Oral Word Association Test
	Category Test

Conclusions: *GBA* mutation status may be a risk factor for early cognitive impairment in PD. Longitudinal studies may determine if memory and executive performance predict PD dementia in *GBA* carriers.

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Quantitative gait assessment in parkinsonian patients with or without mild cognitive impairment

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Objective: To perform a quantitative assessment of gait in parkinsonian patients with or without Mild Cognitive Impairment (MCI).

Background: Originally the construct of MCI has been conceptualized as the transitional condition between physiological aging and Alzheimer's disease (AD). More recently this concept has been also applied to cognition in patients with Parkinson's disease (PD). The relationship between cognition and gait disturbances has received increasing attention and is well established.

Methods: Fourteen PD patients were enrolled. All patients were neither demented nor depressed. The clinical assessment included clinical data collection, Hohen and Yahr scale (H&Y), UPDRS I, II and IV at on state, UPDRS III both at on and off state and an extensive neuropsychological assessment in order to classify the patients according to MCI criteria. Quantitative gait analysis was performed by means of a motion capture system (Qualisys, Sweden) and the tracks were analyzed by a software developed by us. The following conditions, both at off and on state, were investigated: 1) normal gait (Gait-off and Gait-on); 2) motor dual task (Mot-off and Mot-on); 3) cognitive dual task (Cog-off and Cog-on). Statistical analysis was carried out by means of Mann-Whitney test.

Results: Based on neuropsychological testing, seven subjects were classified as patients with MCI (MCI+) and seven subjects were classified as patients with normal cognition (MCI-). There were no significant differences in age, disease duration, H&Y scale, UPDRS and MMSE scores between the two groups. The following gait parameters significantly differed between the two groups: 1) double support time was longer in MCI+ vs. MCI- in Gait-off (p=0,007), Gait-on (p=0,026), Cog-on (p=0,026); 2) velocity was reduced in MCI+ vs. MCI- in Mot-on (p=0,038) and in Cog-off (p=0,011); 3) cadence was reduced in MCI+ vs. MCI- in Cog-on (p=0,038).

Conclusions: As compared to MCI-, MCI+ PD patients displayed specific gait features: slower velocity due to the reduction of cadence and impairment of dynamic stability as revealed by the longer double support time.

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Heterogeneity of cognitive status in Parkinson's disease influences latency and gain of reflexive saccades

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Objective: To examine whether reflexive saccade parameters correlate with cognitive status in Parkinson's disease and provide useful objective markers.

Background: Research on saccades in PD has not previously examined in detail the effects of heterogeneity of cognitive status on key parameters (latency and gain). In particular, no study has specifically included those with mild cognitive impairment.

Methods: We examined reflexive saccades in 97 PD patients with varying degrees of cognitive impairment in comparison to 47 cognitively normal controls to determine the influence of cognitive status on key parameters. Seventeen PD patients had dementia (PDD), 23 had mild cognitive impairment (PD-MCI) and 57 had unimpaired cognition (PD-U). General cognitive status was assessed with the Montreal Cognitive Assessment (MoCA). Reflexive saccades to targets with amplitudes of 5, 10, 15, and 20 degrees and inter-stimulus-intervals of 750, 1000, and 1400ms were examined in 108 mixed randomized trials, incorporating equal numbers of gap, step, and overlap trials.

Results: For each condition mean saccadic latency increased linearly as cognitive status declined in PD patients, as defined by the MoCA (gap, $r=-0.69$, $p<0.001$, step $r=-0.61$, $p<0.001$, overlap $r=-0.61$, $p<0.001$). The PDD group showed prolonged latencies across all conditions (gap, step and overlap) compared to Control, PD-U, and PD-MCI groups ($F(3, 140)=45.15$, $p<0.001$). There was also a linear relationship between MoCA score and primary gain, collapsed across reflexive tasks for all group means ($F(3, 140)=18.73$, $p<0.001$). The PDD group showed reduced gain across all conditions compared to Control, PD-U, and PD-MCI groups.

Conclusions: Our results indicate that increasing cognitive impairment in PD is associated with increasing reflexive saccade latency and reduced gain, even prior to dementia. PD dementia in particular is associated with global prolongation of saccadic latency and reduced gain across all reflexive tasks. Reflexive saccades are thus a promising objective tool for measuring and following disease status in PD.

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Old age, lower education, and activity of daily living are the predictors of cognitive impairment in Mongolian patients with Parkinson's disease

B. Khandsuren, B. Ts, D. Ulziibayar (Ulaanbaatar, Mongolia)

Objective: To evaluate the baseline predictors of the cognitive impairments valued by the using of the Mini Mental Status Examination (MMSE) in PD patients.

Background: It is estimated that the prevelance of dementia in PD is close to 30%. The main risk factors for cognitive impairment are older age, level of education, severe parkinsonism,depression, and mild cognitive impairment at baseline.

Methods: 117 patients with PD in according to criteria of the UKBBPD have been enrolled. The patients were assessed using HY stage, UPDRS II and III parts, MMSE, and Modified Beck Depression Inventory (BDI). Patients with dementia and non dementia were classified using cut-off MMSE scores 25 or below. Linear stepwise regression analyses were conducted to identify predictors of cognitive impairment in PD patients.

Results: Total 117 patients: 48 male (40.2%) and 69 female (59.8%) were included. The mean age was 61.9 years (range 33-88), the mean HY stage was 2.8 (range1.0-5.0) and the mean disease duration was 5.5 years (range1-16). The mean MMSE score was 25.7 (SD 4.0; range 16-30) with the following distribution for categories: non demented in 61.9% of patients (mean MMSE score 28.3 ± 1.6), demented in 38.9% of patients (mean MMSE score 21.4 ± 2.9). Non-parametric Mann-Whitney test revealed that patients with dementia had older aged ($p<0.001$), later onset ($p<0.001$), lower education ($p<0.001$), advanced HY stage ($p<0.005$), greater postural impairment on UPDRS III ($p<0.001$), and lower score of activity of daily living (ADL)on UPDRS II ($p<0.001$) than non demented patients. In contrast, there were no significant differences in disease duration and depressive disorder in BDI. When the predictors were entered into a linear stepwise regression analysis old age ($p<0.001$), education year ($p<0.001$), and reduced ADL ($p<0.005$) on UPDRS II were the most significant predictors (41.7% of the variables) of development of cognitive impairment in PD patients. This association was not seen between MMSE score and depressive disorder in BDI.

Conclusions: Our data supports that cognitive decline in PD patients is associated with old age, lower education, and greater impairment of daily living activity on UPDRS II. We suggest that accurate evaluation of impact of cognitive decline on ADL could be an important step for detecting dementia in PD patients.

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Clinical validation of diagnostic procedures for Parkinson's disease dementia (PD-D)

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Objective: To evaluate proposed diagnostic procedures for detecting Parkinson's disease dementia (PD-D).

Background: Dementia occurs in up to 48-78% of Parkinson's disease (PD) patients. Diagnostic procedures for PD-D based on recent clinical criteria have been proposed by a The *Movement* Disorder Society (MDS) Task Force. A brief, practical, bedside eight-item screening checklist derived from simple assessments with suggested cutoff points has not yet been validated in comparison to results of more extensive neuropsychological testing.

Methods: Subjects were recruited from those scheduled for neuropsychological testing at two specialty PD centers, administered by a neuropsychologist as part of routine clinical care. Independent and blinded clinical neurologists also administered the screening checklist. Kappa coefficient was used to compare outcomes of the checklist and the neuropsychological battery.

Results: We tested ninety-one PD subjects, with mean age 66.3 ($SD=9.7$) and mean disease duration 8.8 years ($SD=6.1$). Seven subjects (7.7%) met all eight checklist criteria for probable PD-D, as compared to 15 (16.5%) with probable PD-D using the full neuropsychological assessment. There was moderate agreement between these two methods for determination of PD-D ($Kappa=0.59$, $p<0.001$). The screening checklist showed 100% specificity and 46.7% sensitivity for diagnosing PD-D as compared to the full neuropsychological assessment. The missed PD-D cases were largely due to two checklist items (positive depression screening and Mini Mental State Examination (MMSE) scores ≥26).

Conclusions: Where subjects met screening checklist criteria, the designation of PD-D was 100% specific. However, for cases that did not meet these criteria, full neuropsychological testing was still needed to differentiate PD-D from milder cognitive impairment. The screening checklist may therefore be used with confidence that cases included under the designation of PD-D are accurate. Modification of cutoff values for the problem items on the checklist may allow adjustments to optimize sensitivity.

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Investigation of attentional deficits among subjects with Parkinson's disease, healthy elderly and young people: Association between clinical and psychophysical tests

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Objective: To investigate differences in the management of the attentional resources in individuals with PD, healthy elderly and young people, using clinical and psychophysical tests.

Background: An efficiency of cognitive functions suffers the effect of age. With aging, occurs a decline in many cognitive domains, such as executive functions, mental flexibility, abstract thinking, attention, memory, and others. This decline is more evident in Parkinson's disease (PD), where subjects have difficulties in managing the attentional capacities between the movements and the external environment demands. So, to investigate these alterations according to different means of measurement is extremely important, in order to improve the methods of study and permeate out better treatment of individuals with PD.

Methods: Eighty subjects participated in the study: 34 with PD, 34 healthy elderly and 12 young people, who performed the tests Trail Making Test (parts A and B); Stroop Color Test (parts W, D and C) and two psychophysical tests which measures sustained and divided attention.

Results: Despite the poor performance of subjects with PD when compared with healthy elderly, there were no significant differences between these groups in both clinical and psychophysical tests. However, among healthy elderly and young people there were significant differences ($p<0,005$) in time of execution of clinical tests, and in accuracy ($p<0,005$) of the psychophysical test of divided attention. Addicionaly, 20 subjects (10 with PD and 10 healthy elderly) performed the tests again, and the results remained the same, thus excluding a possible learning effect.

Conclusions: There are important differences in management of attentional resources between healthy elderly and young people, and less evident alterations between healthy elderly and PD patients, when assessed with clinical and psychophysical tests. So, better ways of measurement of these cognitive domains should be developed and refined in order to be more sensitive in cases of PD, which would help the design of more efficient treatment for these patients.

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A preliminary test of the mnestic hypometria hypothesis in Parkinson's disease

K.D. Black, K.J. Black, T. Hershey (St. Louis, Missouri, USA)

Objective: To determine whether Parkinson's disease (PD) patients show hypometria for remembered distances.

Background: The spatial delayed response (SDR) task is a well-studied measure of working memory in which the subject fixates a central point while a transient target appears peripherally, then after a set delay touches the remembered target position. PD patients touch the target accurately when it remains visible, but show impaired SDR performance with increasing memory load. We hypothesized that their error was biased towards shorter remembered excursions from the fixation point to the target location.

Methods: PD patients (PD; N=9), healthy controls (HC; N=17), and neuroleptic-naive patients with chronic tics (TS; N=5) completed the SDR task (Foster et al, Brain Cogn 2008; 67:1-10) before and after an i.v. infusion, levodopa one day and placebo saline another day, order randomized. PD patients were in a "practical off" state. Target and response locations were converted to polar coordinates r and θ with respect to the fixation point. The dependent variable was $\triangle r = r(\text{response}) - r(\text{target})$. Significance testing used the t test (2-tailed except for the main hypothesis), collapsing across delays.

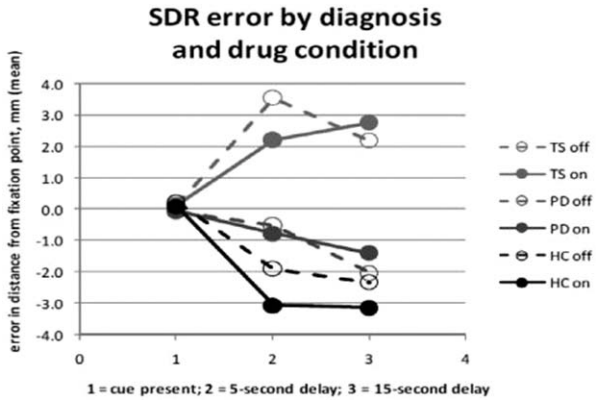

FIG. 1 (396).

Results: PD subjects did on average underestimate recalled distance when in the off state ($\triangle r = -0.86 \pm 9.79$mm, mean±S.D., $p<0.02$). However, so did HCs ($\triangle r = -1.31 \pm 10.34$mm, $p<2\times10^{-5}$). TS subjects overestimated distance ($\triangle r = +1.97 \pm 7.09$mm, $p<3\times10^{-7}$), differing thus from HCs ($p<2\times10^{-11}$). These results were attributable to memory, as all groups were accurate with the cue present. Levodopa had no significant effect on $\triangle r$ in any group ($p>0.10$).

Conclusions: PD subjects did not underestimate recalled distances more than healthy controls, and levodopa did not correct the bias. Crucian and colleagues also found that PD subjects and controls both underestimated distances in different paradigms, though PD subjects did so to a significantly greater degree (abstracts 1997 & 2009). We have not yet examined other trials with a higher memory load, in which PD subjects' SDR performance is poorest, and those trials may reveal the hypothesized effect. Interestingly, TS subjects significantly overestimated recalled distances. This may reflect a cognitive parallel to the hyperkinetic nature of the movement disorder in TS, but this result requires confirmation in a larger sample.

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Probabilistic atlas of neuropsychological outcomes from STN DBS

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Objective: To determine whether DBS-induced activation of regions near the STN is correlated with changes in cognitive and neuropsychological outcomes in PD patients.

Background: While DBS is effective for treating the motor symptoms PD, a high prevalence of neuropsychological effects has been observed in this patient population. Such effects appear more slowly and are more difficult to detect than changes in motor outcomes. The central hypothesis of this work is that cognitive and psychological outcomes in PD DBS patients are correlated with DBS-induced activation of specific brain regions.

Methods: Clinical Evaluation: We compared pre- versus post-operative scores from a battery of 32 neuropsychological tests to measure a range of cognitive functions in 18 PD patients who were good responders to DBS (Fig 1A,B). Computational Analysis: We used a previously published method to predict the volume of tissue activated (VTA) during DBS on an individual patient basis (Fig 1C). MRI volumes for each patient were coregistered with an atlas brain, allowing the electrode locations and VTAs for all patients to be expressed in a common anatomical framework. Clinical scores for each neuropsychological test were assigned to the VTA for each patient at best

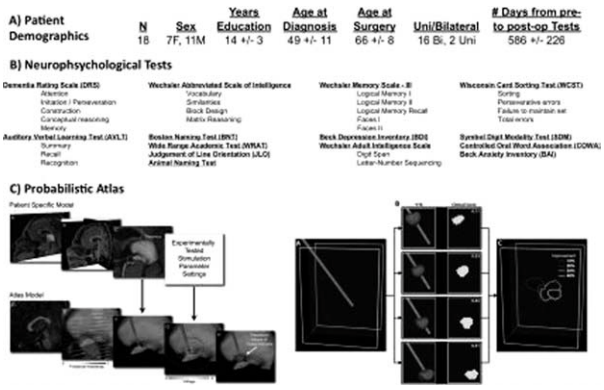

FIG. 1 (397).

therapeutic DBS settings. Statistical analysis was performed on a per-voxel and per-test basis to identify regions where stimulation-induced activation was correlated with differences in test scores.

Results: Of the 32 outcomes, 17 were significantly correlated with DBS-induced activation of distinct regions around the STN (Fig 2). Of these 17 regions: none were in the anterior portion of the STN/thalamus; only 7 overlapped with any part of the STN; 6 showed substantial overlap with the area often targeted for lead placement.

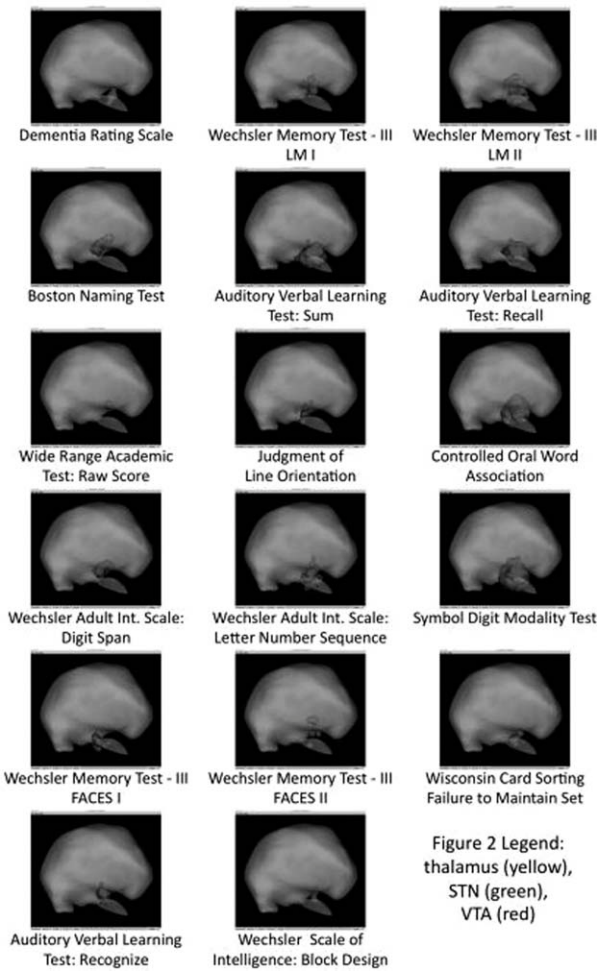

FIG. 2 (397).

Conclusions: Neuropsychological effects could be attributed to several possible sources: DBS; aging; post-DBS changes in medication; disease progression. Here we assumed that these changes were primarily attributable to DBS. We plan to further characterize these results by incorporating age- and disease-matched controls. Our goal is to use this information for pre-operative surgical targeting and post-operative DBS parameter selection to minimize adverse neuropsychological outcomes for PD patients.

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Relationship between apolipoprotein E genotype, dementia and PIB binding in Parkinson's disease

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Objective: The purpose of this study was to explore the relationship between genotype, dementia, and cortical PIB binding potential in PD.

Background: While some evidence suggests that dementia in Parkinson's disease (PD) reflects comorbid Alzheimer's disease (AD), others argue that cortical Lewy bodies account for the dementia. The PET radioligand Pittsburgh compound B (PIB) permits in vivo measurement of amyloid plaque deposition as an indicator of AD pathology.

Methods: A total of 31 PD patients (5 non-demented, 11 with MCI, 15 with dementia) and 7 healthy control (HC) participants completed the Clinical Dementia Rating (CDR) assessment, neuropsychological testing, genetic testing for the ApoE alleles, and PIB PET imaging. PIB binding was calculated for regions known to have high binding in AD.

Results: After controlling for age and education, there was a significant difference in PIB binding based on the presence of the ApoE $\varepsilon 4$ allele. Individuals with the ApoE $\varepsilon 4$ allele had significantly higher PIB binding in the prefrontal cortex ($p=.03$), temporal cortex ($p=.04$), and overall mean cortical binding potential ($p=.04$) and were higher at a trend level in precuneus ($p=.07$) and gyrus rectus ($p=.08$). The proportion of individuals classified as having abnormally elevated PIB was non-significantly greater for those with ApoE $\varepsilon 4$ (5/11) than without (5/27; $p=.087$). However, within the PD group PIB binding did not differ between ApoE $\varepsilon 4$ allele groups (all ps $> .21$). Similarly, there were no differences in CDR scores ($p=.67$) or neuropsychological functioning (all ps $>.15$) between ApoE $\varepsilon 4$ groups for the PD patients.

Conclusions: Although the ApoE $\varepsilon 4$ allele was associated with elevated PIB binding, it was not associated with cognitive impairment or dementia in PD patients. It is possible that although ApoE $\varepsilon 4$ is associated with elevated amyloid burden, dementia in PD is caused by increased Lewy bodies (alpha-synuclein) or another neuropathological process.

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Early motor-dependent impairments of verbal processing in Parkinson's disease and amyotrophic lateral sclerosis

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Objective: Cognitive-motor interactions in Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) are an emerging research area, specially related to the Language domain. Recent studies suggest semantic (verbal) deficits in early PD and ALS. In an attempt to test the hypothesis of motor influence on verbal processing, early PD was diagnosed according to the UKPDSBB criteria, motor symptomatology in patients were examined with the UPDRS

and the Hoehn and Yahr Stage 1 or 2 Scale while on medications. Early ALS/MND, all participants fulfilled the El escorial criteria for 'probable' or 'definite' MND, and control subjects, matched by age, gender and educational level performed the kissing and dancing test (K&D) and a paradigm of reaction times (RTs) based in the action sentence-compatibility effect (ASCE).

Background: A previous reported ASCE was considered in which participants were asked to make judgments on sentences that describe actions performed either with close hands (i.e., She was knocking on the door) or open hands (i.e., She gave a strong applause to the actors).The ASCE effect elicit faster responses when the response requires an hand movement in the same direction as the action described by the sentence. In addition a neuropsychological battery was designed to assess different aspects of motor performance, attention, memory and learning, visual-motor integration, language and frontal/executive functions.

Methods: Compared to controls, PD and ALS presented more errors and less hits in the K&D test. When compared to controls, no ASCE was observed in the PD and ALS. This result was not explained by a general impairment since the basic distinction (open vs close vs neutral) elicited the same RTs differences as controls in PD and ALS.

Results: The ASCE deficit was more accentuated in the Close hand condition in both PD and ALS; but in this last group the performance was more impaired than PD. The motor-language impairment was related to executive functions.

Conclusions: Those results suggest a strong influence of motor impairment on verbal processing in both, PD and ASL, but more accentuated in the last group. The relevance for models of motor influence on language is discussed.

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Motor and cognitive status in a cohort of patients with Parkinson's disease. Cross-sectional study in two different points of time

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Objective: To study the evolution of motor and cognitive status in a group of patients with idiopathic Parkinson's disease (PD).

Background: Cognitive decline may constitute one of the most disabling complications in the evolution of PD. Visuospatial impairment and executive dysfunction affect most of the patients since early stages. Dementia occurs in 20-40% in advanced diseases. There are still some questions regarding their risk factors, evolution, and clinical features.

Methods: Cross-sectional study in two points of time with a mean interval of 8.4 years. Inclusion criteria: PD-patients diagnosed with the UK PD society brain bank's criteria. Hoehn and Yahr (H&Y) classification was used as motor index. Minimental cognitive exam (MEC) (Spanish validated version of MMSE), clock drawing test (CDT), categorical fluency (CF), Necker's cube copy (NCC) and alternating graphic sequences (AGS) were used as neuropsychological tests.

Results: 75 patients were recruited for the 1st evaluation. At the time of the 2nd study, 31 were dead (group 1), 7 were lost and 2 were withdrawn because of changing of diagnosis. Of the remaining 35 patients, 15 (group 2) completed the 2nd motor and cognitive assessment. 1st evaluation: comparing group 1 and 2, group-1 patients were older at the diagnosis of PD (65.97 vs 54.36), and had worse H&Y (2.79 vs 2.14) and lower punctuations in all the psychological tests, with the same duration of disease 2nd evaluation: motor complications (H&Y 3 or higher) occurred in 42.86% of the patients. Cognitive decline affected 14-21% depending on the test used. CDT and AGS were the most sensitive (28% and 53% abnormal results respectively). MEC was within normal ranges in all the patients and did not change with the time.

Conclusions: Diagnosis of PD was very accurate as only 2 patients showed other form of parkinsonism during the long follow up. MEC is not useful to discriminate between normal and impaired patients in PD. Older age at PD-onset seems to be a risk factor for cognitive impairment, worse motor status and higher mortality. In the surviving group of patients the evolution of cognitive decline was slower and slighter than the motor deterioration.

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The Addenbrooke's cognitive examination (ACE) detects cognitive impairment in advanced Parkinson's disease but not in early Parkinson's disease

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Objective: To determine if the Spanish version of the ACE is capable of detecting cognitive difficulties in patients with early Parkinson's disease (PD) and in advanced PD.

Background: Detecting cognitive impairment in patients with PD is crucial for good clinical practice given the new therapeutic possibilities available. The gold standard for detecting cognitive impairment in advanced PD patients is the Mattis Dementia Rating Scale and the neuropsychological testing in early PD but these tests are time-consuming and there is a need for a brief test for detecting cognitive deficit in early PD. The ACE is a practical, brief screening test that has been shown to be useful for the detection of dementia.

Methods: We compared the ACE scores in 32 consecutive patients with early PD and 25 patients with advanced PD. All patients were in the on state at the time of assessment.

Results: Early PD, 20 (62 %) were men, mean age (63, 15±10.09 years), advanced PD patients 60 % were men, mean age (73 ±7.46 years). In the early PD, 25.6 % of patients showed no cognitive deficits on any of the classical neuropsychological tests. Forty one percent of patients exhibited deficit in one or two tests of the battery and 33.4 % presented deficits in three or more tests. Although 74.4 % of the patients had deficits in one or more test of the standard neuropsychological testing, the percentage of subjects scoring below the cut-off of 83/100 of the ACE (suggested to detect mild cognitive impairment) was lower on the early PD group (16 %) than on the advanced PD group (42.3 %) of patients.

Conclusions: This study shows that the Spanish version of the ACE is capable of detecting patients with cognitive impairment in advanced PD but it is not an effective screening tool for early PD patients.

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Posterior white matter hyperintensities are associated with low cerebrospinal fluid beta-amyloid levels in Parkinson's disease

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Objective: To assess the regional burden of white matter hyperintensities (WMH) and its possible association with cerebrospinal fluid (CSF) beta-amyloid levels in Parkinson's disease (PD).

Background: WMH are frequent in the aging brain and commonly viewed as a marker of small-vessel disease. They may also reflect vascular deposition of beta-amyloid, mainly when occurring in posterior subcortical areas. In some studies WMH and low CSF beta-amyloid levels have been found in PD with dementia (PDD), but their relationship has not been explored to date. An association would support a role for beta-amyloid in posterior WMH in PDD.

Methods: Thirty-eight PD patients (19 non-demented –PDND–; 19 demented –PDD–) and 12 healthy controls were studied. WMH in FLAIR images from 3T brain MRI were assessed in several subcortical areas by a radiologist blind to the clinical data, using the scale of the European Task Force on Age-Related White Matter Changes. CSF beta-amyloid levels were determined using a specific and com-

mercially available ELISA technique for beta-amyloid [1-42]. Non-parametrical statistics were applied.

Results: Controls and PD patients did not differ in demographic features. CSF beta-amyloid levels were significantly lower in PDND and in PDD than in controls, and non-significantly in PDD than in PDND. Moderate to severe WMH were significantly more frequent in PDD than in PDND subjects (p=0.05) and controls (p=0.03) in the parieto-occipital (posterior) white matter. PD patients with moderate to severe posterior WMH (n=19; 6 PDND + 13 PDD) had significantly lower CSF beta-amyloid levels than those with none to mild posterior WMH (n=19; 13 PDND + 6 PDD) (p=0.003), with no significant differences in the presence of vascular risk factors (p=0.7).

Conclusions: The burden of posterior WMH was greater in PD patients with dementia and was associated with lower CSF beta-amyloid levels. Vascular deposition of beta-amyloid might account for such findings, which could be related to the well-recognised posterior (parieto-occipital) cognitive deficits of PD.

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Lewy–and Alzheimer–type pathologies in Parkinson's disease with dementia: A comprehensive brain-bank study

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Objective: To examine the individual and combined effect of a-synuclein (aS), amyloid-β (*Aβ)* and tau pathologies in Parkinson's disease (PD) with dementia (PDD) compared to cases without dementia (PDND), and their relationship with progression to dementia and mini-mental state examination (MMSE) scores.

Background: To date the data available on the pathology underlying dementia in PD is diverse, some favouring either Lewy body (LB)-type pathology alone or concomitant Alzheimer's disease (AD)-type pathology.

Methods: We studied 56 PD cases (29 PDD) from the Queen Square Brain Bank, 15 of them with MMSE scores available within last year of life. aS (LB-type) and Aβ and tau (AD-type) pathologies were assessed in multiple cortical areas as recommended by current staging criteria. Cortical LB densities were also determined using a morphometric approach. Genetic risk polymorphisms for APOE ε4 and H1H1 alleles were determined.

Results: Cortical and striatal Aβ load and Braak tau stages were all greater in PDD vs. PDND. Although Braak PD stages did not differ, the cortical density of LBs and neurites was higher in PDD vs. PDND. Each pathology (binary regression model) and combination of pathologies (receptor operative curves) contributed to risk of dementia. APOE ε4 was associated with greater Aβ burden, but only in temporal and parietal cortical areas. Cortical Aβ burden and LB densities (but not the semiquantitative LB score) showed a significant negative correlation with MMSE scores. However, only cortical Aβ burden had a significant negative correlation with time to dementia.

Conclusions: All three pathologies were associated individually, but the presence of all three pathologies in combination best identified PDD. Genetic risk factors only marginally explained the AD pathology burden in PD. Both cortical Aβ and LB pathology reflected cognitive impairment severity, but only Aβ was associated with faster progression to dementia.

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Cognitive deficits in patients with mid- to late-stage Parkinson's disease

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Objective: To assess cognitive function in patients with mid- to late-stage Parkinson's disease (PD).

Background: Cognitive impairment is common among patients with PD. Evidence suggests that cognitive deficits develop early in the course of PD and, as the disease progresses, decline in cognitive function may worsen and affect a greater proportion of patients.

Methods: 656 patients with PD (mean age: 60±9 years) receiving levodopa and other PD medications and experiencing motor fluctuations (>1.5 h OFF time/day) underwent cognitive assessments using Cogtest, a customized, computerized cognitive testing system. The selected Cogtest battery comprised the following tests: Auditory Number Sequencing (ANS), Word List Memory (WLM) test, with delayed recall and recognition (WLMD), Symbol Digit Substitution (SDS), Tower of London (TOL), Strategic Target Detection (STD), and Spatial Working Memory-short (SWMS) and -long (SWML) delay. Data were converted to z-scores based on healthy control data from the Cogtest database (n=240; mean age: 50±17 years). A z-score of 0 represents average performance, and a z-score of -1 represents a performance that is one standard deviation (SD) below the normative group mean. Impairment within a test was defined as a performance >1.5 SD below the normal mean (i.e., z-score <-1.5).

Results: Most patients demonstrated cognitive impairment when compared with age-matched healthy volunteers. In a non-PD population, 7% of people would be expected to show cognitive impairment in any individual test (>1.5 SD below mean), whereas in this study, the percentages of patients showing cognitive impairment in the individual variables at the screening visit were: 84% for ANS, 39% for WLM, 39% for WLMD, 36% for SDS, 48% for TOL, 46% for STD, 48% for SWMS and 64% for SWML.

Conclusions: Of 656 patients assessed, 96% showed impairment in at least one of the 8 cognitive variables when compared with the normative group at the screening visit. Impairment in verbal working memory, assessed by the ANS test, was most common, with 84% of patients affected. These data suggest that cognitive deficits are widespread in patients with mid- to late-stage PD.

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Longitudinal assessment of olfactory dysfunction in early Parkinson's disease

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Objective: To investigate the feasibility of using olfactory dysfunction as a treatment-independent biomarker of disease progression in Parkinson's disease (PD) with a prospective longitudinal assessment of olfaction in early PD patients.

Background: There is an urgent need to develop treatment-independent biomarkers of disease progression in PD. As a non-dopaminergically mediated symptom that occurs very early in PD, olfactory dysfunction is a viable candidate.

Methods: Twenty five early PD patients and 25 age-matched controls participated in baseline and 1-year follow-up assessments of (1) odor identification, using both the University of Pennsylvania Smell Identification Test (UPSIT) and Sniffin' Sticks test, (2) odor detection threshold sensitivity, using the phenyl-ethyl-alcohol (PEA) threshold test, and (3) odor intensity/hedonics. Sniff magnitude was assessed with an automated apparatus.

Results: PD patients performed worse on odor identification and threshold detection tests than controls at baseline but assessments of odor intensity and hedonics were similar. Specifically, control subjects scored higher on the UPSIT (29±5.18, 22.56±6.17; p<0.01), Sniffin' Sticks (11.58±2.52, 8.56±3.22; p<0.01), and PEA-threshold tests (-3.24±1.19, -2.56±1.13; p<0.05). Sniff magnitude was greater among controls than PD patients (0.33±0.02, 0.25±0.01; p<0.01). However, after a one year delay, there were no statistically significant differences in change from baseline between PD patients and controls. Variability in performance from baseline to follow-up occurred in all olfactory assessments with some subjects in both groups exhibiting improved performance after a one-year delay.

Conclusions: Between-group differences in baseline assessments of PD patients and age-matched controls confirmed that olfactory dysfunction occurs in early PD. However, none of the assessment tools used were able to demonstrate a progression of olfactory dysfunction among PD patients relative to healthy controls over a one year interval. In fact, the assessments applied in this study revealed that some variability exists in psychophysical performance over time among both PD patients and healthy controls. These findings suggest that while olfactory dysfunction is present in early PD, it may not be a viable biomarker of disease progression.

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Detecting cognitive impairment in patients with early Parkinson's disease combining two brief screening tests: The Addenbrooke's cognitive examination–(ACE) and the INECO frontal screening (IFS)

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Objective: The goal of the present study was to investigate the usefulness of a combined cognitive screening which includes the Addenbrooke's Cognitive Examination (ACE) and the INECO Frontal Screening (IFS), an executive screening tool designed to detect executive dysfunction (Torralva et al 2009), in the detection of cognitive deficits in early Parkinson's disease (PD).

Background: The ACE is a screening tool which has shown to be sensitive in the detection of cognitive dysfunction in the moderate and severe stages of PD. A recent study showed that the ACE alone is not capable of detecting cognitive dysfunction in early PD (Chade 2008), probably because it does not extensively assess executive functions, which is the most frequent common cognitive dysfunction in the early stages of PD.

Methods: A group of early PD patients (n=20) were assessed with both screening tools as well as with a complete neuropsychological battery including tests of attention, memory, visuoperceptual skills and executive function.

Results: Even though 55% of patients showed deficits in two or more tests of the cognitive battery (z score <-1.5), only 25% showed scores below the cut-off for the ACE and up to 70% showed scores below the proposed cut-off score for the IFS. When both screening tests were combined, however, the proposed cut-off score for this combination (115 out of 130 points) was capable of detecting exactly 55% of the patients; with a 60% overlap with those had shown deficits on the complete neuropsychological assessment battery.

Conclusions: These findings reveal the potential utility of combining a general cognitive status screening tool (ACE) and a more specific executive screening test (IFS) in detecting cognitive impairment in early PD when full neuropsychological evaluations are not available.

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8-OHdG in cerebrospinal fluid as a promising marker of early stages in Parkinson's disease

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Objective: To asses if the 8-hydroxy-2 deoxyguanosine (8-OHdG) as a product of nucleoside oxidation of DNA and a reliable marker in the differentiation between Parkinson's disease (PD) and Parkinson's disease with dementia (PDD).

Background: There is an increasing evidence that oxidative damage is involved in the pathogenesis of various neurodegenerative disorders including Parkinson's disease. Among multiple products of nucleoside oxidation, 8-OHdG is a best characterized forms of DNA oxidation.

Methods: We analyzed the 8-OHdG levels in cerebrospinal fluid (CSF) in 22 patients with the diagnosis of Parkinson's disease and 21 patients with PDD. An enzyme-linked immunosorbent assay (ELISA) was used for CSF assessment. The data were further stratified according to age at the disease onset, disease duration and the severity of dementia.

Results: A statistically significant higher CSF levels (p=0.038) of 8-OHdG in non-demented Parkinson's disease patients (mean 1.14 ±0.38 ng/ml) as compared to demented patients (mean 0.89±0.40 ng/ml) were observed. No differences between CSF 8-OHdG levels and age at the time of lumbar puncture as well as gender were found. Although, no significances were observed in regard to severity of dementia, the group with mild/moderate dementia tend to reach higher 8-OHdG levels as compared to severe dementia stages.

Conclusions: A significant elevated 8-OHdG CSF levels were observed in non-demented PD patients as compared to patients with cognitive impairment. A trend to decrease of 8-OHdG with the disease stage was demonstrated as well. The estimation of 8-OHdG in CSF might be potentially useful in the diagnosing of Parkinson's disease mainly in early stages of disease.

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Silent vascular events and dementia in Parkinson's disease

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Objective: To study the relationship between silent cerebrovascular (CV) events and cognitive decline and dementia in PD patients, and to evaluate a possible correlation between the CV events in the different cerebral lobes and the impairment among the cognitive domains.

Background: Dementia is frequently developed in long duration Pakinson's disease but its pathological substrate is not fully understood. CV pathology is associated with dementia in the elderly population and also in Alzheimer's disease and Lewy bodies dementia. The role of silent CV lesions in the dementia of PD has been poorly studied.

Methods: PD patients older than 60 years with at least 10 years of disease duration were included. Patients with other brain disorders, vascular or severe systemic disease, major psychiatric illness, or previous cerebral surgery were excluded. Evaluations included motor scales (UPDRS-III and Hoehn and Yahr), an extensive battery of neuropsychological tests to asses the different cognitive domains and a 1,5 Tesla MRI study. Patients were classified as cognitively normal (PD-CN), with mild cognitive impairment (PD-MCI) and with dementia (PD-D). MCI was defined as at least 1.5 standard deviations below the expected age corrected mean score in any of the cognitive domains. The DSM-IV was used for the diagnosis of dementia. FLAIR and T2-weighted MRI sequences were used to semi-quantify the silent CV events by counting the white matter hyperintensities (WMH) using 3 different widespread scales: ARWMC-Wahlund, Fazekas and Scheltens.

Results: 111 PD patients in the three groups PD-CN (n=39), PD-MCI (n=46), and PD-D (n=26) were studied. The groups were similar except for the age and UPDRS-III that were higher in the PP-D patients. There were not significant differences in the scores obtained in any of the scales measuring the WMH among the three PD patients groups. There was a negative correlation between the 30 seconds and 1 minute semantic fluency and the Scheltens LH-frontal scores (p=0.048 and p=0.014, respectively).

Conclusions: In contrast with results obtained for AD and LBD, this study indicates a low impact of the silent CV pathology in the cognitive decline and dementia of PD patients. However, the frontal WMH burden implies a relevant worsening on semantic fluency scores.

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Evaluating subtle cognitive changes in hyposmic PARS subjects

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Objective: The overall objective of the PARS study is to identify a biomarker strategy to detect pre-diagnostic PD.

Background: Numerous studies have demonstrated dopamine transporter (DAT) loss and non-motor symptoms including olfactory loss occur during the pre-diagnostic PD period. The ongoing PARS study using a strategy of large scale screening with the University of Pennsylvania Smell identification test (UPSIT) followed by DAT imaging demonstrates that hypsomic subjects have increased risk of DAT deficit. Evidence suggests that cognitive changes may occur at an early stage in PD and present prior to motor symptoms.

Methods: Within the ongoing PARS study the UPSIT and questionnaires evaluating non-motor symptoms were administered to >5,000 subjects by mail. Hyposmic (lowest 15%) and normosmic subjects undergo extensive evaluation including UPDRS, DAT imaging and blood biomarker assessments. Subjects have also undergo cognitive testing including verbal memory (HVL, WMS-R story, RBANS story), spatial orientation (RBANS line orientation), semantic fluency and spatial problem solving (WAIS-III block design). A global cognitive score was derived from these assessments.

Results: In this ongoing study, 101 subjects (53 hyposmic; 48 normosmic), mean age 67.9 (6.3) and 66.9 (10), 47% and 46% female and mean education level 15.7 and 16.4 have undergone cognitive assessments. Comparison of the hyposmic and normosmic subjects revealed statistically significant lower scores in all domains for the hyposmic subjects and 2-tailed t-test effect sizes are as follows: verbal memory 0.55(p=.007), spatial orientation 0.62(p=.002), semantic fluency 0.59(p=.007), spatial problem solving 0.52(p=.01), and global cognition 0.65(p=<.002). 35% of subjects with a global cognition <2 showed abnormal DAT imaging compared to 1.5% of subjects with those >2.

Conclusions: Preliminary data from cognitive testing in this cohort suggests that hyposmic subjects are more likely to have subtle cognitive deficits when compared to the normosmics subjects of similar age, gender and education levels. Early evidence suggest that subjects with even minimal cognitive deficits are more likely to demonstrate DAT deficit. DAT, b-amyloid imaging and longitudinal follow-up are being performed and will ultimately determine whether these findings are early indicators of neurodegeneration.

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Attentional dysfunction and smooth pursuit in Parkinson's disease and Huntington's disease

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Objective: To examine the role of automatic and goal-directed attention in smooth pursuit (SP) eye movements in patients with Parkinson's disease (PD) and Huntington's disease (HD), to determine whether these groups exhibit comparable deficits to those previously demonstrated for saccadic tasks.

Background: Combining sensory input, motor intention and cognitive influences, the basal ganglia (BG) are involved in the preferential selection and suppression of competing responses. PD and HD are two prototypical disorders of the BG that manifest in impaired control over behaviours requiring the efficient resolution of response conflict. Previous research addressing saccadic eye movements demonstrate that these patient groups exhibit distinct deficit profiles, a consequence of altered activity over the BG facilitatory and inhibitory pathways, consistent with the differential sites of BG dysfunction in PD and HD. SP eye movement, however, has attracted relatively little research in these groups, despite accumulating evidence demonstrating a significant overlap in the anatomical substrate and functional mechanisms of saccades and SP.

Methods: Posner-type endogenous and exogenous cueing tasks were adapted to SP. These tasks have previously been used to examine saccades. Eye movements were recorded using an infrared eye tracking system.

Results: Data derive from sixteen people with PD, twelve people with HD and an equivalent number of healthy age-matched controls participated. Preliminary results demonstrate that similar to saccades PD and HD are associated with distinct response profiles, reflecting altered inhibitory output of the BG.

Conclusions: Preliminary results are consistent with impaired conflict resolution processes, reflecting the distinct sites of BG dysfunction associated with PD and HD.

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Assessment of Parkinson's disease with dementia by FDG-PET

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Objective: After a long clinical course, many patients with Parkinson's disease (PD) present with dementia and/or psychosis (11-81%). This condition is classified as Parkinson's disease with dementia (PDD). However PDD includes different conditions, such as drug-induced deterioration, coincident occurrence of Alzheimer's disease (AD), and dementia with Lewy bodies (DLB). Several authors have reported that these dementing illnesses can be differentiated based on patterns of distribution of hypometabolic areas on FDG-PET imaging. There have been no systematic observations of regional cerebral glucose metabolism with FDG-PET in PD patients with a long clinical course. We studied the pattern of regional glucose hypometabolism in patients with PDD by FDG-PET.

Methods: PDD patients were selected from among those with PD being treating in our outpatient clinic based on the following criteria: (i) a 10-year or longer history of PD, (ii) good response to l-dopa and/or anti-PD drugs, and (iii) presence of dementia and/or psychosis. Patients with identifiable causes of dementia and/or psychosis, such as cerebral infarction or brain tumor, were excluded. FDG-PET images were obtained using a PET scanner Allegro (Philips, Holland). A 20-minute emission scan was started 60 min after intravenous injection of 4.4 MBq/Kg of FDG. The FDG-PET images were visually assessed, and 3D-SSP was also used. The pattern of regional glucose hypometabolism was classified as follows: frontal dominant type, parietal dominant type, occipito-parietal dominant type, or normal type (no remarkable reduction found).

Results: Seventeen patients were selected as having PDD with our inclusion and exclusion criteria. The mean age was 68.7 years, mean age was 68.7years, and mean l-dopa dose 534 mg/day. The pattern of regional glucose hypometabolism with normal type was 5 cases, parietal dominant type was 3 cases, and occipito-parietal dominant type in 9 cases. No patients had frontal dominant type.

Conclusions: PDD included several different neurological conditions. Patients with normal type are believed to have symptoms resulting from drug effects or subcortical lesions. The parietal dominant type is considered to be combination of AD cases. The occipito-parietal dominant type is believed to include cases of DLB. FDG-PET is useful for understanding the dementia and psychosis in PD.

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Striatal amyloid-β pathology and dementia in Lewy body and related disorders

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Objective: To examine the extent and severity of striatal amyloid-β peptide (Aβ) deposition in Lewy body and related disorders and its association to dementia.

Background: Recent neuropathological studies have described widespread amyloid-β peptide (Aβ) deposition in the striatum of

patients with Lewy body disorders, particularly those with Parkinson's disease with dementia (PDD) or dementia with Lewy bodies (DLB). However, positron emission tomography (PET) studies using the [11C]PIB ligand, which binds to Aβ deposits, only appears to detect the striatal pathology in DLB.

Methods: We examined Aβ deposition in the caudate nucleus (CN) and putamen (put) of 52 PD, 41 PDD, 14 DLB, 7 multiple system atrophy (MSA) and 14 progressive supranuclear palsy (PSP) cases and assessed its association with the presence of dementia. Semi-quantitative assessment (0-3+; absent to severe) of Aβ immunostaining in the caudate nucleus and putamen was carried out blind to clinical diagnosis. Differences between diagnostic subgroups were analyzed with the non-parametric Mann-Whitney U-test.

Results: PD, MSA and PSP cases showed no or minimal Aβ pathology in the striatum. In contrast, comparison of the PD, PDD and DLB cases revealed a signifcantly greater Aβ burden in PDD and DLB cases in both the caudate nucleus and putamen [PD vs. PDD (CN: $p<0.0001$, put: $p<0.0001$) and [PD vs. DLB (CN: $p=0.0002$, put: $p=0.0004$)]. By contrast MSA and PSP cases showed similar Aβ burdens to those of PD cases. Interestingly, no statistically significant difference in Aβ deposition was observed between PDD and DLB cases (CN: $p=0.37$, Put: $p=0.47$).

Conclusions: We conclude that striatal Aβ pathology is common in PDD and DLB and likely contributes to the development of dementia in these conditions. The lack of agreement between neuropathological and imaging studies may be due to the nature of the ligand used in the latter studies, in that it is likely to detect the β-pleated sheet structure of mature amyloid plaques rather than the diffuse deposits we observe at post-mortem.

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Executive dysfunctions: A premotor biomarker of familial Parkinson's disease?

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Objective: To investigate the hypothesis that executive dysfunctions are a preclinical marker of Parkinson's disease (PD) in first-degree relatives (FDR) of patients with familial forms, we report longitudinal data from a group of 41 FDR.

Background: Early PD diagnosis is essential for the development of potential neuroprotective treatments. As asymptomatic parents may be at risk to develop PD, familial forms of PD have a particular interest. In 1999, we showed that 15 among 41 FDR were already impaired, compared to controls, on executive function tests.

Methods: Over a follow-up period of 11 years, we were able to compare 26 FDR to 23 healthy controls. A large battery of tests was administered included parkinsonism and sleep rating scales, executive function tests, smell identification test, neurophysiological study of movement-related cortical activation and a single photon emission computed tomography using I-123-FP-CIT as a dopamine transporter ligand.

Results: Compared to controls, FDR were impaired on 2 tests measuring executive functions. Abnormalities on cortical activation (event-related desynchronisation) and minimal signs of parkinsonism were also evidenced. No olfaction nor sleep dysfunction was described. No FDR met criteria for probable PD. No significant reduction was found in striatal dopamine transporter binding. A factorial discriminant analysis allowed isolation of 2 subgroups of FDR who differed from controls on neuropsychological and neurophysiological variables.

Conclusions: Our results confirm executive dysfunction and motor abnormalities among FDR of patients with familial PD. As none of FDR developed probable PD, we cannot conclude that cognitive disorders are pre-clinical marker of PD. The abnormalities we evidenced may be due to early dopaminergic impairment in cortico-striatal loop. Longitudinal follow-up of these FDR need to be continued to assess executive dysfunction as a premotor marker.

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Significance of subjective memory complaints in non-demented patients with Parkinson's disease

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Objective: To compare the motor and cognitive function scores in non-demented patients with Parkinson's disease (PD) with and without subjective memory complaints (SMC).

Background: In PD, executive function is impaired early in the disease process as a result of frontal lobe dysfunction. The utility of the FAB as a valid screening tool for executive dysfunction and its correlation with motor symptoms, among Asian patients with PD has not been established.

Methods: 115 PD patients were recruited from the PD and Movement Disorders Centre, National Neuroscience Institute over a 5-month period. Patients were prospectively evaluated with the MMSE, FAB, UPDRS, Hoehn and Yahr staging. All patients met the National Institute of Neurological Disorders and Stroke criteria for the diagnosis of PD and did not meet DSM-IV criteria for dementia. Patients with limbs deformities or contractures were excluded from the study. Parametric, non-parametric tests and correlation statistics were performed with statistical significance taken at $p\leq0.05$

Results: 28 of these non-demented PD patients had memory complaints on the question on amnesia on the DSM-IV. Their mean age was 69.8±11.4, years of education was 6.18±6.04, H&Y stage was 2.52±0.81, UPDRS motor score was 26.5±10.0, bradykinesia was 17.5±6.34 and instrumental ADL (IADL) was 21.36±2.73. For the 87 PD patients without SMC, their mean age was 66.3±9.7, years of education was 7.7±5.4, H&Y stage was 2.24±0.73, UPDRS III motor was 22.1±11.18, bradykinesia was 14.3±6.87 and IADL was 22.6±1.4. Patients with SMC had lower MMSE (22.1±5.44), FAB (10.5±3.63) & design copy scores (0.43±0.5), than patients without SMC (25.1±3.68, 12.4±4.07 & 0.54+0.5) respectively. A significantly greater percentage failed the education-adjusted FAB (78.6% with SMC vs 49.4% without, $p<0.05$) compared to the memory-based MMSE test (35.7% with SMC vs 25.3% without).

Conclusions: Non-demented PD patients with SMC performed worse compared to those without SMC. The FAB may be a more sensitive instrument than the MMSE in detecting cognitive decline amongst non-demented PD patients which might suggest earlier frontal dysfunction.

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Withdrawn by Author

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Cerebrospinal fluid biomarkers and cognitive performance in non-demented Parkinson's disease

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Objective: To examine the relationship of cerebrospinal fluid (CSF) biomarkers and cognitive performance in a group of Parkinson's disease (PD) subjects without dementia.

Background: The pathophysiologic processes underlying cognitive impairment (CI) in PD are uncertain. By the time an elderly PD patient develops frank dementia, several processes may be contributing to CI including Lewy body disease, Alzheimer's disease (AD) and vascular disease. To better understand the processes underlying CI in PD it may be better to examine patient prior to the development of frank dementia. Therefore, we examined the relationship of CSF biomarkers linked to PD and AD and cognitive performance in a group of non-demented PD subjects.

Methods: Subjects were 22 PD patients enrolled in a longitudinal study of motor and non-motor complications of PD. All subjects ful-

filled UK Brain Bank criteria for PD. Subjects underwent paired neuropsychological testing and research lumbar puncture. CSF samples were analyzed with a multianalyte profile including three biomarkers of interest (Aβ42, tau, brain derived neurotrophic factor (BDNF).

Results: Mean age, duration of PD and MMSE score were 68.1 years, 8.9 years, and 28.3 respectively. Significant Spearman correlation were found between between digit symbol performance and CSF Aβ42, BDNF and the ratio of CSF Aβ42 to tau. Verbal fluency for vegetables was also significantly correlated with the ratio of CSF Aβ42 to tau. CSF Tau was not significantly correlated with performance on any of the neuropsychological tests. UPDRS score was not significantly correlated with any CSF biomarker.

Conclusions: We found evidence, in a non-demented PD sample, for an association between cognitive performance and CSF biomarkers. Of interest, reduced BDNF, a marker linked to PD, was associated with a poorer performance on Digit Symbol, but not to motor impairment. CSF Aβ42 was also associated with performance on this same test, but not Tau levels. This latter finding suggests that classic neuropathologic AD (i.e., neurofibrillary tanlges and senile plaques) is not likely contributing to the neuropsychological performance in this PD sample. However, our finding of lowered CSF Aβ42 in those with poorer cognitive test performance suggests that this pathologic change might be linked to CI in PD.

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Gait variability in Parkinson's disease: Impact of dopamine and attention

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Objective: To investigate the explanatory characteristics of gait variability in Parkinson's disease (PD) *on* and *off* medication under single and dual task conditions. The hypotheses were: i) explanatory characteristics would in part reflect non-dopaminergic pathways; ii) executive function would predict gait variability under dual task conditions.

Background: Gait variability, expressed as the Coefficient of Variation (CoV) derived from individual step data, has potential utility as a predictive measure of dysfunction. The underlying neural mechanisms of gait variability in PD are not clear, although current understanding implicates contribution of non-dopaminergic pathways.

Methods: Fifty people (mean (SD) age 69.2 years) with PD and median Hoehn & Yahr score of 3 were assessed twice at home (*on* and *off* L-dopa) whilst walking under single and dual task conditions. Gait speed, stride time and double limb support (DLS) time were recorded with a stride analyser, and CoV calculated for stride time variability and DLS time variability. Hierarchical regression analysis was used to identify predictors. The first block of variables included age, gait speed, depression (Hospital Anxiety and Depression Scale) and fatigue (Multidimensional Fatigue Inventory) and the second block included motor severity (UPDRS III), executive function (Hayling & Brixton), and attention (Test of Everyday Attention).

Results: R^2 values ranged from 0.32 to 0.84 for all models. Motor severity predicted stride time variability and DLS time variability independent of L-dopa during single and dual task gait. Dual task gait yielded a more complex picture. For stride time CoV, depression made a unique contribution of 9.0% *on* medication and 5.0 % *off* medication. Visual attention and younger age contributed to DLS variability *on* medication explaining 3% and 2% respectively. Motor severity predicted DLS variability *off* medication explaining 74% of variance. Gait variability was independent of gait speed for all models.

Conclusions: Non-dopaminergic characteristics contribute to gait variability in PD under complex (dual task) walking conditions. Different characteristics explain the two measures of gait variability pointing to different control mechanisms. Surprisingly, depression featured more strongly than executive function or attention, potentially implicating norepinephrine mechanisms.

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Cognitive deterioration rates, based on Montreal cognitive assessment, in patients with Parkinson's disease from Northeastern China

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Objective: In the present study, we tried to define and compare the cognitive profiles and clinic features of the PD patients with slow or rapid CDR, and then identify the risk factors for rapid CDR in PD patients.

Background: Cognitive impairment (CI) is common in Parkinson's disease (PD), and the cognitive deterioration rate (CDR) differs significantly in PD patients. However the studies depicting the features and risking factors of PD patients with rapid CDRs are lacking. Montreal Cognitive Assessment (MoCA) is considered to be a sensitive and reliable approach to detect mild cognitive impairment (MCI).

Methods: A cross-sectional study of cognition with MoCA were performed in the convenience sample of 73 PD patients and 41 age-, sex-, education-matched controls.

Results: Our results showed that, compared with the slow CDR group, the rapid CDR group had older age (58.8 vs 64.1 $p=0.02$), older disease-onset age (52.7 vs 61.7 $p<0.001$), faster movement symptoms deterioration rate (19.5/year of increment in UPDRS III score vs 4.4/year of increment in UPDRS $p=0.03$), and lower MoCA subscores including Clock Drawing Test (CDT), attention, verbal fluency, and abstraction, and higher rate in multiple domain impaired CI (38.9% vs 10.8%). Based on the univariate logistic regression model, onset age, movement deterioration rate, multiple domains CI, and executive function impaired CI were risk factors for rapid CDR. However, only movement deterioration rate ($p=0.01$) and onset age ($p=0.05$) remained independent predictors for rapid CDR in the multivariate logistic regression model.

Conclusions: A subset of PD patients progress to dementia more rapidly, defining this population may not only predicts the development of PD dementia, but also raise the necessity for therapeutic intervention at early stage.

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Prevalence and predictive factors of cognitive impairment and dementia in Parkinson's disease

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Objective: To estimate the prevalence of cognitive impairment (CI) and dementia (DEM) in patients with Parkinson's disease (PD) attending a specialist clinic and to identify the main predictive factors.

Background: CI is common in PD, although its prevalence depends on the population studied and the diagnostic criteria used.

Methods: We selected 60 consecutive patients with PD (London Brain Bank criteria) in Hoehn-Yahr stage ≥ 2 with disease onset at ≥ 45 years of age, after excluding those with other diseases that could be associated with CI or interfere with the evaluation. After a complete clinical, cognitive (orientation, attention, memory, language, praxis, executive functions), behavioral, and functional study, they were classified by an independent researcher as: without CI; with CI without DEM (CInD); or with DEM. Multivariate logistic regression analysis was used to identify predictive factors for the presence of CI or DEM.

Results: CI was presented by 71% of patients (43% CInD and 28% DEM). Subjective memory complaints were reported by 63% of patients but were not related to the final cognitive diagnosis. For the same values of the other variables (age, time with PD, main motor symptoms, medication dose) the main factor associated with CI was low educational level (unfinished primary schooling; OR=10.86; p<

0.001) and the main factor associated with DEM was the Hoehn-Yahr stage (> 3; OR=10.97; p=0.001).

Conclusions: A high proportion of PD patients attending specialist clinics have CInD or DEM. Screening tests are required to identify these conditions independently of subjective complaints, especially in patients with low educational level or more advanced PD.

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fMRI investigation of the effects of l-dopa on cerebral activity linked to finger movement complexity in Parkinson's disease

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Objective: Our aim was to investigate the effects of L-dopa on brain activation patterns of patients affected by Parkinson's disease (PD) using a finger-movement task.

Background: Patients with PD have both cognitive and motor symptoms. Using fMRI, we have previously shown that cortical activity in PD varies according to striatal requirement while performing a cognitive task. Also, L-dopa helped restore a normal pattern in the motor but not the cognitive cortico-striatal loop during the Wisconsin Card Sorting Task. Furthermore, when comparing self-initiated (SI), externally-triggered (ET), and repeated (Ctl) movements in healthy participants, we found activations in the motor loop for SI and ET movements, and in the cognitive loop for SI movements only.

Methods: 15 PD patients underwent two fMRI sessions, once on, once off medication. Participants used their right hand to perform SI, ET, and Ctl movements. 15 healthy controls also participated in one fMRI session.

Results: Preliminary results indicate increased activity in the PFC and striatum with increasing task complexity in controls and patients ON, but not OFF medication. There is no change in activations for SI movements with L-dopa, whereas there is an increase in putamen activity with L-dopa for ET movements.

Conclusions: Our results show that L-dopa has no effect on the cognitive component of our task, but partially reestablishes activity in the motor loop. Furthermore, L-dopa restores the effect of task complexity on striatal activity in PD patients. Finally, our results suggest that cortical hyperactivation seen in PD patients is due to long-term medication usage rather than the pathology of the disease.

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The development of a questionnaire to assess everyday multi-domain cognitive functioning in people with Parkinson's disease: The Parkinson's disease everyday cognition questionnaire (PD-ECQ)

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Objective: To develop a questionnaire-based tool that measures the everyday manifestations of multi-domain cognitive impairments in early-stage Parkinson's disease (PD).

Background: Neuropsychological tests indicate that, even during early stages of PD, patients exhibit impairments in memory, attention and executive function. How these changes affect cognitive functioning in patients' everyday lives, however, is largely unknown. The Parkinson's Disease Everyday Cognition Questionnaire (PD-ECQ) is being developed to address this issue of validity and clinical relevance.

Methods: A telephone questionnaire consisting of 136 items was given to a group of patients with PD (N=60) and healthy age-matched controls (N=33). The groups were screened for dementia and matched for years in education. Items measured everyday cognitive functioning, for example "How often do you forget things people tell you?" and "How often do you begin one task and get distracted into doing something else?". Participants were asked to repeat the questionnaire, to assess reliability, and asked to complete a battery of neuropsychological tasks, to assess validity. Partners or relatives were asked to complete a reduced-item version of the questionnaire.

Results: Thirty-five questions were selected from the larger questionnaire to form the PD-ECQ. Preliminary data suggest the tool successfully measures the everyday manifestations of cognitive dysfunction in early-stage PD. For example, the group with PD made more overt attentional errors ($p<.001$) than the control group.

Conclusions: The PD-ECQ is a valuable and easy to administer assessment. The tool is currently being validated in a longitudinal study of the incidence of cognitive impairment in people with PD.

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Pattern of cortical thickness associated with cognitive impairment and dementia in Parkinson's disease

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Objective: To explore cortical thickness changes in Parkinson's disease (PD) patients with mild cognitive impairment (MCI) and dementia (PDD), compared to cognitively intact (CgInt) patients and healthy controls.

Background: PD patients eventually develop dementia. Knowledge on the neural bases involved in the transition from MCI to PDD would help to detect and treat earlier patients in progression to dementia. Cortical thickness, a more reliable measure of atrophy than grey matter volume changes, seems specially sensitive to detect early neocortical degeneration.

Methods: We randomly selected 44 PD patients (15 CgInt, 15 PD-MCI, 14 PDD; age 73.2±5 years, education 9.4±4 years, disease duration 7.2±4 years) and 12 age- and education-matched healthy controls. Cognitive status was assessed by the DSM-IV criteria for dementia, the Clinical Dementia Rating Scale, and neuropsychological testing. Cortical parcelation and cortical thickness quantification were assessed by using 3T MRI (3D-FFE) and the Freesurfer software in a GRID environment. One-way ANOVA and t-tests were used to study differences between groups.

Results: Significant cortical thickness decline was observed bilaterally in the enthorrinal/parahipocampal cortex and in the precuneus when PDD patients were compared with both PD-CgInt and PD-MCI groups ($p<0.001$, uncorrected). In addition, a decrease in cortical thickness was also observed in the left posterior cingulate gyrus, right temporo-parieto-occipital areas, and right medial-orbital frontal cortex ($p<0.001$, uncorrected).

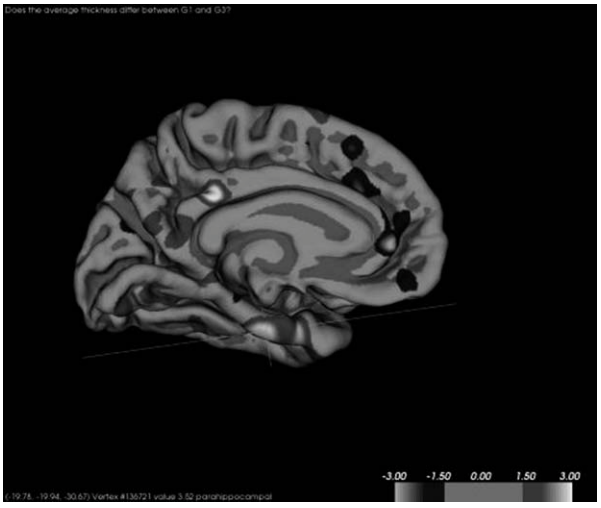

FIG. 1 (422).

Conclusions: Selective decrease of cortical thickness in PDD patients was characterized by a predominant medial temporal and posterior cortical atrophy, which reinforces the importance of posterior cortical versus frontal-striatal disturbances in the progression to dementia in PD.

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Regional frontal lobe cortical atrophy in Parkinson's disease without dementia

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Objective: to assess the regional frontal lobe cortical atrophy in non-demented Parkinson's disease (PD) patients using high-resolution structural magnetic resonance imaging (MRI).

Background: the extension of neurodegenerative process in PD goes beyond the basal ganglia and underlies clinical motor and non-motor symptoms of the disease. Despite the observation that frontal lobe dysfunctions may be identified since the early clinical stages of PD, the related brain pathology of these altered processes are not fully understood at present.

Methods: Fifteen PD patients and 13 age- and sex-matched healthy volunteers (HV) underwent a 3.0 T MRI and the Mini Mental State Examination (MMSE). PD patients were also submitted to the Unified Parkinson's Disease Rating Scale part III (UPDRS-III). Using an automated reconstruction of the brain cortical surface (Freesurfer), we measured the differences in the right and left regional frontal lobe cortical thickness (CTh) between PD and HV. A correction for multiple comparisons was applied with a significant level of $p=0.002$.

Results: there was no evidence of dementia in PD patients (MMSE 27.0±1.9). The mean disease duration was 5.3±3.0 years (range 2-12). The mean score of UPDRS part III was 13 (±7.7, 4-29). Among all frontal cortical areas, we found a significant difference ($p=0.0007$) in the CTh of the right rostral middle frontal gyrus. A trend toward significance was also observed in the CTh of the left rostral middle frontal gyrus ($p=0.008$).

Conclusions: our preliminary results provide further evidence that frontal lobe cortical atrophy occurs early during PD. These results show that in non-demented PD patients the prefrontal cortex (i.e., areas 9, 10, 46) is precociously affected, as suggested by the dysexecutive syndrome occurring since the early stages of the disease.

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Study about cognitive performances in the patients with Parkinson's disease treated with neurotrophic therapy

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Objective: The aim of this study was to investigate the evolution of cognitive function in patients diagnosed with Parkinson's disease (PD) and treated with neurotrophic factors.

Background: PD clinical features comprise both motor and non-motor manifestations.Cognitive dysfunction is common in PD, but are frequently overlooked or undertreated.

Methods: We studied 42 patients (19 men and 23 women) diagnosed with PD in stage one or two on Hoehn-Yahr Scale, aged between 65-75 years, at least 10 years of education and 5 years duration of the disease.The patients received treatment with L-Dopa 600-750 mg/day (12 patients), L-Dopa 400 mg/day associated with dopamine agonists (16 patients) and only dopamine agonists (14 patients).In addition to this treatment they received neuro trofic factor (Cerebrolysin) 10 ml/day, 10 days/month for 6 months. Cognitive function was evaluated by Mini Mental State Examination (MMSE) and Cambridge Cognitive Examination (CAMCOG). The patients were examined at baseline, after 3 months and 6 months later.The results were analysed by Student Test.

Results: In the beginning of the study all patients presented cognitive dysfunction and they obtained scores below those corresponding to their age and education level on MMSE and CAMCOG. After 3 months, the results were better, but not significantly statistic.In the end of the study, they showed significantly statistic better performances in comparison to baseline.

Conclusions: The treatment with neurotrophic factors improved cognitive performances in patients with PD, but we consider that further more accurate studies are needed in order to decide if neurotrophic factors represent a hope for these patients.

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Convolution of cognitive load and walking along curved paths exacerbates freezing of gait in Parkinson's disease

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Objective: To test if cognitive loading increases the propensity for Freezing Of Gait (FOG) among patients with Parkinson's disease (PD) and if walking along curved paths (an action that putatively places high demands on bilateral coordination), further exaggerates the risk for FOG.

Background: An association between cognitive impairments and FOG has been observed in PD. Bilateral coordination of gait in PD patients with freezing (PD+FOG) was also found to be impaired.

Methods: In preliminary evaluation, 8 PD+FOG patients (age: 68.9±5.1 yrs; disease duration: 11.6±6.1; H&Y scale: 2.7±0.4; UPDRS motor part: 34.8±11.4) were tested during the "Off" state. Patients performed two gait tasks at a self-selected pace: 1) 2 X 36 m long straight line; and 2) 10 X ~7 m figure 8 shaped laps. These tasks were also executed while performing dual tasking (DT), i.e., serial 3 subtractions. Post hoc analysis of mute video segments determined the number of FOG episodes and their duration.

Results: Three patients did not exhibit even one FOG episode during the experiments. For the other five, the number of FOG was higher during 8 shaped paths, and their duration increased in response to DT. For all subjects, mobility as expressed by gait speed, was compromised in the DT tasks (see table 1).

Conclusions: Although a limited number of subjects were evaluated, the data suggest that curved trajectories are more likely to trigger FOG episodes in PD patients. Cognitive load leads to an increase in FOG 'burden' on mobility, in particular if curved trajectories are involved. Further research should investigate why the most challenging task did not invoke FOG in a subset of PD+FOG patients and unravel the intriguing relationship between FOG, cognitive function and walking trajectory.

TABLE 1 (425). *Characteristics of FOG episodes and patient mobility*

	Straight Line Walking			Figure 8 shaped walking		
	Usual	Dual Task	P value*	Usual	Dual Task	P value*
Number of FOG episodes	5	10	n/a	26	46	n/a
Mean duration of FOG episodes ± SEM (sec)	0.5± 0.3	2.8± 2.5	0.414	5.0± 3.0	15.7± 3.9	0.043
Inter-ictal gait speed ± SEM (m/sec)	0.99± 0.05	0.67± 0.05	0.012	0.51± 0.03	0.37± 0.04	0.028

* Non parametric analysis.

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A funny thing happened on the way to the conference: Perception of humor in Parkinson's disease

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Objective: As a first step towards utilizing humor as a coping tool in a PD population, we are conducting an ongoing study on its perception by PD patients in comparison with a healthy control.

Background: Situations and content perceived as humoristic may help patients cope with chronic disease ramifications and symptoms such as pain, discomfort and depression. Frontal and temporal lobes in the brain and the limbic system are involved in humor comprehension and are also areas damaged in Parkinson's disease (PD).

Methods: A study of 7 PD patients (5 men, 2 women, age 63.7 ± 9.3 education years 15.7±2.36, illness duration 7.8 ±4.8,) and 7 healthy control (5 women, 2 men, age 57.6 ± 6.8, average education years 19±2.44), not demented according to Montreal Cognitive Assessment (MoCa) > 26. Participants underwent Unified Parkinson's Disease Rating Scale (UPDRS), cognitive screening (Frontal Assessment Battery (FAB) + MoCa) and completed questionnaires: Geriatric Depression Scale (GDS 15), Spielberger Trait –State Anxiety Inventory, Parkinson's disease quality of life (PDQ 8), Sense of Humor Questionnaire (SHQ- 6). Patients were also asked to rate as humorous 3 non verbal cartoons with punch lines, 3 audio 3 visual presentations, portraying different humor styles (blatant, subtle, macabre).

Results: No significant differences were found in FAB and MoCa scores. Significant differences were demonstrated in GDS15 education and age. Significant differences in appreciation of humoristic content were demonstrated in 2/3 video presentations (p=0.04, p=0.002). No significant differences were noted in audio and cartoon presentations.

Conclusions: PD patients experienced more difficulties in perceiving video content as humoristic than healthy controls probably due to the attention load required in watching videos. It appears a less effective medium for utilizing humor in PD, although age and education might also impact.

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Gender differences in motor and non-motor clinical manifestation of Parkinson's disease–analysis of the E.W.O study

I. Rektorova, M. Bares, R. Jech, K. Farnikova, I. Rektor, J. Roth, E. Ruzicka, P. Kanovsky, K. Chroust, T. Pavlik (Brno, Czech Republic)

Objective: To compare the differences between men and women with respect to both motor and non-motor clinical manifestation of Parkinson's disease (PD) based on the results from a national, multicenter, epidemiological E.W.O study (Epidemiology of Wearing-Off symptoms in PD patients chronically treated with L-dopa for ≤ 10 years).

Background: Some gender differences have been decribed in PD including motor and non-motor symptoms manifestation, and response to treatment.

Methods: Data analyzed from 563 consecutive PD patients (219 women, 344 men); detailed records on medical and drug history, clinicians' assessment, and WOQ-9 questionnaire used. Additional testing of non-motor symptoms of PD (as measured by NMS30, MADRS, HAMA, MOCA) performed by movement disorders specialists in 217 out of 563 patients (83 women, 34 men).

Results: No differences between both groups found with respect to demographic data, symptoms manifestation, Hoehn and Yahr (H-Y) stage, prevalence of wearing-off symptoms. Median L-dopa equivalent dose was similar in both groups. Regarding NMS 30 results, both groups differed significantly in the subscore evaluating sexual dysfunctions (indicated by 26% of women and 45.5% of men; p=0.006). When selected questions from the questionnaire were taken into consideration, drooling and excessive saliva was indicated significantly more frequently in men compared to women (18.1% of women and 32.1% of men; p=0.027) whilst women expressed sad/ depressed mood feelings significantly more frequently than men (50.6% of women and 33.6% of men; p=0.016). Concerning other scales, no significant differences were observed between both sexes.

Conclusions: We found no differences between men and women with respect to motor manifestation of PD or the prevalence of wearing off phenomena. Regarding non-motor outcomes, slight differences were identified in the presence of sexual dysfunction and drooling (more frequent in men), and sad/ depressed mood feelings (more frequent in women).

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Non-motor symptoms in 217 patients with Parkinson's disease as measured by MOCA and MADRS–analysis of the E.W.O. study

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Objective: To assess depressive and cognitive symptoms of Parkinson's disease (PD) using Montgomery and Asberg Depression Rating Scale (MADRS), and Montreal Cognitive Assessment (MOCA) based on the results from a national, multicenter, epidemiological E.W.O study (Epidemiology of Wearing-Off symptoms in PD patients chronically treated with L-dopa for ≤10 years).

Background: Non-motor symptoms of PD have drawn special attention since they significantly impact on patients' quality of life.

Methods: Data analyzed from 217 out of 563 consecutive PD patients (83 women, 34 men); detailed records on medical and drug history, clinicians' assessment, WOQ-9 questionnaire, NMS30, MADRS, HAMA, MOCA used.

Results: Sadness, sleep problems, inner tension, and inability to concentrate were the most frequent depressive symptoms. Only 17.1% of patients had MADRS score > 14. Patients with the first symptom manifestation on the right side had higher MADRS scores compared to those with the left-sided or bilateral manifestations (results adjusted for current Hoehn and Yahr [H-Y] score; p=0.015). MADRS scores were significantly influenced only by the H-Y score with two peaks at stage 1 and 3 (p=0.005), and they significantly correlated with HAMA scores (r=0.681; p<0.001), NMS30 scores (r=0.645; p<0.001), and MOCA scores (p=0.023, r=-0.155). Current intake of DA agonists or its daily dose had no impact on MADRS scores. The most frequent cognitive deficits included impairment of delayed recall and visuospatial/ executive functions. 43.8 % of patients had MOCA scores <26. MOCA scores were significantly correlated with patients' age (p<0.001, r=-0.308), MADRS scores and NMS30 scores (p=0.010, r=-0.224). MOCA results were not influenced by the cumulative dose of any class of antiparkinsonian medication.

Conclusions: Using the suggested cut-off scores, MADRS revealed depression in 17%, and MOCA revealed dementia in 43.8% of our patients. We demonstrated a significant effect of laterality of the first motor symptom manifestation, and H-Y score on the MADRS results, while the current intake or daily dose of DA agonists had no impact on MADRS. Antiparkinsonian medication did not influence MOCA results.

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Emotion recognition in early Parkinson's disease and its relation with cognitive functioning

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Objective: The goal of this study was to investigate emotion recognition in a cohort of early diagnosed Parkinson's disease and to

investigate its relationship with medication and with cognitive functioning.

Background: Due to the fact that the neural correlates of emotion recognition are involved in Parkinson's disease (PD) pathology, emotion recognition in this disease is now becoming an important subject of study. Even though emotion recognition deficits have already been reported, there is contradictory evidence regarding the specificity of those deficits. While some authors have described specific deficits in anger, others have found deficits in other emotions such as disgust. The differences between these studies may be related to the variability of tasks and the lack of control of confounding factors such as medication or overall cognitive ability.

Methods: We compared the performance of patients with early PD receiving medication (n=13), patients with early PD receiving no medication (n=15), and matched healthy controls (n =9) with an emotion recognition test and a complete neuropsychological battery. The experimental task used in this study was the Emotion Hexagon Task. Patients were also assessed with a test of recognition of famous faces to control for face processing and with a complete cognitive battery.

Results: Significant differences between PD patients (both medicated and unmedicated) and normal controls were found on the recognition of most emotions assessed, including faces portraying happiness, surprise, anger, fear and sadness. When performance was compared between PD patients with and without dopaminergic medication, no significant differences were found. Within the patient group, significant correlations were found between the emotion hexagon total score and cognitive performance measured by tests of attention, memory, executive functions and language.

Conclusions: Significant differences were found on the capacity to recognize facial emotions in patients with early Parkinson's disease. The failure in the emotion recognition may be related to performance in other cognitive tasks.

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Impairments in social cognition in early medicated and unmedicated Parkinson's disease

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Objective: The objective of the present study was to assess social cognition in patients with early Parkinson's disease (PD).

Background: Previous research has shown social interaction problems in patients with Parkinson's disease. Originally based on social psychology, social cognition intends to explore the way in which the actual or implied presence of others influences thoughts, feelings, and behavior. More specifically, Theory of Mind (ToM) refers to the ability to infer others' mental states, including intentions and feelings, and is considered to be a critical part of social cognition. Studies investigating ToM in individuals with PD have yielded equivocal findings. A possible reason for this variability may lie in several methodological issues such as overlooking of potentially different profiles within the PD population, and the disregard of important clinical variables such as disease severity and dopaminergic medication intake.

Methods: In the present study, we compared medicated (n=16) and unmedicated (n=20) patients with early PD and a control group of healthy subjects (n=38). Patients were assessed with two ToM tasks designed to differentially detect subtle deficits in the affective and cognitive aspects of ToM, as well as with a battery of classical executive tests.

Results: Our results are the first to indicate that ToM is affected in the early stages of PD. Such deficits seem to be related to the cognitive aspects of this domain, and were not related with performance on executive functioning nor depression.

Conclusions: It is suggested that the frontostriatal circuits affected in PD are involved in social behavior.

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The relationship between executive functions and fluid intelligence in early Parkinson's disease

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Objective: In the present study we aimed to determine the role of fluid intelligence in frontal deficits shown by patients with Parkinson's disease.

Background: Deficits in cognitive functions dependent upon the integrity of the prefrontal cortex are common in Parkinson's disease. In a recent study (Roca, 2009) we showed that fluid intelligence (g) is a substantial contributor to frontal deficits. For some classical executive tasks,frontal deficits were entirely explained by g. However, on a second set of frontal tasks, deficits remained even after fluid intelligence was statistically controlled. These latter tasks were associated particularly with anterior brain damage and included tests of Theory of Mind (Faux Pas) and Multitasking (Hotel Task), among others.

Methods: By assessing a group of patients in the early stages of the disease (n=32) and a group of control subjects (n=22) with the aforementioned frontal tests, using the Raven Progressive Matrices to assess fluid intelligence.

Results: In line with our previous results, the significant differences found in some classical executive tests, such as the WCST and Verbal Fluency, became non-significant once fluid intelligence was introduced as a covariate. However, for tasks of Theory of Mind (Mind in the eyes) and multitasking (hotel task), deficits remained after fluid intelligence was statistically controlled.

Conclusions: The present results suggest that clinical assessment of neuropsychological deficits in PD should include tests of fluid intelligence, supplemented with one or more specific tasks that allow for the assessment of residual frontal deficits associated with Theory of Mind and Multitasking.

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Effect of levadopa on the working memory in Parkinson's disease: An fMRI study

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Objective: This study relates dopaminergic administration to short term memory loss in Parkinson's disease patients.

Background: Non motor effects of dopa therapy on functional state of brain remains obscure.

Methods: 11 patients {(mean age 56.92±15 years, disease duration 4.81±3.2years) with early PD and Hohen and Yahr stage 1.5±0.79} and 8 controls (mean age 48.6±5.24 years) were recruited. The patients rated on UPDRS III as 20.5±11.0 and MMSE 27.45±2.58. L-Dopa equivalent intake was 394.79±190.80mg. Functional scans were conducted in both "off" state and "on" states. The subjects observed the 24 pictures presented for 2000ms each as target images that were to be recollected and registered using Superlab software. Blood oxygen

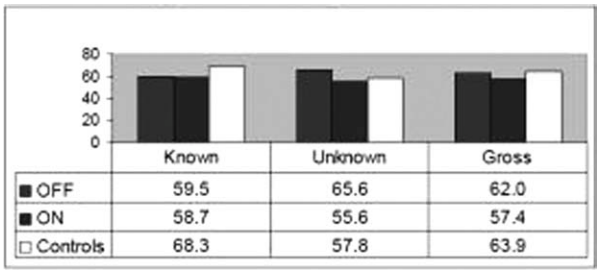

FIG. 1 (432). Bar diagram representing the memory response for known and unknown images; in "on" and "off" states in patients compared to controls.

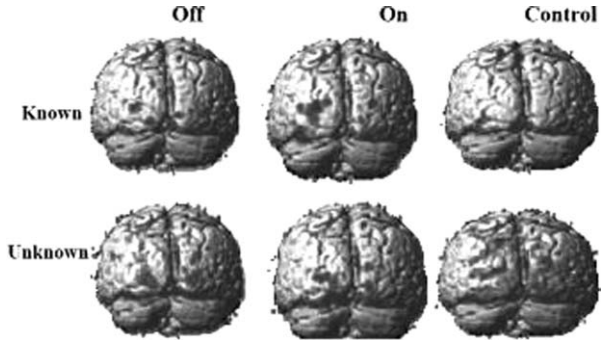

FIG. 2 (432). The comparative BOLD activation pattern in the three groups.

level dependent imaging using single-shot EPI in the whole brain was conducted on 1.5 T. One way ANOVA ($p < 0.001$)) was used for group analysis, while paired t-test was applied for "on" and "off" states.

Results: The activation pattern in PD patients and controls for known and unknown images are depicted in Fig 3. It seems the aPFC a memory buffer (BA 7) undergoes degeneration in PD patients. The patients recruit more of the occipital gyrus in observing the images as compared to controls. The superior temporal gyrus (BA 21, 22) could be attributed for registering new facts. The cognitive deficit could be attributed to loss of neurons in the prefrontal cortex specifically BA 7, 10 and 18.

Conclusions: The dopaminergic therapy has no role in memory enhancement.

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Is L-Dopa response in Parkinson's disease gender dependent? An fMRI study

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Objective: We wish to determine whether dopaminergic therapy is gender influenced.

Background: The striatal dopamine depletion in Parkinson's disease (PD) leads to motor dysfunction. The abnormal activation of Primary motor cortex (M1) could be normalized to an extent by dopaminergic replacement.

Methods: Subjects (details as in table 1), were recruited from the movement disorder clinic of our institute. Two functional MRI scans were conducted in supine position at 1.5T (using head coil on Siemen's Avanto Scanner); one in the practically "off" state (i.e. after 12 hours of last dopa administration) and the other after 2 hours of dopa administration in the "on" state. Single-shot echo planar images (EPI) were acquired to study the Blood oxygen level dependent (BOLD) effects in the whole brain. (slices: 31, slice thickness 4.0 mm; TR/TE: 4000/44 ms, FOV: 230mm, resolution: 128 x 128). The block design was a simple finger tapping action during the active state, and rest in baseline. Pre- and post-processing was carried out on an offline server using SPM2. One way ANOVA ($p<0.001$, cluster threshold 5) was used for group analysis, while paired t-test was carried out for comparing the results during "on" and "off" states.

Results: The "off-state" in males showed activation in the left Pre- and post-central gyrus (BA6) apart from the left superior frontal gyrus (BA8) and left inferior parietal lobule (BA40) and right superior temporal gyrus (BA42). During the "on-state" maximum activation was observed

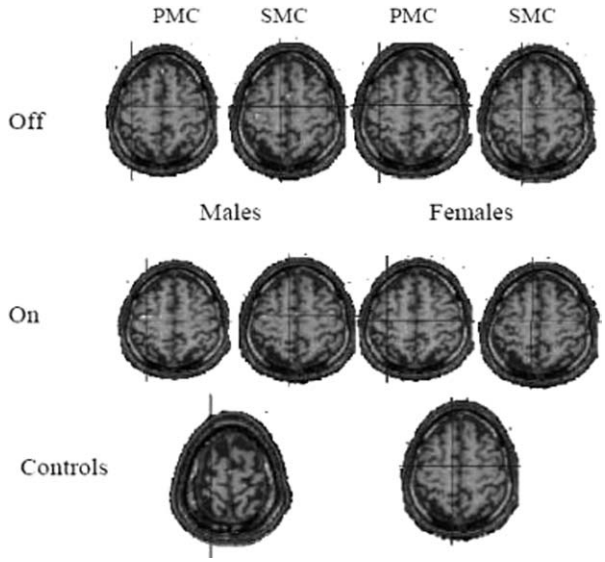

FIG. 2 (433). The brain activation pattern showing difference in activity in the primary motor cortex (PMC) and supplementary motor corte (SMC) in response to dopaminergic administration.

in the left pre-central gyrus (BA4) and left middle, medial and superior frontal gyri (BA6). In females the cerebellar activation was observed even in the "off-state". Major activation was observed in the off state in bi-hemispheric SMA (BA6) and occipital gyri (BA18, 19) though left M1(BA4), was also activated. The females in the on-state showed improved M1 activation (BA4) and reduced SMA (BA6) interestingly, right SMA was suppressed. The cerebellar activation was present.

Conclusions: It seems males respond better to dopaminergic therapy.

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Dopamine dysregulation syndrome and its relationship to executive functioning in idiopathic Parkinson's disease

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Objective: To present a case of dopamine dysregulation syndrome (DDS) in an individual with early-onset Parkinson's disease (PD), focusing on neurocognitive function (particularly executive functions) as a means to further understand DDS.

Background: DDS is a relatively rare yet well-documented neuropsychiatric condition arising in a minority of individuals with PD, associated with dopamine overuse. Various conceptualizations of DDS have been proposed, ranging from those focused on premorbid risk factors to addiction theory. A further possibility (less frequently discussed) is that DDS is associated with behavior dysregulation occurring secondary to executive dysfunction, which frequently occurs in individuals with PD-related cognitive impairment.

Methods: The patient is a 57-year-old, right-handed gentleman with PD onset at age 40. He had a long history of DDS symptoms including transvestic fetishism, punding (i.e., 'walkabouts'), and exhibitionism. Premorbid baseline was high, including 2 Master's degrees and prior work as an engineer/inventor. Although he could understand and articulate the negative consequences of his behavior, he

Type	Subjects	No. of subjects recruited	Age	Disease Duration	Mean daily dopa intake	Stage of the disease	MMSE	UPDRS III
PD	18	11 M, 7 F	59.8 ± 14.3	6.53 ± 3.5	712.5 ± 308.5 mg	H & Y 1.7 ± 0.61	27.2 ± 2.67	20.5 ± 10.8
Controls	8	5M 3F	48.6 ± 5.2	-	-	-	29.0 ± 1.0	-

FIG. 1 (433).

reported that "in the moment" of dopamine overuse he lacked impulse control or judgment to desist the behaviors. The patient underwent comprehensive neuropsychological examination in the context of pre-surgical workup for deep brain stimulator (DBS) surgery.

Results: Premorbid intellectual functioning was estimated to be in the superior range, with most current cognitive functions being average, albeit a decline from superior baseline. Both self-report and family scores on the Frontal Systems Behavior Scales indicated significant symptoms of disinhibition and cognitive-executive dysfunction. However, neuropsychometric scores of executive functions were largely average (including abstract reasoning, conceptualization, and inhibition), with those in the low average range due to speed of completion, not accuracy of performance.

Conclusions: In this case, DDS could not be explained by executive dysfunction arising in the context of PD. Here, DDS might be conceptualized as a state (i.e., during dopamine intoxication) rather than trait (i.e., due to interaction of dopamine overuse and persistent cognitive dysfunction) phenomenon. Implications for understanding of DDS are discussed.

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Withdrawn by Author

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Neuropsychological assessment of monolingual Spanish speaking Parkinson's disease patients in the United States pre and post STN-DBS

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Objective: 1. Present neuropsychological outcomes pre and post bilateral subthalamic nucleus deep brain stimulation (STN-DBS) for monolingual Spanish speaking patients diagnosed with Parkinson's disease (PD) and 2. Discuss the significant health disparity in the field of neuropsychology with this population.

Background: A consensus is underway regarding the cognitive changes post STN-DBS in the English speaking community of the US, with declines reported in verbal fluency, verbal memory, and visuo-spatial skills. However, a significant gap exists in the STN-DBS outcome research of monolingual Spanish-speaking PD patients in the United States.

Methods: Utilizing a comprehensive Spanish neuropsychological battery, neurocognitive functioning prior to STN-DBS was examined in 14 monolingual Spanish-speaking PD patients recruited from the Parkinson's Disease and Movement Disorders Clinic at Baylor College of Medicine. Our post-operative outcome study is on-going; we will report on a subset of these patients who have undergone post-surgical neuropsychological and neurological evaluations.

Results: Our sample was comprised of 8 males and 6 females of Hispanic descent. All participants were right-handed, with an average age of 55 years, 13 years of education, and 10 years duration of PD at baseline. Prior to surgery, 29% percent reported a mild history of depression, 35% experienced hallucinations and 14% reported delusions. Information regarding levodopa and psychotropic medications for this sample will be presented. Motor improvement was found for those tested approximately 18 months post STN-DBS. A subset of 3 patients, who completed the post-operative neuropsychological evaluation to date, revealed declines in verbal fluency and verbal memory. Reliable Change Indexes (RCIs) for neuropsychological outcome measures will be presented. Moreover, an introduction to the Spanish neuropsychological measures administered will be provided.

Conclusions: Monolingual Spanish speaking candidates for STN-DBS should be evaluated using Spanish neuropsychological measures which are currently available and being validated and normed for this population. Patients should be counseled regarding the possible cognitive changes associated with this surgical procedure.

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fMRI neurofeedback and its effect on Parkinson's disease

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Objective: Neurofeedback is a functional magnetic resonance imaging (fMRI) technique where the participants are trained to influence local brain activity while receiving real-time feedback on their performance. In the present study our aim was to train patients with Parkinson's disease (PD) to increase activity in the supplementary motor complex (SMC) and assess the effects of successful upregulation on motor and cognitive tasks and everyday functioning.

Background: PD patients show reduced metabolic activity of the SMC that is directly related to impaired motor output (Nachev et al., Nature Neuroscience 2008). All parts of the SMC are connected to the basal ganglia which is primarily affected in PD.

Methods: Four patients (2M: 2F) with PD on medication between the ages of 39-63 years and in the first 3 stages of the disease participated in the experiment. We used MRI compatible surface EMG to measure muscle activity during fMRI. We identified the individuals SMC through a functional localiser experiment (Johnston et al., Neuroimage 2010) with hand movements. In the next two 5 minute runs the participant was asked to increase the signal in the SMA during periods of 20 seconds without active movement, alternating with rest periods. They were also assessed before and after the scan on their mood and motor speed.

Results: All patients were able to increase activity in the SMC after about 5 minutes of receiving feedback in the scanner and reported using imagery of complex movements to control SMC activation. A comparison of the pre and post assessments outside the scanner showed a slight improvement in motor speed. One patient carried on the exercise at home for two weeks and assessed himself at the end of every week on a particular activity that he found difficult. He reported that he found himself improving on the task. The other patients scanned will start practicing the technique at home. All participants will undergo a refresher session of neurofeedback before the final assessment. We are currently recruiting more participants.

Conclusions: Patients with Parkinson's disease are able to control activity in higher motor areas through neurofeedback training. Preliminary outcome data suggest that this training may contribute to improvement of motor fluency and everyday activities, especially when the imagery strategies are practiced at home.

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Effects of continuous intraduodenal levodopa infusion therapy on cognition and depression in patients with advanced Parkinson's disease

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Objective: To investigate how continuous dopaminergic stimulation (CDS) delivered by intraduodenal L-Dopa therapy affects cognition and depression in patients with advanced Parkinson's disease.

Background: Intraduodenal CDS seems become increasingly important in the management of all aspects including the non-motor symptoms of advanced Parkinson's disease (PD).

Methods: 11 patients participate in this investigation. Inclusion criteria: CDS for at least 6 months continuously; ability to walk a few steps; no severely limiting co-morbidities. Cognition is investigated with the PDQ39 (questions 30-33), MMSE and UPDRS subpart I. Depression is investigated with the geriatric depression scale (GDS) and compared with questions 17-19 of the PDQ39. The concurrent change in antidepressants is reported.

Results: The following changes are observed comparing the scores before the switch and 6 months later: a) Cognition: PDQ39 (questions 30-33): improvement in 10 patients, 1 patient remains the same (patient on antidepressants); MMSE: in 10 patients either no change or improvement of up to 3 points; 1 patient presents with 1 point

less after 6 months; UPDRS part I: improvement in 9 patients, no changes in 1 patient, 1 patient presents with a slight worsening of the score (patient on antidepressants). b) Depression: according to GDS positive changes in all 11 patients, according to PDQ39 (questions 17-19) positive changes in 9 patients, no change in 2 patients (one with score 0, the other with score 1). Before the switch to intraduodenal CDS 9 patients present with possible depression according to GDS and 5 patients take antidepressants; afterwards 3 of the 9 patients present with possible depression and 2 of the 5 continue with their antidepressant agents.

Conclusions: The results suggest that L-Dopa therapy delivered intraduodenally by CDS may influence cognition and depression positively, i.e. the mode of delivery may play a part in the management of these non-motor symptoms. However, it is not clear how an improvement in depression influences cognition and vice versa.

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Is appearance of applause sign conected with cognitive deficit in Parkinson's disease patients

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Objective: To analyse correlation of applause sign and cognitive deficits in patients with idiopathic Parkinson's disease.

Background: Applause sign is test used in patients with neurodegenerative disease with subcortical structure lesion. Patient is asked to clap only 3 times as quickly as possible and after it was showen by examiner. Test is negative (normal) if patient clap only 3 times and positive (pathological) if clap more than 3 times.

Methods: Patients with idiopathic Parkinson's disease were tested with Dementia Rating Scale (DRS) for cognitive deficit and made aplausse sign test. Depressed patients were excluded from study using Geriatric Depression Scale (GDS). Data were analysed using method of descriptive statistic, Spearman coefficient of correlation, analysis of variance and student t-test with $p<0.05$.

Results: There were 26 patients, 12 female and 14 male, average age 71,4 years (in the range from 56-86 years). Eighteen of them had negativne applause sign (69%) and 8 of them had positive sign (31%). Patients with negative applause sign had average disease duration of 4,33 years, while those with positive sign had 6,13 years. There is no statistical difference between this two group of patients ($t(24)=0.817$, $p>0.05$). Patients with negative applaus sign had average DRS score 127,7±10,4, while those with positive sign had 120.6±14.7. There is no correlation between applause sign and DRS score ($r_s=-0.234$, $p>0.05$), neither between applause sign and subscales of DRS (attention $r_s=-0.045$, $p>0.05$; initiation/perseveration $r_s=-0.298$, $p>0.05$; construction $r_s=-0.277$,$p>0.05$; conceptualisation $r_s=-0.106$, $p>0.05$; memory $r_s=-0.078$, $p>0.05$).

Conclusions: Our data suggest that applause sign is not conected with deficit in executive function, attention, initiation/perseveration, conceptualisation or memory in patients with Parkinson's disease.

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The relationship between theory of mind and decision-making in patients with early Parkinson's disease

M. Roca, T. Torralva, E. Gleichgerrcht, G.J. Gomez Arevalo, A.R. Chade, O.S. Gershanik, F. Manes (Capital Federal, Buenos Aires, Argentina)

Objective: The goal of the present study was to investigate the relationship between theory of mind (TOM) and decision-making deficits in a group of early Parkinson's disease (PD) patients.

Background: Theory of Mind (ToM) and decision-making deficits have been described in patients with Parkinson's disease (PD), however the relationship between both deficits in this pathology remains unclear.

Methods: We studied a group of patients with early PD (n=28) and a group of matched normal controls (n=22) on the Iowa Gambling Task (IGT) of decision-making, and the "Reading the Mind in the Eyes" and "Faux pas" tests of ToM.

Results: As predicted, the PD group was impaired in reading the mind in the eyes ($p<0.05$), the Faux Pas test ($p<0.01$) and the Iowa Gambling Task ($p=0.01$). Performance measures from ToM were not associated with each other or with Iowa Gambling Task performance.

Conclusions: This finding suggests that both Theory of Mind tasks may be assessing different subcomponents of this function and that, in early PD, deficits in ToM and Decision Making may have distinct but additive effects upon the development of social behavior.

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Comparing the usefulness of the INECO frontal screening and the frontal assessment battery (FAB) in early Parkinson's disease

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Objective: The goal of our study was to compare the utility of the INECO Frontal Screening (IFS) (Torralva et al. 2009) and the Frontal Assessment Battery (FAB) (Dubois et al. 2000) in the detection of executive dysfunction in a group of early Parkinson's disease (PD) patients.

Background: Although several brief sensitive screening tools are available to detect cognitive dysfunction in Parkinson's disease, few tools have been developed exclusively to quickly assess executive function, which is the most common cognitive dysfunction in early PD. The IFS and the FAB are two brief screening tests known to reflect executive functioning.

Methods: A group of early PD patients (n=21) and a group of healthy controls (n=28) were assessed with a general cognitive screening test, as well as the IFS and the FAB.

Results: Using previously proposed cut-off scores, the IFS showed a sensitivity of 71.3% and a specificity of 89.3%. While the FAB showed a specificity of 100%, its sensitivity for the detection of executive deficits in PD was as low as 38.1%. The discriminatory accuracy between PD patients and controls, as determined by the area under the ROC curve, was higher for the IFS (.86, SE=.05) than for the FAB (0.82, SE=.06). Both tests correlated significantly with classical executive tasks.

Conclusions: While both the IFS and the FAB are brief, sensitive, and specific tools for the detection of early executive dysfunction, the IFS is recommended for assessment of PD patients because of its superior capacity to detect executive impairment.

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Time-course and qualitative analysis of unconstrained oral naming abilities in non-demented Parkinson's individuals

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Objective: The goal of the present study was to provide a quantitative and qualitative analysis of the word production of patients with Parkinson's disease (PD) and of control matched individuals looking at the characteristics of words produced, their time-course evolution and their correlation with executive deficits.

Background: Semantic and phonological oral naming tests (ONT) are often used to assess cognitive dysfunction in PD. In general, results have shown that patients with PD produced fewer words in both tasks than control matched individuals, even in initial stages of this illness. However, results of studies that have analyzed qualita-

tively the PD's word production are contradictories. While some studies have shown that the average size of phonemic and semantic clusters do not seem to be reduced in PD, other studies have shown that switching and clustering are reduced in PD's patients. Theses contradictories results could be partially explained by the different criteria used (semantic and phonologic) for its evaluation.

Methods: For avoiding this aspect, we have decided to use an unconstrained oral naming task (UON). In this task, 10 non-demented PD and 10 control individuals, matched for gender, age and education, are invited to produce words within a limited time period (150 second), without having to respect any production criterion. Participants also have to perform a short neuropsychological battery, which was also used to evaluate the executive functioning level of participants.

Results: Many different aspects of word production were analyzed, such as number of words, frequency, word familiarity, word concreteness, grammatical class, word naming strategy used (number and size of clusters) and the time course analysis (the number of words produced for each 30 seconds period). Moreover, analysis production was correlated to their neuropsychological profile.

Conclusions: In general, results showed that while clustering seems not to be impaired in PD's patient, switching seems to be impaired. The results of this qualitative analysis are consistent with the proposition according to which the oral naming production of Parkinson's patients reflects a disruption of frontal-basal ganglia circuits mediating efficient shifting between categories.

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Clinical comparison of early onset PD vs late onset PD

B. Ts, G. Baigalmaa, B. Handsuren, J. Ariunaa (Ulaanbaatar, Mongolia)

Objective: To compare baseline clinical characteristics in early onset versus late onset Parkinson's disease and evaluate whether age at onset was predictive of the subsequent progression of clinical symptoms.

Background: PD is characterized by clinical heterogeneity, association of signs and symptoms, and rate of progression depending on age at onset. It is reported that motor deficit, quality of life and cognitive impairment in patients with early onset PD (EOPD) less severe than those in patients with late onset PD (LOPD).

Methods: 117 patients with PD in according to criteria of the UKBBPD have been enrolled. The patients were assessed using Hoehn and Yahr stage, UPDRS II and III parts, Mini Mental Status Examination (MMSE), de Boer's quality of life (QOL) questionnaire, and Modified Beck Depression Inventory (BDI). The patients with early onset PD (EOPD) and late onset of disease (LOPD) were classified using cut-off age at onset 55 years below or more.

Results: Total 117 patients: 48 male (40.2%) and 69 female (59.8%) were included. 54 EOPD (45.7%) patients (mean age at onset, 52.1±7.9 yrs; range, 33-55; mean duration of PD, 7.5±4.7 yrs) were matched with 46 LOPD (54.3%) patients (mean age at onset,70.2±6.0 yrs; range, 56-88; mean duration of PD, 4.2±2.3 yrs). Nonparametric Mann-Whitney test revealed that EOPD patients had younger aged ($p<0.001$), longer duration of disease ($p<0.001$), less severe motor symptoms on UPDRS III ($p=0.038$), greater tremor subscore on UPDRS ($p=0.008$), and higher score on MMSE ($p<0.001$) than LOPD patients. In contrast, there were no significant differences in akinesia, rigidity subscore on UPDRS, QOL on Boer, and depressive disorder in BDI. When the predictors were entered into a linear stepwise regression analysis age at onset could predict tremor symptoms ($p<0.001$), and cognitive impairment in PD patients ($p<0.001$) (38.7% of the variables). The Pearson's correlation analysis showed that age at onset significantly correlated to MMSE score ($r=-0.438$; $p<0.001$) and tremor symptom ($r=-0.198$: $p=0.009$), while no other clinical characteristics was not correlated with age at onset.

Conclusions: Our results confirmed that specific patterns of clinical symptoms and cognitive functions of PD seem to be associated with different age at onset. We suggest that age at onset could be predictive of the subsequent progression of tremor and cognitive impairments in PD patients.

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Prosopagnosia and higher-order visual deficits in Parkinson's disease

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Objective: We present 3 PD patients who developed recurrent and short-lasting episodes of paroxysmal prosopagnosia.

Background: Prosopagnosia defined as the inability to recognize faces has been extensively described in Alzheimer's disease, but is not referenced in Parkinson's disease (PD).

Methods: Case report of 3 PD patients who complained for prosopagnosia.

Results: Case 1: 78-year-old man, rigid-akinetic PD (20-year evolution, H&Y 4), in treatment with levodopa 900 mg/day. He exhibited increasing memory difficulties that accomplished criteria for dementia 3 years ago. In the past 24 months he reports recurrent episodes of difficulty in recognizing his wife's face, but recognizing her by her voice. He also experienced recurrent complex visual hallucinations and episodes suggestive of optic ataxia. Neuropsychological examination revealed moderate-severe cognitive impairment (MMSE 21, DRS 106) with marked executive, memory and visuospatial deficits, but without anosognosia, language, or semantic memory impairment. Case 2: 65-year-old man, rigid-akinetic PD (10-year evolution, H&Y 3), receiving levodopa 550 mg/day. Four years-ago, he presented minor hallucinations and mild but progressive memory problems (MMSE 26, DRS 127). Different visual disturbances, with recurrent, short-lasting (10-15 minutes) and isolated episodes of diplopia, macropsia, optic ataxia, and prosopagnosia (towards family members and friends), were present in the past 2 years. Case 3: 79-year-old woman, tremor dominant PD (6-year evolution, H&Y 3) receiving levodopa 400 mg/day and pramipexol 0.18 mg TID. In the past year she complained of progressive cognitive decline and frequent minor hallucinations. Transient episodes of prosopagnosia, with difficulty recognizing relatives' faces that resolve when hearing their voices, and two episodes of micropsia lasting 20-30 minutes, were present in the last six months.

Conclusions: We present the first formal description of prosopagnosia in PD. The association of prosopagnosia with other higher-order visual deficits and progressive cognitive impairment highlights the importance of posterior cortical deficits in the development of mental symptoms in PD.

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Association between gray matter atrophy and severity of cognitive impairment in Parkinson's disease

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Objective: The Center of Excellence for Research on Neurodegenerative Diseases (CERND) at the University of Pennsylvania developed and evaluated biomarkers to detect the neural substrate of cognitive decline in Parkinson's disease (PD) patients.

Background: There is growing recognition that diffuse gray matter atrophy occurs in PD patients with dementia (PDD), but atrophy across the range of cognitive impairment that occurs in PD is not well known. This study assessed regional gray matter atrophy in PD patients with normal cognition, mild cognitive impairment, and dementia as defined by standardized Mattis Dementia Rating Scale (DRS-2) score.

Methods: 107 subjects (PD-normal cognition [PD-N; n=61], PD-mild cognitive impairment [PD-MCI; n=12], PDD [n=11], and healthy controls [HC; n=23] underwent structural MRI on a 1.5 T Siemens scanner. Quantification of regional brain volumes was performed with an elastic atlas warping algorithm that co-registered a template of brain anatomy with individual scans based using 92 regions of interest (ROIs). Linear regression models (controlling for age, sex, educational level, disease severity, and intracranial volume) were used to explore between-group differences in regional brain volumes. Partial correlations were performed for DRS-2 total scores and regional brain volume measurements.

Results: HCs and PD-N patients had similar regional brain volumes in a multivariate model. Within the PD group, there were group-level differences in parietal lobe gray matter (GM), temporal GM, medial temporal lobe, and hippocampal volumes. Comparing cognitive subgroups, PD-MCI patients had smaller medial temporal lobe (beta coefficient [β]=-0.37, p=.003) and hippocampal (β=-0.37, p=.001) volumes than PD-N patients. PDD patients had additional atrophy in parietal GM (β=-0.24, p=.006) and temporal GM (β=-0.19, p=.04) volumes. Hippocampal volume was correlated with total DRS-2 score (r=0.46, p<.001).

Conclusions: Atrophy of the medial temporal lobe, including the hippocampus, may be associated with the development of MCI in PD. Subsequent atrophy of parietal-temporal neocortical gray matter regions may contribute to ongoing cognitive decline and progression to dementia.

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Neuropsychological effects of deep brain stimulation of the subthalamic nucleus in advanced Parkinson's disease: A clinical, neuropsychological and neurophysiological study

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Objective: to investigate the possible neuropsychological abnormalities in patients with Parkinson's disease (PD) after deep brain stimulation (DBS) of subthalamic nucleus (STN) evaluating neuropsychological and neurophysiological tests.

Background: neuropsychological impairment may be observed in PD patients after DBS especially in elderly; nevertheless the definite extent of this condition still raises different opinions.

Methods: we studied 9 patients mean age of 63.88 years treated with DBS of STN (the mean duration DBS treatment is 3.5 years; range 1-7 years) with great improvement of motor functions. They all underwent to a complete neuropsychological assessment prior and after surgery. We also performed cognitive event-related potentials (P300) after DBS. In three patients P300 was evaluated before and after DBS. We also studied the difference of P300 latency and morphology with DBS-ON (in bipolar setting to reduce the artifact signal) and DBS-OFF, in all patients. We investigated also the Mini Mental State Examination (MMSE) with DBS-ON immediately before P300 execution.

Results: Mean MMSE before P300 with DBS-ON was 24.31. The mean latency of P300 after surgery with DBS-ON was 385.3 msec; with DBS OFF was 401.7 msec. In the three subjects we could study P300 before and after surgery, the mean latency of P300 was 422 msec before DBS; after surgery with DBS-ON the mean latency was 366 msec and with DBS-OFF 388 msec. The amplitude of P300 in DBS-OFF was reduced in respect ON stimulation. Neuropsychological tests before and after DBS disclosed a moderate worsening of fonemic fluency, but not as a selective variable and mild general cognitive profile decline.

Conclusions: Our survey displays a slight improvement of attention and discriminatory abilities after surgery. On the contrary neuropsychological evaluation figured out a moderate decline of general cognitive abilities with reduction of verbal fluency. Selective frontostriatal loops abnormalities might be considered as possible responsible of cognitive dysfunction in these patients.

POSTER SESSION 2
TUESDAY, JUNE 15, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

PARKINSON'S DISEASE: DYSAUTONOMIA

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Alpha-synuclein immunoreactivity in minor salivary glands: A potential pathological biomarker for Parkinson's disease?

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Objective: To determine whether there is alpha-synuclein (α -SYN) immunoreactivity in the minor salivary glands of patients with Parkinson's disease (PD).

Background: The degenerative process in PD affects not only the central but also the peripheral autonomic nervous systems. The accessibility of peripheral tissues makes them an attractive source to identify potential pathological biomarkers of the disease. Reduced salivary secretion is a common and early finding in PD which provides rationale for studying the salivary gland in these patients.

Methods: Labial minor salivary gland biopsies were obtained from three PD patients who complained of dry mouth and 3 matched controls with suspected Sjögren disease. PD duration was 4 years with a Hoehn and Yahr stage 2 in the three cases. Immunohistochemical studies were performed in paraffin tissue slices using a rabbit polyclonal antibody against α –SYN. Immunolabeling was visualized using a peroxidase method. Specificity of the immunostaining was determined by omission of the primary antibody and the use of a specific blocking recombinant protein.

Results: α -SYN immunoreactive profiles were observed in 2 of the 3 PD and none of the control cases. The immunostaining was distributed primarily around the acini, corresponding to the distribution of nerve fibers innervating the gland.

Conclusions: This preliminary data suggest that α -SYN pathology involves the salivary glands in some cases of PD. Although these findings may be potentially relevant, they should be confirmed in a large number of cases. Further studies using specific neurochemical markers for different population of nerve fibers are necessary to identify the nature, distribution, and potential significance of α –SYN inclusions in the salivary glands in PD.

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Deep brain stimulation of the subthalamic nucleus regulates peripheral glucose metabolism in patients with Parkinson's disease: Evidence of a brain-liver crosstalk in human

I. Rieu, M. Batisse, C. Guillet, B. Morio, J.J. Lemaire, Y. Boirie, F. Durif (Clermont-Ferrand, France)

Objective: To evaluate if Subthalamic Nucleus-deep brain stimulation (STN-DBS) could modulate glucose metabolism, especially the endogenous glucose production (EGP) in Parkinson's disease.

Background: Animal studies suggest a link between hypothalamus sensing of substrates and glucose metabolism. STN-DBS is an alternative treatment for patients with uncontrolled symptoms of Parkinson's disease. As subthalamic nucleus is located close to hypothalamus, we hypothesized that DBS may induce changes in the hypothalamus activity and modulate glucose metabolism.

Methods: The study enrolled eight patients with Parkinson's disease (4 men, 4 women) aged 60.6±2.7 years with a mean duration of disease of 12.9±1.51 years and an acute efficacy of STN-DBS of 54.4±1.71% (assessed using UPDRS part III). EGP was measured during 5h infusion of D-[6,6-$^2H_2$]-Glucose in STN-DBS treated patients after DBS interruption (Stim OFF) and under DBS (Stim ON) conditions. EGP was then compared to EPG of eight matched healthy control subjects (control group) together with plasma concentrations of insulin, glucagon and free fatty acids.

Results: In Stim OFF conditions, EGP was higher in patients than in the control group (2.62±0.09 vs 2.27±0.10 mg/kg/min, $p<0.05$). Despite no significant change in plasma glucose, a significant and consistent decrease of EGP was observed in the patients between Stim OFF (2.62±0.09 mg/kg/min) and Stim ON (2.04±0.07 mg/kg/min) ($p<0.05$), and there was no more difference between control group EPG (2.27±0.10 mg/kg/min) and parkinsonian patients in Stim ON (2.04±0.07 mg/kg/min) (p=NS). No difference in insulin, glucagon or free fatty acid levels was observed between the patients in Stim OFF and Stim ON and with the control group. Finally, basal plasma glucose was higher in parkinsonian patients (1.00±0.04 g/l) than in control group (0.92±0.01 g/l) ($p<0.05$).

Conclusions: Deep brain simulation in patients with Parkinson's disease affects endogenous glucose production independently of changes in pancreatic hormones, suggesting that a cross-talk between central nervous system and peripheral tissues regulates glucose homeostasis.

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Deep brain stimulation of the subthalamic nucleus increases blood glucose in patients with Parkinson's disease

I. Rieu, Y. Boirie, F. Durif (Clermont-Ferrand, France)

Objective: To evaluate if Subthalamic Nucleus-deep brain stimulation (STN-DBS) affects blood glucose in Parkinson's disease and could increase the risk to develop a diabetes.

Background: STN-DBS is a clinically effective therapy to treat motor symptoms for advanced form of Parkinson' disease (PD). However, STN-DBS alters energy expenditure and body weight control. Furthermore, we recently showed that STN-DBS could modulate glucose metabolism by modifying endogenous glucose production. Some studies provided evidence for higher diabetes prevalence in non operated PD patients but the effect of STN-DBS on blood glucose remains largely unknown.

Methods: The study included 23 patients with Parkinson's disease (12 women and 11 men) aged 61.9±1.5 years. Before surgery (M-1) and one year after the surgery (M+12), blood samples were taken in all patients after an overnight fast to determinate plasma glucose. Body weight and height of each patient were also measured at M-1 and M+12 in order to calculate their Body Mass Index (BMI). Furthermore, 23 healthy controls aged 60.0±1.4 years were recruited to match patient for sex, age and body composition (weight and height) at M+12.

Results: One year after surgery, body weight and BMI were significantly increased by 8.1 ±1.2 kg and 2.8±0.4 kg/m^2 respectively ($p<0.0001$). At M-1, 4 patients were overweight (25<BMI<30 kg/m^2) and 3 were obese (BMI >30 kg/m^2). One year after surgery 6 patients were overweight and 4 were obese. Plasma glucose concentrations were significantly increased between M-1 (4.97±0.16 mmol/l) and M+12 (5.81±0.36 mmol/l) (p=0.0005). A positive correlation was found between body weight gain and glycaemia variations (R^2=0.367, p=0.022). Plasma glucose concentrations measured in matched control group (4.99±0.09 mmol/l) tended to be lower than in patient group (5.81±0.36 mmol/l) (p=0.0768).

Conclusions: These results demonstrate for the first time that STN-DBS significantly increase blood glucose level in PD patients suggesting that the risk to develop an impaired glucose tolerance or diabetes could be enhanced after this surgical procedure. This study emphasizes on the importance of an adequate nutritional follow up care for parkinsonian patients.

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Overweight after deep brain stimulation of the subthalamic nucleus in Parkinson's disease: A 5 year follow up study

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Objective: To follow-up the weight gain changes in patients with Parkinson's disease, 5 years after Subthalamic Nucleus-deep brain stimulation (STN-DBS).

Background: STN-DBS is a clinically effective procedure for patients with advanced form of Parkinson' disease (PD) leading to a great improvement in its major motor symptoms (eg, akinesia, rigidity, tremor and motor complications). However, this chirurgical procedure also induces a rapid and strong body weight gain and sometimes obesity that may limit the benefits of surgery and induce critical metabolic disorders. Several studies have described the post-operative overweight, but few of them have examined the long term changes in body weight.

Methods: The study included 20 patients with Parkinson's disease (6 women and 14 men) aged 59.7±1.4 years. Body weight and body composition were evaluated before surgery, (M-1), 3 months (M+3), 16 months (M+16) and 5 years (M+60) after surgery using dual X ray absorptiometry.

Results: Before surgery, 55% of patients were overweight or obese (n=11/20). This rate increased to 70% (n=14/20) at M+3 and to 85% (n=17/20) at M+16. This rate is identical between M+16 and M+60. At M+3, body weight (BW) and body mass index (BMI) were significantly increased by + 3.12 ±0.55 kg and + 1.07±0.18 kg/m^2 respectively ($p<0.05$). Between M+3 and M+16, BW and BMI continued to increase (+ 3.03±0.58 kg and + 1.03±0.19 kg/m^2 respectively) ($p<0.05$). BW and BMI gains were associated with a significant increase in fat free mass and fat mass between M-1 and M+3 and between M+3 and M+16. On the contrary, there was no more increase in BW and BMI between M+16 and M+60. BW of patients were not significantly different between M+16 (78.33±2.30 kg) and M+60 (77.10±2.48 kg) (p=NS). In accordance fat mass and fat free mass levels were similar between these two periods.

Conclusions: STN-DBS implantation in patients with Parkinson's disease leads to a rapid body weight gain which is already significant 3 months after surgery. This weight gain slightly increases to 16 months after surgery and is stabilized 5 years after surgery. This stabilization could be in part explained by an adequate diet management and nutritional advices.

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Peripheral vascular responses to an orthostatic challenge and plasma volume in Parkinson's disease patients with orthostatic hypotension

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Objective: To compare plasma volume and peripheral vascular responses to an orthostatic challenge in Parkinson's disease (PD) patients with orthostatic hypotension (OH) versus PD patients without OH and healthy controls.

Background: OH is present in up to 60% of PD patients and is negatively correlated with daily life activities and quality of life. The pathophysiological mechanism of OH in PD is unclear. Since in PD a generalized sympathetic denervation is present, a reduced peripheral vasoconstriction may play a role. Also an inadequate plasma volume could be a contributing factor to orthostatic intolerance, especially since plasma volume expansion is considered to be an effective therapy.

Methods: Superficial femoral artery flow in 15 PD patients with OH (PD+OH), 17 PD patients without OH (PD-OH) and 15 age and gender matched controls was examined using Doppler ultrasound during a 10-minute 60° head-up tilt. Leg vascular resistance was calculated as the arterial-venous pressure gradient divided by blood flow. In a subset (9 PD+OH, 9 PD-OH and 8 controls), we deter-

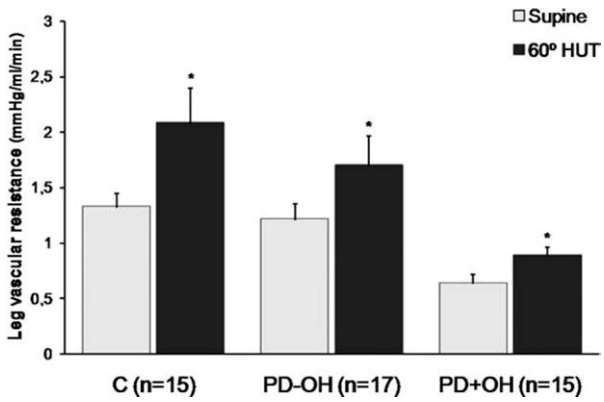

FIG. 1 (451).

mined plasma volume by indicator dilution method with radiolabelled albumin (^{125}I-HSA).

Results: Supine leg vascular resistance was significantly lower in PD+OH (0.6±0.3 mmHg/ml/min) compared to PD-OH (1.2±0.6 mmHg/ml/min) and controls (1.3±0.5 mmHg/ml/min). Leg vascular resistance significantly increased during 60° head-up tilt with no difference among the groups (PD+OH +0.3; PD-OH +0.5; controls +0.7 mmHg/ml/min, respectively). Plasma volume was significantly higher in PD+OH (3869±265 ml) compared to PD-OH (3123±377 ml) and controls (3204±537 ml).

Conclusions: PD patients with OH have an attenuated leg vascular resistance in combination with a larger plasma volume compared with PD patients without OH and controls. Although PD patients with OH can increase their leg vascular resistance during 60° head-up tilt to a similar extend as PD patients without OH and controls, they are unable to maintain their blood pressure in an upright position, possibly due to the attenuated basal leg vascular resistance.

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Spontaneous "sleepy" pupillary oscillations in Parkinson's disease

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Objective: To develop novel measures of autonomic physiology in PD–namely, spontaneous changes in pupil diameter (pupillary oscillations)–and characterize their relation to sleepiness.

Background: Pupil diameter is under autonomic control. In healthy adults, spectral power of pupillary oscillations is positively correlated with sleepiness. Since autonomic dysfunction and sleep disorders are common in PD, we predicted pupillary oscillations would differ in PD relative to controls.

Methods: Spontaneous pupillary oscillations were measured in darkness in 27 participants (12 PD and 15 age and sex-matched controls), who were asked to fixate on a dim point of light of constant luminance for 11 min while horizontal pupil diameter was measured with an infrared camera. Each participant also completed the Epworth Sleepiness Scale. Changes in pupil diameter were investigated using fast Fourier transformation. A power spectrum was plotted from 0 to 0.8 Hz. Outcome measures were: total power, dominant frequency (frequency with highest power), percent dominant frequency (power of dominant frequency/total power X 100) and Epworth score. Univariate linear regression was applied with PD or Epworth scores as predictors and total power as outcome.

Results: Comparing PD to controls, total power (mean(SD)) of pupillary oscillations was higher (0.038(0.028) vs. 0.022(0.018), p=0.037), however there was no difference in dominant frequency (Hz) (0.022(0.008) vs. (0.025(0.009)) and percent dominant frequency (44.7(17.9) vs. 43.7(17.2)). There was a trend for higher Epworth scores in the PD group (9.5(4.5) vs. 6.4(4.7), p=0.065). Among all participants, PD diagnosis was not a significant predictor of total power, however Epworth scores were positively correlated (p=0.036, R^2=0.20).

Conclusions: Pupillary oscillations are non-invasive measures of autonomic physiology that can be applied to PD. They are of higher spectral power in PD compared to controls. This observation was not specific to PD and correlated with sleepiness, demonstrating that autonomic function in PD may be affected by common comorbidities such as sleep disorders.

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Parkinson's disease and sexuality

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Objective: The purpose of this study was to evaluate the sexual function in a group of young patients with PD.

Background: Parkinson's disease can affect sexuality through loss of neurological control of body movements or medication side effects.

Methods: 18 patients (13 males and 5 females) from the Movement disorder unit at the University Hospital Center Mother Theresa were included in the study. Mean age 45 years old, (SD +_ 5,3 years) The duration of disease was 1 -7 years. Four patients were in stage 1, five patients in stage 2 and 9 in stage 3 Hoenh and Yahr. All of them were taking levodopa therapy. A structured interview concerning sexuality was performed to them.

Results: 9 patients (50%) reported sexual problems. Five males (40%) and four females (80%) reported changed libido; while four males (30%) and five females (100%) experienced changed sexual activity after onset of PD. A tendency to changes in libido and sexual function was seen with increasing time to treatment and advanced Hoehn et Yahr stages.

Conclusions: It is concluded that changes in libido and sexual function occur more frequently than previously reported, especially in females, They can be present since the beginning of disease and are connected with the progression of the illness and the time of treatment. More attention should be paid to these problems.

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Pathological burden in the colon of living Parkinson's disease patients correlates with disease severity

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Objective: To correlate alterations of the enteric nervous system (ENS) with clinical measures in living Parkinson's disease (PD) patients.

Background: The presence of Lewy bodies (LB) and Lewy neurites (LN) has been demonstrated in the ENS of PD patients. Routine colonic biopsies enable a histological analysis of the ENS in living patients and thus provide a new tool to develop a biomarker of PD.

Methods: A total of 10 controls and 29 PD patients divided into 3 groups according to disease duration were included. PD symptoms were assessed using the Unified Parkinson's Disease Rating Scale, part III (UPDRS-III) with and without medications. All patients and controls underwent a total colonoscopy and 4 biopsies were taken from the ascending and descending colon. Immunohistochemical assessment of the biopsies was performed using antibodies against phosphorylated alpha-synuclein and neurofilaments NF 220 kDa (NF). Density of LN labeled by the anti-phosphorylated alpha-synuclein antibodies was evaluated using a semi-quantitative rating score.

Results: Lewy pathology was evidenced in the colonic biopsies from 21 patients and in none of the controls. The amount of Lewy neurites in the ENS was inversely correlated with the density of neurons immunoreactive for NF and positively correlated with the severity of levodopa-unresponsive axial features.

Conclusions: Routine colonic biopsies allow a neuropathological assessment of disease severity in living patients with PD and could thus be regarded as a new and original biomarker of disease severity. (ClinicalTrials.gov number, NCT00491062).

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Autonomic nerve dysfunction in early Parkinson's disease and essential tremor

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Objective: To study autonomic nerve dysfunction and depression in patients with early Parkinson's disease (PD) and essential tremor (ET).

Background: Non-motor symptoms occur in almost all Parkinson's disease (PD) patients and these symptoms influence patients' quality of life [1]. Essential tremor (ET) is another common movement disorder. An extensive literature suggests an association between ET and PD [2, 3]. Patients with ET are four times more likely than controls to develop PD during prospective follow-up. These data confirm and begin to establish a link between these diseases.

Methods: The Unified Parkinson's Disease Rating Scale - motor examination (UPDRS-III) and the Hoehn and Yahr scale were used in 89 PD patients to evaluate the severity of the disease. The Tremor Rating Scale for Tremor was performed in 53 ET patients. A questionnaire that focuses on the autonomic system in PD (SCOPA–AUT) was used to evaluate autonomic nerve function in both groups.

Results: Compared to the ET patients, PD patients suffered more severe autonomic dysfunction, involving the gastrointestinal, urinary, cardiovascular, thermoregulatory, and pupillomotor systems. Gastrointestinal and urinary dysfunctions were more frequent in dopamine-treated PD patients.

Conclusions: Autonomic dysfuction is more common in Chinese early PD patients than in ET patients and normal controls. Dopamine therapy is associated with gastrointestinal and urinary dysfunction in PD patients. Autonomic dysfuction indeed occurs in ET patients, especially in the urinary and thermoregulatory systems. Therefore, we should pay attention to autonomic dysfuction not only in PD, but also in ET patients. Common symptoms of autonomic dysfunction between PD and ET suggests the two disease may share common pathophysiologic mechanisms.

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Effect of medical treatment on autonomic and sensory symptoms in Parkinson's disease one year after diagnosis

B. Müller, J.P. Larsen, O.-B. Tysnes (Bergen, Norway)

Objective: To investigate changes in the frequency and severity of autonomic and sensory symptoms dependent on the type of medical treatment one year after diagnosis in a population-based cohort of patients with Parkinsons's disease (PD).

Background: Autonomic and sensory disturbances are common in PD. The effect of antiparkinsonian treatment on these symptoms is discussed and poorly described for the early disease stage.

Methods: 201 patients with PD, followed up for one year after the initial diagnosis in the Norwegian ParkWest study, were included. The presence of urinary dysfunction, constipation, drooling, dysphagia, increased sweating and pain were based on the UPDRS and a ParkWest score created for this study. A score ≥ 1 indicated the presence of a symptom. Orthostatic blood pressure was measured and orthostatic hypotension was defined according to standard criteria. The severity of urinary dysfunction, constipation, drooling, dysphagia, pain and lightheadedness when standing was assessed with a preliminary version of the MDS-UPDRS. Data from baseline and after one year were compared. Here we present preliminary results.

Results: One year after diagnosis, nine patients were treated with a MAO-B inhibitor (MAO-Bi) only, 74 with levodopa (with or without a COMT-inhibitor and/or MAO-Bi) and 79 with a dopamine agonist (with or without any of the previous substances including levodopa). 37 patients received no antiparkinsonian medication. For the total group, the frequency of autonomic and sensory symptoms was similar after one year compared to baseline both for each single symptom and for the sum of symptoms per individual (mean 2.2 ± 1.4). The frequency of the symptoms was also unchanged for the different treatment groups. The severity of dysphagia tended to be reduced in patients treated with dopaminergic agents and increased in the untreated patients. The severity of the other symptoms was similar after one year compared to baseline for all treatment-groups.

Conclusions: These preliminary results indicate that the influence of antiparkinsonian treatment on autonomic and sensory symptoms in the early stage of PD is limited. Dysphagia may be reduced by dopaminergic agents. The early stage of the disease and the short duration of treatment have probably contributed to these results and longer follow-up of the current cohort is needed.

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Dysphagia and sialorrhea associated with Parkinson's disease

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Objective: To correlate dysphagia, sialorrhea and Parkinson's disease.

Background: Dysphagia and sialorrhea are frequently associated with Parkinson's disease (PD). The sialostasis and sialorrhea are both characterized by the increase of saliva volume in the oral cavity secondary an inefficient saliva clearance. Dysphagia can be associated with mechanic or degenerative causes, nevertheless neurological diseases are the main cause of dysphagia. Therefore, when the PD patients present dysphagia this swallow compromise is attributed to the neurological disease without further investigations. Nevertheless dysphagia can be present in PD patients by another etiology.

Methods: Three groups of PD patients from the same Movement Disorders Ambulatory were studied. In the first one, 17 dysphagic patients were evaluated by videofluoroscopic method. In the second, 14 patients with sialorrhea and 8 healthy controls had the salivary glands dynamic evaluated by scintigraphic method. In the third, 66 patients were evaluated to establish the correlation of dysphagia, sialorrhea and PD.

Results: First group - Besides the presence of rigidity (5 patients), xerostomy, lack of the teeth, deficiency of the oral bolus organization and ejection, dental prosthesis unadjusted and others dysphagic causes were found. Second group–Sialorrhea could not be related with age, time or severity of the disease. We noticed no difference between the results of the uptake of pertechnetate by the parotid gland in the two groups (PD patients and control group), but the excretion speed of the parotid gland in PD patients was greater than that observed in healthy individuals. Third group–We found sialorrhea in 39 patients, dysphagia in 11 and both complain in 16.

Conclusions: Our results allow concluding that sialorrhea and sialostase is not directly dependent of the PD. They are secondary to dysphagia, that in the PD can be produced or intensified by another associated etiology, usually neglected.

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Factors related to orthostatic hypotension in Parkinson's disease

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Objective: To assess the concordance between a BP fall after orthostatism and the presence of hypotensive symptoms as well as to explore factors related to the presence of OH.

Background: Orthostatic hypotension (OH), a frequent feature of Parkinson's disease (PD) can contribute to falls or other morbidity, thus warranting its diagnosis and treatment. They can be related to the disease itself or to drugs.

Methods: Non-demented, non-operated PD out-patients were recruited at the Toulouse's movement disorders clinic. Subjects were

questioned about the presence of any hypotensive symptoms such as head lightness, blurred vision, falls or nausea after standing up or vertigo. Afterwards, BP was measured 5 min after lying down and 2 min after standing up. OH was defined as systolic and/or diastolic BP fall $\geq$ 20 and/or10 mmHg within 2 min after orthostatism plus the presence of hypotensive symptoms. Subjects without OH were defined as those without a BP fall after ortostatism and not reporting any OH-related symptom.

Results: 64 patients were included in this study. Mean age 67±10 years; 72% were males; mean UPDRS II or III in ON-state were 12±6 or 24±11. They were on L-Dopa/Agonists (99%), COMT-I (22%), Baroreflex-modifying (BR-M) drugs such as alpha-, beta-antagonists, Ca-channel blockers, amiodarone or Cholinesterase-inhibitors (17%), MAOB-I (12%) or fludrocortisone/midodrine (3%). Twenty-seven subjects (42%) showed hypotensive symptoms and 28 (42%) had exaggerated BP fall. The agreement between the BP fall and the presence of hypotensive symtoms was kappa=0.16±0.12 (p=0.2). Twenty-four (37%) subjects were diagnosed with OH (i.e. BP fall + symptoms), whereas 14 (21%) were labeled as non-OH (i.e. no BP fall + no symptoms). Compared to non-OH, OH subjects has higher UPDRS II in ON (14±1 vs 10±1, $p<0.05$), higher tremor score (4±1 vs 2±0.5, $p<0.04$) and were more frequently on amantadine (36% vs 8%) or BR-M drugs (37 vs 8%). Independent factors related to OH as disclosed by logistic regression were amantadine (OR=8.0, IC95%=1.2-55.2) or BR-M drugs administration (8.2, 1.1-55.5).

Conclusions: In our study, the presence of orthostatic hypotension (defined as an exaggerated BP fall after orthostatism plus hypotension symptoms) was related to amantadine or drugs able to modify baroreflex.

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Intraduodenal levodopa infusion and blood pressure in patients with advanced Parkinson's disease

V. Pursiainen, E. Pekkonen (Helsinki, Finland)

Objective: To evaluate the effect of intraduodenal levodopa infusion on blood pressure and motor symtoms in advanced Parkinson's disease.

Background: Both motor fluctuations and autonomic nervous system dysfunction are common problems in Parkinson's disease (PD). Intraduodenal levodopa infusion (Duodopa®) is effective in the treatment of advanced PD and has been shown to alleviate motor fluctuations. It's effect on autonomic nervous system has not yet been studied.

Methods: We studied six consecutive patients referred to us for intraduodenal levodopa infusion. All patients fulfilled the UK PD Brain Bank's clinical criteria for PD and had daily motor fluctuations that could not be sufficiently controlled by oral medication. All patients were graded using Unified Parkinson's Disease Rating Scale (UPDRS). The patients were advised to gradually discontinue all PD medication apart from levodopa two weeks before hospitalisation. UPDRS evaluation and ten minute orthostatic test were performed during on-phase and off-phase. Naso-duodenal infusion tube was inserted in fluoroscopy control and levodopa infusion was tested for 4 to 6 days. All patients had favorable response, and PEG-infusion tube was inserted in gastroscopy control. UPDRS evaluation and orthostatic test were repeated before discharging and two months later.

Results: Mean UPDRS total score was 41 (range 32-51) at the first visit and 27.1 (range 16-40) at two month follow-up, the difference was significant ($p<0.001$). UPDRS motor scores, supine systolic BP values and orthostatic BP responses are presented in Table 1

There was a trend towards lower supine systolic BP during test phase (p=0.07) compared to on-phase. There was no difference in orthostatic BP responses between the test phase and two month follow-up. The number of patients with orthostatic symptoms did not change. One patient had local infection after PEG insertion that resolved with antibiotics without further sequelae.

Conclusions: In our study, intraduodenal levodopa infusion was effective and well tolerated. It increases orthostatic BP drop in advanced PD patients previously treated with oral levodopa. Although the orthostatic BP drop at two months was on average 19.1mmHg higher than during on-phase, prevalence of orthostatic symptoms didn't change.

.TABLE 1 (459). *Supine blood pressures and orthostatic blood pressure responses*

	UPDRS motor score	Supine systolic BP	Orthostatic systolic BP drop	Initial orthostatic systolic BP drop
On-phase	20.5 (16-26)	143.8 (32.3)	14.5 (9.7)	11.1 (8.2)
Off-phase	36.7 (29-42)	166.1 (24.2)	18.7 (11.5)	13.7 (5.5)
Test phase	12.8 (8-20)	128.3 (20.5)	26.1 (4.0)*	25.5 (3.7)**
2 mo follow-up	11.4 (8-21)	138.5 (13.5)	33.7 (15.7)**	24.1 (7.8)*

BP values presented as mean (SD). * = $p<0.05$, ** = $p<0.01$ compared to on-phase (paired samples t-test)

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Botulinum toxin treatment of sialorrhea in 25 patients suffering from Parkinson's disease, MSA, PSP, and brain injury in early childhood

A. Stenner, G. Reichel (Zwickau, Germany)

Objective: Sialorrhea may occur in various neurological diseases. It can be caused by intense salivation as well as irregular swallowing. Benefits from botulinum toxin (Btx) treatment may vary, because, frequently, the primary disease as well as the pathophysiology of salivation is not taken into account.

Background: The question is as follows: Is it possible to apply specific approaches with Btx for the various diseases that can cause sialorrhea?

Methods: We examined 25 patients who were seriously affected by sialorrhea. Three diagnostic groups were involved: Parkinson's disease (n=13), brain injury in early childhood (n=10) and two patients with MSA and PSP, respectively. Our first step was Btx treatment of parotid glands; if this did not show adequate results submandibular glands and sublingual glands were injected as well. Some of the injections were administered under ultrasound guidance.

Results: All of the Parkinson patients experienced reduced salivation after only one injection into their parotid glands. None of these cases showed the required subjective benefits; the actual reduction was still inadequate. Subsequent injection of only the submandibular gland resulted in clearly reduced salivation in all of the 13 patients, therefore all following Btx injections were placed only into this salivary gland. In the group of patients with brain injuries in early childhood, treating only the parotid gland, or the submandibular gland, respectively, did not produce adequate results. Injecting both salivary glands finally resulted in beneficial effects for the patients. Additional injections into the sublingual glands did not lead to any further improvement. Results for the 2 patients suffering from MSA or PSP were similar.

Conclusions: Successful Btx treatment of sialorrhea in patients with Parkinson's disease (predominantly production at rest) can be accomplished with injections into only the submandibular gland (responsible for 70 % of saliva production at rest). On the contrary, patients with brain injuries in early childhood (predominantly reflex production) will need injections into the parotid and the submandibular glands. This will lead to a 90 % decrease in saliva production. Injecting the sublingual gland is not necessary at all.

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Analysis of epicardial fat tissue as a potential tool for *in vivo* evaluation of autonomic nervous tissue in premotor Parkinson's disease (PD): A pilot study in cardiac surgery

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Objective: To prospectively study epicardial fat tissue from neurologically unimpaired individuals undergoing programmed cardiac surgery for the suitability to detect autonomic nervous (AN) tissue in epicardial fat and to study the presence of alpha-synuclein (AS) aggregates in peripheral cardiac AN system.

Background: In PD AS aggregates occur frequently in the peripheral AN system and cardiac involvement has been detected in patients with motor symptoms and in those without parkinsonism but with Lewy body pathology (incidental Lewy body disease) in *postmortem* studies. In vivo imaging data (cardiac scintigraphy) support also early and premotor cardiac involvement in PD but objective in vivo documentation of Lewy body pathology is lacking.

Methods: Formalin-fixed and paraffin-embedded samples of epicardial fat tissue (0,5-2cm, 5-6 areas) obtained during cardiac surgery, evaluated by histology and immunohistochemistry using anti-tyrosine-hydroxylase and anti-alpha-synuclein antibodies. Samples form 14 individuals (8 male; mean age 65 years) have been studied so far. Areas more likely to contain autonomic nerve fibres and/or ganglia were selected: fat tissue close to cavoatrial confluence, Waterson-Sondergaard sulcus, right atrio-ventricular sulcus, left coronary artery, and surrounding aorta and pulmonary artery. The study has been approved by the Ethics Committee.

Results: AN tissue (small nerves, ganglia and/or TH positive fibres) has been identified in each of the 14 cases, in 2 to 4 from the 5-6 samples obtained from each individual. No AS aggregates have been detected.

Conclusions: Access to AN tissue in epicardial fat during cardiac surgery is feasible and has no significant additional risk during surgery. If AS aggregates can be detected *in vivo* by this method in individuals without parkinsonism, their presence would suggest the diagnosis of incidental Lewy body disease, possibly representing premotor PD. In these individuals, additional studies (e.g. DAT imaging or smell tests) and appropriate follow may contribute to a better understanding of the premotor phase of PD and the involvement of the cardiac AN system in the early disease stages.

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Clinical availability of skin biopsy in the diagnosis of Parkinson's disease

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Objective: To determine clinical availability of skin biopsy in premortem diagnosis of Parkinson's disease (PD).

Background: Phosphorylated α-synuclein immunohistochemistry is a practical tool in pathological diagnosis of PD. A postmortem study has demonstrated that Lewy pathology is found in the skin in 70% of patients with pathologically diagnosed PD. These results led us to examine whether skin biopsy combined with α-synuclein immunohistochemistry is useful as a clinical test method for the diagnosis of PD.

Methods: Skin biopsy was performed from 20 patients with clinically diagnosed PD. Under local anesthesia, 6-mm punch biopsies were undergone from the anterior chest wall and the right leg. Samples were fixed and embedded in paraffin. Serial 6-μm-thick sections were cut and 3 sections 30 μm apart were immunostained with anti-phosphorylated α-synuclein antibody.

Results: Abnormal accumulation of α-synuclein was found in the chest skin from two (10%) of 20 patients, but not in the leg. These abnormal structures were located in the unmyelinated fibers near the blood vessels and sweat glands. One patient with Lewy neuritis was a 64-year-old female with 3-years' disease duration (Hoehn-Yahr stage 2). The other patient was a 61-year-old male with 10-years' disease duration (Hoehn-Yahr stage 4).

Conclusions: We could firstly demonstrate Lewy pathology in biopsied skin tissue. However, the sensitivity of skin biopsy combined with the conventional immunohistochemistry for α-synuclein was low. This result suggests that the method is not clinically sufficient for diagnosis of PD. However, the skin remains to be a promising tissue to be explored in PD.

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Autonomic dysfunction in patients with early and later onset Parkinson's disease

Y.A. Trufanov (Calgary, Alberta, Canada)

Objective: To analyze the prevalence of autonomic dysfunction in patients with the early and later onset Parkinson's disease (PD).

Background: PD is often complicated by autonomic dysfunction which can significantly influence quality of life in patients, but has not been studied to the same extent as motor symptoms.

Methods: 73 consecutive patients with idiopathic PD (50 males and 23 females, age range from 42 to 88) were questioned at time of routine clinic visits with respect to presence and onset of constipation, bladder symptoms and postural dizziness. BP was measured lying and standing. Retrospective chart review was carried out to confirm findings. The patients were divided into two groups: PD onset prior to 61years (35 persons) and PD onset at age of 61 and older (38 persons). Average age of patients was 67.9, and average disease duration was 7.7 years.

Results: Symptomatic postural hypotension was observed in 32.9% of PD patients, with no differences found between the two groups (34.3% vs 31.6%, $p > 0.05$). During the first 5 years of the illness, symptomatic postural hypotension was observed twice more frequently in the group of patients with onset of illness after age 60 (15.8% vs. 8.6%, $p<0.001$). Frequent urination was observed in 39.7% of PD patients, and was twice more common in the group of patients with onset after the age of 60 (55.3% vs. 22.9%, $p<0.001$), and began in the first 5 years of the illness (42.1% vs. 14.3%, $p<0.001$). Urinary retention related to parkinsonism was observed at 6.8% of patients and only in the group of patients with onset after the age of 60. Constipation was observed in 53.4% of patients, and was more common PD onset after age 60 (63.2% vs. 42.9%, $p<0.02$), and began in the first 5 years of the illness (44.7% vs. 22.9% vs $p<0.001$).

Conclusions: All 3 autonomic symptoms, postural hypotension, frequent urination and constipation, are common in PD patients; frequent urination and constipation were observed more frequently in PD patients with disease onset after the age of 60. In addition, these symptoms tended to occur more frequently within the first 5 years of the illness in the older age group. All PD patients should be queried with respect to autonomic symptoms even in the early stages of disease.

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Weight loss in Parkinson's disease across different stages

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Objective: Determine incidence of and predictors for weight loss (WL) in PD across different disease stages.

Background: PD patients lose weight. Existing clinical trial databases provide weight data and detailed demographic and clinical information.

Methods: We used clinical trial databases of the Parkinson Study Group to study the baseline prevalence and the incidence for low body mass index (BMI <22 kg/m^2), very low BMI (<18.5 kg/m^2), and $\geq 5\%$ WL from baseline in non-demented samples of early PD not requiring dopaminergic treatment (DATATOP), early PD requiring dopaminergic treatment (CALM-PD), and moderate PD with

motor fluctuations (PRESTO-baseline prevalence only due to 6 months study duration).

Results: At baseline, the prevalence of low BMI was 13.9% (95% CI: 11.4, 16.4) in DATATOP, 10.1% (6.6, 13.7) in CALM-PD, and 15.1% (11.8, 18.3) in PRESTO. The prevalence of very low BMI was <2% in all 3 studies. Low BMI at baseline was associated with female gender (p=0.0001) and increased disability due to dyskinesia (p=0.01, PRESTO). The cumulative incidence for low BMI at 4 years was 15.5% (12.4, 18.6) in DATATOP and 6.9% (3.5, 10.2) in CALM-PD. The cumulative incidence for ≥5% WL at 4 years was 51.9% (47.9, 56.0) in DATATOP and 27.4% (21.7, 33.1) in CALM-PD. Increased age and severity of parkinsonism (especially, axial features), occurrence of depression or apathy, and worse cognitive function (all time-dependent measures) were significantly associated with earlier time to weight loss. Deprenyl had a significantly protective effect against WL, whereas cumulative levodopa exposure showed a trend for association with WL. Presence of urologic, dermatologic, gynecologic symptoms at baseline were associated with WL. Presence of ApoE-ε4 allele (DATATOP) showed a trend for association with WL.

Conclusions: Weight loss in PD affects a substantial proportion of patients at different stages and progresses with advancing disease. WL in PD is associated with age, female gender, motor dysfunction, apathy, depression, treatment (potential symptomatic motor/antidepressant effect or "neuroprotective" effect by Deprenyl), dyskinesia, potential autonomic dysfunction, and cognitive impairment suggesting a multifactorial process with possible genetic contribution.

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Character of urinary dysfunction in drug-naïve patients with Parkinson's disease

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Objective: The aim of this study was to evaluate the character and incidence of urinary dysfunction in a cohort of drug-naïve patients with Parkinson's disease (PD).

Background: Urinary dysfunction, mainly storage dysfunction, was reported to be common in PD. However, most previous studies have been based on the patients receiving anti-parkinsonian drugs, which can influence urinary function. Little is known regarding the urinary dysfunction in early and drug-naïve patients with PD.

Methods: A total of consecutive 49 drug-naïve patients with PD were recruited except the patients with complication influencing bladder function, who were mean age of 67, mean disease duration of 23 months and mean Hoehn & Yahr scale (H&Y) of 1.9. We questioned their urinary symptoms and performed urodynamic studies including sphincter needle EMG.

Results: Thirty two patients out of 49 (65%) complained of urinary symptoms (storage symptoms: 61%, voiding symptoms: 27%). Thirty six patients out of 49 (73%) had abnormal findings of urodynamic studies (In storage phase, detrusor overactivity: 61%, increasing bladder sensation without detruor overactivity: 8.2%; In voiding phase, detrusor sphincter dyssynergia: 8.2%, Non-relaxiing urethral sphincter obstruction: 16%). None had low compliance bladder or neurogenic change of sphincter motor unit potential (MUP) (mean duration: 6.8±1.4msec, number of over 10msec: <40%). Eleven patients out of 17 with H&Y 1 (64%), 16 patients out of 20 with H&Y 2 (80%), and 9 patients out of 12 with H&Y 3 (75%) had urinary dysfunction. Compared with PD patients between tremor/mixed type and akinesia type, tremor/mixed type have nocturia and urinary urgency more frequently than akinesia type (52% : 24%, 41% : 29%, respectively).

Conclusions: Urinary dysfunction, mainly storage dysfunction without neurogenic change of sphincter MUP, may commonly occur pathologically in early and drug-naïve patients with PD. In case with severe voiding dysfunction and/or with neurogenic change of sphincter MUP, other Parkinson's syndrome or complications influencing urinary function should be considered.

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Behavioral therapy to treat urinary incontinence in Parkinson's disease (BETTUR PD)

C.P. Vaughan, J.L. Juncos, K.L. Burgio, P.S. Goode, T.M. Johnson II (Atlanta, Georgia, USA)

Objective: To determine if older adults with Parkinson's disease (PD) and urinary incontinence (UI) can achieve significant reductions in weekly episodes of UI using behavioral therapy.

Background: While lower urinary tract symptoms, including UI, affect between 30% and 60% of persons with PD, current recommendations for treatment typically involve the first-line use of antimuscarinic agents. To date no randomized controlled trials of these drugs have been performed in the PD population. Behavioral interventions, which have demonstrated efficacy in other populations, including post-stroke patients, might be useful for PD as well.

Methods: PD subjects ≥ 50 years old were recruited from Movement Disorders clinics. Participants meeting inclusion criteria were enrolled if they recorded ≥ 4 UI episodes on a 7-day bladder diary. Participants were taught a) pelvic floor muscle exercises using computer-assisted, dual-channel biofeedback, and b) to utilize the pelvic floor muscles as part of an urge suppression strategy to prevent UI. A total of 6 visits over 9 weeks were used to reinforce techniques and monitor the primary outcome of weekly UI frequency using bladder diaries. Secondary outcomes included other lower urinary tract symptoms and quality of life ratings using the International Consultation on Incontinence Questionnaire for Overactive Bladder (ICIQ-OAB).

Results: Fifteen subjects (92% male, mean age 67.0±5.8, with PD for mean 7.7±5.5 years) completed the pilot study. The median (IQR) weekly frequency of UI at baseline was 9 (4–11) and following intervention was 1 (0–3), representing a median (IQR) 83.3% reduction (45.5–100.0, p-value 0.0001). Quality of life scores on the ICIQ-OAB improved from a mean (±SD) of 71.0 (±25.1) to 53.9 (±16.3, p-value for change 0.008).

Conclusions: In this uncontrolled pilot study, participants with PD and UI demonstrated significant and clinically meaningful reductions in weekly frequency of UI and improvement in quality of life using an exercise-based behavioral intervention reinforced by computer-assisted biofeedback. Further studies are warranted to assess behavioral therapies in PD patients in randomized controlled trials. 1) This abstract has also been submitted to the 2010 American Geriatrics Society Annual Scientific meeting (May 12–15, 2010).

POSTER SESSION 2
TUESDAY, JUNE 15, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

PARKINSON'S DISEASE: ELECTROPHYSIOLOGY

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Neural basis of the detection of incongruity of competing stimuli in Parkinson's disease

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Objective: To evaluate the cortical areas involved in the selection and suppression of competing responses in PD patients.

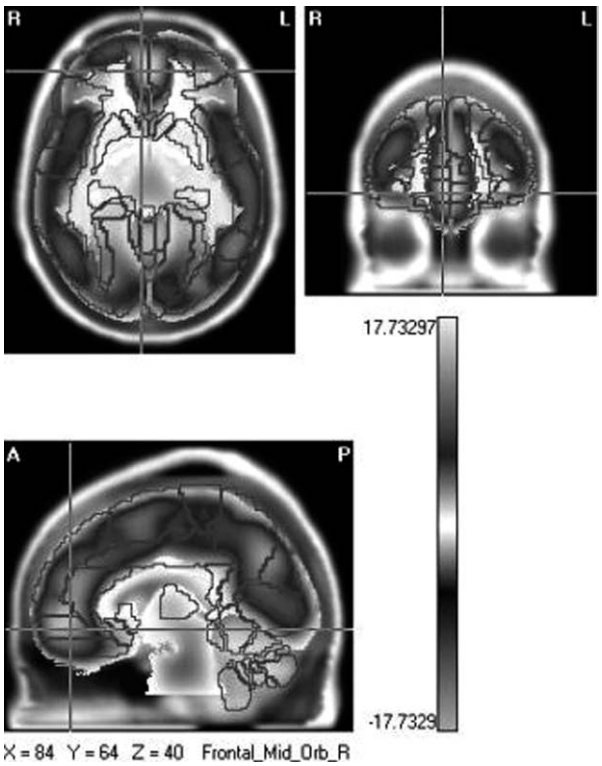

FIG. 1 (467).

Background: There is evidence that the basal ganglia are involved in the selection and suppression of mutually incompatible responses. Dysfunction in these structures in PD should alters this capacity, making it difficult for this patients to suppress interference arising from the automatic activation of salient responses. EEG source imaging of the detection of incongruity in these patients should reveal the neural circuitry of these deficits.

Methods: 20 PD patients (I-III Hoehn and Yahr stage, medicated, 41-65 years old) and 20 healthy controls matched in age and educational level, performed an Eriksen flanker task which required to select specific responses with the letter H or S that was flanked by the same HHHHH (congruent) or different SSHSS letter (incongruent) condition. ERPs were recorded simultaneously with the task using a 64 channels EEG system.

Results: Consistent with previous findings, reaction time (RT) increased with incongruent flankers compared to congruent and this cost of incongruity was greater among PD patients ($p=0.026$). This difference was significant (using a permutation test) at the 56, 204, 490 and 580 milliseconds after the presentation of the stimuli, revealing the conflict at early and late steps of processing of information. The percent of mistakes in the PD group is significant higher ($p=0.0003$) than for controls, indicating reduced efficiency in the suppression of competing responses. A N2 scalp potentials reflecting conflict monitoring on correct response trial appeared instead of the error-related negativity expected in the PD group. A tomographic solution using LORETA (average brain, volume constraints, 116 structures MNI atlas) found the generators of the component N2 in temporal superior pole and insula right and the late negativity at frontal medial orbital and cingulated anterior right.

Conclusions: These findings suggest that although poor suppression of conflicting responses is an important feature of PD the discrimination between the two competing conditions is processed by the brain in relevant areas of the fronto-striatal circuitries of right hemisphere.

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The effects of vibrotactile feedback on protective stepping response in Parkinson's disease (PD) patients

P.-Y. Lee, M.J. Naushahi, K. Gadareh, S. O'Riordan, S.A. Molloy, P.G. Bain, D. Nandi, M.A. Gresty, A.M. Bronstein (London, United Kingdom)

Objective: To characterise PD patients' stepping response to unpredictable postural stimuli and to assess whether vibrotactile feedback enhances protective stepping response of PD patients.

Background: PD patients have a high incidence of falling due to inadequate stepping balance response. A vibrotactile feedback prosthetic device to improve step generation has been developed [J Neurol (2007) **254**: 1555]. The present study aims to characterise PD patients' stepping response to unpredictable postural stimuli and to assess whether vibrotactile feedback enhances protective stepping response of PD patients.

Methods: 21 PD patients (68.6±10.3 years; 14 in Hoehn-Yahr stage I-II and 7 in stage III or above) and 16 healthy volunteers (67.8±10.6 years) were recruited. Subjects stood on a computer-controlled movable platform that unpredictably accelerated forwards or backwards, thus requiring protective step(s) to maintain balance. Subjects wore an elastic hat incorporating two small vibrators (frontal-occipital) as biofeedback to aid step generation (forwards-backwards, respectively). Step reaction time and length were measured from leg gyroscopes and foot-contact electrical switches. ANOVA statistics compared subject groups, with-without vibration, forwards-backwards step direction.

Results: Backward protective steps had significantly shorter reaction times and smaller step length than forward steps ($p<0.05$) in all subject groups. Advanced PD patients used shorter steps than the healthy elderly and mild PD patients ($p<0.05$) both forwards and backwards. No significant differences due to vibrotactile feedback during the perturbation were observed.

Conclusions: Backwards protective steps are quicker but shorter than forwards steps. This characteristic, probably dictated by biomechanical constraints, is preserved in all stages of PD. Since reaction times are preserved, the critical abnormality of protective stepping response in PD is insufficient (short) step length. The study showed that this abnormality is also present in unpredictable conditions both in forwards and backwards direction. The prosthetic vibrotactile device did not improve stepping responses.

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Contribution of intramuscular mechanisms to rigidity in parkinsonism

V. Stanislaus, J.A. Burne (Sydney, New South Wales, Australia)

Objective: To quantify the non-neural or intramuscular factors contributing to rigidity in parkinsonism.

Background: In 2009, we reported to the society that the gain of the tonic stretch reflex was reduced by more than 50% in Parkinson's disease compared to age-matched controls and the reflex correlated poorly with concurrent estimates of joint stiffness. Further, no effect of medication was found on TSR gain. It was concluded that the rigidity present in these patients was not due to increased TSR activity. In these studies, the metacarpophalangeal joint's resistive torque was noted to be highly nonlinear during sinusoidal stretching and, in contract to normal controls, could not be modeled as a second order system.

Methods: In the current study, this nonlinearity was quantified by plotting the joint's resistive torque against passive sinusoidal changes in joint angle over several frequencies.

Results: The area of the enclosed hysteresis loop quantifies the viscous joint stiffness component and was found to be substantially increased (to x10) in patients relative to controls.

Conclusions: This study suggests that intramuscular factors, potentially related to crossbridge attachment-detachment mechanisms, contribute significantly to the rigidity of parkinsonism. Further investigation of intramuscular mechanisms and their place in the disease pro-

cess is indicated so that their potential to provide biomarkers and a target for therapy in PD can be assessed.

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Factors contributing to joint stiffness at the wrist joint in parkinsonism

J.A. Burne, C. Yiannikas (Lidcombe, New South Wales, Australia)

Objective: This study aimed to confirm at the wrist joint results collected from the metacarpophalangeal (MCP) joint suggesting a significant intramuscular contribution to rigidity in parkinsonism.

Background: Stanislaus and Burne (accompanying poster this meeting) recorded resistive torque and sEMG data in response to small amplitude sinusoidal perturbation of the index finger about the metacarpophalangeal joint in normal subjects and rigid Parkinson patients (PD). In contrast to normal data, the resting resistive torque data from patients showed a markedly non-sinusoidal (nonlinear) relation to the joint perturbation which could not be correlated with EMG activity, inferring a significant intramuscular contributor to rigidity. In the current preliminary study, resistive torque and sEMG data were collected in response to sinusoidal wrist joint perturbations.

Methods: Resistive torque and wrist flexor/extensor sEMG were collected during low and high frequency wrist joint perturbations of small and large amplitude while patients attempted to relax. Correlation analysis of the perturbed joint angle against resistive torque and rectified sEMG were used to determine joint stiffness and reflex gain from each record.

Results: In most records from the wrist, the resistive torque recordings were approximately linearly related to the perturbation. This was generally the case for large amplitude perturbations (>2 deg) or frequencies >0.5 Hz. Prominent reflex EMG bursts were present in some 'resting' wrist flexor or extensor muscles but the torque signal remained approximately linear in these patients. However, some evidence of nonlinear torque profiles was seen in recordings from low frequency (<0.2 Hz), small amplitude (<2deg) perturbations in patients able to achieve minimal or silent EMGs at rest.

Conclusions: The wrist data is consistent with data from the MCP joint that infers an intramuscular factor may contribute to rigidity in PD. This feature may be best observed using perturbations of small amplitude and low frequency which will most strongly demonstrate enhanced short range muscle stiffness.

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Cerebellar theta burst stimulation in Parkinson's disease

F. Carrillo, F.J. Palomar, V. Conde, P. Porcacchia, F. Diaz-Corrales, G. Koch, P. Mir (Seville, Spain)

Objective: The aims of this study were to investigate whether repetitive transcranial magnetic stimulation (rTMS) of the lateral cerebellum could be able to modulate the excitability of the contralateral M1 in Parkinson's disease (PD) and to evaluate the role of dopaminergic treatment.

Background: The cerebellum takes part in several motor functions through its influence on the motor cortex and corticospinal outputs. Recent studies have suggested that there are also changes in cerebellothalamocortical networks occurring in PD. Functional or metabolic changes in the cerebellum have been reported in patients with PD treated with deep brain stimulation or pallidotomy of the globus pallidus.

Methods: Twelve PD patients with (ON) and without dopaminergic treatment (OFF), and twelve control subjects with similar age and sex distribution were included in the study. Motor evoked potencials (MEPs) amplitude, short intracortical inhibition (SICI), long intracortical inhibition (LICI) and short intracortical facilitation (SICF) were tested in the contralateral M1 before and after applying cerebellar theta burst stimulation at 80% of the active motor threshold

Results: Cerebellar rTMS reduced MEPs and SICI at interstimulus intervals of 2 and 3 ms in control subjects. However, PD patients in OFF and ON medication compared to controls did not show any change in MEPs amplitudes or reduction in SICI following cerebellar rTMS.

Conclusions: Cerebellar rTMS modulates the excitability of the cerebellothalamocortical pathway in control subjects, but not in PD patients, suggesting abnormal interactions of the cerebellothalamocortical pathway in PD patients. These findings do not appear to depend on dopaminergic treatment.

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Oculomotor abnormalities in early stage unilateral Parkinson's disease

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Objective: The aim of this study was to analyses the oculomotor abnormalities in unilateral PD patients and the differences between two sides.

Background: Oculomotor abnormalities in Parkinson's disease (PD) patients have been reported for many years, but there are no systematic studies of oculomotor deficits in early stage unilateral PD patients and of the differences between symptomatic and asymptomatic sides.

Methods: We recorded eye movements such as saccade (SEM), smooth pursuit (SPEM), and optokinetic nystagmus (OKN) by means of video-oculography in 44 patients with early stage unilateral PD (modified Hoehn & Yahr stage 1) and 26 controls.

Results: PD patients had significantly slower saccadic velocity, lower pursuitic gain, slower OKN velocity and lower OKN gain than controls, whereas no differences in saccadic latency and accuracy between PD patients and controls. The gain of the SPEM toward symptomatic side was significantly decreased than that toward asymptomatic side, but other parameters of saccade and OKN did not show any difference between symptomatic and asymptomatic sides.

Conclusions: This study shows that examination of eye movements is a useful adjunct in the diagnosis of early stage PD and SPEM systems are involved asymmetrically in early stage unilateral PD.

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Dopamine but not sub-thalamic DBS restores the altered somatosensory temporal discrimination in PD patients

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Objective: To investigate whether deep brain stimulation (DBS) modulates somatosensory temporal discrimination threshold (STDT) in Parkinson's Disease (PD) and if it does, whether the DBS-induced effects on STDT are comparable to those produced by levodopa.

Background: STDT measures the ability to perceive as temporally separated two incoming tactile stimuli arising from the same body part.

Methods: STDT was tested bilaterally in three body regions (eye, neck and hand) in 13 PD patients implanted with unilateral and bilateral sub-thalamic DBS in four different conditions: medication on/DBS on, medication on/DBS off, medication off/DBS on, medication off/DBS off. PD patients underwent also clinical and neuropsychological evaluations under each experimental sessions.

Results: STDT values improved when patients were tested under dopaminergic therapy compared to medication-off condition, whereas switching-on DBS worsened STDT. Conversely, when the patients were off dopaminergic therapy, no significant changes in STDT values were found between on/off DBS. The distinctive finding in our study is therefore that in PD patients levodopa but not DBS improves STDT. Neurocognitive tests did not significantly change across the experimental sessions.

Conclusions: Dopamine directly modulates neural circuits of somatosensory temporal discrimination processes restoring the inter-

play between the interconnected areas of the cortico-subcortico-cortical loop. Conversely the worsening on STDT during "DBS on" condition, could be caused by the interference of DBS-related field potentials on somatosensory pathways at sub-cortical level.

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STN-GPe functional connectivity in healthy and 6-OHDA lesioned rats

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Objective: We have previously shown that changes in firing rates and oscillations in Parkinson's disease (PD) impact the entropy within the external globus pallidus (GPe) network. However, it is not known how interactions between nuclei are affected. Here we investigate the functional connectivity between the subthalamic nucleus (STN) and the GPe in lesioned and control animals.

Background: Chronic dopamine loss in cortical-basal ganglia (BG) circuits in PD induces disorders of movement and cognition. Classical models suggest that alterations in the firing rates of BG neurons lead to the deficits seen in patients. Nonetheless, other perturbations in the dynamics of neural activity have also been observed during PD. For example, recordings from deep brain stimulation electrodes implanted in PD patients have shown that dopamine depletion in the BG is linked to an increase in beta frequency (13-30 Hz) oscillations at the single-cell and neuronal population levels. Less is known, however, about changes in interactions between BG nuclei in this disorder.

Methods: We recorded single-neuron activity in the GPe and in the STN of control and 6-hydroxydopamine-lesioned rats, the latter of which is a PD model that shows exaggerated beta oscillations after selective destruction of dopaminergic neurons. We then examined the network dynamics and the functional connectivity between GPe and STN pairs of neurons by the means of a nonlinear causal model.

Results: Dopamine depletion led to significant decreases in the firing rates of GPe neurons and increases in the firing rates of STN neurons. Additionally, we found that in the lesioned animals there was an increase of the connectivity between STN and GPe nuclei in both directions in comparison with what we observed in the control network. The subthalamopallidal and pallidosubthalamic projections were characterized by the model as being excitatory and inhibitory, respectively, as would be expected from the known neurochemistry of these nuclei.

Conclusions: We found that dopamine lesions lead to substantial changes in the interactions between the nuclei, measured with causal mutual information. Furthermore, the time-scale of the interactions shows pronounced beta dynamics. Our findings suggest that changes in interactions may reflect increased synaptic coupling between the nuclei.

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Blink and startle reflex analysis in patients with Parkinson's disease and essential tremor

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Objective: In the presented study, sporadic PD patients with early and late onset ET and PD patients without ET were included and seperated into groups. We aimed to examine the features of startle and blink reflexes in these groups and to gether knowledge whether there is a functional abnormality in brainstem circuitry contributing to the pathogenesis.

Background: Essential Tremor (ET) is the most common movement disorder and a heterogenous disease rather than a single entity. Both ET and Parkinson's disease (PD) are commonly encountered movement disorders and based on recent publishments they share the same clinical and pathogenetic aspects.

Methods: 14 ET, 15 ET+PD, 13 PD patients and 10 healthy subjects aged between 40-75 presented to Istanbul University Cerrahpasa Medical Faculty, Neurology Department, Movement Disorders outpatient clinic were included into this study. Blink reflex responses were taken via superficial recording electrodes from orbicularis oculi muscle with supraorbital electrical stimulus. To induce and record startle reflex, subjects were given a auditory burst signal binaurally with earphones and superficial recording EMG electrodes were placed on orbicularis oculi, masseter, sternocleidomastoid, biceps brachi, forearm flexor muscles.

Results: Blink and startle reflex responses of ET,ET+PD and PD groups were compared with each other and the control group. No statistically significant difference was found.

Conclusions: Blink and startle reflex responses of ET,ET+PD and PD groups were compared with each other and the control group. No statistically significant difference was found.

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Theta burst stimulation over the primary motor cortex does not induce cortical plasticity in Parkinson's disease

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Objective: To investigate whether a period of continuous theta burst stimulation (cTBS) induces cortical plasticity and thus improves bradykinesia of the upper limb in Parkinson's disease.

Background: Transcranial magnetic stimulation can be used to induce lasting effects on the excitability of the cortico-spinal motor output and can thus induce plastic changes within cortical tissue and motor pathways. In this context, plasticity is defined as lasting changes in the efficiency and/or number of synaptic connections in the motor circuits of the brain. Previous worked showed, that changes in cortical plasticity in PD can be induced by paired associative stimulation (PAS) or repetitive transcranial magnetic stimulation (rTMS) as evidenced by changes in the size of motor evoked potentials (MEP), the length of contralateral silent period (CSP) or ipsilateral silent period (ISP). The plasticity effects of cTBS remained to be elucidated.

Methods: In 8 patients with Parkinson's disease (two females; mean age: 68.5±5 years; disease duration: 4±3 years) electrophysiological (motor evoked potentials, contralateral and ipsilateral silent period) and behavioural (Purdue Pegboard test, UPDRS motor subscore) parameters were evaluated before (baseline condition) and after a 40-second period of (i) real or (ii) sham continuous theta burst stimulation over the primary motor cortex contralateral to the more affected body side off dopaminergic drugs.

Results: Compared to baseline, cTBS did change neither measures of cortical excitability (MEP, CSP, ISP) nor behavioural measures (Purdue Pegboard Test, UPDRS motor subscore).

Conclusions: cTBS over M1 has no significant effects on either cortico-spinal excitability or motor behaviour of the upper limbs in PD subjects off dopaminergic drugs. This data suggest that cortico-spinal plasticity is impaired in PD.

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Mechanisms underlying pathological oscillations in the rat 6-hydroxydopamine model of Parkinson's disease

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Objective: To establish the roles of the indirect and hyperdirect pathways in the genesis of pathological oscillations in rats with nigrostriatal lesion.

Background: The globus pallidus and subthalamic nucleus (STN) show increased oscillatory activity spanning a broad range of frequencies in patients with Parkinson's disease. This increased oscillatory activity is also present in rats with nigrostriatal lesion induced by 6-hydroxydopamine (6-OHDA), a widespread model of Parkinson's disease. Both in humans and rats, the enhanced basal ganglia oscillations are synchronized with cortical oscillations. Although there are several studies exploring the correlation with clinical signs

and dopamine dependence of parkinsonian oscillatory activity, the mechanisms underlying it remain obscure.

Methods: Recordings were performed in control rats and rats with nigrostriatal lesion showing motor deficiencies reminiscent of parkinsonian akinesia, under urethane anesthesia. In one set of experiments we explored the effect of blocking striatal NMDA receptors with the competitive antagonist AP-5 (100-200 μM) on oscillatory activity in the external globus pallidus (GPe). In another set we studied the short latency (presumably monosynaptic) response of STN neurons to cortical stimulation. GPe spiking activity was recorded with 16 channel silicon probes, STN activity with glass microelectrodes allowing juxtacellular labeling. In all experiments we also recorded the frontal cortex local field potential.

Results: In control rats, GPe activity was not modified by intrastriatal AP-5 administration. However, the abnormal synchronization between GPe and cortical oscillations (Zold et al., 2007) as estimated by coherence analysis, was reduced by 80% during intrastriatal AP-5 administration in rats with nigrostriatal lesion ($p<0.01$, five rats per group). Preliminary analysis of peristimulus time histograms (100 trials) suggest that STN neurons show enhanced monosynaptic responses to cortical stimulation in rats with nigrostriatal lesion.

Conclusions: Striatal NMDA receptors activation support the enhanced synchronization between the frontal cortex and GPe in rats with nigrostriatal lesion. Further studies are needed to establish how the hyperdirect pathway contributes to GPe and STN oscillations.

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Effects of levodopa and subthalamic nucleus stimulation on the oscillatory activity of the pedunculopontine nucleus area in Parkinson's disease

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Objective: To test the hypotheses that pedunculopontine area (PPNa) oscillatory activity is modulated by a locomotor task and levodopa (Ldopa), and that subthalamic nucleus (STN) stimulation modulates differently the neuronal activity of its output targets depending on its stimulation frequency.

Background: The motor triad of Parkinson's disease (PD) is improved by Ldopa and high-frequency STN stimulation, while Freezing Of Gait (FOG) responds poorly to Ldopa but may be improved by low-frequency STN and PPNa stimulation. Little is known about the pathophysiology of FOG in PD and the effects of stimulating the STN at different rates on its output targets.

Methods: Seven PD patients aged 63±6 years with previous STN stimulation had bilateral PPNa stimulation for disabling FOG. We recorded the local field potentials of the PPNa from quadripolar leads at rest and during 30-second step-on-place trials, under OFF and ON Ldopa, and with STN stimulation OFF, ON 20 Hz, and ON 130 Hz. STN stimulation was bipolar and effective on parkinsonism at 130 Hz. Fast Fourier Transforms were used to calculate the power of PPNa oscillatory activity from all dipoles, in the alpha (5-12 Hz), beta (13-18 and 22-35 Hz), and gamma (62-98 Hz) frequency bands.

Results: At rest and under OFF Ldopa/OFF STN stimulation, the alpha, beta, and gamma powers were 3.99±1.76, 2.78±1.41, and 1.67±0.10 respectively. Switching STN stimulation ON at 20 Hz or 130 Hz did not change the power of alpha, beta, or gamma band oscillatory activities of the PPNa. Under OFF Ldopa/ON STN stimulation, the relative alpha and beta band powers did not differ at rest or during step-on-place, but FOG was associated with gamma power desynchronization. Ldopa enhanced the synchronisation in the alpha band during FOG ($p<2x10-6$). The more severe the FOG under Ldopa, the lower the alpha and the higher the gamma powers.

Conclusions: FOG is associated with an imbalance between low and high frequency oscillatory activities of the PPNa that is enhanced under Ldopa in patients with Ldopa-resistant FOG. STN stimulation has no direct or indirect effects on the PPNa oscillatory activity which is independent on the classical parkinsonian motor triad, only improved by 130 Hz STN stimulation.

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Holmes tremor responsive to quetiapine

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Objective: To describe response to quetiapine treatment in a patient with Holmes Tremor (HT).

Background: HT, also called rubric or mesencephalic, first described by Benedikt in 1889 and then by Holmes in 1904, is characterized by rest, postural, intention, low frequency, and usually severe tremor, being one of the most disabling tremors. It is usually refractory to pharmacological treatment, and its etiology is diverse. Damage to dopaminergic and non dopaminergic systems, mainly the nigrostriatal pathway and cerebellar output tract represented by both dentothalamic and dentorubric bundles, have been described. Some weeks or even months usually elapse between the acute episode and the clinical presentation.

Methods: 76 year-old male with a previous history of myocardial infarction, hypertension and non anticoagulated atrial fibrillation. He was hospitalized with a left cerebelar ischemic infarct with hemorrhagic transformation, pontine infarction and right cerebellar ischemic stroke. Two months later he developed a severe postural, intentional and resting tremor. A diagnostic of HT was made and treatment with different drugs (levodopa, phenobarbital, amantadine, clonazepam) failed to improve symptoms. Quetiapine was then titrated up to 100 mg daily.

Results: With the 100 mg /day quetiapine dose, resting tremor was successfully controlled, and an 80% improvement in position and intentional tremor was observed. After stopping quetiapine tremor worsened, and improved once the drug was restarted.

Conclusions: Quetiapine, an atypical neuroleptic, might be an alternative therapeutic option for patients with HT. Poster presented at the XLIV Argentine Congress of Neurology. Mar del Plata, Argentina. November 14-November 17, 2007.

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Electrophysiologic analysis of reaction time variability in patients with Parkinson's disease

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Objective: We performed this study to evaluate (1) the relationship between RT variability assessed with surface EMG recording and clinically measured scores in patients with Parkinson's disease (PD) and (2) if RT variability changes as PD progresses.

Background: Variability or unsteadiness in motor performance is an important marker that used to evaluate motor function of the individual. Reaction time (RT) variability adversely affecting the patient's ability to adapt to environmental changes.

Methods: Simple RT of 31 patients with PD was obtained with electromyographic muscle recording from bilateral wrist flexor/ extensor muscles and ankle dorsi-flexor muscles during isometric contraction. RT variability was defined as the intra-individual standard deviation of RT based on the raw EMG data. The mean of the standard deviation of acquired signal parameters from each subject was calculated as an indicator of the range of RT responses. Motor function was assessed using UPDRS part III and progression of the disease was graded with H&Y stage. All participants also underwent neuro-cognitive function tests.

Results: Reaction time variability was greater in PD than in controls ($p<0.001$), and clinical data according to the UPDRS revealed that bradykinesia, rigidity, and the sum of the UPDRS motor scores

were correlated with RT variability, but RT variability was not influenced by the degree of disease progression.

Conclusions: Greater RT variability are characteristic motor features of PD and it could be used for assessment of the motor function of PD patients in a clinical practice. Further investigation are required to clarify the clinical impact of the RT variability on the activity of daily living of patients with PD. Individual movement could be quantified through surface EMG recording.

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Chronic local field potential recordings for adaptive deep brain stimulation

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Objective: Because novel deep brain stimulation (DBS) systems retroacted through local field potentials (LFPs) have been recently proposed, we tested whether and how LFPs can be still recorded one month after the surgery for DBS electrode positioning.

Background: Because LFPs recorded 2-7 days after DBS surgery provided physiological information on basal ganglia functions and correlate with the clinical state of Parkinson's disease (PD) patients, they can be used as a control variable in novel closed-loop DBS systems. However, changes in the tissue surrounding the electrode that occur after DBS surgery could be relevant for DBS electrode impedance and LFP recording.

Methods: We recorded LFPs and impedances from 11 patients with PD at 4 time points: immediately after (T-0h), 2 hours after (T-2h), 2 days after (T-48h), and one month after (T-30d) DBS surgery. LFP rhythms in the low frequencies (LF, 2-7Hz), low-beta (LB, 8-20Hz), and high-beta (HB, 21-35Hz) were considered.

Results: Impedances at T-0h were significantly higher than at all the other time intervals (T-2h, $p=0.0005$; T-48h, $p=0.0002$; T-30d, $p=0.003$). Correlated with this change ($p=0.005$), the LF band decreased at all time intervals ($p=0.0005$). Conversely, the LB and the HB increased in time (LB, $p=0.003$; HB, $p=0.022$), but did not change between T-48h and T-30d.

Conclusions: DBS electrode impedance and LFP pattern are a function of the time interval between electrode implant and LFP recordings. Whereas impedance decrease correlated with LF decrease could be related to changes in the electrode/tissue interface, beta modulations be the result of neural adaptation mechanisms. These findings show that LFPs can be also recorded 30 days after DBS surgery and are comparable with LFPs recorded 2-7 days after surgery, confirming that LFPs can be used in novel closed-loop DBS systems.

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Altered parieto-motor functional connectivity in Parkinson's disease

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Objective: To explore intra-hemispheric posterior parietal cortex (PPC)-primary motor area (M1) connections using paired pulse bifocal transcranial magnetic stimulation (ppTMS) in Parkinson's disease (PD) and its possible modulation by dopaminergic treatment.

Background: PD is commonly diagnosed by a clinical triad of motor symptoms as tremor, rigidity and bradikynesia. This latest symptom could be related to a difficulty in programming motor skills and its execution. PPC has connections with several brain areas as different primary sensory areas, pre-motor and ipsilateral M1 and is critically involved in movement planning and execution. Functional connectivity between the PPC and M1 can be tested in humans by ppTMS, a technique that allows to investigate the cortical connections between interconnected brain areas.

Methods: Twelve PD patients with (ON) and without (OFF) dopaminergic treatment and twelve age-matched healthy controls were included in the study. TMS was delivered over right PPC for the conditioning stimulus (CS) and over right M1 for the test stimulus (TS). Motor evoked potentials (MEPs) were recorded in left first dorsal interosseus (FDI). We used three different CS intensities set at 70%, 90% and 110% of the resting motor threshold (RMT) of right M1. TS intensity was set to evoke MEPs of 1 mV peak to peak amplitude over left FDI. We tested seven interstimulus intervals (ISIs) between the CS and TS corresponding to 2, 4, 6, 8, 10, 15 and 20 ms.

Results: In control subjects, we observed a significant facilitation of MEP amplitude at ISI of 4 ms when CS intensity was set at 90% of RMT. This significant facilitation was not observed in PD subjects in OFF condition and tended to normalise in ON condition.

Conclusions: The facilitatory intra-hemispheric functional connection between PPC and ipsilateral M1 is not observed in PD patients in OFF condition suggesting functional impairment of this circuit. This impairment could be related to functional or motor deficits observed in PD.

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Modulation of dysarthropneumophonia in advanced Parkinson's disease by low-frequency subthalamic nucleus deep brain stimulation

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Objective: To compare the effects of high-frequency (130 Hz) and low-frequency (60 Hz) subthalamic nucleus deep brain stimulation (STN DBS) on parkinsonian dysarthria in an objective, acoustic, aerodynamic analysis.

Background: Parkinsonian dysarthria is characterized by a breathy, harsh voice, hypophonia, monotony of pitch, a variable speech rate and imprecise consonants. This disabling, L-Dopa-resistant, axial symptom is frequently associated with gait disorders, such as freezing and festination. Conventional STN DBS shows little long-term benefit for speech, which often becomes increasingly unintelligible over time (Pinto et al., 2004).

Methods: Eleven Parkinson's disease patients (5 women and 6 men) on STN DBS were included in the study. The mean time since disease onset was 19 years and the mean time since initiation of stimulation was 6 years. All patients complained of gait disorders. We analyzed the patients' speech under three double-blind, randomized conditions (off-drug, off-stim ("worst off"), 60 Hz stimulation and 130 Hz stimulation) by recording (i) clinical speech intelligibility, (ii) aerodynamic parameters in an analysis with the EVA 2 system (intra-oral pressure (IOP), laryngeal resistance (LR), forced expiratory volume (FEV) and maximum phonation time (MPT)) and (iii) acoustic parameters (fundamental frequency (F0), its coefficient of variation (CV) and the intensity (I) after reading a sentence, in order to assess speech dysprosodia).

Results: We observed a clinically significant improvement in speech intelligibility in the 60 Hz condition, with higher IOP, FEV ($p=0.02$), MPT (+30%; $p=0.01$) and speech intensity than in the 130 Hz and "worst off" conditions. There were no differences between 60 and 130 Hz stimulation in terms of the LR. We observed a decrease in F0 and its CV during 130 Hz stimulation (-30%; $p=0.02$).

Conclusions: Our preliminary data suggest that the improvement in speech intelligibility observed during low-frequency (60 Hz) STN DBS in advanced PD patients with severe axial disorders may be related to better pneumophonic coordination. Moreover, the significant worsening of speech dysprosody during 130 Hz STN DBS may be linked to current diffusion to non-dopaminergic mesencephalic areas.

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Radicular and nonradicular back pain in Parkinson's disease patients

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Objective: The aim of our study was to analyze the clinical features and electroneurographical aspects of back pain in a group of PD patients.

Background: Back pain is a frequent feature in Parkinson's disease (PD) patients. The published data show a prevalence of up to 74 %. Back pain is a part of the spectrum of nonmotor symptoms, but it can be caused by degenerative problems of the spine. In many cases a syndrome of radicular irritation may be revealed by clinical and/or electroneurographical examination.

Methods: 74 PD patients were included in this study. Pain was quantified on the visual analogue scale (VAS). The duration, localization and characteristics of pain were taken into account. The syndrome of radicular irritation was defined on clinical grounds and/or electroneurographical aspects. Electroneurography was performed for all patients. The patients who presented back pain underwent an MRI of the spine.

Results: The average age of the patients was 67, 56±8, 18 years, with a mean severity of PD of 2.57 on the Hoehn and Yahr scale. Back pain occurred in 64, 86 % of the patients with an intensity of 61, 66 on VAS. Back pain was mainly present at the cervical and lumbar level. 34 patients (70.83 % of those who had pain) showed a radicular syndrome as well. In 10 patients the radicular syndrome was reveled only after neurophysiological assessment.

Conclusions: Back pain is frequent in PD patients. Electrophysiological assessment supplements the clinical evaluation of these patients. It brings useful data about the etiology of the back pain and quantifies the degree of radicular involvement.

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Effects of deep brain stimulation at individual frequencies in the treatment of Parkinson's disease and essential tremor

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Objective: Hypotheses: 1) β and θ oscillations are antikinetic and γ oscillation is prokinetic (oscillation model) 2) The main frequencies within each band are specific for each patient. 3) The oscillation model applies to conditions other than PD.

Background: Brain oscillations can be divided into frequency bands of δ (delta, 1-4 Hz), θ (theta, 4-10 Hz), β (beta, 10-30 Hz) and γ (gamma, 30-80 Hz). The *oscillation model* of the basal ganglia (BG) proposed that synchronization in the 8-30 Hz (θ and β) bands antagonize novel motor processing. Therapeutic deep brain stimulation (DBS) is typically set at high frequencies (HFS, >130Hz). Information on how local field potentials (LFP) power spectrum changes with stimulation and its relationship to clinical status is critical in understanding the mechanism of action of DBS.

Methods: The studies were performed 2 to 5 days after DBS electrode implantation while the DBS leads are externalized. Parkinson's disease (PD) patients with electrodes in the subthalamic nucleus (STN) and essential tremor (ET) patients with electrodes in the ventral intermediate nucleus (VIM) of the thalamus were recruited. In Experiment 1, LFP were recorded from DBS electrodes at rest and during self-paced and externally triggered wrist extension tasks. Patient specific frequencies within each band that showed the greatest change with dopaminergic medication and movement were identified. Experiment 2 investigated which frequency and type of stimulation was most effective in producing clinical benefit and modulating the LFP power spectra. We used single pulse, multiple pulses, and random stimulation protocols at the specific frequencies from Exp. 1. Exp. 2 was performed one day after Exp. 1 with DBS electrodes connected to an *external stimulator*. PD patients were tested randomly in the "OFF" and "ON" medication states. The clinically more affected side was studied and the LFP recorded during stimulation.

Results: Stimulation with specific gamma frequencies was comparable to therapeutic HFS in modulation of the recorded LFP power spectra and clinical effects.

Conclusions: Each patient has individual main frequencies within each band. Stimulation at the selected gamma peak may be at least as effective as HFS.

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Involvement of cerebellothalamocortical pathway in generating tremor in Parkinson's disease

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Objective: To investigate the excitability of the cerebellothalamocortical pathway in Parkinson's disease (PD).

Background: Rest and postural tremors are common in PD. The cerebellum may be involved in the generation of tremor. Lesion or stimulation of the cerebellar thalamus is an established treatment for medication refractory tremor. Tremor reset occurs with transcranial magnetic stimulation (TMS) of the primary motor cortex (M1) but not of the cerebellum in patients with essential tremor. The cerebellothalamocortical pathway can be assessed by TMS of the cerebellum which suppresses the contralateral M1 5-7 ms later, a phenomenon termed as cerebellar inhibition (CBI).

Methods: We studied 10 mild to moderate PD patients and 10 healthy controls. The more affected side of PD patients and the right arm of healthy subjects were tested. Surface electromyogram was recorded from the first dorsal interosseous (FDI), extensor carpi radialis and flexor carpi radialis muscles. Cerebellar stimulation was set at 5% below the threshold for evoking motor evoked potentials (MEP) in FDI muscle. M1 stimulation was adjusted to generate 1 mV MEP in the FDI muscle. Tremor reset from TMS delivered to the ipsilateral cerebellum or the contralateral M1 were assessed at rest and with arms extended. CBI was assessed by delivering cerebellar stimulation followed by M1 stimulation at interstimulus intervals (ISI) of 3-8 ms and was tested at rest and during arm extension.

Results: PD rest tremor was reset by M1 stimulation but not by cerebellar stimulation. PD postural tremor was reset by both types of stimulation, with M1 stimulation producing more prominent reset. CBI at rest was pronounced at ISI of 5-7 ms in the controls but was reduced in PD patients. Arm extension decreased CBI in healthy subjects and turned CBI into facilitation in PD patients. CBI correlated with the degree of tremor reset caused by the cerebellar stimulation in PD patients.

Conclusions: Resetting of tremor with cerebellar stimulation suggests that the cerebellothalamocortical pathway is involved in the generation of tremor in PD. Decreased excitability of the cerebellothalamocortical pathway in PD causes reduced inhibition in M1, which may be a factor leading to tremor.

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STN hole in Parkinson patients

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Objective: In this study we found a hole in subthalamic nucleus during elelctrophysilogy recording of about 10% of patients with Parkinson's disease who underwent deep brain stimulation. This finding has never been reported before in litarutre review.

Background: The Subthalamic nucleus (STN) becomes overactive in Parkinson's disease (PD) as a result of a decrease in striatal dopamine level. It is widely believed that in PD, neuronal degeneration occurs as a consequence of these changes in neuronal activity of the basal ganglia circuitry. Neuronal damage due to excitotoxicity is one possible mechanism. In 10.3% of sides which underwent STN-DBS we came across a hole in STN in MRI image and a silent area in

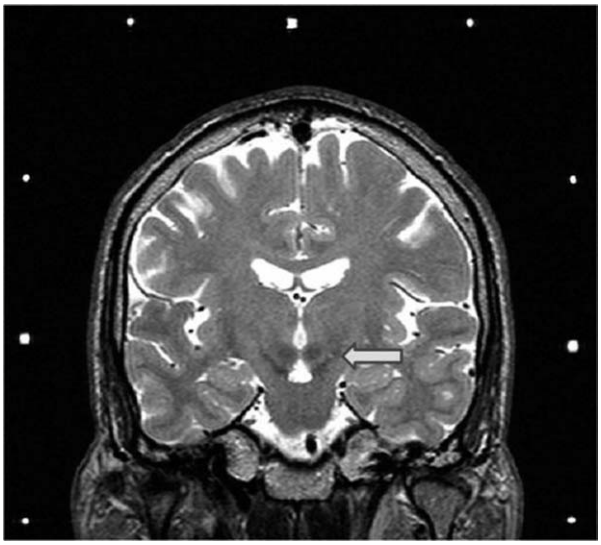

FIG. 1 (487).

electro-physiologic recording. In literature review nothing was found regarding this issue.

Methods: In 34 cases with PD who underwent bilateral STN-DBS surgery (68 sides) we came across a hole in STN in 10.3% of sides (7 sides in 68 sides) shown in MR imaging. It was correlated with a central silent area in electro-physiologic recording of STN at the same side. These findings were unilateral in all cases except one.

Results: The hole was in the affected side that the symptoms of the patients were more severe and longer. It is possible that some neuronal damage also occur within the STN itself due to its hyperactivity in the course of the illness and the hole in STN is the result of this pathologic phenomenon. We were not able exactly to decide weather this finding is just anatomical variation or represent the pathologic degeneration change in the STN during the course of the disease.

Conclusions: Although STN lesions potentially might help controlling the PD symptoms but this type of lesion that lead " hole" formation in STN maybe actually represent a more widespread neuronal pathology in the basal ganglia circuitry as the disease progress. Weather inhibition of the STN over activity by STN-DBS operation in ***earlier*** stages of PD can halt further progression of neuronal injury in the basal ganglia should be further investigated.

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Mu rhythm and rigidity in parkinsonian patients with DBS

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Objective: To observe the effects of STN DBS on somato-motor mu rhythm in patients with advanced Parkinson's disease (PD).

Background: 15-35 Hz somato-motor cortical beta oscillatory activity has been associated with the maintenance of the posture in healthy subjects. In PD, the strength of beta oscillation correlates with the estimated rigidity [1]. A new artifact suppression method called spatiotemporal signal space separation (tSSS) has made it feasible to record the cortical oscillations of PD patients with DBS by MEG, despite the strong stimulator-related artifacts [2].

Methods: We measured nine medicated PD patients with STN DBS (Medtronic®) both on and off. UPDRS motor scores were estimated in both conditions. Spontaneous brain activity was recorded by 306-channel MEG (Elekta Neuromag®) in eyes open and closed conditions. The strong magnetic artifacts caused by DBS were suppressed by the tSSS method. Minimum current estimates (MCE) and frequency domain MCE (MCEfd) were calculated to identify the oscillatory activity strength and location in the somato-motor region.

Results: The peak–and mean strengths of the mu rhythm within 18–22 Hz range correlated significantly with the summed UPDRS rigidity scores of upper and lower limbs ($r=0.786$ and $r=0.6587$, $p<0.05$), with eyes open and DBS on. With eyes closed or DBS off, the respective correlations were non-significant. The mean strength of the mu rhythm did not differ significantly between the DBS on and off conditions, whether the eyes were open or closed.

Conclusions: With DBS on and eyes open, the mu rhythm correlated significantly with rigidity. However, DBS had no effect on the mean strength of the 20-Hz mu rhythm. Apparently, DBS modifies the regulation of the mu rhythm by making it more physiologically relevant. Modulation of DBS with the components of mu rhythm contributing to the maintenance of posture vs. movement is one possible explanation. 1 Kühn AA, Kupsch A, Schneider GH, Brown P (2006): Reduction in subthalamic 8-35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease *Eur. J. Neurosci.* 23: 1956-1960 2 Airaksinen K, Mäkelä J, Taulu S, Ahonen A, Nurminen J, Schnizler A, Pekkonen E: Effects of DBS on auditory and somatosensory processing in Parkinson's disease (submitted).

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Subthalamic deep brain stimulation in Parkinson's disease: Influence of pulse width on motor, verbal and depressive symptoms

A.M. Reis, F. Rossato, T.T. Reis, J.V. Pinto, A.S. Schuh, P. Abreu, O.P. Dalligna, C.M. Rieder (Porto Alegre, RS, Brazil)

Objective: This study was designed to access DBS of the subthalamic nucleus (STN) in Parkinson's diesase (PD) with different electric pulse width settings on verbal fluency and depressive symptoms.

Background: Deep Brain Stimulation (DBS) is one of the treatment options for advanced idiopathic PD. Some studies have suggested that verbal fluency (VF) and mood symptoms may suffer impairment after STN DBS. However, no clearly definition about the influence of certain electrical parameters, especially pulse width (PW), on verbal fluency and mood symptoms was obtained.

Methods: Eleven patients with advanced PD with DBS in STN were randomized in a double-blind trial and were assessed about VF, semantic and categorial, and mood aspects with some questions of the Beck Depression Inventory (BDI), in all three electrical categories: a) with stimulator turned off; b) with stimulator turned on with the lowest possible PW (60μs) and; c) stimulator turned on with PW in the best motor result obtained previously. Beside that, the scores obtained in VF in the BDI previously to surgery were compared with the scores with DBS on at least 5 months after the surgery. UPDRS were performed during evaluations.

Results: There was no impairment in the VF when compared scores previous to the surgery with the performance after DBS implantation. In the assessment of VF associated with different PW, there are no statistical differences in the three electrical modalities. When depression symptoms were evaluated, there was a significantly improvement in irritability scores after the surgery with DBS on, compared to before surgery ($p<0.024$). Although some symptoms were markedly worst in some patients when the DBS was switch-off, there were no statistically differences between the different PW and depressive scores. Reduction of PW did not change significantly the UPDRS.

Conclusions: Our evidences show that changes of PW in subthalamic DBS do not produces significantly changes in the VF. Apparently, reductions of PW will not produce significantly impairment of UPDRS suggesting that the smallest PW must be tried once it will reduce the battery discharge. The irritability symptoms present previous to DBS surgery are improved by subthalamic DBS.

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Enhanced intrinsic excitability of striatal cholinergic interneurons in a rat model of Parkinson's disease

G. Sanchez, M.J. Rodriguez, M.G. Murer (Buenos Aires, Argentina)

Objective: To establish the mechanisms underlying enhanced excitability of striatal cholinergic interneurons in rats with nigrostriatal lesion.

Background: An enhanced cholinergic tone has been regarded as a core feature of Parkinson's disease pathophysiology and cholinergic antagonists have been used in patients. Moreover, cholinergic interneurons loss their typical pause response to reward in animals with nigrostriatal lesion. Although cholinergic hyperactivity and the lack of reward responses in cholinergic interneurons could be important in Parkinson's disease pathophysiology, the involved mechanisms remain to be clarified.

Methods: Whole-cell patch clamp recordings of striatal cholinergic interneurons have been performed in slices of control rats and rats having a nigrostriatal lesion induced with 6-hydroxydopamine (6-OHDA), under current and voltage-clamp conditions, at 32-34°C. Computer simulations were run in Neuron software.

Results: Cholinergic interneurons fire two times more spikes during current depolarizing pulses in rats with nigrostriatal lesion ($n=70$) than in age matched adult control rats ($n=74$; $p<0.01$). This is mainly because cholinergic interneurons of control rats show a marked adaptation during the current pulse that is almost absent in 6-OHDA rats. Thus, the interspike intervals are two times longer at the end than at the beginning of the current pulse in controls, but do not change along the pulse in the parkinsonian condition ($p<0.01$). Voltage clamp experiments and computer simulations show that a Barium sensitive delayed outward current could be responsible for firing adaptation and the differences between control and lesion rats.

Conclusions: Striatal cholinergic interneurons show reduced firing adaptation during sustained depolarization in dopamine depleted rats. This change can contribute to the hypercholinergic state and lack of pause response to reward in Parkinson's disease. Preliminary findings indicate that an outward current mediating firing adaptation in controls is reduced in the parkinsonian condition.

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Intermittent synchronous neural oscillations in subthalamic nucleus in Parkinson's disease

C. Park, R.M. Worth, L.L. Rubchinsky (Indianapolis, Indiana, USA)

Objective: To describe the properties and to understand the potential origin of the synchronized neural activity in parkinsonian basal ganglia using data analysis and modeling methods of nonlinear dynamics.

Background: Recent studies indicate that patterns of oscillatory synchronous activity in basal ganglia are strongly relevant to basal ganglia physiology and basal ganglia disorders, such as Parkinson's disease. Multiple experiments lead to a conjecture that pathologically synchronous and excessively oscillatory neural activity contributes to the generation of hypokinetic symptoms of Parkinson's disease. This dictates the interest in the properties of this synchronous activity and in its potential mechanisms.

Methods: We use time-series analysis methods of nonlinear dynamics to study oscillatory activity in extracellular units and local field potentials (LFP) in subthalamic nucleus (STN) of parkinsonian patients. In particular, we study the phase locking of the neural activity on the short time-scales. We further use conductance-based models of subthalamo-pallidal circuits to identify network mechanisms, which are responsible for the generation of synchronous patterns, similar to the ones, which we observe in our data.

Results: Experimental data analysis reveals that the phase-locking of the extracellular units and LFP is interrupted by the intervals of non-phase-locked dynamics. Although numerous, these desynchronization events tend to be short, which appears to be a characteristic feature of the observed oscillations. The study of conductance-based models of subthalamo-pallidal circuits indicates that this characteristic feature of oscillations can be prominent without external modulation of oscillations, if the synaptic coupling in the network is strong enough, but not excessively strong.

Conclusions: The results suggest that the intermittent synchronous dynamics is an intrinsic generic feature of basal ganglia activity, which may be augmented in Parkinson's disease and lead to the generation of symptoms. Attempts to suppress the synchrony (whether through the deep brain stimulation or pharmacologically) need to recognize that the oscillations are not fully synchronous to begin with, but rather frequently interrupted by brief desynchronized dynamics.

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Intraoperative microelectrode recording in Parkinon's disease reveals STN subdivisions by means of discharge pattern and waveform

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Objective: The aim of the study was the intraoperative identification and characterization of subterritories of the subthalamic nucleus (STN).

Background: The STN is the currently most effective target for deep brain stimulation (DBS) in advanced Parkinson's disease (PD). As the STN is divided into sensorimotor, limbic, and associative subareas, implanting the electrode in the dorsolateral sensorimotor region is regarded as crucial for the optimum motor benefit and for the prevention of cognitive and behavioural adverse events of the procedure.

Methods: In 12 PD patients, stepwise intraoperative microelectrode recordings (MER) were performed using five concentrically configured electrodes (Medtronic, Minneapolis, USA) starting from 10 mm above until 4 mm below the calculated target point. MER were made over 30 sec at each height in the awake patient (drug-off state). Subsequent off-line analyses were performed with the Spike 2™ (Version 4.03, Cambridge Electronic Design, Cambridge, UK) and Neuroexplorer® (Version 4, Nex Technologies, Massachusetts, USA) software. According to the individual extension of typical STN activity, the target region was subdivided into three commensurate parts: dorsolateral (DL), transition zone (TZ), ventromedial (VM).

Results: In a total of 313 neurons, we found a higher occurence of bursty ($p=0.001$) and oscillatory ($p=0.05$) spike patterns in the DL region, whereas irregular discharges were more frequent in the VM area ($p=0.005$). In the DL region, triphasic waveforms were predominantly present ($p=0.017$) while biphasic potentials were more frequent in the VM area ($p=0.013$). No significant differences were found for frequency, coefficient of variance, asymmetry index as well as spike duration and amplitude.

Conclusions: The sensorimotor DL region of the STN can be electrophysiologically distinguished by bursty and oscillatory discharges and triphasic waveforms. These characteristics presumably reflect pathological synchronization in the basal ganglia motor circuit in PD. We conclude that MER can be helpful for the delineation of the dorsolateral STN and for the precise implantation of DBS electrodes.

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High frequency stimulation of subthalamic nucleus restore to a normal level the enhanced group II spinal excitation observed at cervical level in patients with Parkinson's disease

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Objective: The modulation of the excitability of upper limb cervical spinal reflexes involving group I-group II afferents, by High Fre-

quency Stimulation of the subthalamic nucleus (STN-HFS) was investigated in 7 bilaterally STN implanted patients with Parkinson's disease (PD).

Background: The contribution of group II spinal pathways in parkinsonian upper limb rigidity and the modulation of spinal excitability of these Group II pathways by L-DOPA has been recently shown (Marchand-Pauvert et al 2010 submitted), using a new method (Lourenčo et al 2006) in a group of medically treated PD patients.

Methods: The effect of ulnar nerve electrical stimulation on Flexor Carpi Radialis electromyogram (FCR EMG) was studied in 7 STN bilaterally implanted PD patients (DBS group) without L-DOPA (MED-OFF) and in two randomized conditions: with stimulation being switched OFF (STIM-OFF) or ON, (STIM-ON). Results obtained in STIM-OFF conditions were compared to those obtained in a control group (10 subjects).

Results: The ulnar nerve stimulation produced short latency and long duration facilitation in the FCR EMG, mediated by group I and group II afferents. No significant change was found in the group I excitation but the mean amplitude of the group II excitation was significantly enhanced in the rigid upper limb of patients in DBS GROUP in MED OFF and STIM OFF conditions compared to controls (P=0.01). STN-HFS had no effect on group I excitation but decreased significantly the mean amplitude of the Group II excitation in the DBS GROUP (P=0.01) as it was previously shown with a single dose of L-DOPA.

Conclusions: These results give further support to the contribution of group II spinal pathway in the pathophysiology of PD and show for the first time that HFS-STN can restore to a normal level the enhanced spinal excitability of group II pathways observed in rigid PD patients.

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Effect of micro lesion during complex tasks in basal ganglia dysfunctions

A. Singh, J. Levin, K. Boetzel (Munich, Germany)

Objective: In the present study, we investigated the effect of micro lesion to perform fast ballistic movements in both Parkinson and dystonic patients.

Background: Slowness in the execution of movement is termed as bradykinesia which is a prominent feature of Parkinson's disease (PD) and other disorders of basal ganglia (BG) while in dystonia, sustained muscles contractions cause repetitive movements. Now days, electrodes are implanted in subthalamic nucleus (STN) and globus pallidua internus (GPi) for the deep brain stimulation (DBS) against Parkinson and dystonic patients respectively. Electrodes implantation has been explained to elicit motor improvement not only after stimulation but also before the stimulation.

Methods: Present study is based on 16 patients who underwent DBS, for PD (9 cases) and dystonia (7 cases). The experimental task required seated subjects to perform self paced movements with their right and left arm under two conditions. In one paradigm subjects executed repetitive fast ballistic (complex) movement with touching the boxing hammer with fist (BT) while in another they stopped themselves just before the hammer (BWT).

Results: PD subjects executed BT movement significantly faster than dystonic subjects while in BWT movement no differences was observed. During BT movement, PD subjects were found faster compare to BWT, but not in dystonic subjects. In addition, no significant differences were observed in the coefficient of variation (CV) of BT and BWT velocity. CV results were indicating that all movements performed by both the groups were not irregular.

Conclusions: The effect of micro lesion is more prominent in PD rather than dystonia and apparent explained by kinematic properties. PD and dystonia both have different pathophysiological circuit and the micro lesion may affect them differently and also in different basal ganglia dysfunctions.

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Rate-dependent impairments in repetitive finger movements in Parkinson's disease are associated with tonic suppression of movement-related cortical oscillations

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Objective: To examine the effects of movement rate on movement-related cortical oscillations (MRCOs) associated with repetitive finger tapping in patients with Parkinson's disease (PD).

Background: Repetitive finger movements in PD are characterized by a marked loss of amplitude (hypokinesia) and hastening when movement rate nears or exceeds 2 Hz. Currently, the cortical mechanisms contributing to the loss of movement control near this frequency are unknown. This study examined the changes in MRCOs associated with the emergence of rate-dependent movement impairments.

Methods: Ten subjects with PD in the off-medication state and 10 matched controls were studied. Subjects performed finger flexion/extension movements cued by a tone presented from 1 to 3 Hz in 0.25 increments. Spectral power from 5-40 Hz was derived from a 72-channel EEG recording obtained during rest, listen-only, and move conditions.

Results: In both PD and control subjects, low movements rates (<1.75 Hz) were characterized by MRCOs in the alpha and beta bands. Movements were preceded by a suppression of MRCOs in both bands immediately prior to and during movement and enhancement of MRCOs between movements. This pattern of MRCOs and movement performance was maintained in the control subjects up to 3 Hz. PD subjects showed marked decrements in movement performance at rates near 2 Hz and above. The movement rate at which the impairment emerged was associated with a near-tonic suppression of MRCOs in both bands and was maintained up to the tone rate of 3 Hz.

Conclusions: The rate-dependent impairment of repetitive finger movements in patients with PD (off medication) is associated with the manifestation of prolonged and maintained suppression of MRCO's in both the alpha and beta bands. These findings show that the hesitations and arrest of repetitive movements are not due to the re-emergence of beta band oscillations that have been proposed to mediate the akinetic state of PD.

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Effect of partial weight supported treadmill gait training on cardio autonomic modulation in patients with Parkinson's disease

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Objective: To evaluate the effect of Partial weight supported treadmill gait training (PWSTT) on Heart rate variability (HRV) in patients with Parkinson's disease (PD).

Background: HRV represents one of the most promising markers of cardiao-autonomic functions. PWSTT is widely used in rehabilitation of gait in patient with PD. However, its effect on cardio-autonomic modulation in PD has not been studied widely.

Methods: Twenty seven patients with idiopathic PD (age 57.4±8.6yrs, M:F::20:7), on stable doses of dopaminomimetic drugs were assigned into two groups. Group I (n=13;duration of illness 4.3±4.2yrs) were only on medications & Group II (n=14;duration of illness 4.9±4.2yrs) along with medication, underwent PWSTT (Biodex, USA) with 20% unweighing for 30 minutes/day, 4 days/week, for 4 weeks (16 sessions). Both the groups were evaluated in best 'ON' state at basal and after 4 weeks. Five minutes of resting HRV (time domain in millisec and Frequency domain in Hz) parameters of PD were compared with fourteen healthy volunteers (age 56±4.8 yrs, M:F::10:4).

Results: Compared to healthy volunteers, HRV of PD patients showed significantly lower values in. Mean NN (p=0.04), SDNN (standard deviation of NN interval) (p=0.004), RMSSD (root mean square successive difference) (p=0.049), LF (low frequency) (p=0.018) and total power (p=0.003). Following PWSTT, Group II

had significant improvement of Mean NN (pre=747.8±69.6, post =829.6±115.3, p=0.002), SDNN (pre=17.5±7.1, post=26.7±11.4, p<0.001), RMSSD (pre=11.3±5.1, post=21.4±10.5, p<0.001), Total power (pre=388.4±326.4, post=861.0±837.1, p=0.001), LF (pre=106.1±103.4, post=256.8±320.7, p=0.007), HF (high frequency) (pre=57.8±74.7, post=179.1±178.2, p=0.001) and HFnu (28.2±9.2, post=37.3±13.1, p=0.03). In addition, decreased LFnu (58.6±13.3, 49.8±18.0, p=0.03), and LF/HF ratio (pre=2.3±0.8, post=1.5±1.1,p=0.03) was observed.

Conclusions: PD patients had lower HRV compared to healthy volunteers. PWSTT improved HRV in patients with PD. Four weeks training was optimum for achieving significant change in cardio-autonomic modulation in PD. PWSTT can be used as an adjunct in rehabilitation PD with autonomic dysfunction.

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Patients with Parkinson's disease have a less differentiated muscle activation pattern than healthy controls during manual circle movement

C.M. Toxopeus, B.M. de Jong, G. Valsan, B.A. Conway, J.H. van der Hoeven, K.L. Leenders, N.M. Maurits (Groningen, Netherlands)

Objective: To investigate changes in modulation of agonist and antagonist activity in patients with Parkinson's disease (PD) during execution of continuous circle movement.

Background: PD patients experience changes in the organization of motor execution inducing problems with initiation and inhibition of movement. This leads to impaired starting and stopping of (purposeful) movement. On the other hand, purposeful movement requires a motor system in which initiation and inhibition of successive movements are adequately organized; the continuous modulation of agonist and antagonist activity. Yet, it is not clear how changes in initiation and inhibition, regarding the agonist-antagonist adjustment, in PD patients cause a decline in the ability to execute purposeful movement. A continuous circle task could provide further insight in specific changes in modulated muscle activity in PD patients.

Methods: We employed a two-directional, continuous circle task (clockwise and counter clockwise) using a manipulandum with visual feedback. Kinematic and electromyographic (EMG) parameters of 4 lower arm muscles were used to compare (ant)agonist activity between a group of mildly affected PD patients (N=15, stage 1-2 Hoehn Yahr) and 2 groups of healthy subjects (elderly, N=16 and young subjects, N=16).

Results: Comparison of kinematic parameters showed that PD patients perform circle movements significantly slower, make more errors and show more variability in task execution compared to both young and elderly subjects. The EMG data showed that PD patients use a less differentiated muscle-activation pattern than young subjects, when executing circle movements. The muscle activation pattern of elderly was found to be slightly less differentiated than in young subjects, but still substantially better than in PD patients.

Conclusions: We conclude that PD patients, compared to healthy subjects, show changes in kinematics and muscle activation patterns during execution of a continuous circle task. These changes in execution of continuous movement might provide an objective measure of both bradykinesia and rigidity, potentially useful for diagnosis, follow-up of disease progression and further fundamental investigations into these phenomena.

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Initiation and inhibition of wrist movements in parkinson patients and healthy controls

C.M. Toxopeus, J. Gooijers, B.M. de Jong, G. Valsan, B.A. Conway, J.H. van der Hoeven, K.L. Leenders, N.M. Maurits (Groningen, Netherlands)

Objective: This study investigated, whether findings of impaired motor function due to aging and Parkinson's disease (PD) could be replicated on two movement tasks focused on initiation and inhibition of movement using a custom made wrist device.

Background: Motor performance has been found to decline as a result of aging and PD. Elderly, compared to young subjects, are known to have a decreased movement speed, longer reaction times and a greater motor output variability. PD patients experience additional problems with movement initiation.

Methods: 16 young (mean age 23.8 years, 7 males) and 16 elderly (mean age 64.3 years, 6 males) healthy subjects and 16 PD patients (Hoehn-Yahr 1-2, mean age 60.6 years, 11 males) performed a ballistic wrist movement, with no intentional stops, and a fast, controlled wrist movement with intentional stops (4 stop) using a wrist manipulandum with visual feedback.

Results: PD patients and elderly performed worse than young adults concerning reaction time, errors and motor output variability during the ballistic task. Remarkably, PD patients were not impaired on velocity and acceleration measures. Group comparisons on the fast, 4 stop movement (only performed by both control groups) revealed more errors and greater variability for the elderly. Besides group comparisons, direction comparisons also revealed interesting findings. Higher reaction times, increased velocity and increased acceleration were demonstrated for wrist flexion as compared to wrist extension movements. Electromygraphic (EMG) activity, recorded from the forearm, demonstrated a complete triphasic EMG pattern for most subjects, indicating an intentionally terminated ballistic wrist movement. For some subjects a triphasic EMG pattern with a diminished or abolished antagonist activity was found, indicating a non-intentionally terminated ballistic wrist movement.

Conclusions: Overall performance on the ballistic movement task, was better in young than in elderly subjects and better in elderly subjects than in PD patients. Differences were smaller for the 4 stop movement. Further, differences in wrist flexion and extension were found, independent of age and PD.

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Antidromic activation of subthalamic neurons by contralateral subthalamic deep brain stimulation in Parkinson's disease

H.C. Walker, R.L. Watts, C.J. Schrandt, H. Huang, B.L. Guthrie, E.B. Montgomery (Birmingham, Alabama, USA)

Objective: To characterize the response of subthalamic neurons to contralateral subthalamic deep brain stimulation (STN DBS).

Background: Multiple studies have shown bilateral improvement in motor symptoms in Parkinson's disease (PD) following unilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) and internal segment of the globus pallidus (GPi), yet the mechanism(s) underlying this phenomenon are poorly understood. We hypothesized that STN neuronal activity is altered by contralateral STN DBS.

Methods: Patients undergoing staged STN DBS surgery were awake and at rest in the "practically defined off" medication state. Microelectrode recordings identified the sensorimotor STN, and two stimulation paradigms were tested for 120 seconds each. First, the contralateral STN stimulator was activated at 160 Hz at settings previously determined to be clinically effective in the outpatient setting. Second, 30 Hz stimulation was delivered at otherwise identical settings. Baseline STN activity was recorded for 120 seconds before, between, and following the two stimulation conditions. An analysis routine discriminated neurons in the deartifacted data based upon waveform morphology using a validated template-matching algorithm. Raster plots and histograms for each neuron were constructed centered on the time of the contralateral stimulus pulse, and neuronal activity in the resting state was compared to that during high and low frequency contralateral STN stimulation.

Results: We demonstrate short latency, temporally precise, stimulation frequency-independent responses from contralateral stimulation consistent with antidromic activation. Furthermore, the total discharge frequency in response to contralateral 160 Hz stimulation was greater than during 30 Hz stimulation and the resting state (12.3±1.7

versus 10.6±1.7 and 9.7±1.5 Hz, p=0.006 and p<0.001, respectively, one-way repeated measures ANOVA with bonferroni pairwise comparisons).

Conclusions: These findings demonstrate complex responses to DBS and imply that output activation throughout the basal ganglia–thalamic–cortical (BG-Th-CTX) network rather than local inhibition is the therapeutic mechanism of DBS. STN activity was increased by contralateral high frequency STN DBS.

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Effects of STN DBS on saccade latency–analysis using a probability distribution (the LATER model)

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Objective: To investigate the effects of subthalamic stimulation (STN DBS) on saccade latencies using a probability distribution (the LATER) model in Parkinson's disease (PD) patients.

Background: Reciprocals of saccade latencies are considered to show a Gaussian distribution (Carpenter 1981). This model (LATER model) allows us to investigate the rate of information processing and a total amount of information by plotting the cumulative probability of latency distribution against the reciprocals of latencies (reciprobit plot).

Methods: 32 PD patients (HY II-IV, age 58.3±7.9, 15 men, 17 women) with STN DBS performed visually guided (VGS), gap (GS), memory guided (MGS), and anti (AS) saccade tasks when DBS was on and off.

Results: STN DBS significantly shortened the latencies of VGS, GS, and AS. STN DBS evoked a leftward parallel shift of the reciprobit plots, except for MGS. The latencies of MGS were not affected by STN DBS. The reciprobit plots were not swiveled by STN DBS in any tasks.

Conclusions: Parallel shift of reciprobit plots suggests changes in the rate of information supply during a decision making. Their leftward shift suggests that STN DBS induced an acceleration of the visual information processing. In VGS, GS, and AS tasks, the direction and eccentricity of saccade were assessed after a target appearance, although it was done before a target appearance in MGS task. The acceleration of processing by STN DBS must be more in VGS, GS, and AS than in MGS. Furthermore, swiveling of reciprobit plots is thought to reflect the change of the starting and threshold level of information signals for decision making. STN DBS did not induce their swiveling, and it must not affect the starting and threshold level of signals. The LATER model indicates that the effects of STN DBS on saccade latency are provided by an acceleration of the processing rate of the visual information, rather than by changing of the starting and thresholds for decision making.

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Levodopa and deep brain stimulation partially harness different therapeutic mechanisms

A. Zaidel, H. Bergman, Z. Israel (Jerusalem, Israel)

Objective: In this study we reassess the notion of congruency between the therapeutic mechanisms of levodopa and subthalamic nucleus deep brain stimulation (STN DBS) in Parkinson's disease (PD) through both clinical and physiological analyses.

Background: It has become widely accepted that in PD, the extent of preoperative levodopa responsiveness predicts the extent of responsiveness to STN DBS. However, this notion may be the result of statistical methods and primary assumptions. In addition, physiological studies have shown that pathological STN oscillations are suppressed by dopamine replacement therapy, and by STN DBS in some studies, but not others. Hence the relationship between levodopa responsiveness, STN beta oscillations and responsiveness to STN DBS requires reassessment.

Methods: We compared preoperative responsiveness to levodopa, as well as STN microelectrode recordings to the outcome of STN DBS, as evaluated by the third section of the Unified Parkinson's Disease Rating Scale (UPDRS-III, motor score).

Results: We were able to reproduce previously published correlation results on our data (N=48 patients). Yet, these same results were demonstrated even after random shuffling of our data. Notably, we did not observe a correlation between STN DBS efficacy and preoperative levodopa responsiveness when using their respective baselines and fractional scores of motor improvement. Furthermore, postoperative responses were not limited by preoperative scores, with tremor demonstrating the greatest discrepancy. Hence, preoperative levodopa responsiveness does not predict or limit the outcome of STN DBS. We found that the spatial extent of beta oscillations in the STN predicted a favorable response to STN DBS (p<0.0001), however, different beta frequencies were associated with improvement of the axial symptoms due to DBS, on and off medication (~15Hz and ~25Hz, respectively). In contrast, a strong response of limb symptoms (rigidity and limb-bradykinesia) correlated with wideband over-activity. This association between limb symptom improvement and over-activity was only seen for DBS with medication and not for DBS alone.

Conclusions: These clinical and physiological results imply different therapeutic mechanisms for levodopa and STN DBS and therefore question the validity of using substantial preoperative levodopa responsiveness as a selection criterion for STN DBS.

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Abnormal interhemispheric interactions in ATP13A2 mutation carriers: A TMS study

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Objective: To determine electrophysiological characteristics of ATP13A2 mutation carriers.

Background: Kufor-Rakeb syndrome (PARK9) is an autosomal recessive multisystemic neurodegeneration characterized by juvenile-onset parkinsonism, pyramidal signs, dementia and supranuclear gaze palsy and caused by mutations in the ATP13A2 gene. Investigations by transcranial magnetic stimulation (TMS) in idiopathic Parkinson's disease (IPD) and parkin mutation carriers (MutC) revealed specific alterations of motor cortex excitability. As yet it is unclear whether these alterations are due to neurodegeneration per se or represent compensatory adaptive mechanisms.

Methods: Four heterozygous, one clinically affected compound-heterozygous ATP13A2 MutC and nine healthy subjects were investigated with TMS. Apart from standard measurements including resting motor thresholds and MEP latencies, the ipsilateral silent period (ISP) was determined using TMS pulses over the left and right primary motor cortex (M1) during ipsilateral pinch grips of maximal voluntary contraction (MVC). The contralateral silent period (CSP) was determined by application of TMS during contraction of the target muscle with 50% MVC. Interhemispheric inhibition (IHI) was investigated using conditioning stimuli with an intensity of 120% RMT applied over left/right M1 followed by a test stimulus (intensity 120% RMT) over the contralateral M1 at interstimulus intervals of 6–10 msec. Short afferent inhibition (SAI) was tested by applying electrical stimuli to the right index finger followed by TMS pulses over the left M1.

Results: MEP latencies and the CSP duration were increased bilaterally in the compound-heterozygous MutC. Left iSP duration was increased both in the compound-heterozygous MutC and in the asymptomatic heterozygous MutC. IHI and SAI were normal in MutC.

Conclusions: In line with clinical signs of pyramidal tracts damage, MEP latencies were increased in the compound-heterozygous MutC. In asymptomatic heterozygous ATP13A2 mutation carriers, some interhemispheric interactions were abnormal which might be a direct consequence of the ATP13A2 mutation or represent compensatory adaptive changes.

POSTER SESSION 2
TUESDAY, JUNE 15, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

PARKINSON'S DISEASE: RATING SCALES

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Investigation of the psychometric properties of the short Parkinson's evaluation scale/scales for outcomes in Parkinson's disease (SPES/SCOPA)

R.E. Wilson, L.C. Seeberger, P.O. Buck, J.B. Conner, J. Castelli-Haley (Kansas City, Missouri, USA)

Objective: To further investigate the reliability and validity of the Short Parkinson's Evaluation Scale/Scales for Outcomes in Parkinson's disease (SPES/SCOPA) motor clinical examination, a brief scale to evaluate motor impairment in Parkinson's disease (PD) patients.

Background: The SPES/SCOPA was developed as a reliable and valid scale that can be completed in less time than the Unified Parkinson's Disease Rating Scale (UPDRS); however, relatively little research in the US has investigated its psychometric properties.

Methods: The BRAVURA study was designed to investigate order effects associated with the UPDRS motor examination at 2 centers in the US. Patients, stratified by center and previous Hoehn and Yahr (H&Y) stage, were randomly assigned to 1 of 2 UPDRS item sequences. All scale evaluations occurred during a single clinic visit. In addition to the 8-item SPES/SCOPA motor clinical examination and the 14-item UPDRS motor examination, scales included current H&Y stage and patient- and physician-rated Schwab and England Activities of Daily Living (ADL). Data were analyzed using Cronbach's alpha and Spearman's correlation.

Results: Complete data were available for 112 patients (mean time from diagnosis=6.4 years; 50.9% previous H&Y stage 2.0 or less). Relationships among the scales were comparable across the 2 experimental groups, thus data were pooled for these analyses; SPES/SCOPA mean score=9.5 (SD=5.2). The SPES/SCOPA demonstrated good internal reliability (alpha=0.79). Construct validity was supported with the SPES/SCOPA correlating 0.76 with the UPDRS. Furthermore, the SPES/SCOPA correlated 0.47 with current H&Y stage and -0.39, -0.45 with patient- and physician-rated ADL, respectively.

Conclusions: In this US sample of PD patients with varied disease severity, the SPES/SCOPA exhibited good psychometrics, including evidence of construct validity with the current standard of motor impairment measurement. The SPES/SCOPA also had good internal consistency and correlated with 3 broad evaluations of disease disability in a similar fashion to the UPDRS. Additional research on short scales of motor impairment will help clinicians evaluate their patients as easily, consistently, and accurately as possible.

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The use of the original and new UPDRS in Tanzanian patients with Parkinson's disease

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Objective: To describe the use of the new and original Unified Parkinson's Disease Rating Scale (UPDRS) in a group of patients with Parkinson's disease (PD) in Tanzania and to offer practical tips from our experience.

Background: The most widely used rating tool in PD is the UPDRS. Recently, the UPDRS has been updated to incorporate more items on non-motor (NM) symptoms and to make it more widely culturally acceptable. Several of the original questions, e.g. eating with cutlery, handwriting and buttoning clothes were not valid in our population in Tanzania, or other societies world-wide. We used the original UPDRS in our prevalence study in 2006 [1] and continued to follow up patients annually. Medication was started in April 2007.

Methods: At the 2008 follow up, all patients were assessed in their own homes including completion of both the original and new UPDRS.

Results: Both new and original UPDRS were easy to carry out in patients' homes. The new UPDRS took 5 -10 minutes longer. In 2008 the mean original UPDRS score was 43 (range 15-95) and the mean new UPDRS was 59 (17-141). It should be noted that the handwriting question, which is still in the new version, was difficult to score. It could be either "no change" to their handwriting as they have never been able to write, or "cannot write at all", but this suggests they have very severe PD. The NM section has been significantly expanded, and these questions were acceptable to the study population. 7/19 complained of illusions or hallucinations, 9/19 reported being depressed, 7 were anxious and over half reported day time sleepiness. Urinary symptoms (14/19) and constipation (10/19) were common and 14/19 complained of fatigue. All of our patients are now treated. In both scales, section IV refers to complications of treatment. Patients who are untreated may therefore have a low score overall on the UPDRS as they have scored very little on section IV, but this may be misleading. In this situation, UPDRS part III may be the most useful and comparable score.

Conclusions: Both original and new UPDRS were easy to use in this setting. Although slightly more time consuming, the new UPDRS took into account more NM symptoms which may be very troublesome for patients. Even after cultural adaptation, there are still some questions that are not entirely transferrable to a sub-Saharan African population.

505

Comparison of the toe tapping component of the MDS-UPDRS motor scale with leg agility and finger tapping

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Objective: To evaluate the utility of the MDS-UPDRS toe tapping score, by comparing it to MDS-UPDRS leg agility and finger tapping.

Background: Toe tapping, a novel component of the MDS-UPDRS motor scale that was not part of the original UPDRS, measures distal lower extremity function. The clinical value of toe tapping, relative to leg agility which also measures lower extremity motor function, is unknown.

Methods: This is a sub-analysis of an observational study of subjects with Parkinson's disease, in random motor states. MDS-UPDRS was performed along with a questionnaire that included questions about frequency of falls and Freezing Of Gait (FOG). Averages of left and right sided toe tapping, leg agility, and finger tapping scores were calculated, for subjects whose data were available for analysis (N=75). R^2 and p values were calculated using SPSS, correlating toe and finger tapping, leg agility, and the total MDS-UPDRS motor score with other items of interest.

Results: Mean (standard deviation) MDS-UPDRS motor subscores were 1.1733 (0.9462) for toe tapping, 0.7533 (0.7684) for leg agility, and 0.8933 (0.88261) for finger tapping. Correlation of these items and the total motor MDS-UPDRS score with measures of motor function, gait, and falls appear in the table.

Conclusions: The new toe tapping component of the MDS-UPDRS motor scale generally correlated better with measures of motor function, gait, and falls, compared to leg agility. However, toe tapping and leg agility both poorly correlated with H&Y, gait, FOG,

TABLE (505). *Toe Tapping, Leg Agility, and Finger Tapping Versus Other Measures of Motor Function and Gait*

R^2 (p Value)					
	Toe Tapping	Leg Agility	Finger Tapping	MDS-UPDRS Motor Score	
MDS-UPDRS Motor Score	0.435 (<0.001)*	0.385 (<0.001)*	0.496 (<0.001)*	----------	*N=75*
Modified Hoehn and Yahr	0.167 (<0.001)*	0.054 (0.024)*	0.097 (0.003)*	0.379 (<0.001)*	*N=74*
MDS-UPDRS Part 2 Walking and Balance	0.039 (0.045)*	0.007 (0.236)	0.033 (0.059)	0.124 (0.001)*	*N=75*
MDS-UPDRS Part 2 Freezing	0.023 (0.098)	0.000 (0.425)	0.013 (0.169)	0.062 (0.016)*	*N=75*
Falls per Month	0.073 (0.009)*	0.006 (0.262)	0.123 (0.001)*	0.112 (0.002)*	*N=75*
Freezing Episodes per Month	0.001 (0.379)	0.016 (0.145)	0.013 (0.172)	0.038 (0.128)	*N=71*
Finger Tapping	0.323 (<0.001)*	0.220 (<0.001)*	----------	0.496 (<0.001)*	*N=75*

* *indicates p<0.05.*

R^2 was higher for toe tapping than for leg agility, when compared with MDS-UPDRS motor score, modified Hoehn and Yahr score (H&Y), and finger tapping. Toe tapping but not leg agility significantly correlated with fall frequency and MDS-UPDRS Part II walking and balance. Toe tapping, in comparison with leg agility, showed a trend toward a higher correlation with MDS-UPDRS Part II freezing but not frequency of FOG.

and falls. This suggests that both toe tapping and leg agility are not strong predictors of practical sequelae of lower extremity dysfunction. Nevertheless, this study suggests that toe tapping may be a useful component of the MDS-UPDRS.

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Validation of a motor screen for undiagnosed parkinsonism: The baylor functional assessment screen (BFAS)

C.B. Hunter, M.K. York, J. Jankovic (Houston, Texas, USA)

Objective: Evaluation of sensitivity and specificity of a motor screening questionnaire designed to identify individuals with undiagnosed parkinsonism in a community setting.

Background: Validated screening instruments designed to detect undiagnosed symptoms of parkinsonism with high sensitivity and specificity are currently lacking. We have previously piloted and now have validated the BFAS, a brief self-administered motor screen consisting of 12 items highlighting key parkinsonism motor symptoms.

Methods: The BFAS (table 1) was administered to persons with clinically diagnosed Parkinson's disease (PD), other movement disorder controls (MDC), and healthy community controls (HC). In a subset of the community cohort, participants with positive scores on the screen were examined using the Montreal Cognitive Assessment (MOCA), Unified Parkinson's Disease Rating Scale (UPDRS) and Cumulative Illness Rating Scale (CIRS).

Results: The BFAS was administered to 56 PD, 52 MDC, and 111 HC. Using a cut-off of one standard deviation below the mean for the PD group, the BFAS demonstrated a sensitivity of 82% and specificity of 90% with a positive predictive value (PPV) of 80% and negative predictive value (NPV) of 91% for the PD versus HC populations. In the PD versus MDC populations the BFAS demonstrated a sensitivity of 73% and a specificity of 76%, with a PPV of 80% and NPV of 67%. Out of 68 HC participants, 3 were found to be false positives based on nil scores on the UPDRS and were further examined with the CIRS and MOCA. The CIRS revealed high total and severity index scores for 2 of the participants (e.g., sinusitis, hypertension, low MOCA). The final participant did not report any comorbid diagnosis to explain the false positive finding.

TABLE 1 (506). *BCM Functional Assessment Screen (BFAS)*

1. Have you been getting slower in your usual daily activities?
2. Is your handwriting smaller?
3. Is your speech slurred or softer?
4. Do you have trouble arising from a chair?
5. Do your lips, hand, arms and/or legs shake?
6. Have you noticed more stiffness?
7. Do you have trouble buttoning buttons or dressing?
8. Do you shuffle your feet and/or take smaller steps when you walk?
9. Do your feet seem to get stuck to the floor when walking or turning?
10. Have you or others noted that you don't swing one arm when walking?
11. Do you have more trouble with your balance?
12. Have you or others noted that you stoop or have abnormal posture?

Conclusions: The BFAS is a brief self-administered questionnaire that may be useful as a screening tool to detect undiagnosed parkinsonism, but further validation in a larger sample is required to determine its diagnostic utility. If these findings are confirmed by a large prospective study, the BFAS may be used for epidemiological studies and for referrals to appropriate health care or research facilities.

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Developing a better UPSIT for PD

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Objective: To create a "PD-specific UPSIT" by identifying subsets of UPSIT items that distinguish PD from controls with similar or improved test characteristics (sensitivity/specificity) compared to the full test.

Background: The 40-item University of Pennsylvania Smell Identification Test (UPSIT) effectively detects hyposmia in PD. However, its widespread clinical use has been limited by time and cost required for administration. Shorter versions of the UPSIT exist, and prior studies indicate that identification of particular odors may be selectively disrupted in PD suggesting that shorter, more PD-specific versions of the UPSIT could be created.

Methods: Discriminatory power of each item was examined using existing UPSIT data from 315 PD patients and a similar number of age and sex-matched controls and ranked using multiple methods (including odds ratios, regression coefficients and discriminant analysis). Sensitivity, specificity and receiver-operator curves were calculated for candidate subsets.

Results: The UPSIT effectively distinguished PD in our population (Sensitivity 0.77, Specificity 0.71) and individual item odds ratios varied significantly (range: smoke=4.5, gingerbread=0.91) similar to prior studies. Multiple novel 12-item subsets (and the previously described BSIT-B) had test characteristics that were similar to the full UPSIT and better than12 random items. To investigate whether subsets derived from our cohort were applicable to the wider PD population, we calculated test characteristics using data from two independent cohorts (totaling 306 PD patients and 343 controls). Although multiple subsets retained test characteristics similar to the full UPSIT, they did not perform better than 12 random items.

Conclusions: Discriminatory power of individual items is not conserved across independent cohorts arguing against selectivity of hyposmia in PD. Multiple 12-item subsets distinguish PD as well as the full UPSIT. These subsets could form the basis for shorter tests allowing routine inclusion of olfactory testing in the clinical evaluation of parkinsonism.

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The feasibility study of the Indonesian version of activities-specific balance confidence (ABC) scale for Parkinson patients

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Objective: This study was purposed to measure the feasibility of using ABC scale in daily clinical practice.

Background: Falls are common in older subjects with Parkinson and result in loss of confidence and independence. Measuring the risk of falls and the confidence scale of the patients is very useful. The Activities-specific Balance Confidence scale (ABC) was developed in North America to quantify these entities, but contain has not been tried for Indonesians.

Methods: The process of cross-cultural adaptation and validation followed the guidelines provided in the existing literature. First, three bilingual health professionals independently translated the original questionnaire into Indonesian and a consensus version was generated. Then, three other translators, blind to the original questionnaire, performed a back translation into English to confirm the accuracy of the translation. This version was then compared with the original English questionnaire. Discrepancies were discussed and solved by a panel of physicians. The field-testing for face validity was done in a group of nurses. Reliability was assessed with test-retest reliability and construct validity was confirmed with factor analysis.

Results: The questionnaire was tested in a group of 32 Parkinson patients. The mean age was 62 years old. The group consist of 22 male and 10 female. The mean time of questionnaire administration was 4 minutes and 45 seconds. The test-retest reliability was 0.75, and Cronbach's coefficient alpha was 0.71 for the entire sample.

Conclusions: The overall findings of this study indicate that the Indonesian version of the ABC scale sound tool with satisfactory measurement characteristics including construct validity and internal consistency reliability. This instrument may be useful in assessing confidence of falls in elderly with Parkinson.

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Use of smell test identification in Parkinson's disease in Mexico

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Objective: To establish cut-off values for the use of Brief Smell Identification Test (BSIT) to differentiate Parkinson's disease (PD) patients from neurologically healthy controls in Mexico.

Background: Smell tests have been shown to be useful to differentiate PD patients from non-degenerative tremors, but they need to be culturally adequate for each population in which it is applied. The BSIT is a quick smell test which has been designed to be cross-cultural and we have aimed at providing practical parameters for its application to Mexican subjects.

Methods: We created a Spanish translation for the BSIT and tested 70 neurologically healthy control subjects and 70 non-demented PD patients fulfilling UKPD Society Brain Bank diagnostic criteria. Patients and controls were matched by age and gender. To study the influence of various factors on the smell test we collected data on sociodemographic variables including age, age of onset, disease duration, tobacco use, income and place of residence in rural or metropolitan area. We used multiple linear regression analyses to determine which factors influence the result of the BSIT in Mexico, and logistic regression analyses to determine the cut-off, sensitivity and specificity of the BSIT to differentiate PD from controls.

Results: Patient data is shown in table 1.

37% of the patients were on levodopa treatment, 22 (31%) were on levodopa and pramipexole and 18 (26%) were on pramipexole alone; the rest were on a monoamine oxidase inhibitor. The median for the Hoehn-Yahr was 2 (range 1-5) with 61.4% having a mild disease (HY 1-2), 34.2% moderate disease (HY 2.5-3) and 4.4% having a severe disease. The multiple linear regression analysis showed that age ($p<0.001$) but not gender, number of years of schooling, monthly family income or place of residence were significant determinates of the BSIT result. The subjects were then divided into 2 age groups (age<60 or age≥60) and a logistic regression showed that when separating in two age groups the BSIT had 71.4% sensitivity and 85.7% specificity to differentiate PD from control, with an overall accuracy of 78.6%, using a cut-off of 7 or less for those aged ≥60, and 9 or less for those aged <60.

Conclusions: The BSIT has good reliability to differentiate PD patients from control subjects in Mexico and can be used with the adequate translation.

TABLE (509). *Clinical data of PD patients*

N	70
Age (years, Mean ± SD)	66.4 ± 8.7
Age at onset (years, Mean ± SD)	59.7 ± 9
Disease duration (years, Mean ± SD)	6.7 ± 5
Female gender (%)	29 (41%)
Non-smokers (%)	51 (73%)

SD: Standard deviation.

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Evaluation of autonomic dysfunction in Parkinson's disease using SCOPA-AUT scale

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Objective: To evaluate autonomic dysfunction in Parkinson's disease (PD) using SCOPA-AUT scale and to determine its correlation with other disease related features.

Background: Despite increasing interest in autonomic impairment in PD, few studies have used validated instruments for evaluation. SCOPA-AUT scale has been suggested to be one such instrument but not many studies have reported its clinimetric properties.

Methods: PD subjects and age matched controls were prospectively enrolled from a movement disorders clinic in a VA hospital at Little Rock, Arkansas. Significant comorbid conditions interfering with autonomic assessment were excluded. Control subjects were enrolled from other Neurology clinics like Pain, Headache, Peripheral Neuropathy and Epilepsy. Participants answered the questionnaire in the waiting room. Demographics and disease related assessments: UPDRS, MMSE, Hoehn & Yahr (H&Y) and Schwab & England scales were documented. SCOPA-AUT has 26 questions; each autonomic item evaluates the frequency of the problem and has four comprehensible response options ranging from 0 ("never") to 3 ("often"). Gastrointestinal, Urinary, Cardiovascular, Thermoregulatory, Pupillomotor, Sexual (men and women) and Medication are included domains.

Results: Sixty-six patients with PD and 63 controls, all men, were recruited. The mean age for the PD group was 74.5±8.2 years for the control group was 70.8±7.9 years, mean disease duration, 8.7±5.9 years, mean H&Y 2.1, mean UPDRS Total 48.5, mean Schwab & England score was 74.5. SCOPA-AUT total score mean (median) was 17.55±9.35 (15.5) points for the PD cohort and 12.1±7.9 (10.0) for the control, respectively ($p=0.001$). SCOPA-AUT total for both groups was free of a ceiling effect; however those hitting the floor in PD group were 3% and 2% in the control group. Overall Cronbach α was 0.81 for PD cohort while the domains ranged from 0.38 to 0.81. The SCOPA-AUT for the PD group failed to display any correlation with age, PD duration, H&Y, UPDRS total, UPDRS III, Schwab & England, and levodopa dose.

Conclusions: SCOPA-AUT was helpful in identifying PD subjects with autonomic impairment but lacked convergent validity with other disease related scales.

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Expression of psychotic symptoms in Parkinson's disease as assessed by the scale for the assessment of positive symptoms (SAPS)

H. Williams, D. Bahr, P. Peters, R. Mills (San Diego, California, USA)

Objective: This analysis examined the clinical expression of psychotic symptoms in 298 patients with Parkinson's disease psychosis (PDP) using the Hallucinations and Delusions (H+D) domains of the SAPS.

Background: The SAPS is a recommended scale for the assessment of psychosis in Parkinson's disease as reported by an MDS Task Force. The SAPS was originally developed and validated for schizophrenia and comprises 5 domains (hallucinations, delusions, bizarre behavior, positive formal thought disorder, and inappropriate affect). The scale has been used in clinical studies of clozapine and pimavanserin in PDP. Previous validation analyses have been reported (Ravina et al., 2008 and Mills et al., 2008) which show the SAPS scale to be a responsive measure of treatment effect in PDP, a condition characterized predominantly by hallucinations and delusions. In addition, a previous factor analysis of the H+D domains in a 60-patient sample (Bahr et al, 2009), suggested that only part of the scale (8 of 20 items measured) were relevant in this population. The current analysis was conducted using baseline pre-treatment SAPS H+D data from a Phase III international study of pimavanserin in 298 patients with PDP.

Methods: Principle components and factor analyses with orthogonal (varimax) rotation were performed to evaluate the factor structure of the SAPS H+D domains (20 items) in the PDP population. Items with a low incidence of moderate to severe ratings (<10% of patients) were excluded from the analysis.

Results: In this 298 patient sample, 8 of 20 items on the SAPS H+D domains had an incidence of ≥10% of patients. These items included auditory hallucinations (H1), hallucinations of voices conversing (H3), somatic or tactile hallucinations (H4), and visual hallucinations as well as persecutory delusions (D1) and delusions of jealousy (D2). Both global items (H7 and D13) also met criteria for analysis. The PCA yielded similar results identifying three distinct constructs: auditory hallucinations, visual hallucinations and delusions.

Conclusions: These data are similar to those previously reported and suggest 8 items of the SAPS H+D domains are most reflective of PDP symptoms. This analysis provides additional insight into relevant scale properties for PDP.

POSTER SESSION 2
TUESDAY, JUNE 15, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

PARKINSON'S DISEASE: PHENOMENOLOGY

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Relationship of constipation with dopamine and dopamine metabolites in the caudate and putamen: The Honolulu-Asia aging study

R.D. Abbott, D.B. Miller, G.W. Ross, J.P. O'Callaghan, C.M. Tanner, L.R. White, H. Petrovitch (Charlottesville, Virginia, USA)

Objective: To examine the association of constipation with dopamine and dopamine metabolites in the caudate and putamen in decedents from the longitudinal Honolulu-Asia Aging Study (HAAS).

Background: Constipation is common in Parkinson's disease (PD) and has been associated with incidental Lewy bodies (ILB) in the substantia nigra. Whether constipation is associated with the earliest signs of nigral degeneration in the absence of PD and ILB is unknown.

Methods: Bowel movement frequency was assessed at clinical examinations that were given from 1991 to 1993 in 269 HAAS participants who died and underwent autopsy. Dopamine and dopamine metabolites (ug/g) were measured in the caudate and putamen. Metabolites included dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 3-methoxytyramine (3MT). Constipation was defined as having <1 bowel movement/day.

Results: Dopamine, was 48% lower in 18 decedents with a past history of constipation versus 251 without constipation (5.2 versus 2.7 ug/g, $p=0.004$). Compared to those without constipation, constipation was associated with 40% lower levels of DOPAC ($p=0.019$) and HVA ($p<0.001$). 3MT was 37% lower in the presence of constipation ($p=0.012$). Findings remained significant after adjustment for age at death and midlife cigarette smoking and coffee intake. Although statistical power declined after removing 18 cases of PD and ILB, magnitudes of association persisted. The association remained significant for HVA ($p=0.008$).

Conclusions: Constipation is associated with nigral degeneration in the absence of PD and ILB. Findings suggest that constipation emerges during the early pathological stages of PD and is a preclinical marker of PD.

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The blink reflex hyperexcitability in Parkinson's disease is not reversed by repetitive transcranial magnetic stimulation

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Objective: To evaluate the effect of repetitive transcranial magnetic stimulation (rTMS) on blink reflex (BR) excitability in Parkinson's disease (PD).

Background: BR is hyperexcitable in PD and it returns to normal after LDOPA and deep brain stimulation. The rTMS is an alternative therapy for PD, which improves motor and other symptoms. However it's mechanism of action is not fully understood.

Methods: 14 (six women) PD patient's (mean age 64.8±9.4 yr, mean Hoehn&Yahr stage 2.3±0.5) were treated with 10 daily sessions of 15 Hz rTMS over both primary motor cortices. The stimulation intensity was 120% of the resting motor threshold and in every session 2000 pulses for every hemisphere were elicited. Before and after rTMS the BR and cortical excitability, intracortical inhibition as well as clinical symptoms were assessed. The BR excitability was measured as the amplitude ratio of the conditioned to nonconditioned answers. The conditioning was done with a somatosensory stimulus applied to the median nerve, 100ms before the test stimulus, which was applied to the contralateral supraorbital nerve. The cortical excitability and intracortical inhibition were assessed with motor evoked potential (MEP) amplitude and central silent period (CSP) respectively. The BR, MEP and CSP were recorded bilaterally, from orbicularis oculi and abductor digiti minimi respectively. The clinical effect of rTMS was measured with UPDRS.

Results: After rTMS the ratios of contitioned to nonconditioned answers in BR and the CSP did not change, the UPDRS improved (29.5±12.2 vs 21.1±10.8, $p<0.01$) and the MEP increased (1.0±0.6 vs 2.6±1.5 mV, $p<0.02$; 1.4±1.3 vs 2.6±1.6 mV, $p<0.04$ for right and left abductor digiti minimi respectively).

Conclusions: The rTMS did not influenced the BR excitability in contrast to the other therapeutic methods. The clinical improvement of PD symptoms observed after rTMS can be mediated by different mechanisms than the effect of pharmacotherapy and of the deep brain stimulation.

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Objective voice evaluation in Parkinson's disease

T. Arakaki, N.S. Garretto, N. Molina, M.I. Rosa, C. Larceri, A. Ciuro, M.M. Miranda, C. Giannasi Guallart (Buenos Aires, Argentina)

Objective: To evaluate objectively the voice disorders in patients (p) with Parkinson's disease.

Background: Many p with PD have voice and speech abnormalities. These abnormalities impair the communicative ability and quality of life leading to social isolation.

Methods: We evaluated 28 p with PD, 13 male, 36 to 71 y/o, evolution between 1 to 15 year; H&Y stage I - III. All the p were evaluated in ON state. Subscale II of UPDRS was performed to evaluate phonatory symptoms. Acoustic voice analysis (ANAGRAF) was used to get an objective voice analysis. The acoustic measures analyzed were: Fundamental Frequency; frequency of vibration of the vocal cords; Jitter; frequency perturbations (pitch); Shimmer: amplitude perturbations; H/N: Relationship between the harmonic components respect to the noise components; and Formants and Bandwidth: natural resonance frequencies of the supraglottic cavities ordered from low to high. A control group was used to compare the results. Patients were analized in 2 groups. Group 1: diagnosis less than 1 year, without Levodopa treatment. Group 2: diagnosis more than 1 year, with levodopa treatment. All the p (22 p) were evaluated in ON state after habitual levodopa dosis and 6 of them in OFF state too.

Results: All the patients showed abnormalities during the objective analysis of the voice, although only 68% of them noticed it. Group 1: Bandwidth B1, B2, B3 out of range plus abnormal H/N could suggest an important vocal effort in some of this p. In 4/6 p (66%) we observed regular tremor and hard voice onset. Group 2: Jitter, H/N relationship and vocal tremor were affected. Pathological Jitter variations were correlated with high values in voice tremor in all the p. Hard voice onset was abnormal in 82%. Jitter and tremor parameters were statistically significant between ON and OFF state. High-pitches in one or two tones in Fundamental Frequency during the ON state improve the vocal quality.

Conclusions: While in Parkinson's disease the p may not refer voice alteration, we could observe abnormalities in the mayority of them during the objective analysis. This type of study would permit an early diagnosis of voice abnormalities and an appropiate speech therapy.

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Retinal morphology in Parkinson's disease (PD)

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Objective: To assess macular and retinal nerve fibre layer morphology in people with PD compared to an age-matched healthy control (HC) group.

Background: Visual symptoms are common in PD and range from subtle visual complaints (blurred vision, difficulty reading) through to complex visual hallucinations. Retinal thinning has been reported in PD using non-invasive retinal imaging techniques, raising the possibility that such methods could provide a potential biomarker for disease progression.

Methods: Consecutively recruited PD patients over the age of 50 years underwent comprehensive ophthalmological assessment including visual acuity, contrast sensitivity, cataract grading, intraocular pressure measurement and slit lamp examination. All patients had macula and peripapillary retinal nerve fibre layers imaged using optical coherence tomography (OCT - Zeiss Stratus 3000). Spousal controls supplemented HCs recruited from a research database. OCT scans with a signal strength<5/10 or with a macular protocol confidence limit >20 microns were reviewed for "best fit" automated contour lines. Those scans with "poor fit" contour lines were excluded from analysis.

Results: 51 PD and 25 HC participants were assessed. 5/25 (20%) HCs were excluded due to the presence of macular degeneration, glaucoma or optic atrophy and 7/51 (14%) PD subjects were excluded for similar reasons. Four further PD patients (9%) were unable to tolerate the OCT protocol due to tremor, dyskinesia or anterocollis. Participants with scans suitable for analysis were well matched for age, gender, presence of cataract and intraocular pressure. LogMAR visual acuity and contrast sensitivity were significantly lower in the PD group. No significant differences were seen between groups in terms of retinal nerve fibre layer thickness, foveal thickness or macular volume.

Conclusions: Contrary to earlier publications, we did not find evidence to suggest that PD affects retinal morphology. Our patient group was older than previous studies, while the consecutive recruitment may mean our sample is more representative of the typical PD population. Co-existing eye disease and poor quality OCT scans were common, resulting in a significant proportion of data being discarded. Longitudinal assessment may resolve outstanding questions over the role of OCT in assessing patients with PD.

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Asymptomatic pulmonary dysfunction in Parkinson's disease

M. Arias, G. Morís, J.M. Terrero, F.A. Navascués (Aviles, Asturias, Spain)

Objective: To describe the severity and pattern of subclinical pulmonary dysfunction in a sample of patients diagnosed with Parkinson's disease (PD) while these patients were on dopaminergic therapy.

Background: Pulmonary dysfunctions of obstructive, restrictive and mixed types have been described in patients with PD. Pulmonary function abnormalities are caused by an increased parasympathetic activity, a dysfunction of the upper-airway muscles or a poor coordination of the respiratory muscles. Dopaminergic therapy may improve this respiratory dysfunction.

Methods: A total of 17 PD patients without symptoms of pulmonary or cardiac dysfunction were evaluated using the Hoehn and Yahr stages and the following scales: the motor score on the Unified Parkinson's Disease Rating Scale (UPDRS-III), Schwab and England scale and Medical Research Council Dyspnea Scale (MRCDS). A basal pulsioxymetry was obtained. Pulmonary function tests included spirometry with standard spirometer and maximal inspiratory and expiratory flow-volume curves. Values of FVC, FEV1, peak expiratory flow, maximum midexpiratory flow and maximum midinspiratory flow were obtained and were expressed as percent predicted.

Results: The mean age was 69'6 years and the mean disease duration was 5'5 years. Thirty per cent of them had smoked. The mean UPDRS-III score was 14.9 and only one patient had a score higher than 3 in MRCDS. In our sample, all patients had a basal pulsioxymetry higher than 95%. There was a pulmonary dysfunction of obstructive type in six patients and three patients had a restrictive type. There were no pulmonary alterations in eight patients.

Conclusions: More than fifty percent of patients with PD in ON state had pulmonary dysfunction although they were not concerned about respiratory symptoms. The majority of the respiratory abnormalities were of the obstructive type. Based on our data, it seems a need to take into account this aspect in the assessment of these patients, to accomplish an affordable and appropriate treatment of PD.

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Learning perspective on paradoxical kinesia (PK) in Parkinson's disease (PD)

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Objective: To draw attention to the phenomena known as paradoxical kinesia as a key factor to study and apply for patients' rehabilitation.

Background: Kinésie Paradoxale (PK) is the name that the French Neurologist M.A. Souques gave to a phenomena observed in PD patients: "Il consiste en ce fait que, certain malades, à peine capable de marcher lentement et difficilement, deviennent, par moments, capables de courir" (Souques, 1921:559). Before him, Dr. J. Parkinson (1917/2002) had called "Shaking Palsy" to this neurological disease, name that reflects the paradox that PD presents.

Methods: We conducted a bibliographical review and non-systematic observational study of PK in the "Taller de Parkinson (TdP)" (UNLP and Hospital Dr. A. Korn, Argentina). We also got data from the application of a quality of life scale (PDQ-39) which was answered by the patients who attend the TdP.

Results: PK is contemporary described as a phenomena which is (1) not only a property of PD but also a motor system quality, (2) an unusual behavior elicited by urgent circumstances or a frequent phenomena in patients' life, (3) elicited by auditory or visual stimuli, or a combination of them, and (4) based on some dopaminergic plasticity and/or cerebellar

circuits. Also, PK could be related to perceptual deficits reported in PD. None of the bibliography revised propose our conception that PK can be used as a rehabilitation tool, which is the notion that has underlain the TDP from its creation in 2002. We have observed that the PD patients who attend the activities show subjective and objective improvements in their mobility. Following Vygotsky's perspective on learning, the stimuli (balls, teachers, classmates, etc) help patients trespass a "zone of proximal development" and consciously or unconsciously use the possibility their movement system has to move better.

Conclusions: We propose that PK underlies the possibility of the results. Furthermore, the combination of external stimuli and internal possibilities help patients reach some improvement that they couldn't get by themselves without the intervention of appropriate stimuli. Systematic research is being conducted by us to improve our understanding and use of the phenomena.

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Accuracy of archimedes spiral analysis in differentiating tremor dominant Parkinson's disease from tremulous subjects without evidence of dopaminergic deficit (SWEDDS): An FP-CIT validated study

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Objective: To analyse the accuracy of simple spiral analysis in distinguishing cases of tremor dominant PD from tremulous SWEDDs cases.

Background: Patients with tremor and parkinsonism are diagnostically challenging. It is likely that a significant proportion of the 5-15% of *de novo* patients recruited for recent clinical trials with anti-parkinsonian drugs who had no evidence of nigrostriatal dopamine denervation on functional imaging (subjects without evidence of dopaminergic deficit or SWEDDS) had tremulous syndromes other than Parkinson's disease (PD). Recording of spiral drawings is one of the clinical assessments commonly performed in the analysis of tremor and PD. A previous study compared the accuracy of this technique in distinguishing essential tremor (ET) from PD although there have been no previous studies distinguishing SWEDDs from PD.

Methods: All analyses were carried out by observers blinded to the clinical details and supplied with just the spiral drawings, from which tremor severity, 3-turn spiral diameter and spiral density were measured. A spiral coefficient, averaged for the spirals drawn by the right and left hands, was derived from these 3 measurements. A cut off of<4 in the spiral coefficient was taken to indicate PD.

Results: Of the 65 cases analysed, the data was felt to be of insufficient quality in 6. Of the remaining 59 cases, the sensitivity and specificity for differentiating tremor dominant PD from tremulous SWEDDs was 65.2% and 61.1% respectively. An analysis was also performed looking at the individual components measured from the spirals. This showed that the sensitivity and specificity of tremor severity were 62.5% and 74.3%, 3-turn diameter 75% and 77.8% and spiral density 28% and 67.3% respectively in predicting the correct classification.

Conclusions: These results indicate that a very simple measure, the 3-turn spiral diameter, has similar sensitivity and specificity in distinguishing tremor predominant Parkinson's disease from SWEDDs cases as previously reported for two expert movement disorder specialists assessing these patients from standardized videotapes (Bajaj et al. Mov Disord 2009; 24 (suppl 2): S521).

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Epidemiology of Parkinson's disease in Argentina. National registry of Parkinson's disease Parkinson en movimiento program

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Objective: To analyzed the epidemiological characteristics among Argentinean Parkinson's disease (PD) patients.

Background: Epidemiological study in PD has not been performed in Argentina since 1991. Registries are an important design to describe the demographics and epidemiological data of a disease and to identify trends in our population. We performed the first confidential national database, called "Parkinson en movimiento".(www.parkinsonenmovimiento.com.ar).

Methods: According to the methodology of the National Registry of PD, after informed consent has been signed PD patients were invited to participate. Data on educational level, residency, and environmental exposures as tobacco, coffee, and toxicants were analyzed.

Results: The population consisted of 283 PD patients, 117 women and 169 men, mean age 64.9 ys (43-94). The median disease duration was 7.3 ys (months-24 ys) and the median age at onset 56.9 ys. 18.66% of patients were residents at the metropolitan area, 2.7% living in rural area. 86.28% individuals possess drinking water and main sewer. 3.57% smoked more than 20 cigarettes/day and 60.71% reported never smoke or less than 5 cigarette/d. 3.5% drunk more than 3 cups of coffee per day. Twenty five patients reported environmental toxic exposure. The analysis of the educational level showed that elementary school was performed by 46.94% of patients, while high school and college was achieved by 41.98% and 9.9% respectively. The 67% of PD patients of this series were retired, the retirement was accomplished because of PD in 52.41% of them.

Conclusions: The present study constitutes an attempt to identify epidemiological conditions among an Argentinean PD population. Although Argentina is recognized as a farming country, the majority of individuals were living in urban areas and curiously environmental toxic exposure (pesticides) was reported in only few cases. Epidemiological studies will contribute to our best understanding of the environmental, cultural and social factors involved in PD in our region.

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Valosin-containing protein (VCP) gene mutation and Parkinson's disease (PD): A case report

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Objective: To identify the possible association between VCP gene mutations and PD.

Background: It is increasingly clear that genetic factors play an important role in the development of PD and approximately 5% of cases do have a familial etiology. More than 15 loci and 11 causative genes have been identified and are involved in mitochondrial function, the ubiquitin-proteasomal system (UPS), autophagy/lysosomal pathways and membrane trafficking. VCP is a member of the type II AAA ATPases and is involved in a wide variety of cellular functions. Mutations in the VCP gene affecting its ubiquiting binding domain have been associated with a rare autosomal dominant disease characterized inclusion body myositis, Paget's disease of bone and Frontotemporal dementia (IBMPFD).

Methods: We conducted a chart review of a patient with PD and confirmed VCP gene mutation with a significant family history of IBMPFD.

Results: The patient is a 54 year old American man with confirmed R159C VCP gene mutation and a strong history of IBMPFD in 11 family members. He presented at age 44 with subtle signs of decreased dexterity and rigidity in his left arm with rest tremor involving the left side. He has since then followed a typical disease course with sustained responsiveness to dopaminergic medications and mild motor fluctuations including non disabling dyskinesias and wearing off. He has otherwise remained cognitively intact but only recently started to develop mild signs of myopathy with scapular winging without significant weakness.

Conclusions: We report the first case of a patient presenting with typical PD associated with a VCP gene mutation. We cannot be

certain that the mutation is causative in this single case report, but given hypothesized pathogenic processes of PD and VCP disease, further investigation of their association is warranted. It is intriguing that a single mutation in a gene can result in diverse phenotypes in one family. Classic L-dopa-responsive PD may be added to the potential consequences of VCP mutations. Additionally, it adds further support to the possible role of the UPS in the etiology of PD.

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Congenital mirror movements associated with Parkinson's disease: Clinical and neurophysiological observations

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Objective: To describe the previously unreported association of Parkinson's disease (PD) and persistent congenital mirror movements (MM).

Methods: We report two women, ages 79 and 61, affected by sporadic congenital MM not associated to other congenital abnormalities, with a 4- and 11-year history of PD, respectively.

Results: Parkinsonian symptoms were bilateral from the onset. Strong and sustained MM were observed during intended unilateral movements of either upper limb. In patient 1, focal transcranial magnetic stimulation (TMS) of either primary motor cortex (M1) elicited bilateral motor evoked potentials of normal latency in the resting hand muscles, reflecting the presence of ipsilateral fast-conducting corticomotoneuronal projections. Moreover, focal repetitive TMS of either M1 during intended unilateral thumb-to-index tapping failed to produce a complete disruption of EMG activity in either hand, suggesting an abnormal contribution of both M1 to the motor output.

Conclusions: The presence of dual M1 output and ipsilateral fast-conducting corticomotoneuronal projections in patients with comorbid PD and congenital MM may explain their relative symmetry of parkinsonian symptoms from the outset.

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Some clinical and epidemiological features of a Peruvian cohort of patient with Parkinson's disease

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Objective: To determine the clinical features of the motor syndrome in Parkinson's disease (PD) as well as some epidemiological features in peruvian PD patients evaluated at a referral center.

Background: PD is a worldwide neurodegenerative and progressive disorder. There is limited information about epidemiological and clinical features of PD in South America especially in Andean countries.

Methods: This was an observational, cross-sectional study. Consecutive PD outpatients of all ages and in all stages of the disease who fulfilled the UKPDBB criteria were included. They were seen at the Movement Disorders Unit of the Instituto Nacional de Ciencias Neurologicas and systematically examined by experts in movement disorders.

Results: A total of 308 PD patients were studied in a one-year period. Mean age was 63.9 (range 37 to 87) years, male 58.1%. Mean disease duration was 6 years (1 to 35 years). Mean age at onset was 57.92 years (26 to 84). Familial history of PD was positive in 17.85% (55/308) of the cases. 170 patients were born in rural areas and 138 in urban areas. 301 patients were right-handed. Asymmetrical onset of symptoms was reported in 306 patients being right side the most commonly affected (189 patients). Tremor was the first motor sign in 224 patients, bradykinesia in 49 and rigidity in 35. 217 patients already presented bilateral involvement of the body while 79 still had unilateral motor signs. Mean time for bilateralization was 3 years (6 months to 14 years). 272 patients were on levodopa therapy. 240 of them reported marked improvement of symptoms. 145 patients presented levodopa-induced motor complications.

Conclusions: This is the first report of clinical and epidemiological characteristics of PD peruvian patients. Most features are very similar to those reported in different countries.

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Clinical management of depression and apathy in early Parkinson's disease: The animo study

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Objective: The main purpose of this study was to estimate the frequency of depressive symptoms (DS) and apathy, and to describe the medical management of these symptoms in a large representative sample of patients with early idiopathic Parkinson's disease (PD).

Background: DS and apathy are common in PD and significantly impact on patients' disability.

Methods: We studied a sample of patients with early PD (disease duration $\leq$ 2.0 years), recruited from a Spanish cross-sectional survey (the ANIMO study), measuring health-related quality of life (HRQoL) by the EuroQoL-5D, apathy by the Lille apathy rating scale, and DS by structured questionnaires. Depression was diagnosed according to DSM-IV-TR criteria, and disease severity by the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn & Yahr staging scale (HY). Comparison was performed using parametric or non parametric tests as needed.

Results: A total of 705 PD patients were enrolled from 147 neurology clinics (60% males, 40% females) with a mean age of 69.5$\pm$10.9 years, motor UPDRS of 20.8$\pm$11.2, and median HY stage of 1 (1-2). Depression (minor or major depression disorders) was diagnosed in 313 PD patients (44.4%) and apathy in 257 (36.5%). Women suffered from depression more frequently than men ($p<0.001$), in contrast to apathy where not significantly differences were found in terms of gender. Apathy was moderately correlated with DS ($r_s=0.49$), but both similarly correlated with the UPDRS ($r_s=0.45$ and 0.39), antidepressants use ($r_s=0.45$, and 0.34), the levodopa dose ($r_s=0.26$ and 0.12), and inversely correlated with HRQoL ($r_s=-0.39$, 0.45), respectively. Compared to non-apathic PD patients, patients with apathy were on lower dose of levodopa ($p<0.0001$), and received antidepressants more frequently ($p<0.0001$). Likewise, compared to non-depressed, depressed PD patients were on lower dose of levodopa ($p<0.001$), and received antidepressants more frequently ($p<0.0001$).

Conclusions: In this representative cohort of patients with early PD, apathy and depression were common and significantly associated with HRQoL. Apathy and DS are frequently seen in patients receiving lower dose of dopaminergic drugs, highlighting the broad importance of identifying these symptoms and optimizing medical treatment in this population.

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Split-belt locomotion in Parkinson's disease reveals how asymmetry interferes with interlimb coordination

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Objective: To explore the interaction between lower limb bradykinesia and asymmetry in the pathogenesis of parkinsonian gait.

Background: So far, the role of asymmetry in the pathogenesis of the poor inter-limbs coordination has been poorly investigated.

Methods: Ten patients (age: 60.5$\pm$8.8 years) affected by Parkinson's disease since 12.2$\pm$5.7 years have been enrolled. The most affected body side was equally distributed. They were examined on a motor-driven treadmill carrying two belts (one for each leg); gait analysis was performed by a 3D opto-electronic analysis system. Patients were evaluated without medication in the following three conditions: Tied (the two treadmill belts running at the same velocity); worst side reduction (WSR): the belt corresponding to the slowest leg run 0.4 m/s slower; best side reduction (BSR): the belt corre-

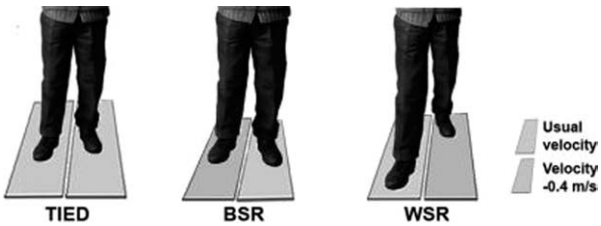

FIG. 1 (524).

sponding to the fastest leg run 0.4 m/s slower. The bilateral coordination of gait was assessed by the Phase Coordination Index (PCI).

Results: During tied condition, the step lengths of the slowest and fastest leg were respectively 26.5±3.0 and 34.9±3.9 cm (p=ns) with a fastest/slowest ratio of 1.3±0.5. During the BSR condition these values resulted respectively 31.1±4.9 cm, 29.9±4.0 cm (p=ns) and 1.1±0.8 (p=0.03 vs. *tied*), thus revealing a more symmetric gait as compared to the tied condition. During WSR, these values were respectively 22.5±2.5 cm, 41.0±2.8 cm (p=0.0003) e 1.8±0.2 (P=0.002 vs *tied*), thus revealing a more asymmetric gait. However, when examining the bilateral coordination of the lower limbs, gait was significantly more coordinated during WSR than during tied (p=0.05) or BSR (p=0.02): the PCI values were 39.8±10.3, 47.3±10.7, and 52.3±11.5, respectively. As a consequence the global performance of gait resulted improved during the WSR as compared to the tied condition: stride length increased from 61.0±5.0 to 64.1±5.9 cm (p=0.05) whereas cadence decreased from 147±17 to 118±9 steps/min (p=0.04).

Conclusions: Our findings reveal that during normal gait (tied) the locomotor system reduces the step length of the less affected side in order to preserve the symmetry between legs. In fact, during the WSR condition, in spite of the increased asymmetry, gait improves in terms of stride length and coordination.

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Gait analysis using a wearable accelerometer system: Comparison between control subjects and patients with Parkinson's disease

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Objective: To examine specific gait parameters using a wearable accelerometer system in PD patients as compared with normal individuals.

Background: Walking is one of the most universal human activities and disorders of gait are one of the most cumbersome symptoms in Parkinson's disease (PD). Quantitative gait analysis using external devices is particularly relevant to detect and characterize walking disorders, particularly in patients with neurological diseases.

Methods: Ten PD patients (mean age: 63±9 years and body mass index: 23±3 kg/m^2) and 10 control subjects (mean age: 64±9 years and body mass index: 24±2 kg/m^2) were included in the study. PD patients were studied on medication. Mean disease duration was 8 years and mean score on Hoehn & Yahr scale was 2 Participants were asked to walk at their comfortable speed under standardized experimental conditions in a 40 m-long hospital corridor. The gait analysis system used in this study (Locometrix^{TM}) included an acceleration sensor, a recording device and a software for signal processing. The sensor was composed of two accelerometers placed perpendicularly and was incorporated into a semi-elastic belt placed over the L3-L4 intervertebral space. We extracted the following gait parameters during a 20-second period of stabilized walking: stride frequency, stride length, stride regularity (similarity of cranio-caudal movements over successive strides) and step symmetry (similarity of left and right cranio-caudal movements). Walking speed was also measured.

Results: Walking speed and stride length were significantly lower in PD patients in comparison with healthy controls (Table 1). Stride regularity and step symmetry were also altered in the PD group but this difference did not reach statistical significance.

Conclusions: Although this study is limited by a small sample size, our preliminary results showed that quantitative gait parameters can be easily studied in PD patients using a wearable accelerometer system. This approach still needs to be validated in PD but opens interesting perspectives to track modifications of quantitative gait parameters associated with disease progression and to evaluate more accurately the effects of specific therapeutic interventions.

TABLE 1 (525).

Gait parameters	Controls	PD	p value
Walking speed (m/s)	1.39 ± 0.19	1.16 ± 0.3	0.05
Stride frequency (Hz)	0.92 ± 0.04	0.92 ± 0.1	NS
Stride length (m)	1.51 ± 0.18	1.26 ± 0.26	0.02
Stride regularity (au)	270 ± 47	239 ± 67	NS
Step symmetry (au)	214 ± 52	185 ± 79	NS

m=meters; s=seconds; au =arbitrary unit; NS=not significant.

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Ambulatory monitoring of energy expenditure and physical activity levels using the SenseWear Armband^{TM} system in Parkinson's disease

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Objective: To monitor physical activity levels and energy expenditure in daily life using the ambulatory SenseWear Armband^{TM} system in Parkinson's disease (PD) patients and control subjects.

Background: One goal of therapeutic interventions in PD is to improve the level of mobility and physical activity during daily life but these important outcomes remain difficult to quantify with a high accuracy.

Methods: We recruited 11 PD patients (mean age: 63.33±7.81 years and B.M.I.: 25.1±3.24 kg/m2) and 11 control subjects (mean

TABLE 1 (526). *Parameters derived from 24h ambulatory SenseWear Armband^{TM} recordings*

	Controls	PD	P value
TEE	2286 ± 563	2336±584	NS
0-1 MET			
EE (cal)	687±166	894±224	NS
Time (min)	658±163	768±179	NS
1-2 MET			
EE (cal)	392±119	560±176	NS
Time (min)	408±163	424±211	NS
2-3 MET			
EE (cal)	562±155	361±121	0.002
Time (min)	222±74	147±55	0.01
3-6 MET			
EE (cal)	628±557	506±442	NS
Time (min)	150±103	100±80	NS
>6MET			
EE (cal)	17±20	12±4	NS
Time (min)	2.2±2.4	6±7	NS
Number of steps	7563±3194	5279±1820	0.045

TEE=total energy expenditure (EE); cal=calories; min=minutes.

age: 63.34±2.6 years and B.M.I.: 22.54±2.77 kg/m2). PD patients were studied on medication. Mean disease duration was 9.2 years and mean score on Hoehn & Yahr scale was 1.9. The SenseWear Armband™ system was placed on the right upper arm during 24 hours on a week-end day. The system includes a two-axis accelerometer, a galvanic skin response sensor, a heat flux sensor, a skin temperature sensor and at least a near-body ambient temperature sensor. We recorded the total energy expenditure (T.E.E.), and both energy expenditure (E.E.) and time (T.) at 0-1, 1-2, 2-3, 3-6 & >6 metabolic equivalents (MET=3.5 mlO2.Kg-1.min-1) as well as the total number of steps. On a separate day, PD patients also performed a triangular aerobic test at 10 watts/min on a cyclo-ergometer to estimate their VO2max and maximal heart rate (MHR).

Results: Despite PD patients were on medication, E.E. & T. at 2-3 METs and steps number were significantly lower than in healthy controls (Table 1).

Mean group VO2max and MHR were 25 ml/kg/min and 125/min, respectively. There was no significant linear correlation between VO2max and T.E.E. or between VO2max and steps number in the PD group.

Conclusions: Although this study is limited by a small sample size, our results showed that energy expenditure and physical activity levels can be easily monitored during everyday life using the ambulatory SenseWear Armband™ system. This device still needs to be fully validated in PD but it opens interesting perspectives to monitor sustained motor effects after therapeutic interventions including a physical reconditioning program. In this case, the aerobic triangular test may also be indicated for longitudinal follow up.

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Nine-hundred patients with Parkinson's disease: A twenty-year experience in a public hospital

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Objective: To analyze the clinical features and treatment trends of PD patients treated in our Movement Disorder Clinic in the last twenty years.

Background: There are guidelines for the treatment of the early stages of PD. However, for many patients levodopa is still a choice as an initial treatment.

Methods: We performed a retrospective study of 3,590 medical records from the period 1988-2008. We selected 900 patients with idiopathic PD (25%). We analyzed age, gender, family history, stage of the disease, features of the progression of the disease, and treatments.

Results: *Demographic data*: Age at onset: 57.9±10.6 years (51.8% men). Family History of PD:10%. *Clinical features at first visit*: duration of disease: 48 months[1-360], previous diagnosis of PD: 88,3% (in 70% of patients, diagnosis was made immediately when symptoms began); motor fluctuations: 39.9%, dyskinesia: 29.2%, Hoehn&Yahr stage I: 24.1%, II: 63.3%, III: 11.4%, IV: 0.9%, V:0.3%. *Progression during follow-up* (FU): dyskinesia: 42.1% (FU: 72 months [4-252]), motor fluctuations: 54.3 % (FU: 60 months [2-252]), cognitive impairment:13.1% (FU: 108 months [24-336]), hallucinations: 16% (FU: 120 months [24-336]), depression: 31.4% (FU: 54 months [1-360]). *Initial treatment with levodopa* 1988-1997: 85%; 1998-2008: 79%; in patients aged<65 years: 83.7% and 75.8%, respectively.

Conclusions: The demographic and clinical features in our patient population are coincident with those in the literature. The large number of patients with a prior diagnosis of PD is accounted for by the fact that ours is a referral center. Levodopa remained the first choice for initial therapy in most patients, in spite of the availability of more optional drugs in the last decade and the recommendations for early disease treatment. We suspect that economical factors are an important determinant in the choice of the initial therapy, although limited knowledge of other alternatives by non-experts could be the cause in some cases.

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Dyskinesia-hyperpyrexia syndrome: Another Parkinson's disease emergency

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Objective: To present a case of dyskinesia-hyperpyrexia in a patient with Parkinson's disease (PD), a new PD emergency different from the parkinsonism-hyperpyrexia syndrome (PHS).

Background: PHS is a rare though life-threatening PD complication. It is characterized by hyperthermia, autonomic dysfunction, consciousness disturbances, rigidity and elevated serum creatinekinase (CK). No PD patients with a dyskinetic status- instead of severe rigidity- associated with hyperthermia, rhabdomyolisis and a confusional state have been previously described.

Methods: A 68-year-old female, with a twelve-year history of PD complicated with motor fluctuations and dyskinesias, was treated with levodopa/carbidopa/entacapone, pramipexole and amantadine. She experienced transient visual hallucinations that became more frequent over the last six months. Two days before her admission severe continuous generalized dyskinesias appeared followed by confusion, drowsiness and fever. There has been no change in her usual antiparkinsonian treatment. On examination she was conscious but disoriented and with prominent visual hallucinations. Temperature was 41.2 °C. No meningeal signs were found. Severe generalized choreatic dyskinetic movements were observed, more intense in the lower limbs. Only a mild bilateral akinetic-rigid syndrome was detected. The remainder of neurological and general examination was normal. High plasma CK was found (up to 1455 IU/L). Blood, urine and cerebrospinal fluid cultures, a cranial computerized tomography, and a chest radiography showed no abnormalities.

Results: Treatment was started with intravenous fluids, antipyretic measures and pramipexol was tapered and withdrawn within five days. A small dose of quetiapine (25 mg/day) was added. Patient's clinical status progressively improved. Temperature and CK levels normalized in few days and the severity of dyskinesias was greatly reduced. Hallucinations remitted almost completely. Two months later her neurological state remained unchanged.

Conclusions: We describe a patient with dyskinesia-hyperyrexia syndrome, a severe complication of PD which, although shares some of the features of the PHS, has some clinical differences (severe dyskinesias instead of rigidity) and a different therapeutic approach.

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Risk factors for freezing of gait in Parkinson's disease

A. Contreras, F. Grandas (Madrid, Spain)

Objective: To determine possible risk factors for Freezing Of Gait (FOG) in Parkinson's disease.

Background: FOG is a major source of morbidity and poor quality of life in patients with Parkinson's disease (PD). Although a common motor complication of PD, the risk factors for FOG are not well understood.

Methods: Cross-sectional study involving 160 consecutive PD patients. We screened patients for the presence of FOG and assessed 19 variables regarding clinical, neuroimaging and therapeutics aspects, as well as gait and balance functional scales and timed tests. A comparison between PD patients with and without FOG was performed using statistical univariant analysis, followed by multivariant logistic regression, Kaplan-Meier and ROC curves, and Cox models.

Results: 43,8% experienced FOG. Age of PD onset, disease duration, MMSE score, motor fluctuations, dyskinesias, UPDRS, Hoehn-Yahr stating, Schawb-England score, balance and gait Tinetti Score, falls and number and length of steps were significantly different between patients with and without FOG. There were no differences in antiparkisonian treatments and cerebrovascular disease. Hoehn-

Yahr stating (OR 2,021) and UPDRS (OR 1,036) were the best predictors for FOG, followed by falls, Balance Tinetti, disease duration, and age of PD onset. FOG was more frequent in younger patients at the onset of PD.

Conclusions: Disease progression appears to be the main responsible for FOG in PD. FOG is a cause of falls in advanced PD, frequently in association with balance dysfunction. FOG occurs more frequently in younger patients, with longer PD duration.

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Plasma homocystein levels in patients with Parkinson's disease

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Objective: To determine whether there is any relationship between homocystein (Hcy) level and Parakinson disease (PD).

Background: Hcy may be involved in the cell damage and considerede to implicated in PD pathogenesis.

Methods: A total of 50 PD patients were participated and secondary parkinsonism were excluded. The cardinal parkinsonian signs were divided into a group according to severity from 1 to 3,in which 1 is a mild and 3 indicates severe state. The control group consisted 50 healthy people.

Results: There were no statistically different for Hcy levels between PD and control groups. Correlatin coefficient in the PD patients showed no significant relationship among variable age, sex, duration, and the severity of cardinal parkinsonian features.

Conclusions: The prsent study indicates no significant differences of Hcy between PD and control.Serial change or CSF levels of Hcy are further needed for the evaluation of PD.Considering the hypothesis that Hcy may be marker of neurodegeneration and restore of Hcy remains to be warranted.

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Polineuropathy in Parkinson's disease patients

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Objective: To describe the clinical, and electrodiagnostic findings of peripheral neuropathies in PD patients.

Background: Polineuropathy has been described in patients with PD. There are very few studies dealing with this problem.

Methods: We studied retrospectively the files of parkinsonian patients admitted to our service of neurology and diagnosticated for PN during the period 2005-2009. The diagnosis of PD was made according the UK Parkinson Disesae Soicety Brain Bank Clinical Criteria for diagnosis of PD. The diagnosis of polineuropathy was based upon the clinical, electroneuronography and electromyography findings. Patients with PN of known etiology were excluded from the study. We found 15 patients (7 females and 8 males) with PD and PN. The mean age was 71,2 years. (SD$\pm$5.2). The patients were in different Hoenh and Yahr stage. Three patients were in stage 2,five patients were in stage 3 and seven patients in stage 4 (H&Y). All patients were taking levodopa. PN was diagnosed 1-5 years after the diagnosis of PD.

Results: 12 patients had minor positive sensory complaints; 3 patients had worsening gate and 10 patients had atrophy and osteotendinose areflexia in lower extremities. Electrodiagnostic test revealed out 6 patients (40%) with axonal sensory-motor PN; 9(60%) patients with axonal sensory PN. We did not found any correlation between the presence of PN and duration or the severity of the disease.

Conclusions: The diagnosis of PN in PD patients is difficult and represents a challenge even for an expert neurologist. It may be suspected in the presence of worsening gait or sensory complaints.

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Lower serum levels of uric acid (UA) in Japanese patients with Parkinson's disease (PD): Relationship between serum UA levels and disease courses

Y. Nakamura, K. Kawabe, K. Ikeda, Y. Iwasaki (Tokyo, Japan)

Objective: Little is known how serum levels of UA influence clinical profile of PD in Japanese patients. We aimed to elucidate serum levels of UA and the relationship to clinical variables in Japanese PD patients.

Background: Oxidative stress plays an important role in the pathogenesis of neuronal degeneration. UA, an endogenous antioxidant, may protect dopaminergic neurons in PD patients. Higher serum levels of UA decrease PD risk in men. Serum UA levels contribute to disease progression in European, North American and Canadian men and/or women with PD.

Methods: PD was diagnosed according to the clinical criteria of the UK PD Society Brain Bank. Serum levels of UA were compared between 119 PD patients (56 men and 63 women) and 120 control subjects (57 men and 63 women) matched by age, sex and body mass index (BMI). We also analyzed correlation between serum levels of UA and clinical variables of PD patients, including age, sex, Yahr stage, disease duration and BMI. Users of UA-lowering agents or diuretics were excluded from this study. Statistical analyses used pared Student's t-test and Spearman's rho correlation.

Results: Mean age (SD) of PD was 73.4 (8.7) years, 72.3 (9.4) years in men and 74.3 (7.8) years in women. Mean Yahr stage (SD) was 3.1 (0.9) in men and 3.4 (0.9) in women. PD duration (SD) was 6.9 (5.1) years, 6.2 (4.8) years in men and 7.5 (5.3) years in women. Serum UA levels (SD) of PD patients was 4.5 (1.1) mg/dL, 4.9 (1.0) mg/dL in men and 4.0 (1.0) mg/dL in women. That of controls was 5.8 (2.1) mg/dL, 6.4 (2.8) mg/dL in men and 4.6 (1.8) mg/dL in women. In both controls and PD patients, serum levels of UA were significantly higher in men than those in women ($P< 0.001$). As compared to controls, serum levels of UA were significantly reduced in male ($P< 0.01$) and female PD patients ($P< 0.05$). Serum levels of UA were correlated inversely to Yahr stage and PD duration in male ($P< 0.01$) and female patients ($P< 0.03$). There were no statistical differences between serum UA levels and other clinical variables in PD patients.

Conclusions: Our data of Japanese PD indicate a significant reduction of serum UA levels and significant inverse correlations between serum UA levels and disease progression in men and women. Potentiation of serum UA levels may have a therapeutic potential for PD.

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Differences in myocardial sympathetic degeneration and the clinical features of subtypes of Parkinson's disease

E.J. Chung, S.J. Kim (Busan, Korea)

Objective: We analyzed the correlations between MIBG uptake and the clinical features of the subgroups of PD.

Background: In PD, the myocardial MIBG uptake is reduced significantly, even without apparent autonomic failure, which enables early diagnosis of the illness.

Methods: We enrolled 14 age-matched healthy controls and approximately 27 patients with PD. Based on the motor score (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS), we divided the patients into three clinical subtypes of PD: tremor-dominant (TDT), akinetic-rigid (ART), and mixed (MT) subtypes. All of the subjects were given an intravenous injection of 111 MBq of ^{123}I-MIBG. The entire cardiac MIBG uptake was expressed as the heart-to-mediastinum activity ratio.

Results: The MIBG uptake was decreased in order of TDT (1.69$\pm$0.39), MT (1.45$\pm$0.32), and ART (1.35$\pm$0.22) (p=0.049, respectively); it differed significantly between ART and TDT (p=0.02). The UPDRS motor score also differed significantly among the subgroups (ART, 34.6$\pm$18.28; MT, 24.63$\pm$7.78; TDT,

16.22±4.15, p=0.002), especially between ART and TDT (p=0.022). The MIBG uptake was inversely correlated with the severity of hypokinesia in ART (r=–0.75; p=0.01) and MT (r=-0.8; p=0.02), but was not correlated with the severity of any parkinsonian motor symptoms in TDT.

Conclusions: These results imply that hypokinesia is strongly associated with sympathetic myocardial degeneration; however, the pathogenesis associated with development of tremor in PD was not clear.

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Characteristics of veterans with dual diagnoses of Parkinson's disease and melanoma

E.C. Lai, S. Moore (Houston, Texas, USA)

Objective: To combine use of an electronic medical record and a regional data warehouse to identify and characterize a group of patients seen at any of ten Department of Veterans Affairs Medical Centers and diagnosed with both Parkinson's disease (PD) and malignant melanoma (MM).

Background: Parkinson's disease patients have been reported to be at greater risk for melanoma. The Veterans Health Administration (VHA) utilizes the same electronic medical record system nationwide. Information on patients seen at 10 regional medical centers is transmitted within the VHA to a regional electronic data warehouse. Combined use of these resources allows greater detail to be gathered on a greater number of patients than would be available from only an administrative database or one facility.

Methods: The regional data warehouse for the eastern part of Texas, all of Arkansas, Louisiana and part of Mississippi was queried to find patients who received health care as outpatients during the period 10/01/1997–09/30/2007 and who received ICD-9CM diagnostic codes for both PD/parkinsonism and melanoma. The data warehouse provided basic demographic information along with prescription drug use. Use of the electronic medical record supplemented data warehouse information by providing additional diagnostic information, as well as information on military service, weight, smoking history, comorbidities and pathology.

Results: Of 367 patients with at least one code for Parkinson's disease (PD), Parkison's plus syndrome, or tremor plus at least one code for melanoma or history of melanoma (MM), 163 patients had codes for PD and MM. Of these 163, 99% were men and 56.4% resided in rural areas. This compares with 36.3% of VHA enrollees overall who reside in rural areas. Patients resided, on average, about 46 miles from the nearest VA medical center. PD patients whose medical records did not contain evidence of melanoma generally did show a history of other skin cancer. Characteristics and risks for combined PD/MM cases will be presented.

Conclusions: Combined use of data warehouse and electronic medical record resources can be successfully utilized to identify and characterize PD/MM cases.

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A decade of delayed diagnosis in two cases of monogenetic parkinsonism

H. Ling, M. Braschinsky, P. Taba, S. Luus, A. Lees (London, United Kingdom)

Objective: We report 2 cases of monogenetic parkinsonism who had been misdiagnosed as psychogenic movement disorder for over a decade by multiple medical specialists (video).

Results: Patient 1 was a 31-year old British woman who developed gait freezing followed by hand tremor, falls and urge incontinence of micturition. She had 5 younger siblings; 1 had committed suicide, 3 others had depression. At age 32, a somatoform motor conversion disorder was diagnosed and she underwent psychotherapy for 2.5years. She was seen by 6 neurologists over 14 years. At age 45, she had awkwardness of hand movements with a very slow gait, freezing and postural instability which confined her to a wheelchair. She was admitted to the National Hospital for Neurology and Neurology where Parkinson's disease was suspected. An abnormal DAT-SPECT led to genetic testing which revealed *parkin* mutations. After 3 weeks of L-Dopa, she regained full functional independence, UPDRS-III score improved from 56 to 7. She had dyskinesia 7 weeks after treatment. Patient 2 was a 33-year old Estonian nurse who developed depression, slowing of movement and hand tremor 1 year after a minor car accident. She was diagnosed with post-traumatic stress disorder and severe depression. She later had hypophonic speech, dysphagia and a 'bizarre' slow gait. Two neurological admissions concluded that she had psychogenic movement disorder. At age 42, she was bedridden with generalized rigidity and contractures. Neurologists at the University Hospital of Tartu suspected parkinsonism. An abnormal DAT-SPECT then led to genetic testing which revealed duplication in the alpha-synuclein gene. She had excellent response to L-Dopa but developed dyskinesia 1 week after treatment.

Conclusions: In both patients, the early mislabelling of psychogenic movement disorder may have led to an uncritical acceptance of the diagnosis by subsequent specialists. The young age of onset and the fact that one patient had a strong family history of depression and the other was a health care worker may have compounded the initial error. Regular follow up of all psychogenic movement disorders is recommended and if relentless progression continues over years, critical appraisal of the diagnosis and a trial of L-Dopa should be considered. DAT scanning may help in confirming the clinical suspicion of nigrostriatal dopamine denervation.

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Bradykinesia in Parkinson's disease and related conditions

H. Ling, L. Massey, A. Lees, P. Brown, P. Schwingenschuh, K. Bhatia, B.L. Day (London, United Kingdom)

Objective: To assess 'bradykinesia' objectively using measurements of finger tapping in patients with PD, PSP and SWEDDS (suspected parkinsonism with a normal DAT-SPECT).

Background: Bradykinesia is a sine qua non for the diagnosis of Parkinson's disease. The Queen Square Brain Bank Criteria define bradykinesia as 'slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive action'. Finger tapping is a simple bedside assessment of bradykinesia.

Methods: 11 PD, 10 PSP, 5 SWEDDs patients and 11 healthy age- and gender- matched controls were recruited. Subjects were instructed to repeatedly tap their index finger and thumb as rapidly and as widely as possible for 15s. Infrared-emitting diodes were fixed to 8 designated regions on digits and back of hand, and motion was recorded in 3D (Coda). Amplitude and frequency were used to measure each cycle of finger tap from one finger-thumb separation to the next. Aperture rate measures the rate of change in aperture over a cycle. Decrement (fatigue) was assessed by the percent of reduction

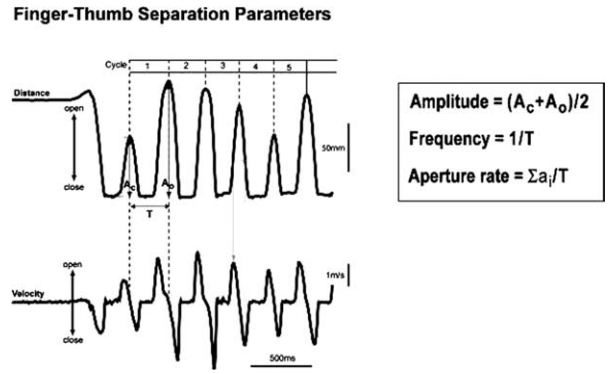

FIG. 1 (536).

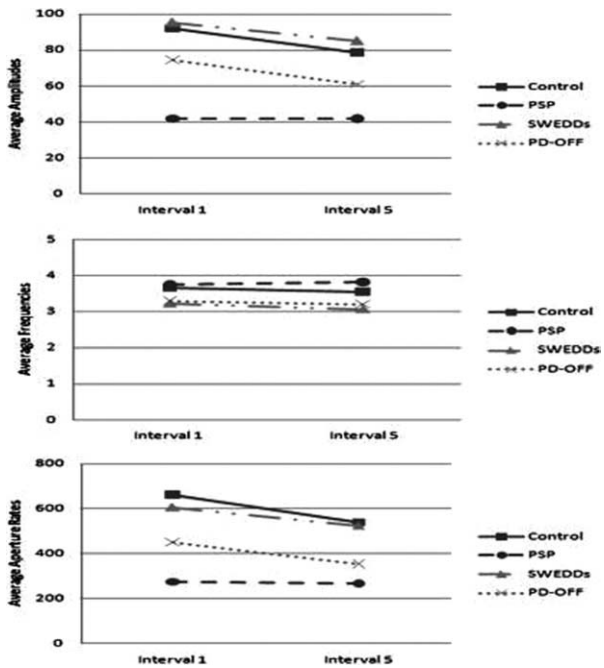

FIG. 2 (536).

in average aperture rate from the first 20% to the last 20% of cycles within 15s.

Results: The controls and SWEDDs patients had similar amplitude, frequency and aperture rate and 'fatigued' similarly by about 16%. For PD, amplitude and frequency were similar to controls but aperture rate was significantly lower during both 'Off' and 'On'. PD-On and Off both 'fatigued' by about 25%. A high UPDRS-III score correlated with small average amplitude and aperture rate. For PSP, frequency was similar to controls but amplitude and aperture rate were less than 50% of controls ($p<0.001$) and 66% of PD-On (rate: $p<0.05$). PSP 'fatigued' by 4%, significantly less than PD. In PSP, a prolonged disease duration correlated with a small amplitude ($p=0.03$), whereas a high Frontal Assessment Battery score seemed to correlate with a low aperture rate ($p=0.06$).

Conclusions: PSP patients have a specific finger tapping pattern which is different from PD. The small amplitude movements performed at normal frequency might reflect hypokinesia coupled with frontal dysfunction and perseveration. PD-On has a low aperture rate suggesting that symptoms are not completely alleviated despite dopaminergic treatment. SWEDDs patients have some fatiguing but this do not differ from controls.

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Speech difficulties in Parkinson's disease need more attention

K.K. Martikainen, R.J. Marttila (Turku, Finland)

Objective: To assess the prevalence of subjective speech problems in PD.

Background: Voice and speech abnormalities have been reported among PD patients[1] but only few of them has any speech therapy. In our previous study among 937 working-aged PD patients only 20 (2%) used speech therapy.[2]

Methods: A questionnaire study among PD patients referred to multidisciplinary rehabilitation.

Results: Of the 1000 consecutive patients 656 (373 men and 283 women) participated in the questionnaire study. Their median age was 67 years, the median duration of the disease since diagnosis was four years (range <1 to 8 yrs). The frequency of subjective speech problems was assessed by PDQ-39 and the severity of the problem by UPDRS II. Two percent of patients had problems in speech always, four percent often and 22 per cent sometimes. Four percent assessed the problems to be so severe that they were often asked to repeat what they say and 18% were asked to repeat sometimes. Thirty percent had at least sometimes problems in communication and 25% had the feeling to be ignored. Only 38% had never problems in speech and 42% assessed their speaking as normal. In addition most of the patients had also impaired writing. Speech problems and depressive moods were statistically associated.

Conclusions: Speech problems are common already in the early phase of Parkinson's disease and they often limit communication and social participation and are also associated with depression. Voice problems should be asked actively and speech therapy should be offered already in the early phase. [1]Ramig LO, Sapir S, Countryman S et. al. Intensive voice treatment (LSVT®) for patients with Parkinson's disease: a 2 year follow up. J Neurol Neurosurg Psychiatry 2001;71:493-498. [2]Martikainen K, Luukkaala T, Marttila R. Työikäinen Parkinson-potilas. Suom Lääkäril 2007; 62:389-393.

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DeNoPa Kassel–a long-term follow-up study on biomarkers and non-motor symptoms for PD

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Objective: To conduct a long term follow-up study for early diagnostic and prognostic marker for Parkinson's disease (PD). We hypothesized that (1) an algorithm out of several markers will help to improve the early differential diagnosis of PD when compared to healthy controls (HC) and movement disorder controls (MDC) and (2) predict different clinical courses of non-motor symptoms in PD.

Background: Clinical diagnosis of PD still relies on expert opinion or years of clinical follow-up. Different fluid and non-fluid markers have been shown to be useful in the early and differential diagnosis of PD.

Methods: We established the protocol and initiated the recruitment for a long-term follow-up study with *de novo* PD, HCO and MDC subjects. The protocol includes (1) neurological examinations with UPDRS (2) Levodopa testing, (3) neuropsychological testing, (4) venous and lumbar puncture, (5) smell testing (6) autonomic tests, (7) electroencephalography, (8) polysomnography (9) brainstem ultrasound, (10) MRI, (11) DAT Scan as well as (12) scales and scores on non-motor symptoms. All subjects are hospitalized Monday thru Friday for completing investigations. Most tests are carried out at baseline in all three groups and every two years for 15-20 years with autopsy in case of death.

Results: We established the test protocol according to feasibility, current knowledge and publications on markers for PD and started to enroll PD and MDC patients in September 2009 from convenience samples of the clinic. Within three months we enrolled 13 subjects including 11 PD patients (9 male, 2 female). Average age at enrollment was 62 ± 8 years. We aim to enroll 150 PD patients as well as 100 HC within 2 years. A pre-analysis of the enrollment data will be carried out in April 2010 and presented in more detail.

Conclusions: We present the first data set from a newly established study of PD, MDC and HCO subjects designed to evaluate early diagnostic and prognostic biomarkers for non-motor-features in PD. We showed that enrollment of two patients every week carrying out all investigations within five days is feasible. We conclude that an algorithm of different biomarkers will improve the early diagnosis of PD and for prognostic evaluation of non-motor symptoms in PD.

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Predicting non-motor features of Parkinson's disease

R.P. Munhoz, H. Eleftherohorinou, H.H.A. Teive, L.J. Coin, L.C. Werneck, A.J. Lees, L. Silveira-Moriyama (Curitiba, Parana, Brazil)

Objective: To evaluate which features predict the development of four key non-motor features of Parkinson's disease (PD): psychosis, dementia, REM sleep behavioural disorder (RSDB) and restless legs syndrome (RLS).

Background: We have attempted to identify subgroups of PD patients who are more at risk of morbidity from non motor symptoms.

Methods: A total of 775 patients with PD were examined using a standardized protocol that assessed demographics, disease and treatment of PD, H&Y staging, the UPDRS part III and its subscales and the presence of the four key non-motor features using validated criteria. The selection of variables which best predicted the occurence of each key non-motor feature were performed using logistic regression models, the diagnostic accuracy of which was examined by ROC curves.

Results: The clinical variables that best predicted the non-motor features were: age ($p<0.001$, CI 1.1-1.2) and H&Y stage ($p<0.001$, CI 2.3-8.5) for dementia; age ($p<0.001$, CI 1.0-1.1), disease duration ($p<0.02$, CI 1.0-1.1), H&Y stage ($p<0.001$, CI 2.3-6.2), use of anticholinergics ($p=0.008$, CI 1.3-4.5), dopamine agonists ($p=0.02$, CI 1.1-2.5) and COMT inhibitors ($p=0.02$, CI 1.1-4.3) for psychosis; disease duration ($p=0.03$, CI 1.0-1.1) for RSBD; symmetry of motor signs ($p=0.01$, CI 0.2-0.8) for RLS. The ROC curves for each non-motor variable are displayed in Figure 1. Figure 1: ROC curves for the accuracy of the models in predicting the occurence of each non-motor variable investigated.

Conclusions: The occurence of dementia and psychosis could be accurately predicted by the models, indicating that dementia should be screened in older patients with more advanced disease, and psychosis in older patients with more advanced disease and also in patients using anticholinergics, dopamine agonists or COMT inhibitors. RSDB and RLS were poorly predicted by the models. The association of RLS with symmetric motor feaures is a novel finding and further studies are warranted.

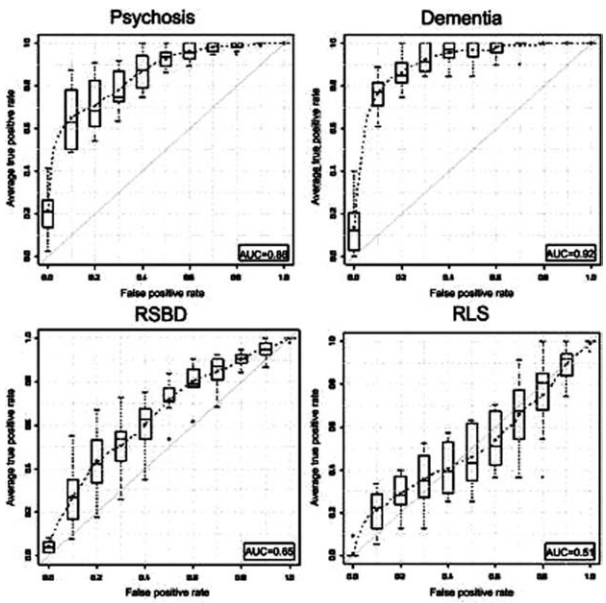

FIG. 1 (539).

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Prevalence of non-motor symptoms in Parkinson's disease using NMSQuest in a Peruvian cohort of patients

Y. Nunez, C. Cosentino, L. Torres (Lima, Peru)

Objective: To determine the prevalence of non-motor symptoms in peruvian PD patients as well as the relationship to sex, duration of disease and Hoehn-Yahr scale.

Background: The NMSQuest is a self-completed screening tool designed to draw attention to the presence of NMS in PD patients.

Methods: This was an observational, cross-sectional study. Non demented consecutive PD outpatients of all ages and in all stages of the disease were included. They were seen at the Instituto Nacional de Ciencias Neurologicas between november 2008 and august 2009. Patients were asked to complete the NMSQuest (spanish validated version). Caregivers were allowed to help patients in this phase.

Results: Two hundred patients completed the questionnaire. Mean age was 64.74 ± 9.51 (range 40 - 86) years, male 57%. Mean disease duration was 6.13 ± 4.73 (4 months to 30 years) years. The mean total NMS was 12.5 ± 5.38. Ninety-nine percent of patients presented at least one NMS. A continuous increase in the number of NMS was observed through the stages of the Hoehn-Yahr scale. Most frequent NMS were sadness/depression (81.5%), nocturia (79%) and urgency (67.5%) while bowel incontinence and delusions were least prevalent (7.5% and 10% respectively).

Conclusions: This is the first study using a validated auto-questionnaire to assess the presence or absence of NMS in a large number of peruvian PD patients. A clear correlation between total NMS and disease severity (HY scale) and duration of disease was found.The prevalence of NMS in PD patients is very high being the most prevalent sadness, depression, and urinary complaints.

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Detection of falls in fluctuated Parkinson's disease: Combination of fall reports and motion recordings

Y. Okuma, H. Mitoma, B.R. Bloem (Izunokuni, Shizuoka, Japan)

Objective: To detect and investigate the characteristics of falls in Parkinson's disease (PD) patients with motor fluctuations in home and community.

Background: Recurrent falls are a disabling feature of PD and have a significant negative impact on the patient's quality of life. Although there have been a number of studies on falling associated with PD, the characteristics of falls in relation to motor fluctuations have not been well elucidated.

Methods: (1) Thirty-five PD patients who showed wearing off phenomenon and recurrent falls participated in this prospective study and kept a fall diary (fall reports) for six months. (2) We developed a motion recorder (body-fixed accelerometer) with a long-lasting battery. Healthy volunteers mimicked various kinds of falls such as those with Freezing Of Gait (FOG), and acceleration signals were analyzed. (3) Walking and motions of recurrent fallers were recorded continuously (up to 40 hours) using the device in their everyday life.

Results: (1) Twenty of the 35 patients (57%) fell predominantly during the on-state, and 7 patients (20%) fell during the off-state. Seven patients (20%) fell preferentially in the transition state between on and off. Most of the off-/transition-state fallers and about half of the on-fallers reported FOG as the main cause. (2) By mimicking falls, characteristic patterns of acceleration signals and motions were found when falling forward after FOG and when turning around or falling backward. (3) In PD patients, falls were typically detected by impact acceleration. Fall reports and motion recording data complement each other.

Conclusions: FOG appears to be the most frequent cause of falls in PD, particularly during the off- or transition-state. Motion recording with our device is useful for detecting and analyzing falls in everyday life in PD patients.

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Paradoxical kinesia in parkinsonian patients surviving earthquake

L. Bonanni, A. Thomas, F. Anzellotti, D. Monaco, F. Ciccocioppo, S. Varanese, S. Bifolchetti, M. Onofrj (Chieti, Italy)

Objective: We are reporting the effect of paradoxical kinesia, as a consequence of a life-threatening event (earthquake), in a group of 14 patients affected by severe parkinsonism with Hoehn/Yahr (H/Y) stage 3-4.

Background: Paradoxical kinesia is the sudden transient ability of a patient with PD to perform a task he was previously unable to perform, usually when facing an immediate threat.

Methods: Before the earthquake, 31 patients with parkinsonism resident in the epicentre area were followed in our Movement Disorder Clinic. All patient were regularly assessed by independent raters with Unified Parkinson's Disease Rating Scale (UPDRS) scores and Freezing of Gate queationnaire (FOG)8 every 2-4 months. 15 days to one month after the earthquake and in the following 6 months at least twice, all patients were assessed by different raters unaware of observations by the referring clinician. UPDRS scores were compared in all patients with H/Y stage 3-4 who had escaped during earthquake despite their level of inability was such as to impair unassisted walking.

Results: All our patients presented an extraordinary motor response during the earthquake that has recently stricken the Italian city of L'Aquila, making them able to safely escape unaided and, in some cases, to assist their families. In 5 patients we observed a definite improvement of motor disabilities, particularly of freezing, which lasted for 2-5 months.

Conclusions: We could collect evidence of PK in a large group of patients whose disability had been regularly documented in our clinic.

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Lateral spine deviation in Parkinson's disease

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Objective: To report on a Parkinson's disease (PD) patient with marked lateral spine deviation (LSD), who significantly improved the abnormal spinal posture after increasing the levodopa dose.

Background: As part of an ongoing study of LSD in PD, we previously reported that the radiological features of PD/LSD were a single and smooth curve without vertebrae rotation, differing from the classical findings of Scoliosis. Since the etiological causes of such spinal deformities remain to be determined, the observation of a clear improvement of LSD in a patient of the study after increasing the levodopa dose was considered useful to contribute knowledge on basal ganglia functioning and therapeutic strategies.

Methods: The patient underwent a neurological examination, an UPDRS evaluation and a spinogram before and after the increase of levodopa. In the spinogram, the degree of the angle resulting from a line drawn between the center of Lumbar 5 and Cervical 7 defined the degree of LSD.

Results: We present a 78 years old, female patient, who started in 2002 with ocassional right thumb tremor and insomnia. Two years later she developed shuffling gait, reduced arm swing, and PD was diagnosed, UPDRS III=16. The patient started treatment with amantadine 200mg/day, which was stopped because of dizziness and fatigue in July 2004. From 2004 to 2006 levodopa was indicated several times but discontinued because of nausea or dizziness. In January 2007, she was receiving 200mg/day levodopa, however, a progressive worsening of tremor was observed. By May 2007 the patient was on 400mg/day levodopa, when she perceived a progressive leaning to the left. A spinogram showed a 22 degree LSD, UPDRS III=21. Rehabilitation was prescribed as well as a progressive and careful increase of levodopa. In July 2008 the patient was on 1675 mg/day levodopa and the abnormal posture had greatly improved, observing in a new spinogram a 7 degree LSD.

Conclusions: LSD was contralateral to PD signs, involving lumbar and thoracic spine. The improvement of LSD was very remarkable after the increase in levodopa dose, which may suggest a decrease in the inhibitory output of the striatum and cortical deactivation.

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The relationship between balance, as measured by clinical posturography, and vitamin D in Parkinson's disease

A.L. Peterson, J.F. Quinn, F.F. Horak, J.G. Nutt (Portland, Oregon, USA)

Objective: To evaluate the relationship between balance performance, using computerized posturography, and vitamin D levels in persons with Parkinson's disease (PD).

Background: Postural instability is one of the 4 cardinal features of PD. Balance problems and falls are a major source of morbidity and mortality late in the disease largely because there are no affective treatments. Vitamin D supplementation reduces falls and improves balance in elderly fallers. The overall goal of this study is to examine the relationship between vitamin D levels and balance performance in persons with PD. The immediate goal is to determine the most appropriate balance tests for a future vitamin D intervention study.

Methods: Subjects underwent a battery of 5 balance tests on the Neurocom posturography platform, were tested for possible confounders: Parkinson's severity (motor UPDRS), cognitive function (trails A & B, MMSE, verbal fluency, and clock draw), dyskinesias (mAIMS), had concurrent medications reviewed, and had serum drawn for vitamin D levels.

Results: The balance data for the first 20 (of 40) subjects has been analyzed. Out of 5 balance tests, 2 tests were very difficult for a number of patients: unilateral leg stance and walk and turn (because of narrow platform). Two tests did not show abnormalities in most subjects: sit-to-stand and backwards translation (resulting in forward body sway). The most informative test was the sensory organization test (SOT), involving measures of quiet stance under 6 sensory conditions; 3 on a static platform and 3 on a sway referenced platform each with eyes open, then closed, then with a sway-referenced visual surround. The SOT composite score, based on the average of anterior-posterior center of mass sway, correlated well with performance on the pull test, question 30 of the motor UPDRS. Subjects with a normal pull test (0) had a mean SOT composite score of 77 (SD=6.37), subjects with mildly abnormal pull test (1) had a mean SOT composite score of 59.6 (SD=12.4), and subjects with loss of balance on pull test (2) the mean SOT composite was 34.5 (SD=27.0). Correlations between the SOT, other balance measures, and plasma vitamin D levels will be reported.

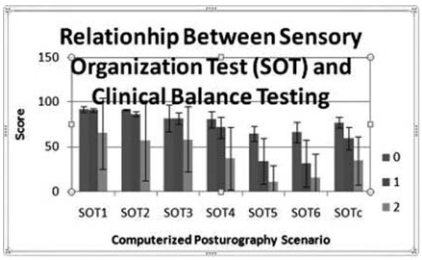

FIG. 1 (544). Shows the 6 SOT scores for PD patients with normal (0), mildly affected (1) and severely affected (2) balance on the UPDRS Postural Response test. The bese possible score for the SOT is 100; a fall is 0.

Conclusions: The SOT is the most appropriate balance test for a clinical trial examining the effects of vitamin D on balance in people with PD.

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Relationship of brain organochlorine levels with total dopamine concentration in the caudate and the putamen: The Honolulu-Asia aging study

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Objective: To examine the association of brain organochlorine levels with total dopamine concentration in the caudate and putamen in decedents from the longitudinal Honolulu-Asia Aging Study (HAAS).

Background: Organochlorine exposure can induce alpha-synuclein aggregation in mesencephalic cells over-expressing human alpha-synuclein. Organochlorines have been reported to be higher in Parkinson's disease (PD) brains than in controls. Whether organochlorines are associated with declines in total dopamine concentration is unknown.

Methods: Organochlorine levels, measured by gas chromatography, were obtained from frozen occipital lobe brain samples from 190 HAAS decedents who underwent measurement of total dopamine concentrations (ug/gm) in the caudate and putamen.

Results: Among 17 organochlorine compounds found to be present in at least one brain, 13 were inversely associated with total dopamine concentration. Results for heptachlor, oxychlordane, and DDE are presented here. Total dopamine concentrations were 3.8 versus 5.0 ($p=0.181$), 3.3 versus 5.0 ($p=0.083$), and 4.6 versus 5.8 ($p=0.053$) in those exposed and not exposed to heptachlor, oxychlordane, and DDE, respectively. When examining exposure to one or more compounds, associations became stronger. For those who were not exposed ($N=40$), mean total dopamine concentration was 5.9. For those exposed to one compound ($N=126$), total dopamine concentration was 4.9. For those exposed to 2 or more compounds ($N=24$), total dopamine concentration was 3.1. As the number of compounds to which a decedent was exposed increased, total dopamine concentrations declined significantly ($p=0.004$). Findings persisted after adjustment for age at death, body mass index, cigarette smoking, and coffee intake ($p=0.014$), and after removing 15 cases of PD or dementia with Lewy bodies ($p=0.006$).

Conclusions: Exposure to heptachlor, oxychlordane, and DDE is associated with declines in dopamine concentration, supporting previous reports of associations of organochlorines with PD, and suggesting that organochlorines may be involved in the process leading to nigral degeneration in the brain.

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Camptocormia in Parkinson's disease: Cystonia, myopathy or something else

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Objective: To discuss the etiopathogenesis of camptocormia in Parkinson's disease.

Background: Camptocormia is defined as an abnormal, severe and involuntary forward flexion of the thoracolumbar spine, which becomes manifest during standing and walking and subsides in the recumbent position. Despite the increasing studied on camptocormia the mechanisms underlying such phenomenon is largely unknown.

Methods: We report the case of a 82 year old men with idiopathic Parkinson's disease with progressive bent spine that responded poorly to any pharmacological treatment. We performed a full clinical, laboratory and neurophysiological investigation, that included MRI, needle EMG, and biopsy of paraspinal muscles.

Results: MRI (T1 sequence) showed fatty replacement and atrophy of lumbar paraspinal musculature and needle EMG examination revealed early muscle recruitment and absence of simultaneous contraction of rectus abdominalis and paraspinal muscles. The muscle biopsy showed alterations compatible with myopathy. We reviewed the literature assessing the possible mechanisms for camptocormia and contextualized it with the data gathered from our patient.

Conclusions: Myopathy of paraspinal muscles may contribute to the pathogenesis of camptocormia at least in some patients with Parkinson's disease. This could explain why some patients with this condition did not respond well to deep brain stimulation neither to botulinum toxin of abdominal muscles.

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Argentinian national registry of Parkinson's disease *Parkinson en movimiento program*

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Objective: To develop a national and multicentric Registry of Parkinson's disease (PD) patients (p) and a database containing the demographic, epidemiological, clinical, pharmacological and surgical aspects of PD. To promote education towards achieving a correct diagnosis of PD. To lead multicentric research to a national level.

Background: The PD National Program is a network of PD specialists and physicians aiming to improve knowledge about the characteristics of the disease in our country. It coordinates sites from different parts of the country at a national level, and participating researchers are trained and certified to be part of the program.

Methods: The recruitment began in July 2009. PD p attending the outpatient clinic at the different sites were invited to participate and the first 2 p accepting to be included in one consultation day were uploaded in a randomized fashion. All p signed an inform consent (IC) and data was anonymously entered onto the database. An approval of the IC and the Program by the ethical committee was requested. Researchers underwent an UPDRS training using an educational kit containing videos to rate p according to the scale (part III). Sites were gradually included starting by sites from Buenos Aires and in a 2nd step, sites from other provinces. Demographic, epidemiological, clinical, pharmacological and surgical data were collected and entered onto the database.

Results: At the moment 13 sites are active: 10 in Buenos Aires, one in the east (Rosario), one in the north (Salta) and one in the centre of the country (Cordoba). We report the first 283 PD p, 169 male, age 64.9 ys, age at onset of PD: 56.9 ys, disease duration 7.3 y; HY I: 20%, II: 57%, III: 18%, IV: 4% and V: 1%. Family history of PD was present in 13% of p (38/283).

Conclusions: This is the first PD registry within the Latin American region. The establishment of a network of PD specialists and physicians will improve our knowledge of the disease in Argentina; furthermore, it will lead to the development of research projects and data sharing with other Registries, and finally, it will contribute to improvement in the care of our p.

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T2* relaxation time in patients with early Parkinson's disease and increased iron cerebral deposition

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Objective: To determine, whether the substantia nigra (SN) iron content was increased in patients with early Parkinson's disease (PD) and whether it could be estimate using gradient echo magnetic resonance imaging (MRI). To make clear whether others cerebral regions like striatum and palidum showed an elevated iron content in patients

with early PD or if this excess iron accumulation is limited to the SN at the biginning of the disease.

Background: PD is the second most common neurodegenerative disorder (after Alzheimer's disease) and results primarily from the death of dopaminergic neurons in the SN. Oxidative stress contributes to the cascade leading to dopamine cell degeneration in PD. Iron is a transition metal capable of generating hydroxyl radicals, the most potent reactive oxygen species. Consequently, a disruption in the metabolism of iron and excessive levels could play a role in the pathogenesis of PD by the formation of free radicals, leading to lipid peroxidation and neurotoxicity. Postmortem studies of patients with PD reveal an increase in iron concentration in the SN.

Methods: Tissue iron levels were evaluated using a gradient echo technique with a 1.5-T MRI system. The T2* relaxation time was measured in height areas: the substantia nigra, globus pallidus, putamen, caudate nucleus, thalamus, ruber nucleus, the frontal white matter and the internal capsule. One group of patients with early PD and one age-matched group of normal control subjects were studied.

Results: In comparison with healthy controls, T2* relaxation time in PD patients were reduced in the following brain regions: substantia nigra, globus pallidus and putamen. However, the shortening of T2* relaxation time did not correlate with disease duration nor with clinical severity.

Conclusions: Our findings support the notion of increased iron deposition in the SN of patients with early PD but not limited to this area. In fact, at the biginning of the disease, increased iron deposition seems to concern the whole nigrostrial dopaminergic system. This deposition is evaluable with a gradient echo technique by the the T2* relaxation time. This technique could be used to evaluate neuroprotective treatment in early PD.

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Handedness and Parkinson's disease

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Objective: To investigate the predictive value of handedness with respect to motor symptoms in veterans with Parkinson's disease (PD).

Background: Handedness is associated with structural and functional asymmetries in brain, the significance of which is largely unexplored in PD. The predictive value of handedness with respect to motor disease asymmetry in PD also remains controversial.

Methods: Using a standardized retrospective chart review approach, medical records of 403 consecutively evaluated PD patients, followed in our Movement Disorders Center (MED VAMC) were reviewed. The selected patient records contained information about pre-morbid handedness, demographic data, description of the initial motor symptom (type and distribution), and a detailed clinical assessment including standardized evaluation of parkinsonism using Unified Parkinson's Disease Rating Scale (UPDRS). The frequency and distribution of handedness was determined. The relationship of handedness with the side of asymmetric onset was studied using Chi-Square analysis. The type and distribution of the initial symptom was analyzed in relation to handedness.

Results: 315 patient records met the inclusion criteria. 289/315 (91.7%) subjects were recorded as right hand dominant (RHD), 24/315 (7.6%) as left hand dominant (LHD), and 2/315 (0.7%) as ambidextrous. In subjects with asymmetric onset (245/315, 78%), 91% (223/245) were RHD and 9% (22/245) were LHD. Motor symptoms emerged first on the dominant side in 69% (154/223) of the RHD group and 63.6% (14/22) of the LHD group, (*p=0.004*). Tremor was the most commonly recalled initial symptom in both groups, 201/223 (90%) in RHD, 17/22 (77%) in LHD, *p=0.139*. Bradykinesia was the only other initial motor symptom recalled, 22/223 (10%) in RHD and 5/22 (23%) in LHD groups respectively. Dominant upper extremity was the site of initial symptom emergence in 65% (145/223) of RHD, and 54.5% (12/22) LHD groups, followed by the contralateral upper extremity 27% in each group. (60/223 in RHD) and (6/22- LHD).

Conclusions: Veterans with PD do not defer from the general population with respect to the distribution of handedness. In this subgroup, handedness has predictive value with respect to the side of onset of asymmetric disease, however it did not seem to confer any specific predisposition with regards to the type of symptom or its distribution in relation to the dominant side.

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Characteristics of PD patients according to the age of onset: Dopaminergic load and motor complications

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Objective: To describe characteristics of Parkinson's disease patients according to the age of onset (AOO).

Background: Younger PD patients have a different spectrum of disease and complications. We have investigated a possible explanation for this difference in our patients.

Methods: A cohort of 298 PD patients was followed for a mean of 5 years from the first presentation; assessment involved PD related parameters at the initial and recent consultation. A note was made of drug therapy, body weight and motor complications. Patients were categorised into three groups according to AOO–young onset $\leq$55 (35), middle 56-66 (101) and older$\geq$66 years (162).

Results: There was a trend for more men (p=0.05) and higher akinetic rigid PD (26%) in young AOO. There was no difference in disease severity on H&Y (p=0.48) and S&E (0.37) scales among the three groups but the older patients had a higher UPDRS score on initial presentation (p=0.02), there was no difference in the depression symptoms on geriatric depression scale (p=0.43), frequency of hallucinations (p=0.17) or falls (p=0.35). There was a trend for lower MMSE in older AOO (p=0.05). Young AOO was associated with higher disease duration on first presentation and on final assessment (p=p<0.001) and they had developed more of fluctuations and dyskinesia (p<0.001). There was no significant difference in mean body weight (p=0.20) among the three groups but there were more weight losers in the older AOO. The young AOO had received a higher absolute levodopa (LD) (p<0.001) and LD dose per kilogram body weight (p<0.001), the LD dose was still higher in young AOO after drug adjustment during follow up (p<0.001). All young AOO had received a dopamine agonist and more often received other medications–selegiline, apomorphine and amantadine i.e. a higher total dopaminergic load.

Conclusions: Our study confirms that younger age of onset is associated with higher motor complications. This may be due to their receiving higher absolute levodopa and levodopa dose per kilogram body weight and higher total dose of dopaminergic medications possibly due to their longer disease duration.

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Mirror movements in Parkinson's disease; disturbance of motor lateralization beyond the level of basal ganglia

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Objective: To evaluate the meaning of mirror movements (MM) observed in Parkinson's disease (PD) patients whose motor symptoms have sustained laterality throughout disease course.

Background: MM in PD have been observed on less affected limbs and were recently reported as more frequently elicited during earlier course of the illness, but their pathophysiology are not fully elucidated.

Methods: PD patients who have been diagnosed based on UK Brain Bank criteria were examined in routine clinical setting. MM of

upper limb (UL) are judged positive when visible pronation-spination movement is observed on asked voluntary pronation-spination movement of contralatetal limb (CL). MM of lower limb (LL) are judged positive when palpable vertical movement of sole is observed on asked voluntary foot tapping of CL. As control, the same examination was done among Alzheimer's disease (AD) patients who have been diagnosed based on NINCDS-ADRDA criteria.

Results: One hundred seventeen PD patients (male 45, female 72; age at disease onset (AO) 64.5±9.3 years old, disease duration (DD) 6.0±4.5 years, modified Hoehn & Yahr stage (mHY) 2.7±0.9) were studied. MM were observed exclusively unilaterally in 52 patients (44%; UL 25, LL 20, both 7) between at first diagnosis and later stage up to 19.4 years DD. Limbs showing MM are less affected ones (judged as less rigid) in 50/52 (96%) cases. Statistical analyses between MM positive (n=52) and MM negative (n=65) groups about AO, DD, treatment duration (TD), clinical subtype (tremor dominant vs tremor plus or nontremor), mHY, and levodopa equivalent daily dosage disclosed significant difference only about DD and TD in male patients (both shorter in MM positive group; 4.1 vs 6.9, $p=0.02$, 3.0 vs 5.5 $p=0.04$ respectively). In AD (male 21, female 51; age at examination 77.9±8.2), MM were observed in 11/72 (15%) patients, of which 3 were on bilateral ULs and 4 including these cases were without rigidity.

Conclusions: MM can be observed in more than one-third of PD patients throughout its disease course. Their higher prevalence and laterality compared with those in AD shows important roles of basal ganglia to elicit them, but the fact that some patients having almost no rigidity manifest MM suggests a role of other than basal ganglia (e. g. cortical circuitry).

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Neuropathic mechanisms contribute to pain in Parkinson's disease: A cross-sectional study

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Objective: To evaluate the contribution of central neuropathic mechanisms to pain in patients with Parkinson's disease (PD).

Background: Pain is a common non-motor symptom of Parkinson's disease (PD), but the underlying mechanisms are unclear. Abnormalities of pain threshold in patients with PD suggest a contribution of neuropathic mechanisms. However, patients with PD have not previously been assessed using validated measures of neuropathic pain.

Methods: We evaluated the characteristics of 29 consecutive idiopathic PD patients with pain recruited from a regional Movement Disorders clinic. Demographic information and details of pain were recorded. The characteristics of pain were assessed using the Short Form-McGill Pain Questionnaire (SFMPQ), Neuropathic Pain Scale (NPS), and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale. Patients also completed the Hospital Anxiety and Depression Scale (HADS).

Results: Eleven patients (38%) had a LANSS score ≥12, and were classed as having probable neuropathic pain. There were no significant differences in disease severity, disease duration or dose of antiparkinsonian medication between patients with probable nociceptive and neuropathic pain. However, patients with probable neuropathic pain had higher anxiety scores (p=0.019). There was a significant correlation between the LANSS, NPS and SFMPQ scores, suggesting their validity in patients with idiopathic PD and related neuropathic pain.

Conclusions: These data suggest that neuropathic mechanisms make a significant contribution to pain in PD, and that they may share a common anatomical substrate with anxiety. This finding has potential implications for the clinical management of non-motor symptoms in PD.

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Referral, consultation and rehabilitation of Parkinson's disease patients in Argentina

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Objective: To evaluate the specialty of physicians most frequently involved in the first consultation of Parkinson's disease (PD) symptoms, in the diagnosis, and in the management of PD in Argentina. To assess how frequently PD patients access to rehabilitation programs (RP).

Background: Since there are differences in the quality of care of PD between general practitioners, neurologists and movement disorders specialists (MDs), knowledge on how the referral system is organized in Argentina and how frequently patients participate of RP is an important issue.

Methods: According to the methodology of the Argentine National Registry of PD, patients were invited to participate. Data on first physician consulted, physician involved in the diagnosis and in the management of PD patients, participation of RP and health insurance were analized.

Results: There were 283 PD patients, mean age 64.9 ys, 169 male, mean disease duration 7.3 ys. Patients first consulted a clinician in 54% of cases, a neurologist in 26 %, a MDs in 6%, and other specialists in 14 %. PD diagnosis was made in 66% of patients by a neurologist, in 23% by a MDs, in 3% by a clinician and in 8 % by other specialists. However, the current treatment was conducted in 96 % of patients by a MDs. In the overall sample, 45% of patients performed any kind of RP: motor in 54% and motor and speech, occupational therapy or physical activity in 46 %. On the other hand, 55% patients had not participated in any RP. Among these, in 22% it was no indicated, 24 % had no nearby center or it was unaffordable, 11% found it unsuccessful, 29% other reasons (non-compliance, refusal) and 14% because of a combination of the different previous reasons. With respect to the health insurance, most patients had some type of coverage.

Conclusions: Clinicians were the first physicians most frequently consulted when initial PD symptoms developed. However, PD diagnosis was most frequently made by a neurologist or a MDs. The adherence to prescribed RP was suboptimal despite the majority of patients having some type of health insurance.

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Vocal rhythm performance in Parkinson's disease

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Objective: The aim of the study was the analysis of vocal rhythm performance based upon different syllable repetition paradigms in patients with Parkinson's disease (PD) as compared to age-matched healthy controls.

Background: Abnormalities of speech timing and rhythm have been described in hypokinetic dysarthria and seem to be caused by a general impairment of rhythm generation.

Methods: N=51 PD patients (32 male) and n=18 (9 male) age-matched healthy controls were tested. Participants were asked to repeat the syllables /pa/, /ta/, /pa-ko/ and /pa-ti/ at least 30 times 1) as fast as possible, 2) in a self chosen steady (isochronous) pace, 3) in two different preset velocities paced by a metronome in a 80/min and 60/min speed. Percentual standard deviation (%SD) of interval length was defined as rate of irregularity (IR). Furthermore, the maximum vowel keeping time (VKT) of the vowel /a/ was obtained to disclose possible difficulties of speech respiration.

Results: Maximum syllable repetition capability (test 1) was similar in the PD and control group, whereas VKT was reduced in the PD group (VKT_{PD} 12,898 s vs. VKT_{Contr} 17,167 s; p=0.025). In the PD group, the ability of steady syllable repetition was significantly

impaired not only when related to the isochronous pace (test 2) (IR_{PD} 9.62 vs. IR_{Contr} 5.98; $p<0.001$), but also when related to the metronome assisted articulation tasks (test 3). In the PD group, the performance in the subtests with alternating syllable production (/pa-ko/ and /pa-ti/ respectively; IR_{PD} 12.14 vs. IR_{Contr} 5.68; $p<0.001$) was even more impaired than in the sub-tests with simple syllable repetition (/pa/ and /ta/ respectively; IR_{PD} 9.72 vs. IR_{Contr} 5.51; $p<0.001$).

Conclusions: PD patients feature disabilities in performing simple steady vocal rhythms, independent from the existence of an external pace generator which might refer to difficulties to internalize and synchronize to external rhythms. Furthermore, the performance is even worse in the subtests containing two equal demands (alternation of syllables and maintaining the speed).

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Vowel articulation in Parkinson's disease

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Objective: The aim of the study was the analysis of vowel articulation in PD speakers suffering from mild hypokinetic dysarthria as compared to healthy controls in correlation to speech rate (NSR) and intonation variability (F_0SD). Furthermore, we intended to reveal possible correlations between vowel articulation and global motor performance and stage of disease.

Background: Vowel articulation has been described to be impaired and is known to contribute to reduced speech intelligibility in hypokinetic dysarthria.

Methods: We examined 68 PD patients (34 male) with mild dysarthria (1 point according to the "speech" item 18 of the Unified Parkinson's Disease Rating Scale / UPDRS III) and 32 age-matched control persons (16 male) using a reading task with subsequent acoustical analysis. F1 and F2 frequency values of the vowels /α/, /i/ and /u/ were extracted from defined words within the text. Description of vowel articulation was based upon measures of triangular vowel space area (tVSA) and vowel articulation index (VAI). PD patients were scored according to UPDRS III and Hoehn&Yahr stages.

Results: VAI values were significantly reduced in male and female PD patients as compared to the accordant control group, whereas tVSA was only reduced in the male PD speakers. NSR was negatively correlated to tVSA and VAI only in female PD speakers. No correlations were seen between vowel articulation and UPDRS III and stage of disease.

Conclusions: VAI seems to be superior to tVSA in the description of impaired vowel articulation in PD. Reduced VAI could be detected in male and female parkinsonian speakers suffering only from mild dysarthria with preserved speech intelligibility and therefore might be applicable to identify subclinical changes of vowel articulation. Moreover, some aspects of altered speech performance in PD seem to feature some gender specific patterns which justify further investigation.

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Steroid responsive camptocormia in a patient with PD showing focal myopathic abnormality of the paraspinal muscles

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Objective: Camptocormia is defined as an extreme forward flexion of the thoracolumbar spine which may worsen during walking or prolonged standing and completely disappears in the recumbent position. The reports about camptocormia in PD and steroid therapy are rare. We report a patient with PD and camptocormia who showed responsiveness to steroid therapy.

Background: Camptocormia can occur in Parkinson's disease or other parkinsonian syndromes. However camptocormia may be associated with a variety of etiologies besides movement disorders. These etiologies are myopathy of paravertebral muscles, motor neuron disease, spine deformities, stroke, and psychogenic cause.

Methods: A 53-year-old woman had suffered from Parkinson's disease for ten years. The initial symptoms were left-sided resting tremor, bradykinesia and masked face. After 3 years of the onset of her symptoms, she first noticed pain of the back area and developed a truncal flexion. She was treated with levodopa, dopamine agonists, and anticholinergics. Her parkinsonian symptoms improved, but her camptocormia continued to worsen. She was admitted to the hospital to evaluate the truncal flexion. The truncal forward flexion was more prominent when standing and walking with complete straightening of the back in supine position, or when she leans against the wall.

Results: Muscle biopsy was taken from the T11 paraspinal muscle, which showed no pathologic findings. She was treated with methylprednisolone 500mg intravenous for 3 days, and discharged with oral steroid 60mg per day. Two weeks after discharge, her back pain and camptocormia was improved.

Conclusions: The pathogenesis of camptocormia in patients with parkinsonism is not known. However, some reports showed that forward flexion of the trunk as a recognized feature of Parkinson's disease may be related to disease of the paraspinal muscles. The characteristic posture in Parkinson's disease may mask weakness of the paraspinal muscles due to focal myopathy. Therefore, in some selected patients who showed abnormal imaging and EMG findings in paraspinal muscles, we suggest to try steroid therapy with caution.

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Gait characteristics during dual tasking in depressed and non-depressed Parkinson's disease patients

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Objective: To compare gait pattern in depressed and non-depressed PD patients in dual-task conditions and correlate to cognitive tests results.

Background: Depression is one of the major non-motor symptoms of Parkinson's disease (PD) disease, and has been associated with alterations in gait. Studies of gait in PD patients found that in depressed patients walking is correlated to both affective and cognitive status. Also, it has been proposed that gait arrhythmicity is correlated to increased risk of falling.

Methods: Demographical and clinical data were obtained for all patients, diagnosis of depression was made according to DSM-IV criteria. Gait parameters were measured on the GAITRite walkway. Subjects performed a simple walking task, dual-motor, dual-cognitive, and combined task. Calculated parameters were gait velocity, stride length, double limb support, stride and swing time and variability of these parameters. All subjests underwent comprehensive neurophsychological testing including CANTAB.

Results: We included 48 patients (25 depressive) that did not differ significantly in age, disease duration, education, UPDRS and MMSE. Neuropsychological testing showed that depressed patients had worse results on set-shifting tasks. Stride time was significantly longer and stride time variabillity was significantly larger in depressed PD patients in repeated measures accross different dual task conditions. Also, depressed patients had significantly longer double-support time and shorter swing-time when expressed as a percetage of the cycle time. Changes in other parametars did not reach statistical significance. There was a correlation of gait parametars to results on tests of executive functions as well as strategic scores, but not to results on memory tests.

Conclusions: Our results implicate that depression affects gait parameters with tendecy to greater variabillity in dual task conditions which might be an indicator of greater fall risk in these persons.

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The effect of saccade intrusion on the latency of subsequent voluntary motor and oculomotor actions in normal subjects and patients with Parkinson's disease

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Objective: We investigated whether inadvertent eye movements made just before a voluntary action (saccadic intrusion) affect the latency of subsequent voluntary motor and oculomotor actions. Furthermore, we studied whether this effect varies with age and how it differs in normal subjects and in patients with Parkinson's disease (PD).

Background: Covert attention tends to be drawn towards suddenly appearing visual signals and we sometimes even make overt eye movements toward it. This tendency is exaggerated in patients with Parkinson's disease (PD), although they have difficulty in initiating voluntary motor and oculomotor actions in the absence of external cues.

Methods: 40 PD patients and 150 normal subjects (age: 5-76) participated in the study. The subjects performed the memory guided saccade (MGS) task and a simple reaction time (RT) task in response to a visual cue, which both required the subjects to keep gazing at the central fixation point until an imperative signal allowed them to initiate a quick voluntary motor or oculomotor response.

Results: n normal subjects, saccade intrusion tended to delay the response time in both tasks. The delay was noted across all age ranges for MGS, although the delay decreased with age for RT. A similar delay was noted in PD patients, but in MGS, the amount of delay was smaller than in normal subjects, whereas for RT the delay was comparable.

Conclusions: Saccade intrusion delays the onset of subsequent motor or oculomotor action, both in normal subjects and in PD patients.

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Laryngeal resistance as a marker of altered aerodynamic mechanism in parkinsonian dysarthria

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Objective: To determine the aerodynamic relevance of laryngeal resistance in Parkinson's disease (PD) dysarthria.

Background: Laryngeal resistance (LR) is a parameter able to further document the laryngeal activity by linking two aerodynamic dimensions (Smitheran and Hixon, 1981, J Speech Hear Disord 46, 138-146): LR is the ratio between the estimated subglottal pressure (ESGP) and the oral airflow (OAF). It is important to consider this parameter as a means to assess globally and dynamically the resistance of the laryngeal valve against the expiratory pressure in PD.

Methods: Using a dedicated system (EVA2, SQLAb, Aix-en-Provence), 51 PD patients were recorded off L-dopa, as well as 50 control subjects. Six measurement points were considered during the production of the French sentence "Papa ne m'a pas parlé de beau-papa" (Daddy did not speak to me about daddy-in-law): ESPG was measured at every p consonants while the OAF was measured on each vowel /a/ following the p consonant. A linear mixed model was estimated (R software) for group analyses integrating patient and p consonant as random terms, with a statistically significance level at $p<0.05$.

Results: For all /pa/ syllables, ESGP and OAF measurements showed significant differences between control subjects and patients off L-dopa, patients presenting reduced values as a reflect of the disease impact. This was not the case for the LR ratio, which displayed a striking increase specifically on the stressed syllable (second /pa/): this data is the result of a supplementary OAF decrease independent of the ESPG reduction, possibly reflecting an "active" strained glottis. No significant difference was observed for the LR ratio concerning the latter syllables, as if the LR was progressively normalized, whereas the ESPG became stabilized thus resulting in a restored OAF.

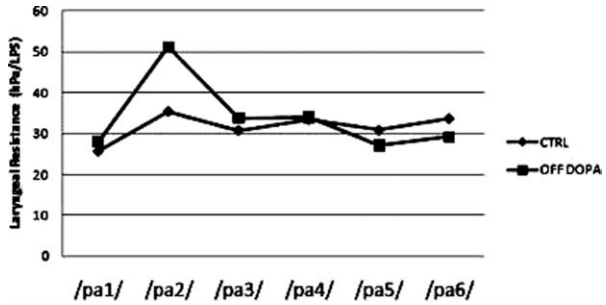

FIG. 1 (559).

Conclusions: LR can thus be considered as a marker of altered aerodynamic mechanisms in PD dysarthria. Its transitory increase on the stressed syllable could result from a defective coordination between the initially phasic expiratory muscles command and the phasic adaptation of the laryngeal valve with an extra-decrease of OAF.

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Association between falls, near falls and measures of gait in Parkinson's disease

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Objective: This study explores the relationship between the risk and frequency of falls and near falls and gait performance in PD.

Background: Falls and near falls in Parkinson's disease (PD) are a multifactorial problem. The relationship between gait and falls is unclear.

Methods: A cross-sectional study of PD patients with Hoehn-Yahr stage 2.5 thru 4 was conducted to improve understanding of the relationship between gait abnormalities and falling in PD. A diary was completed for 4 weeks; near falls and falls are reported as presence of the event (NF, F) and count (NF-count, F-count). Gait measures include Five Time Sit-to-Stand Test (FTSST), Timed Up and Go (TUG; with and without cognitive (CL) and/or physical loads (PL)), and Gait Velocity (GV; with and without cognitive (CL) and/or physical loads (PL)); TUG and GV were recorded as steps and time (seconds-FTSST and TUG; ft/sec-GV). Descriptive statistics and correlations (Pearson for continuous variables and Spearman for categorical variables) were calculated. Correlation results with a significance level of $\leq .05$ are reported.

Results: 338 patients completed the diary and experienced a total of 1,833 events (41% falls). Average age was 71.4±9.0 years; 53.9% male; average years since diagnosis was 10.0±6.9. Age was highly correlated with all measures of gait, but not with NF, F, NF-count or F-count. Gender did not correlate with NF, F, NF-count, F-count; but did correlate significantly with TUG-time and all measures of Gait Velocity. Years since diagnosis correlated with F and F-count but not with NF or NF-count; and with TUG/PL-steps, TUG/CL/PL-steps, GV/PL-steps, and GV/CL/PL-steps. NF correlated with only GV/CL-steps. NF-count did not correlate with any gait measures. F correlated with all gait measures except FTSST, GV/PL-steps and GV/CL/PL-steps. F-count correlated with FTSST, TUG/CL/PL-steps, GV-time, GV/CL-time, GV/PL-time, GV/PL-steps, GV/CL/PL-time.

Conclusions: Gait impairment as assessed by Gait Velocity, Timed Up and Go, and Five Time Sit-to-Stand Test is associated with increased risk of falling and with increased frequency of falling. The same measures do not seem to reflect the risk or the frequency

of near falls. One implication would be that PD patients with abnormal measures are less likely to be able to break a fall.

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Association between cognitive measures and falls and near falls in Parkinson's disease

C.L. Wielinski, S.A. Parashos, R. Wichmann, M.A. Nance, C. Erickson-Davis, S. Lenarz (Golden Valley, Minnesota, USA)

Objective: To explore the relationship between measures of cognition and risk and frequency of falls and near falls in Parkinson's disease (PD).

Background: Cognition has been reported to be associated with the risk of falling in PD. However, it is unclear which aspects of cognition may impact fall risk.

Methods: A cross-sectional study of PD patients with Hoehn-Yahr stage 2.5 thru 4 was conducted to improve understanding of falling in PD. A diary was completed for 4 weeks; near falls and falls are reported as presence of the event (NF, F) and count (NF-count, F-count). Assessments include the Mini-Mental Status Examination (MMSE); Cognitive Linguistic Quick Test (CLQT) with its five domains (reported as z-scores): Attention, Memory, Executive Function, Language and Visuo-spatial Skills; and, the Frontal Assessment Battery (FAB) with its six components: Conceptualization; Mental Flexibility; Motor Programming; Sensitivity to Interference; Inhibitory Control; and, Environmental Autonomy. Descriptive statistics and correlations (Pearson for continuous variables and Spearman for categorical variables) were calculated. Correlation results with a significance level of $\leq$.05 are reported.

Results: 338 patients completed the diary and experienced a total of 1,833 events (41% falls). Average age was 71.4$\pm$9.0 years; 53.9% male; average years since diagnosis was 10.0$\pm$6.9. NF correlated with Language only. NF-count did not correlate with any aspects of cognition. F correlated with Executive Function only. F-count correlated with Lexical Fluency only. There was high correlation between the various cognitive measures.

Conclusions: The measures of cognition included in our study indicate that cognition does not have a robust relationship to falling in PD. However, executive function and lexical fluency appear to have a role in falling in PD. It may be that certain types of falls have a greater cognitive component and grouping falls into a single category masks this impact.

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Categorization of falls and near falls in Parkinson's disease

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Objective: To define categories of falls and near falls in Parkinson's disease (PD).

Background: The risk and attributes related to falling in PD vary across studies. One explanation for this variation is that falls are treated as a single type of event but may be better understood if classified into groups or types of falls based on attributes.

Methods: A cross-sectional study of PD patients with Hoehn-Yahr stage 2.5 thru 4 was conducted to improve understanding of falling in PD. A diary was completed for 4 weeks and data captured included date, time, type (fall or near-fall), direction (forward, backward, side), symptoms (wearing off or off, freezing, dizziness, dyskinesia, fatigue, hallucinations, confusion, depression or anxiety), activity at time of event (walking, standing, turning, on stairs, bending, reaching, carrying, getting up or down), reason for event, and description. Latent class analysis (LCA) was used to determine which variables were informative of falling and these variables were then used to define categories of falling.

Results: 338 subjects completed the diary: 20% experienced no events while the remaining 269 reported a total of 1,833 events (41% falls). 1,364 events contained complete information and were used in the LCA. Variables explaining the model include direction (forward, backward, side), freezing, and activity (walking, standing, bending, reaching, carrying, getting up/down). Variables which did not inform the model and thus were not included were type of event (fall or near fall), wearing off or off, dyskinesia, fatigue, dizziness, hallucinations, confusion, depression or anxiety, reason for event, on stairs, and turning. Model fit (see table) indicated the best model contained 5-classes: Class 1-Rising/Sitting (19.6% of events); Class 2-Falls associated with Freezing Of Gait (28.7%); Class 3-Sideways falls during ambulation (23.9%); Class 4-Retropulsion (10.9%); Class 5-Multi-tasking (17.0%).

TABLE (562). *Model fit statistics*

Model Fit	2-class	3-class	4-class	5-class
AIC	1911.13	1348.85	1150.27	1008.07
BIC	2020.71	1515.83	1374.65	1289.85

Conclusions: These results indicate that categorization of falls in PD is possible. Further investigation is needed to determine if these categories inform the risk of falling in PD.

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Atrophy, autocarnivory amd informatic mismatches determine neurological disability: Lessons from pellagra

A.C. Williams (Birmingham, United Kingdom)

Objective: Why does atrophy rather than discrete pathologies determine disability in neurological diseases ranging from dementia to PD to MS. Perhaps autocarnivory releases energy locally to cope with a mismatch between energy intake and informatics.

Background: Atrophy rather than amyloid, tau, synuclein load, vascular change or demyelination correlates best with clinical status in "degenerative" diseases. Atrophy relates to several discrete pathologies and risk factors combined except in rare early onset genetic cases. Risk factors whether genetic, traumatic, vascular or toxic merge by affecting the redox potential often corrected by adjusting the dose of nicotinamide/NAD(H). The energy supply may not change much with age but the amount of information accumulated does and gets hard to sustain as the energy per byte ratio is high and not all can get returned to co-evolved environments as cues. Autocarnivory like inflammation or proliferative/cancerous disease releases energy as NADH locally.

Methods: Review the low energy low information state Pellagra that was due to lack of dietary nicotinamide.

Results: Pellagra was due to loss NAD(H) the source of energy for all organisms and cells whose gradients largely determine differentiation and dys-differentiation, as part of degenerative processes. Dementia of all sorts along with parkinsonism and other neurodegenerative conditions were common. Homeostatic mechanisms included recruitment of symbionts to boost NAD(H) levels and a reduction in exposure to energy requiring education and physical activity. Pathology was that of ageing with vascular and amyloid and cytoskeletal changes conspiring to cause the clinical phenotype: much the same as modern thoughts on dementia and parkinsonism.

Conclusions: We acquire epigenetic information. This is a double edged sword helping us deal with future stresses but is expensive in energy terms even if some is deposited in environmental "notebooks". Balancing energy intake with informatic needs whether in motoric or cognitive circuitry may be key to long healthy lifes whether nicotinamide the precursor along with glucose to NADH is low or high. When homeostasis is activated local autocarnivory or inflammation/chronic infection or cancerous reactions may in the short-term compensate and we see that as pathology. Information/Energy balances as mirrored in NAD(H) ratios need to be measured and corrected.

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The pathological substrate for clinically diagnosed Parkinson's disease

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Objective: To describe the pathological findings in patients with Parkinson's disease.

Background: The finding of substantia nigra degeneration with α-synuclein immunopositive Lewy bodies is a sine-qua-non for the pathological diagnosis of PD, and is considered to be the substrate for the levodopa responsive bradykinesia and rigidity. Other neurodegenerative disorders may cause parkinsonism with nigrostriatal degeneration and masquerade as Parkinson's disease.

Methods: We retrospectively reviewed 708 patients diagnosed with PD who came to autopsy at the Queen Square Brain Bank for Neurological Disorders (QSBB) from 1989 to early 2009 with a clinical diagnosis of PD.

Results: 593 (84%) had a diagnosis of PD, 76 (11%) of other neurodegenerative parkinsonism, 15 (2%) of vascular parkinsonism, 8 (1%) of Alzheimer's disease and in 9 (1%) no pathological changes were found that could justify the parkinsonism during life. Of these 9, 3 cases were excluded due to insufficient details in the notes to reliably support the clinical diagnosis of PD. Of the remaining 6 patients (4F:2M), the mean age at death was 80y [range 71-90y], mean disease duration was 10y [range 3-18y] and mean age of onset was 70y [range 55-84y]; all patients had tremor, all had rigidity and 4 had bradykinesia; all patients had been treated with levodopa, the maximum dose per day ranged from 200mg to 1250mg (mean 642mg), 3 patients had also used other antiparkinsonian therapy; 3 patients had a good to excellent response to levodopa, and 2 presented dyskinesias.

Conclusions: Of 708 cases the diagnosis of PD was confirmed pathologically in 593(84%) by the presence of Lewy bodies and severe nigral cell loss. A significant proportion presented with nigral neurofibrillary degeneration (tau accumulation) or glial cytoplasmic inclusions (synuclein accumulation) (11%). A smaller number presented with extra-nigral causes including vascular parkinsonism (2%) and Alzheimer's disease (1%). In 6 cases no pathological finding was found to account for the parkinsonian symptoms, despite a mean disease duration of 10 years, and a positive response to levodopa with dyskinesias in some of them.

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Motor fluctuations and pharmacological treatment of Parkinson's disease in Argentina. First national registry of Parkinson's disease: Parkinson en movimiento

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Objective: To evaluate the most frequent initial therapy for Parkinson's disease (PD) in Argentina, and the use of other pharmacological therapies. To describe prevalence of motor fluctuations.

Background: The occurrence of dopaminergic motor complications are more frequent in PD patients receiving initial treatment with levodopa compared to dopamine agonists (DA).Since there is no data available about PD pharmacological treatment in Argentina, the first national Registry of PD patients was developed to advance knowledge on this issue.

Methods: According to the methodology of the National Registry of PD, patients were invited to participate. Data on demography, treatment and motor fluctuations was analyzed.

Results: We report on the first 283 PD patients, age 64.9 ys (43-94), 169 male/114 female, mean disease duration 7.3ys (months-24 ys). Among the 283 PD patients, 158 (56%) received a levodopa preparation as first treatment; 41 (14%) DA, 35 (12%) monoaminooxidase B (IMAO B), 12 (4%) anticholinergics and 11(3.8%) amantadine. Dopaminergic fluctuations were observed in 172 (60%); 107 (62%) of these patients had received levodopa as initial treatment. Among patients on levodopa, 134 (46%) had experienced wearing off (WO), and 6 (2%) ON/OFF fluctuation. In patients experiencing WO, 48% received levodopa as first treatment, and 13(9%) received DA. Dyskinesias were reported in 104 (36%) patients: on dyskinesias=79 (75%), biphasic dyskinesias 25 (25%), and 78 (75%) of these had received levodopa as initial therapy. Patients experiencing WO had longer exposure to levodopa: 7.7 ys vs 3.3ys in patients with no WO, and similarly in patients experiencing dyskinesias: 6.4 ys vs. 4.1ys in patients with no dyskinesia.

Conclusions: Wearing off was observed in 46% of this population and dyskinesias in 36%. Patients experiencing WO had received longer exposure to levodopa than patients with no motor fluctuations or dyskinesias. The most frequent initial therapy for PD was levodopa, followed by dopamine agonists.

POSTER SESSION 3
WEDNESDAY, JUNE 16, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

NEUROIMAGING

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Paroxysmal psychogenic movement disorders. A report of 17 cases

M. Aguirregomozcorta, M.J. Edwards, P. Schwingenschuh, K.P. Bhatia (London, United Kingdom)

Objective: To highlight the clinical characteristics and in particular to identify features which may help differentiate psychogenic from organic paroxysmal movement disorders.

Background: Paroxysmal psychogenic movement disorders (PPMD) have only rarely been described in the literature and represent a diagnostic challenge to clinicians.

Methods: We retrospectively reviewed the medical records of 17 patients who were diagnosed with paroxysmal psychogenic movement disorder in the movement disorders clinic of the National Hospital for Neurology and Neurosurgery, Queen Square, London.

Results: Mean age at onset was 34.4 years and a strong female predominance was found (F:M=4.7:1). The most common types of movement disorders seen were dystonia (24%) and tremor (12%), with 29% presenting with two hyperkinetic phenomenologies. A syndrome that overlapped with psychogenic non-epileptic seizures was observed in 11.8%. Unusual triggers and relieving factors were delineated in 47% and 41%, respectively. Even though all patients described their disorder as consisting of paroxysmal "attacks" only, clinical signs were present in 53% during inter-ictal examination. PPMD and an organic movement disorder co-existed in about 30% of patients.

Conclusions: These patients illustrate the wide spectrum of PPMD. Variability in the degree of responsiveness during attacks may cause diagnostic overlap with psychogenic non-epileptic seizures. Long duration of attacks, "wrong" age at onset, unusual trigger factors, and the presence of non-organic signs during inter-ictal examination may all help differentiate patients with PPMD from organic paroxysmal movement disorders.

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Scans with ipsilateral dopaminergic deficit (SWIDDs): A new entity

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Objective: To highlight patients with resting tremor and ipsilateral dopaminergic deficit in the DaTscan.

Background: Dopamine transporter (DaT) imaging provides in vivo information on the integrity of nigrostriatal terminals and has been proved to useful in differentiating Parkinson's disease (PD) from other tremor disorders. DaT imaging shows reduced uptake in striatum in PD, being more pronounced in the putamen than in the caudate nucleus, greater on the side contralateral to the more severe motor signs.

Methods: We report three patients with resting tremor with ***ipsi***lateral nigrostriatal deficit on DaT scan.

Results: ***Case 1:*** This 74-year-old woman presented a ten year history of resting tremor affecting her left arm. Over the years her symptoms had remained stable without involvement of the contralateral side. No clear signs of bradykinesia were seen and no rigidity or hypomimia were objectivable. A DaTscan was performed which showed reduced uptake in left putamen without other abnormalities. ***Case 2:*** This 71-year-old woman presented with a two year history of resting and postural tremor in the right arm. It was present at rest and when holding things. Occasionally she had mild tremor on the right leg. Mild signs of bradykinesia on the right side were noticed. A DaTscan was performed which showed mild reduced uptake in both putamen being worse on the right. ***Case 3:*** This 71 year-old man presented with a six month history of resting tremor on the left hand. He had mild facial hypomimia, pill-rolling tremor of the left hand and decrease armswing when walking in this side. The DaTscan showed mild reduced uptake in both putamen being more marked on the left.

Conclusions: Previous studies in animals have reported ipsilateral motor control impairment after unilateral nigrostriatal or striatal lesions, and have reported the presence of crossed projections between the basal ganglia and the thalamus. So far, these connections have not been demonstrated in humans. Our patients, together with reports of bilateral improvement of parkinsonian symptoms after unilateral pallidotomy or subthalamic deep brain stimulation, support the complexity of the basal ganglia network. We propose that these patients' scans be called SW***I***DDs (Scans With ***Ipsi***lateral Dopaminergic Deficit).

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Why do clinicians request DaT scans? An analysis of requesting practice and outcome in 455 consecutive scans

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Objective: The aim of this study was to examine the way in which DaT scans are currently used in clinical practice.

Background: Dopamine transporter (DaT) imaging helps evaluate the integrity of the nigrostriatal pathway. Its use is expanding, and what was initially an investigation restricted to use by movement disorder specialists is nowadays accessible to many more neurologists and non-neurologists. It is an expensive technique and using ionising radiation, so it is important to know that it is used appropriately. It has proved very useful in differentiating Parkinson's disease (PD) from other tremor disorders including essential tremor, but currently cannot differentiate PD from most parkinson-plus syndromes.

Methods: We reviewed request forms and results of 455 consecutive DAT scans from one imaging centre.

Results: 91% of the scans were requested by neurologists. The commonest reason for request was to investigate tremor (28.8%), followed by the confirmation of Parkinson's disease (PD) or other parkinsonian syndromes (20.7%). 2.2% of patients were referred to differentiate parkinson-plus syndromes from PD. There were differences in the requesting pattern between neurologists and non-neurologists, with non-neurologists being more likely to request scans to confirm PD. 27.7% of DaT scans were requested for an inappropriate indication.

Conclusions: There is inadequate training of physicians in the rationale for DaT scanning, so the availability of appropriate guidelines would be help improve clinical practice.

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Withdrawn by Author

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A characteristic arterial spin labeling (ASL) MRI perfusion network in Parkinson's disease

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Objective: To distinguish those with Parkinson's disease (PD) from healthy controls by the expression of a characteristic cerebral blood flow (CBF) pattern derived from arterial spin labeling (ASL) MRI.

Background: Radiotracer studies have identified characteristic perfusion changes associated with PD. Non-invasive ASL MRI provides a new method to further investigate potential imaging biomarkers for PD.

Methods: ASL on a 3T GE HDx scanner was used to investigate grey matter perfusion in 59 PD subjects (mean age$\pm$sd: 68.0$\pm$9 years; 43 males) and 30 controls (68.5$\pm$9 years; 21 males). Subjects also completed neuropsychological and motor assessment. The expression of the first 7 components from a principal component analysis (PCA) were entered into a stepwise logistic regression to determine those significantly contributing ($p<0.05$) to the differentiation of PD from control. A linear combination of the significant components was then used to create a PD-related perfusion network. Expression of the PD network in each individual was correlated with neuropsychological scores and disease severity and further examined with ROC analysis. Network reliability was assessed with leave-one-out cross validation.

Results: The identified PD perfusion pattern was characterized by decreased perfusion (blue/green) in parietal-occipital and frontal cortices and left caudate. Preserved perfusion (red) occurred sub cortically and in anterior cingulate. Network expression significantly correlated with cognitive and motor scores, age, and disease duration in PD; ROC yielded an AUC of 0.78. Leave-one-out cross validation showed a classification accuracy of 71.9% (sensitivity: 74.6%, specificity: 56.7%).

Conclusions: This ASL MRI study used a PCA approach to identify a PD-related perfusion network. Cross validation showed generalization to a wider population. Network analysis provides a promis-

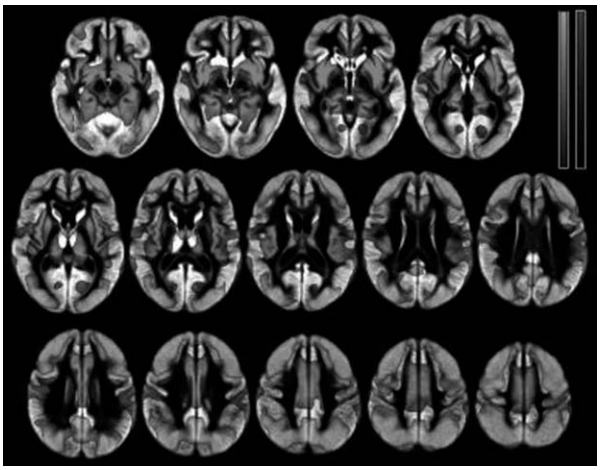

FIG. 1 (570).

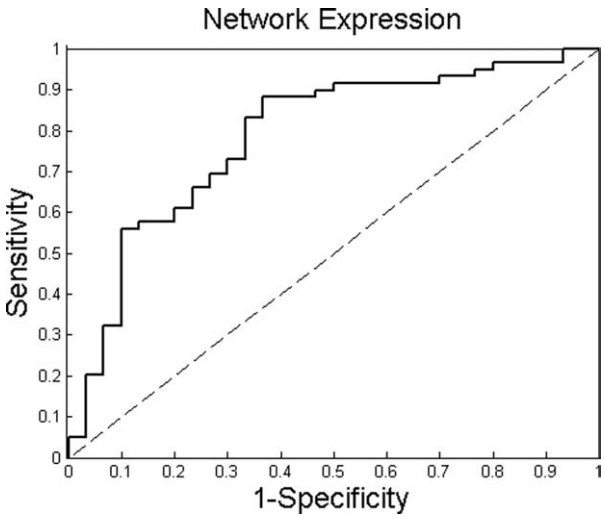

FIG. 2 (570).

ing marker to objectively gauge disease severity and serves as a potential method to longitudinally track disease progression.

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Patterns of morphological change in basal ganglia (BG) structures in Parkinson's disease (PD)

S. Appel-Cresswell, J. Chen, F. Beg, M.J. McKeown (Vancouver, British Columbia, Canada)

Objective: To determine if shape changes in BG structures, as assessed by a newly developed MRI-based shape analysis method in a cross-sectional manner, correlate with clinical deficits in PD subjects.

Background: Unlike Alzheimer's disease, the neurodegenerative process in PD does not lead to gross atrophy with relatively easily identifiable changes in volume of brain structures. In PD, atrophy and possible compensatory hypertrophy in subregions of BG structures are more likely to result in shape rather than overall volume changes. Rather than perform longitudinal studies, another way to deal with intersubject variability is to see if one aspect of shape corresponds with clinical deficits. Combining FreeSurfer and Large Deformation Diffeomorphic Metric Mapping (FS+LDDMM) (Khan et al., 2008) allows for the fully automated segmentation of brain structures in MRI, with demonstrated superior reliability in selecting BG regions in PD subjects (Cheng et al., 2009). The shape of a subject's region of interest (ROI) can then be modeled as a linear combination of basis shapes computed with Independent Component Analysis (ICA).

Methods: 32 PD subjects underwent UPDRS motor testing and MRI scanning (3T, Philips scanner), BG structures were segmented using FS+LDDMM. Basis shapes were determined both on an individual ROI basis as well as combined ROIs. The basis shapes were derived by ICA methods and the ICASSO package.

Results: When examined in isolation, there were significant correlations between UPDRS subscores and basis shapes derived from L&R caudate, L&R thalamus, L&R pallidum, and R putamen. When the BG structures were examined collectively, one independent component, corresponding to a combined shape across ROIs, significantly correlated with symptom duration ($p=0.0004$), UPDRS motor score ($p=0.0148$), rigidity of the right arm ($p=0.0036$), tremor of the head ($p=0.0001$), of the left arm ($p=0.0034$), and of the right arm ($p=0.0211$).

Conclusions: The pilot data presented demonstrates that PD is associated with characteristic changes in the shape of BG structures as shown by the significant correlation of basis shapes with clinical data. The proposed method is able to decompose the ROI shapes into individual components, which might in future allow diagnostic and/or predictive cross-sectional studies instead of longitudinal analysis for PD.

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Effects of levodopa and the feedback process on set-shifting in Parkinson's disease

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Objective: To study the effects of levodopa (LD) and the feedback process on set-shifting in Parkinson's disease (PD). We hypothesize that the ability of PD subjects to set-shift depends not only on the medication status of the subjects, but also on the types of feedback provided.

Background: The mechanisms mediating set-shift deficits in PD subjects have remained controversial. Compared to normal controls, cortical activations may be increased or decreased in PD subjects during set-shifting.

Methods: fMRI studies were performed on 13 PD subjects with mild to moderate disease severity and 17 age-matched healthy controls while they performed the modified card-sorting task. Four experimental time periods were defined: matching following positive external feedback (MCST-PF), matching following negative external feedback (MCST-NF), matching following positive internal feedback (MCST-CR), and matching following negative internal feedback (MCST-IR). PD subjects underwent the experiment twice, once during 'off' medication (PDoff) and the other after LD replacement (PDon).

Results: PD subjects took longer time to respond to set-shift tasks compared to normal subjects during MCST-CR & MCST-PF. The effect was more marked in PDoff than in PDon subjects. During MCST-IR & MCST-NF, no significant differences in task performance were noted across subject groups. Normal subjects activated the dorsolateral prefrontal cortex (DLPFC) during set-shifting, except in MCST-PF where only the left precuneus was activated. Set-shift deficits in PDoff subjects corresponded to deactivations in the right DLPFC during MCST-CR, and activations in the right ventrolateral PFC and right middle temporal lobe in MCST-PF. On the other hand, set-shift performance may be maintained in PDoff subjects despite increase in cortical activations in MCST-NF, and reduced activations in MCST-IR. LD replacement may restore the DLPFC activity in PD subjects, but cannot completely revert the activation patterns to normal.

Conclusions: The cortical activations during set-shifting are modulated by LD-feedback interactions. These findings may represent compensatory changes in PD subjects to cope with the set-shift demands. Set-shift deficits will occur once the shift demands exceed the subject's available cortical resources.

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Magnetic susceptibility of substantia nigra in Parkinson's disease: A 7T *in vivo* MRI study

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Objective: Can MRI susceptibility maps distinguish Parkinson's disease (PD) patients from normal controls by providing a more direct measure of iron content than current approaches.

Background: Dopaminergic neurones rich in neuromelanin (NM) cause the dark appearance of the substantia nigra (SN) at *post mortem*. The SN of PD patients generally show a decrease in NM, perhaps due to oxidative stress, with an increase in ferritin particularly in dopaminergic neurons. Relaxometry-based MRI methods of assessing iron content in the SN depend on the microscopic distribution of

iron. Phase mapping or susceptibility weighted imaging methods are sensitive to the magnetic susceptibility and hence iron content of tissue, but both are affected by the geometrical distortion of the phase information with respect to the underlying susceptibility distribution. We hypothesize that susceptibility mapping will provide a more direct, *in vivo* measure of iron in the brains of PD patients.

Methods: Nine PD patients and controls were recruited under local ethics approval (05/Q2402/87). High resolution T2* weighted MRI scans were acquired using a 7T Philips Achieva MRI scanner. Phase images were acquired and converted to susceptibility maps by unwrapping, filtering and then deconvolving with a dipole field kernel. The relative magnetic susceptibility was measured in the manually outlined whole SN and its medial part representing the pars compacta (PC) compared to surrounding white matter. Values were averaged over both sides all slices. Statistical analyses were carried out using SPSS for Windows v12.0.1 and JMP v7.0.2 (Cary, NC).

Results: A significant difference was found for the PC susceptibility between PD patients and normal control subjects ($p=0.042$) but not for the whole SN ($p=0.18$). Spatial variation of susceptibility with caudal reduction was also noted.

Conclusions: This is the first demonstration of high resolution magnetic susceptibility mapping of the SN of PD patients and shows a focal increase in magnetic susceptibility in the PC only, consistent with an increase in iron. In future the combination of susceptibility mapping (which relates to iron content) and relaxometry (which relates to iron distribution) may provide additional information.

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In vivo marker of substantia nigra depigmentation in Parkinson's disease using optimised neuromelanin sensitive MRI at 3Tesla

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Objective: Optimisation of acquisition and analysis of the neuromelanin (NM) sensitive MRI to better demonstrate the characteristic hypopigmentation of the Substantia Nigra (SN) in Parkinson's disease (PD).

Background: A hallmark feature of PD is the depigmentation of the SN due to loss of dopaminergic cells rich in NM. Surprisingly, until recently, no modern imaging technique allowed visualisation of this macroscopically readily observable and extensive depigmentation of the SN. A newly proposed NM sensitive MRI sequence promises to close that gap, but a first study only demonstrated a 10% reduced NM contrast in the SN of patients with PD (PwPD) (Sasaki, 2006).

Methods: 20 participants comprising 10 patients with mild to moderate PD (HY stages I-II, UPDRS 8-60, age 68.6±11.8 years) and 10 age matched healthy controls (HC, 63.8±9.2 years) were investigated using a clinical 3T MR scanner (Philips Achieva) with an optimised short TE fast spin-echo pulse sequence with additional magnetisation transfer effect through Spectral Presaturation Inversion Recovery (SPIR) pulse in order to assess the NM content of the SN. Image analysis was done by manually outlining the whole SN and surrounding background on two adjacent slices depicting the SN and the red nucleus. The area of the NM rich pars compacta (PC) was defined by the number of hyperintense pixels (x pixel size) within the SN area defined as signal intensities (SI) > mean background SI+3D.

Results: PwPD showed distinctly (>50%) smaller areas of NM rich PC (HC 37.4±12.3 mm^2, PD 17.6±10 mm^2, corrected for age and pixel size, $p=0.001$). Exploratory subgroup comparison revealed an even more marked reduction in more advanced disease (HY stage II and III, n=4, 9.4±6.8 mm^2) compared to early stage disease (HY stage I, n=6, 23.1±9.9 mm^2, $p<0.05$) which represents a relative reduction of NM rich PC by ~38% in mild and ~75% in moderate PD.

Conclusions: This optimised NM sensitive MRI study is to our knowledge the first to demonstrate PC signal abnormalities closely matching the amount of histopathologically observable depigmentation in mild to moderate PD. This preliminary study further supports the promising potential of NM sensitive MRI as biomarker of nigral pathology in PwPD.

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Changes of basal ganglia detected by transcranial sonography and ^{123}I FP-CIT SPECT

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Objective: The aim of our study was to assess correlation among TCS, SPECT findings and diagnosis of PD, other parkinsonian syndromes (PS), essential tremor (ET) and psychogenic movement disorder (PMD).

Background: Diagnosis of Parkinson's disease (PD) could be difficult in early stages of the disease. Transcranial sonography (TCS) is able to detect structural changes in substantia nigra in PD patients. FP-CIT SPECT imaging could detect presynaptic dysfunction in several neurodegenerative disease.

Methods: We examined 25 patients (19 male, mean age 57.2±8.4 years) during 2 years - 4 patients with ET, 12 PD patients, 7 PS patients, and 2 PMD patients. SN echogenicity and SN area were detected using TCS and SPECT evaluation of basal ganglia were performed using SPECT with DAT-ligand (^{123}I-ioflupan) within 2 months after clinical examination. The sensitivity, specificity, positive predictive (PPV) and negative predictive (NPV) values for TCS and SPECT were evaluated.

Results: TCS/SPECT sensitivity, specificity, PPV and NPV for diagnosis of PD or PS were 77.8%/72.2%, 57.1%/100%, 82.4%/100% and 50.0%/58.3%. TCS and SPECT findings correlated in 68% of patients.

Conclusions: TCS has higher sensitivity but significantly lower specificity for detection pathologies in PD/PS patients in comparison with SPECT.

576

Subthalamic-cortical resting state (fMRI-) functional connectivity is increased in early Parkinson's disease

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Objective: To investigate Parkinson's disease (PD) related alterations in the functional connectivity (FC) profile of the subthalamic nucleus (STN) using resting state fMRI.

Background: It is well established that oscillatory activity in STN-cortical networks is pathologically increased in PD [1]. Overactivity is mainly found in the β-frequency band, however, it is currently unknown, whether STN-FC is also altered in the very low frequency range (0.01-0.1 Hz).

Methods: 31 PD patients (OFF-state, H&Y stage I and II) and 44 age matched healthy controls underwent resting-state fMRI in a 3 Tesla Trio system (TR =3s, TE =30 ms, matrix size =64x64, 45 slices, 251 data-points). 16 patients suffered from tremor, which was in 13 cases lateralized to the right body side. Data was corrected for cardiac and respiratory noise, spatially normalized, resampled with 2x2x2 mm resolution, smoothed with a 5 mm Gaussian kernel and regressed for movement using SPM8. The left STN was delineated manually and used as seed region to analyse FC in tremor and non-tremor subgroups.

Results: Tresholded t-maps ($p<0.005$, uncorrected) displaying the contrast FC(PD) > FC(Controls) are shown in Fig. 1: In the tremor subgroup STN-FC was increased solely in the hand areal of left BA

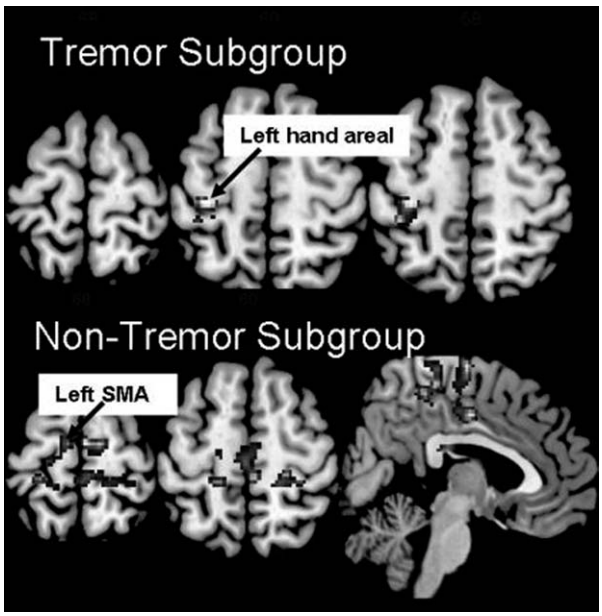

FIG. 1 (576).

4 and 3 (MNI: (-34,-26,60), T=5.1, cluster size: 217, p=0.07, corrected). In the non-tremor subgroup increased FC was found in multiple clusters bilaterally covering midline regions of BA 6 (SMA), BA 4 and BA 3 (max. cluster size:1112, p< 0.001, corrected). Sperical ROIs (5 mm radius, Fig. 1) in the left SMA and hand areal were used for partial FC (pFC) analysis in the non-tremor subgroup (Fig. 2), also revealing an increased STN-hand areal pFC (p=0.04) which was associated with right rigor UPDRS hemiscores (r=0.69, p=0.005), and, additionally, a decreased SMA-hand areal pFC (p=0.02) correlating with UPDRS akinesia scores (r=-0.74, p=0.002).

Conclusions: Here we provide evidence of altered STN-cortical FC in the low frequency range, its pattern showing striking similarity with what we know from electrophysiology. Patients with tremor show increased FC which was specific to the hand areal, arguing for pathologic oscillatory activity in a hyperdirect STN-cortical pathway.

[1] Brown P, 2003. Mov Disord 18, 357-63.

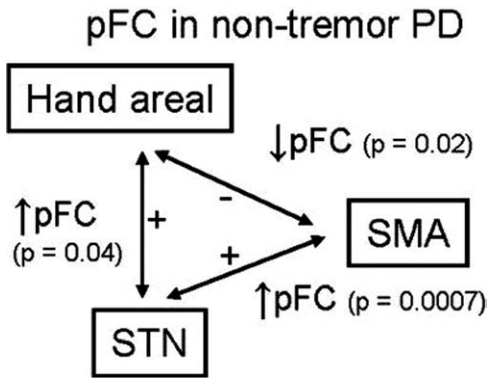

FIG. 2 (576).

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Hippocampal atrophy and ventricular enlargement in newly diagnosed Parkinson's disease; results from the Norwegian ParkWest study

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Objective: To study hippocampal atrophy and ventricular enlargement, and its association with cognitive impairment, in a population based study of patients with Parkinson's disease (PD).

Background: Cognitive impairment is common even in the early stage of PD. The anatomical changes underlying the initial stages of cognitive impairment in PD are not well understood. In a previous study we have found ventricular enlargement, but no significant hippocampal atrophy in a sample of PD patients with long standing disease and dementia. This is the first study to investigate hippocampal and ventricular changes in drug-naïve newly diagnosed PD patients with and without cognitive impairment.

Methods: Patients and controls were recruited from november 2004 to august 2006 for the prospective longitudinal study of patients with incident PD, the ParkWest study. Automated hippocampal and ventricular segmentations were done with two recently validated approaches. Statistical analyses were done using linear regression models, correcting for age and center, with clinical diagnosis at baseline as main predictor. We corrected for multiple comparisons using permutation testing.

Results: The dataset consisted of 258 subjects (controls (NC)=100, PD=128, PD with mild cognitive impairment (PDMCI)=30). Significant difference in age was found between the NC group (youngest) and the PDMCI group (oldest) (p<0.014). PD patients had significant bilateral atrophy of the hippocampus compared to normal controls (NC). Left hippocampal radial distance was

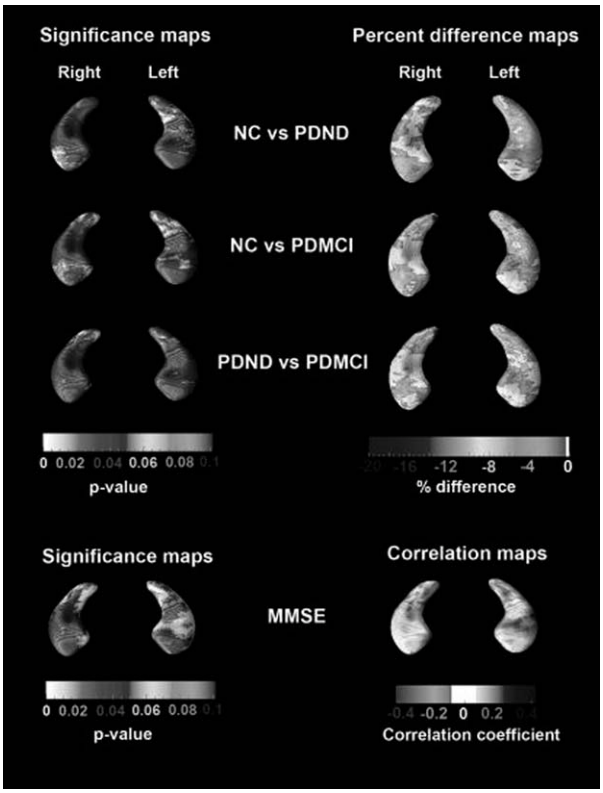

FIG. 1 (577).

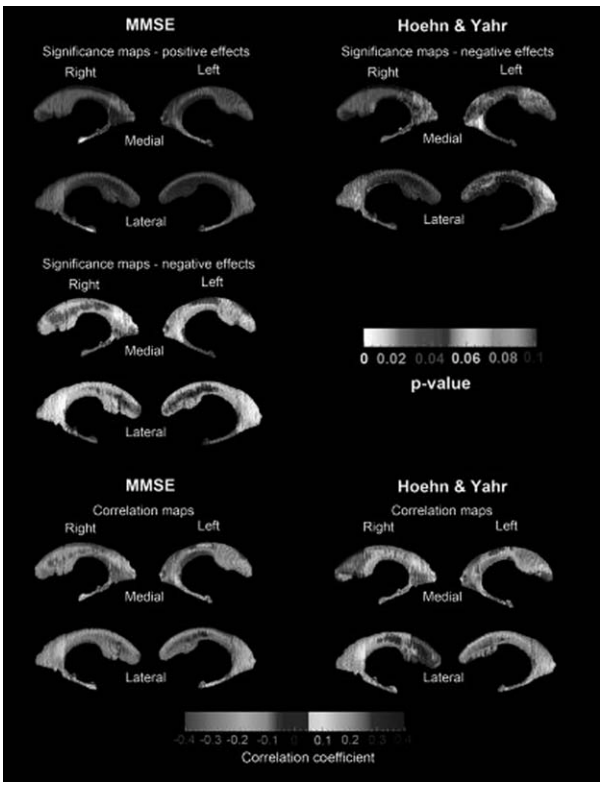

FIG. 2 (577).

significantly smaller in the PDMCI group than in the NC group. (Figure 1) The PDMCI group had significantly larger ventricles in the body/occipital horn and frontal horns bilaterally and in the left temporal horn compared to NC. Comparing the PDMCI group with the PD group we found bilateral differences in the body/occipital, frontal and temporal horns bilaterally. (Figure 2) We found negative associations between MMSE score and radial distance of body/occipital horns and temporal horns bilaterally.

Conclusions: Our results show that drug-naïve PD patients at the time of diagnosis have bilateral hippocampal atrophy and ventricular enlargement, which is associated with cognitive impairment.

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Levodopa-stimulated dopamine release in Tourette syndrome

K.J. Black, J.M. Koller, M.C. Campbell, T. Hseih, M.A. Mintun (St. Louis, Missouri, USA)

Objective: To test whether presynaptic handling of exogenous levodopa (LD) is abnormal in Tourette syndrome (TS).

Background: Several lines of evidence suggest that dopamine-influenced neuronal pathways malfunction in TS, including in nonmotor brain circuits. Some neuroimaging studies suggest presynaptic abnormalities in LD uptake, dopamine (DA) synthesis, or DA release. Alternatively, the downstream response to DA stimulation could be abnormal. The present study directly tested the presynaptic hypothesis: does LD—the body's natural DA precursor—stimulate striatal DA release differently in TS than in control subjects? The PET radioligand [^{11}C]raclopride (*RAC) binds the D2 receptor but can be displaced by synaptic DA.

Methods: Approved by IRB, RDRC (*RAC), and FDA (i.v. levodopa). TS (N=5) and control subjects (N=5) matched for age, sex and handedness. Each subject had 4 *RAC PET scans, 2 on each of 2 days. Study protocol: oral carbidopa, baseline PET, begin infusion of LD or saline placebo (Black et al J Neurosci Methods 2003; 127:19-29), wait 30 min, begin 2nd PET scan, continue infusion. Dynamic 60-min PET scan. T1-weighted MRI to define thalamus, putamen, caudate, accumbens, GP and cerebellar regions. Logan DVR analysis. Repeated measures ANOVA (Region, Time, Drug; Dx), dependent variable BP'=DVR-1.

Results: ANOVA significant for region (p=0.000) and time (p=0.013); time x dx p=0.069. *RAC binding was higher after vs. before saline (8.3% mean, 22.5% in thalamus). Therefore the post-placebo scan is the optimal control for the post-LD scan. Using this comparison, in controls *RAC BP' was lower in all regions on LD vs placebo. By contrast, TS binding was higher on LD vs placebo in thalamus and pallidum, and decreased more than control binding did in accumbens and caudate (NS).

Conclusions: (1) Pre-post *RAC PET designs may be susceptible to a time effect. (2) Control subject data are consistent with increased DA synthesis and release with LD vs placebo. (3) Tic subjects may have an abnormal presynaptic response to exogenous LD challenge in thalamus and pallidum (decreased rather than increased synaptic DA release), but this conclusion is tentative. (4) The presumed decrease in synaptic DA concentration during placebo infusion may indicate that subjects accommodate to the scanner environment. Decreased habituation in TS could explain some of these results.

579

Quantitative measurement of indirect pathway activation and default mode network deactivation by the adenosine A2a antagonist SYN115 in Parkinson's disease

K.J. Black, J.M. Koller, M.C. Campbell, S.I. Bandak (St. Louis, Missouri, USA)

Objective: Use perfusion MRI to answer 2 questions about an investigational new drug, SYN115: 1. Does SYN115 produce regional effects on the brain (either alone or with levodopa)? 2. If so, is the effect of 60 mg p.o. BID greater than that of 20 mg p.o. BID?

Background: Blood flow imaging of human brain is a potential tool for rapidly measuring pharmacodynamic response to new drugs, but successful attempts with relevance to drug development are scarce. Specific adenosine A2a receptor antagonists activate the indirect basal ganglia pathway in animal models and reduce symptoms of Parkinson's disease (PD), but their regional effects on human brain are unknown. We report a successful whole-brain cerebral blood flow (CBF) fMRI study in PD of SYN115, a specific A2a antagonist.

Methods: In 21 subjects with mild to moderate PD, pulsed arterial spin labeling MRI was performed after 1 week of active drug or placebo, in a randomized, double-blind, crossover design. In subjects who took active drug first, >20 half-lives elapsed before measures were obtained on placebo. Statistical inference used SPM8 and a random effects (two-level) analysis with cluster FDR correction for multiple comparisons.

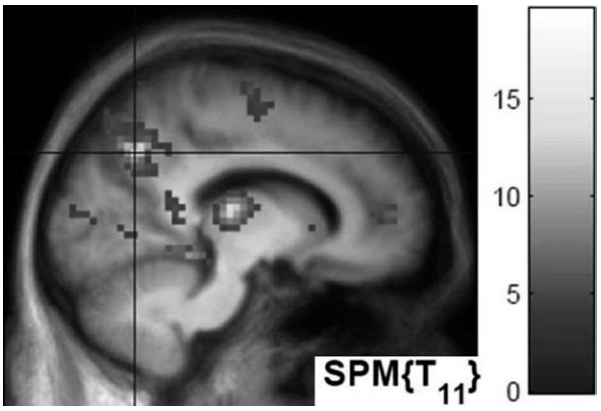

FIG. 1 (579).

Results: SYN115 produced highly significant local decreases in CBF after correcting for a modest decrease in global CBF. The most significant decreases occurred in bilateral thalamus, precuneus and anterior cingulate, all with corrected p=0.000. Other significant decreases occurred in prefrontal Brodmann areas (BA) 9 and 10, posterior cingulate, premotor, and primary somatosensory cortex, and superior parietal lobule. All regional changes were dose-responsive. We exploited sample variation in pharmacokinetics to compute quantitative pharmacodynamic parameter estimates for SYN115 from the rCBF responses.

Conclusions: The bilateral thalamic decrease is consistent with reduced pallidothalamic inhibition via the indirect pathway and with significant motor improvement observed with active drug. The decreases in precuneus and cingulate cortex are consistent with deactivation of the default mode network and with neuropsychological results suggestive of increased alertness with active drug. Perfusion MRI can provide rapid, useful, quantitative and clinically relevant information for pharmaceutical development.

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Imaging gambling severity in patients with Parkinson's disease: Evidence of fronto-striatal disconnection retinal morphology in Parkinson's disease (PD)

R. Cilia, S.S. Cho, T. van Eimeren, G. Marotta, C. Siri, J.H. Ko, G. Pellecchia, G. Pezzoli, A. Antonini, A.P. Strafella (Toronto, Ontario, Canada)

Objective: The aim of the present study was to identify the brain regions associated with the severity of pathological gambling in medicated PD patients. In addition, we used two different connectivity techniques to identify critical neural interactions that differentiated PD gamblers from matched controls.

Background: Pathological gambling may occur in PD patients as a complication of dopaminergic therapy. Previous imaging studies suggested abnormal dopamine transmission within the mesolimbic reward system.

Methods: 30 PD patients (15 with active PG and 15 matched controls, on medication) and 15 healthy subjects underwent brain perfusion SPECT at rest. The severity of gambling was assessed using the South Oaks Gambling Scale. In PD gamblers, we used covariance analysis in SPM5 to identify the brain regions whose perfusion correlated with gambling severity. These regions were then used as seed-volumes-of-interest to identify interconnected regions using voxel-wise covariate analysis in SPM5 (functional connectivity). Finally, we created a path model by means of effective connectivity analysis within the Structural Equation Modeling framework using AMOS 7.0 (effective connectivity).

Results: Increasing gambling severity in PD gamblers negatively correlated with the right ventrolateral prefrontal cortex, anterior and posterior cingulate cortices, medial prefrontal cortex, insula, parahippocampal gyrus, and left striatum; positive correlations were found in the fusiform gyrus and cerebellum (figure A). The main finding of connectivity analyses was the disconnection between striatum and

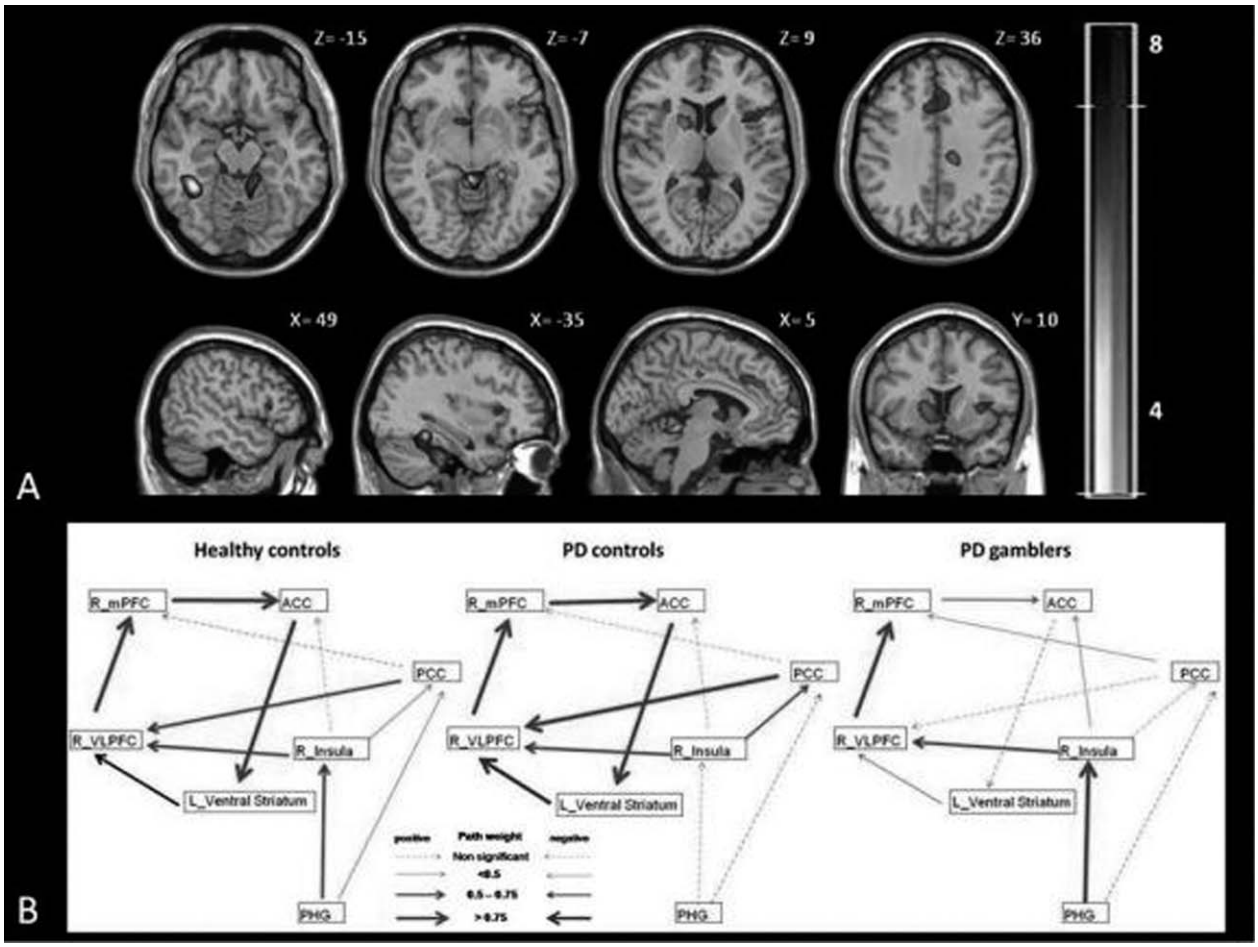

FIG. 1 (580).

ACC in PD gamblers, an interaction that was very robust in both control groups (figure B).

Conclusions: Increasing gambling severity was associated with progressive dysfunction in brain areas involved in risk estimation and the inhibition of inappropriate behaviors. Connectivity analyses identified a disconnection between ACC and striatum: this may underlie the progressive inability of PD gamblers to process negative outcomes and disengage from risk-taking and reward-seeking behaviors.

581

Reduced dopamine transporter density in the ventral striatum of PD patients with impulse control disorders

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Objective: The aim of the present study was to investigate presynaptic dopamine transporter (DAT) density in PD patients with pathological gambling (PG) and other impulse control disorders (ICDs).

Background: ICDs represent a behavioral side effect of dopaminergic therapy in a minority of vulnerable PD patients. Previous imaging studies suggested increased dopamine transmission in the ventral striatum. Striatal DAT regulates synaptic dopamine through active reuptake into the pre-synaptic neuron.

Methods: Eight PD patients with pathological gambling (PG) and other impulse control disorders (compulsive sexual behavior, n=5; binge eating, n=3; compulsive shopping, n=2), 21 matched PD controls, and 14 healthy subjects underwent DAT single photon emission tomography (SPECT) using the tracer FP-CIT. Pathological gambling activity was assessed using the South Oaks Gambling Scale. Statistical parametric mapping (SPM5) applied for voxel-wise analysis ($p<0.05$ corrected at cluster level, Ke>20 voxels).

Results: Analysis of variance (ANOVA) revealed that the three groups differed in bilateral dorsal and ventral striatum. Post-hoc analysis revealed reduced FP-CIT binding in the ventral striatum of PD patients with PG compared to PD controls (figure). Both PD groups (with and without PG) showed bilateral tracer reduction in dorsal putamen bilaterally compared to healthy individuals. There was no correlation between FP-CIT binding and gambling severity.

Conclusions: Reduced DAT density in the ventral 'limbic' striatum may explain the increased synaptic dopamine availability previously shown in PD patients with pathological gambling.[1] Low DAT expression has been previously associated with high impulsivity and addictive disorders in mice and non-PD individuals and we believe that our finding might reflect either functional down-regulation or allelic polymorphisms. [2] **References** [1] Steeves TD et al. Increased striatal dopamine release in parkinsonian patients with pathological gambling: a [11C] raclopride PET study. Brain 2009; 132, 1376-1385. [2] Forbes EE et al. Genetic variation in components of dopamine neurotransmission impacts ventral striatal reactivity associated with impulsivity. Mol Psychiatry 2009; 14(1):60-70.

582

Reduced uptake on [^{18}F]FDOPA pet imaging in welders with occupational manganese exposure

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Objective: To evaluate a cohort of active, asymptomatic welders with manganese (Mn) exposure for signs of in-vivo nigrostriatal neuronal injury using 6-[^{18}F]fluoro-L-DOPA (FDOPA) PET imaging.

Background: Mn is an established basal ganglia neurotoxin but the relative involvement of pre- and post-synaptic dopaminergic system is controversial. Prior dopaminergic imaging studies in subjects with Mn neurotoxicity have demonstrated variable degrees of dopaminergic dysfunction.[1]

Methods: We imaged 20 welders exposed to Mn fumes with FDOPA PET and compared them to 20 individuals with idiopathic Parkinson's disease (IPD) and 20 normal controls. All subjects were examined by a movement disorders specialist including a Unified Parkinson's Disease Rating Scale motor subsection 3. A blinded reviewer traced left and right basal ganglia regions of interest and an occipital control region for each subject. FDOPA PET K_is were generated for each region using Patlak graphical analysis.[2] The lowest K_is for each basal ganglia region (left vs. right) were used for analysis to account for the asymmetry of IPD subjects.

FIG. 1 (581).

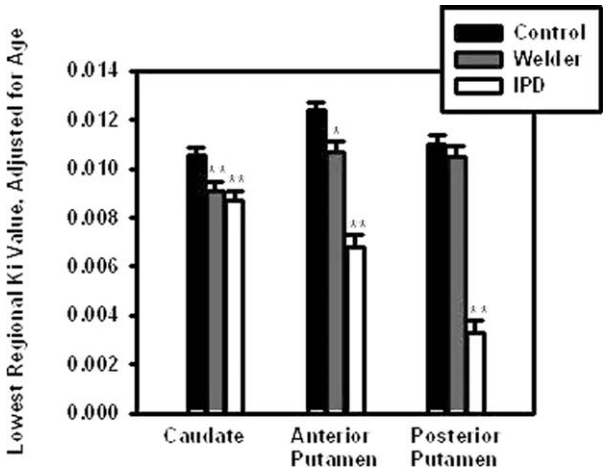

FIG. 1 (582). Average lowest FD OPA PET Ki by region for controls, welders, and IPD subjects adjusted for age. * = different from controls, $p < .05$. ** = different from control $p < .01$.

Results: Repeated measures GLM analysis demonstrated a significant interaction between diagnostic group and region (F=41.443, p<0.001). Welders demonstrated intermediate levels of FDOPA uptake. Welder caudate and anterior putamen K_is were significantly lower than control subjects. FDOPA uptake in welders was most reduced in the caudate > anterior putamen > posterior putamen. This anatomic pattern of FDOPA uptake was inverse to the pattern demonstrated by IPD subjects.

Conclusions: Active, asymptomatic welders with Mn exposure demonstrate reduced FDOPA PET uptake indicating dysfunction in the nigrostriatal dopamine system. The anterior striatal K_i reduction in welders may represent an early (asymptomatic) marker of neurotoxicity or a regulatory effect related to Mn exposure. 1. Aschner M, Guilarte TR, Schneider JS, Zheng W. Manganese: recent advances in understanding its transport and neurotoxicity. *Toxicol Appl Pharmacol* 2007 Jun 1;221:131-147. 2. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. *J Cereb Blood Flow Metab* 1983;3:1-7.

583

Iron accumulation in basal ganglia of patients with Parkinson's disease

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Objective: To compare iron accumulation quantified by susceptibility-weighted imaging (SWI) in basal ganglia between patients with Parkinson's disease (PD) and control subjects.

Background: Iron is the most abundant metal in the human brain and it has a key role in neuronal development. Increase in iron level in the substantia nigra (SN) of patients with Parkinson's disease (PD) has been demonstrated in autopsies and by several different techniques. Haacke et al. introduced a method to estimate iron content in the brain by using a new type of contrast in MRI and referred to this method as Susceptibility Weighted Imaging (SWI).

Methods: 13 patients with PD and 7 control subjects underwent neurological examination and 3.0T brain MRI study. By using the SWI technique and the SPIN (Signal Processing in NMR, SVN Revision 1309) software, the signal intensity was mapped out in the SN and putamen bilaterally. The group differences between PD and control subjects were compared using Mann Whitney test. Statistical analysis was performed with SPSS 17.

Results: In the non-PD group the range of SN mean intensity was -0.0468 to 0.0161, and -0.0104, to 0.0468 radians in the PD group. Statistical analysis indicated significant difference between the two groups (p=0.024) in the SN measurements. Statistical analysis did not show any significant difference between the groups for putamen (p=0.27 and 0.52 for right and left respectively).

Conclusions: Our study suggests that measuring signal changes (an index of iron content) in SN, using SWI as a noninvasive technique may be helpful in detecting PD patients. This study is part of a larger longitudinal study measuring iron accumulation during progression of the disease.

584

Substantia nigra sonography of Parkinson's disease patients with LRRK2 gene mutation

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Objective: to describe ultrasonographic characteristics of the substantia nigra of patients with Parkinson's disease wihch have LRRK2 gene mutation.

Background: Different studies have proved that more than 90% of the patients with Parkinson's disease have hyperechogenic substantia nigra by transcranial sonography. Current data suggest that hyperechogenicity of the substantia nigra is an early marker of preclinical Parkinson's disease.

Methods: We have studied the substantia nigra characteristics and measured its hyperechogenicity by transcranial sonography in six Parkinson's disease patients (three males and three females) with LRRK2 gene mutation. All of them complied the United Kingdom Society Brain Bank Clinical Diagnostic Criteria.

Results: The percentage of increased echogenic size (hyperechogenicity) of the substantia nigra is lower than Parkinson's disease patients without LRRK2 gene mutation. The 66% of our patients had an increased substantia nigra echogenicity. However, 50% of our cases had not a good acoustic transcranial window and couldn't' be evaluated by this technique, all of those were women. All the patients studied which had a good acoustic window had substantia nigra hyperechogenicity.

Conclusions: The ultrasonographic study of the substatntia nigra is an easy, quick and safe test. It could be a good test for Parkinson's disease patients with LRRK2 gene mutation and it may be proposed and practiced in asymptomatic carriers of this mutation. The main limitation of the transcranial sonography is the non existence of a good acoustic sonographic window.

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Neuropshycological profiles and diffusion tensor imaging for the early differentiation of progresive supranuclear palsy and Parkinson's disease

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Objective: To evaluate if neurophysiological profiles of Progressive Supranuclear Palsy (PSP) and Parkinson's disease (PD) and changes in white and grey matter structures using an automated voxel based diffusion tensor imaging (DTI) analysis are useful for the early differentiation of these entities.

Background: PSP and PD show similar motor impairment. Conventional MRI is of little help in their differentiation in early stages.There are only few studies using 3T DTI analysis and their results are contradictory. Furthermore few studies compared cognitive functions in theses disorders.

Methods: A prospective study including 19 PD,14 PSP and 20 matched healthy controls (HC) was performed. Minimental state (MMS), Frontal assessment battery (FAB), Neuropsychiatric Inventory (NPI), UPDRS-III and Hoenh y Yahr score were recorded.Whole brain diffusion Tensor Imaging (DTI) data was acquired in a 3.0 T scanner. An automated voxel based analysis was performed. All statistical parametric mapping (SPM) analysis was performed using the SPM 8 package.The fractional anisotropy (FA) and mean diffusivity (MD) maps were then spatially transformed according to the normalized b0 images and smoothed with Gaussian kernels.

Results: Compared with HC and PD, PSP patients showed a significant (p< 0.001) bilateral decrease in FA and elevation of the MD in frontal and temporal white matter, corpus callosum, internal and external capsule, caudate, thalamus, midbrain, periaqueductal gray matter, basal pontine nucleus, and superior cerebellar peduncles.No significative differences between EP and HC were found. In the neuropsychological study PSP patients showed significantly more apathy and disinhibition. The total FAB was significantly lower in PSP, being verbal fluency the most affected item.

Conclusions: 3T Automated voxel based DTI analysis demonstrates extensive grey and white matter abnormalities in PSP patients in contrast with the lack of findings in PD.These could be helpful in the differentiation of both entities.PSP patients show more severe

frontal and language dysfunction which nicely correlates with the abnormality demonstrated in the DTI analysis in frontal white matter, thalamus and long connecting fibber tracts.

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Transcranial sonography in idiopathic Parkinson's disease, monogenic forms and asymptomatic mutation carriers (*parkin, LRRK2* and *GBA*)

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Objective: To research different forms of Parkinson's disease (PD) by means of transcranial sonography (TCS) and to assess an ability of this method to detect individuals with a predisposition to PD.

Background: Recently many research groups have suggested different biomarkers for an identification of early pathological changes and a predisposition to PD. A number of studies using TCS have shown that a typical finding in patients with PD is a hyperechogenicity of the substantia nigra (HSN). However up to date there are very few reports of TCS application in monogenic forms of PD and asymptomatic carriers of gene mutations.

Methods: In our study applying TCS we examined 90 patients with idiopathic PD (including 28 with familial history), 12 PD patients with confirmed mutations in *parkin, LRRK2* and *GBA* genes, 10 healthy relatives of these carriers, 10 asymptomatic relatives carrying mutations and 50 subjects of control group. To screen for mutations we used real-time PCR (*parkin* exonic rearrangements) and RFLP analysis for common mutations (*LRRK2* - G2019S, *GBA*–L444P, N370S).

Results: The lack of sufficient acoustic window was found in 8% of examined persons. A calculated area of the HSN in the group of PD [31 (25;39,25)] was increased compared with the control [0 (0;16)]. We found no difference between subgroups of sporadic PD and familial cases. In patients with mutations the area of the HSN [26 (19,25;33,25)] was similar to asymptomatic carriers [21 (3,25; 29)]. None of healthy relatives had the HSN. Additionally it seems that there was a smaller area of the HSN in all *parkin* carriers [24 (19;31)] than one in *LRRK2* carriers [29 (24,25;31,75)], but this tendency was not statistically significant.

Conclusions: Our results confirmed that monogenic forms as well as idiopathic PD reveal the HSN as a specific biomarker of PD susceptibility. Promising data were obtained in asymptomatic carriers, the most "disease-prone" group, due to a prevalence of the HSN. In this study we performed a combination of two methods, genetic testing and neuroimaging, to increase specificity in detecting individuals with a high risk to develop PD. This strategy seems more rational to form an appropriate target group for future clinical trials of preventive therapy.

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Clinically unclear parkinsonian syndromes: A SPECT study using TRODAT-1

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Objective: In this study our aim was to evaluate patients with Clinically Unclear parkinsonian Syndromes (CUPS) submitted to brain SPECT imaging using TRODAT-1, a radioligand with high affinity to the Dopamine Transporter (DAT).

Background: Approximately 25% of Parkinson's disease (PD) patients are misdiagnosed in clinical practice. A DAT reduction in the stritum and its nucleus is considered as a surrogate biomarker for pre-synaptic dopaminergic dysfunction.

Methods: For this analysis we included 15 subjects with CUPS and matched then with 13 patients with *probable* PD and 13 healthy control subjects (HCS). SPECT with TRODAT-1 was undertaken at the baseline evaluation and patients from the CUPS were followed-up for 2-years to ensure or not PD diagnosis ("gold-standard").

Results: The mean±SD results from Right and Left striatum Binding Potential (BP) were, respectively, 1.08±0.20 and 1.04±0.16 in the HCS group, 0.47±0.16 and 0.53±0.17 in the PD group, and 0.68±0.11 and 0.84±0.17 in the CUPS group. The rate of disagreement between baseline SPECT in the CUPS group as compared to the "gold standard" diagnosis (clinical diagnosis of PD on follow-up) was of 20%. The sensitivity of the SPECT with TRODAT-1 was 100%, while specificity was 70%.

Conclusions: In conclusion, it is possible to assume from the aforementioned data that brain SPECT imaging using TRODAT-1 as the radiopharmaceutical is a reliable tool to detect pre-synaptic dopaminergic dysfunction in patients with CUPS. The implication of this information has to do with treatment and outcome prognosis, helping treating physicians in the management of their patients.

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Brain SPECT findings in limbic encephalitis

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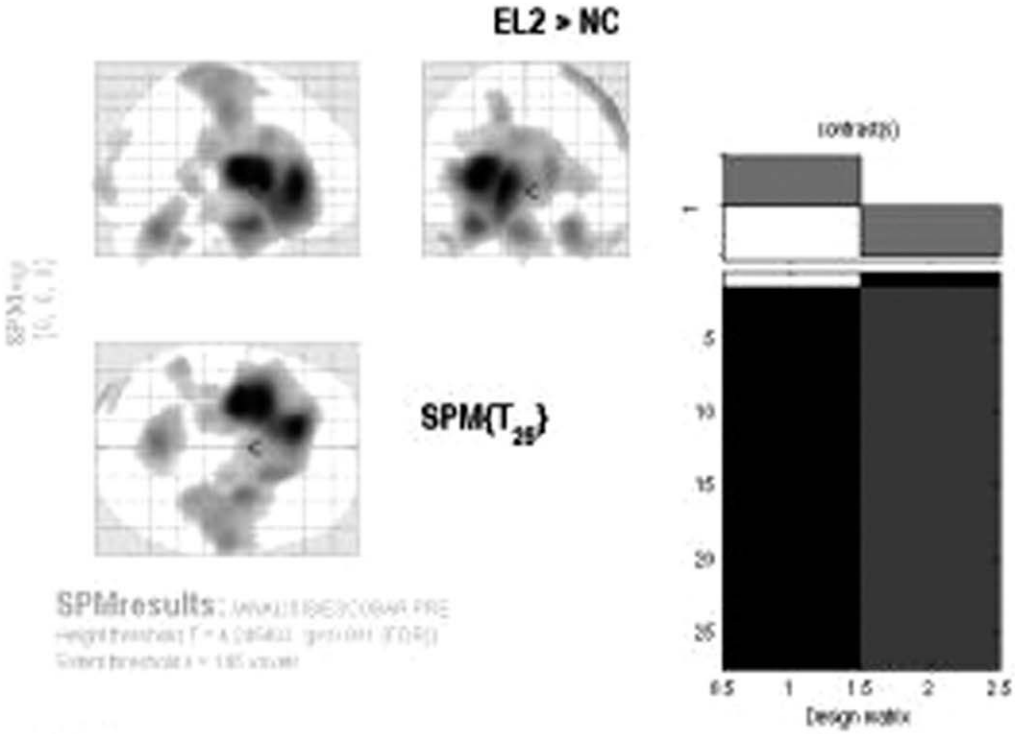
Objective: To describe regional cerebral blood flow (rCBF) changes in patients with limbic encephalitis (LE) and evaluate if brain perfusion SPECT can aid in clinical diagnosis and management.

Background: LE are rare immune mediated neurological disorders, most of them of paraneoplastic origin, that present with subacute onset of cognitive disfunction, abnormal movements or seizures and psychiatric symptoms. Rapid clinical evolution and lack of symptom specificity lead to a challenging diagnosis. MRI medial temporal hyperintensities are not always present and epileptic activity in EEG is not recorded most of the times. Functional neuroimaging is considered a promising tool but references in the literature are very limited, most of them case reports with FDG-PET.

Methods: We report 5 patients (46-78 years, 4 female) with clinical diagnosis of LE (unknown origin) studied with 99mTc-ECD SPECT. In one of them the study was repeated after treatment response. Each scan was compared to a database of 26 normal controls (40-61 years, 15 female) in SPM5. Only highly significant voxels were displayed ($p<0.001$ corrected for multiple comparisons).

Results: All patients presented medial temporal hyperactivity (2 bilateral). Basal ganglia were hyperactive in all of them (3 bilateral). Increased activity was detected in insular (3/5), dorsolateral prefrontal (3/5) and orbitofrontal (2/5) cortex. Cerebellum was hyperperfused in 3 patients. Decreased rCBF was detected in all patients in dorsolateral prefrontal, posterior parietal or temporoparietal and inferior temporal cortex. Normalization of rCBF in temporolimbic structures was seen in the patient studied after treatment response. Hypoperfused areas persisted, as well as less intense hyperactivity in right striatum and paralimbic cortex.

Conclusions: Increased rCBF in LE involves not only medial temporal cortex but also other paralimbic areas, cortical and subcortical conections and cerebellum. Extense hypoperfusion in heteromodal association cortex is also described. This characteristic pattern is similar to that described in peri-ictal SPECT in refractory epilepsy and suggest that persistent epileptic activity might play a major role in the fisiopathology of the disorder. Brain SPECT is a non invasive, widely available tool that may have a role in clinical diagnosis and evolution of LE.



Statistics: *p-values adjusted for search volume*

set-level		cluster-level			voxel-level					mm mm mm
p	c	p_{uncorr}	k_E	$p_{FDR-corr}$	$p_{FWE-corr}$	T	Z_e	p_{uncorr}		
0.000	7	0.000	21833	0.000	0.000	18.29	Inf	0.000	-32 -8 12	
					0.000	0.000	17.98	Inf	0.000	-26 18 6
					0.000	0.000	17.73	Inf	0.000	-12 28 4
		0.000	2439	0.000	0.000	0.000	18.18	8.34	0.000	-2 -58 -20
					0.000	0.000	7.15	5.07	0.000	-6 -48 -12
		0.000	6760	0.000	0.000	0.000	8.88	6.20	0.000	30 8 -24
					0.012	0.000	6.42	4.87	0.000	60 -6 -16
					0.372	0.000	5.48	4.40	0.000	38 2 -32
		0.000	5974	0.000	0.000	0.000	8.18	5.85	0.000	56 -14 50
					0.000	0.000	6.42	5.56	0.000	54 -14 54
					0.000	0.000	6.32	5.51	0.000	44 -28 48
		0.000	232	0.022	0.000	0.000	7.15	5.23	0.000	-50 -44 -32
		0.000	222	0.000	0.000	0.000	6.65	5.03	0.000	30 -28 2
		0.000	208	0.000	0.007	0.000	6.46	4.89	0.000	-34 -64 6
					0.012	0.000	5.39	4.07	0.000	-28 -38 4
					0.122	0.000	5.21	4.01	0.000	-38 -64 32

Table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 4.25, p = 0.000 (0.507) [p=0.001 (FDR)]
Extent threshold: k = 146 voxels, p = 0.000 (0.842)
Expected voxels per cluster, <k> = 37.197
Expected number of clusters, <c> = 0.84
Expected false discovery rate, <= 0.00

Degrees of freedom = [1.0, 25.0]
FWHM = 17.5 19.8 18.8 mm mm mm; 9.8 9.5 9.4 (voxels)
Volume: 1696400 = 212300 voxels = 240.2 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 788.35 voxels)

FIG. 1 (588).

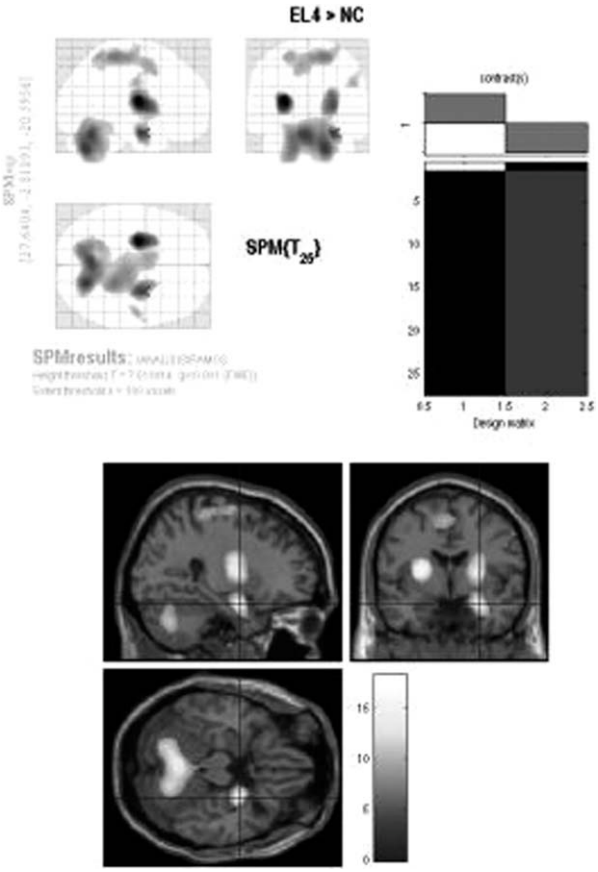


FIG. 2 (588).

589

Automatic brain image reading for the differential diagnosis between atypical parkinsonian syndromes & Parkinson's disease

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Objective: To compare the accuracy of an automatic classifier applied to resting-state 18FDG PET scans collected in patients with degenerative parkinsonism with the clinical diagnosis at follow up several years after PET.

TABLE 1 (589). *Clinical data*

	Final diagnosis	Age (years) at the time of PET (mean ± std)	Disease duration (years) at the time of PET (mean ± std)	Follow up (years) after PET (mean ± std)
Training & testing dataset (N=110)				
PD class	PD (27)/ Norm (28)	59.6 ± 8.47	4.1 ± 4	8.4 ± 4.5
APS class	MSA (22)/ PSP (17)/ CBD (16)	62.8 ± 6.5	3.3 ± 2.1	3.7 ± 3
Validation dataset (N=47)				
PD class	PD (15)	50.4 ± 9.5	5.2 ± 5.2	9.2 ± 3.5
APS class	MSA (9)/ PSP (12)/ CBD (11)	71.4 ± 8.1	4.4 ± 4.1	2.5 ± 2.7

TABLE 2 (589). *Diagnostic yield of automatic brain image reading (APS vs. PD)*

	Training & testing dataset	Validation dataset	Average
Sensitivity	89.1%	96.8%	92.9%
Specificity	92.7%	100%	96.3%
Positive predictive value	92.4%	100%	96.2%
Negative predictive value	89.5%	93.7%	91.6%

Background: Visual inspection of 18FDG-PET scans has proven valuable in discriminating Parkinson's disease (PD) from atypical parkinsonian syndromes (APS: multiple system atrophy [MSA], Progressive Supranuclear Palsy [PSP], and Corticobasal degeneration [CBD]).

Methods: We processed and analyzed 157 resting-state 18FDG-PET scans from patients with degenerative parkinsonism referred to our center because the diagnosis was felt uncertain (Table 1).

After spatial normalization onto a study-specific template and smoothing using SPM8, PET images were analyzed using relevant vector machine (RVM), a supervised multivariate Bayesian machine learning algorithm. The classifier was first trained on 110 scans to learn the differences in image pattern between the 2 classes under consideration (APS vs. PD) and then tested on the same dataset using a leave-one-out (LOO) procedure. Next, the trained classifier was validated using a new set of 47 images with unseen classes obtained on the same tomograph as the first dataset.

Results: After training, the voxels found to contribute the most to image classification into the APS group were distributed in the midbrain, striatum, anterior thalamus and frontal cortex, bilaterally. The LOO procedure on the training dataset led to a 89.1% and 92.7 % classification accuracy for the APS and PD classes, respectively, as compared to the clinical diagnosis at the last available visit. In the validation dataset, only one image from the APS class was misclassified (Table 2).

Conclusions: Automatic reading of 18FDG-PET images of the brain using RVM provides adequate diagnostic yield for discriminating APS from PD patients. Future work should examine how this approach can be generalized to other patient cohorts studied at an earlier stage of the disease. From a broader perspective, results suggest that such multivariate approaches have the potential to assist the clinicians to make accurate predictions at the individual level.

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DTI and probabilistic tractography of the premotor to basal ganglia connections in healthy subjects and patients with Parkinson's disease

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Objective: To study the anatomical differences in the premotor-basal ganglia loops in patients with Parkinson's disease (PD) and healthy controls (HC) by means of diffusion tensor imaging (DTI) and probabilistic tractography.

Background: PD patients do not only suffer from well-known motor symptoms but deficits in also non-motor pathology with impairment of specific domains of memory, frontal cognitive domains, sensory-motor integration and executive function. Although non-motor symptoms significantly impact therapy and course of PD, little is yet known about their anatomical correlates, disease-related morphological changes and their relation to symptom severity in individual subjects. We therefore aimed at characterizing their connectivity within the basal ganglia loop.

Methods: Twelve age matched HC and fifteen patients with idiopathic PD without dementia (7 males, mean age 52.3±7.6, Hoehn and Yahr 2.1±0.8) underwent whole-brain DTI at 3 T (Philips Achieva; 3 acquisitions of 32 directions: b=1000 and five b0 images). The data was pre-processed and analysed using FSL (FMRIBm Oxford, UK) and probabilistic tractographies were run from the dorsal-(PMD) and ventral-(PMV) premotor cortex to a tar-

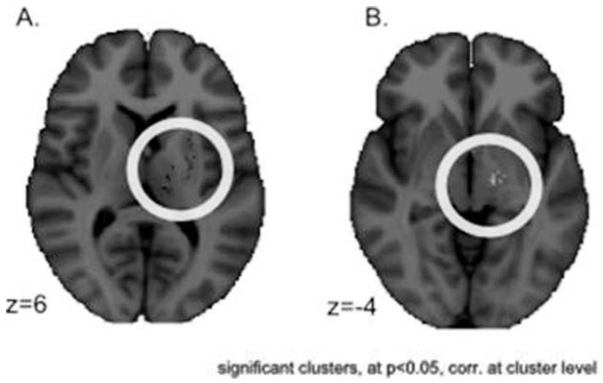

FIG. 1 (590).

get region consisting the basal ganglia, midbrain and diencephalon. A statistical comparison (permutation analysis, corrected at cluster level, $p<0.05$) of the results of the probabilistic tractography to the target was performed between the groups.

Results: In PD patients, we found a significantly altered integrity of premotor-basal ganglia fiber tracts at the level of putamen and ventrolateral thalamus in the connections from the dorsal premotor cortex (A). Furthermore, in PD group there were significant changes in the white matter underlying subthalamic nucleus and ventrolateral thalamus in the combined analysis of PMD and PMV connections. B).

Conclusions: This study, using DTI and probabilistic tractography, demonstrates altered morphological integrity of premotor-basal-ganglia pathways in PD patients. Moreover, it highlights the potential account of this approach for investigating morphological pathologies of basal ganglia and cortical structures in PD. Future studies will need to address the clinical relevance of this morphological finding. In particular one will need to study the relationship between altered connectivity and the severity of frontal executive dysfunction and the potential use of tractography data as a biomarker for the evolution of PD or PD related dementia.

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Diffusion tensor MRI of new brainstem areas can distinguish PSP from PD and MSA-P

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Objective: To test the role of Diffusion tensor imaging (DTI) in differentiating progressive supranuclear palsy (PSP), Parkinson variant of multiple system atrophy (MSA-P) and Parkinson's disease (PD) using already reported and new regions of interests in the brainstem (midbrain tegmentum and superior colliculus) where pathological differences exist among these disorders.

Background: DTI of brain is reported to distinguish PD, MSA and PSP. These observations need to be validated and extended.

Methods: Patients with clinical diagnoses of PD (11), PSP (12) and MSA-P (12) based on established clinical criteria and normal controls (11) participated in the study. Mean diffusivity (MD) and fractional anisotropy (FA) were calculated by using regions of interest (ROIs) over globus pallidus, caudate, putamen, superior cerebellar peduncle (SCP), middle cerebellar peduncle (MCP), superior colliculus (SC), midbrain tegmentum (MTG - to include substantia nigra and red nucleus but not the cerebral peduncles), cerebellar hemispheres, pontine base and the genu of corpus callosum.

Results: In PSP, the MD in SC and MTG were significantly higher when compared to MSA-P group ($p< 0.01$ and $p=0.001$ respectively). MD in MTG and SCP were significantly higher ($p=0.002$ and $p=0.001$ respectively) and FA values significantly lower ($p< 0.01$) in SCP in PSP compared to PD group. The intraclass correlation coefficients (ICCs) of intrarater reliability for the measurement of rADCs and FA were excellent (≥ 0.75). There were no significant differences in MD or FA of other ROIs among the 3 patient groups.

Conclusions: In DTI, higher mean diffusivity of the superior colliculus and midbrain tegmentum can differentiate PSP from MSA-P. Higher mean diffusivity in midbrain tegmentum and superior cerebellar peduncle and reduced FA in the superior cerebellar peduncle can differentiate PSP from PD. The ability of DTI of SC and MTG to distinguish PSP from MSA-P and PD has not been reported earlier. We could not distinguish MSA-P from PSP and PD by DTI of MCP and pons, as reported earlier, probably because there were no cases of MSA-C in our group.

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Comparative neuroimaging study of PD and DLB by diffusion tensor imaging, voxel based morphometry and SPECT

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Objective: To elucidate a correlation among white matter disruption, gray matter atrophy and cerebral blood flow in PD and DLB. We especially focused on a correlation between occipital hypoperfusion and a possible white mater disruption and/or gray matter atrophy of occipital lobe in DLB.

Background: The pathological hallmark of PD and DLB is cytoplasmic and neuritic inclusions named Lewy bodies (LBs) and Lewy neurites (LNs). Pathological study revealed that LBs and LNs were widely distributed in cerebral neocortex accompanied with cognitive impairment but that they were less frequently accumulated in occipital lobe. Recently, hypoperfusion of occipital lobe by perfusion SPECT has been reported in DLB, whose pathogenesis remains to be elucidated.

Methods: Thirty-three PD without cognitive impairment (PDWoCI), 9 PD with mild cognitive impairment (PD-MCI), 8 PD with dementia (PDD), 7 DLB, and 29 healthy volunteers (control subjects) were enrolled in this study. White and gray matter were evaluated and statistically analyzed by diffusion tensor imaging with FMRIB Software Library-tract based spatial statistics (FSL-TBSS), 3 dimensional T1 weighted image with FSL- voxel based morphometry. Cerebral blood flow was evaluated by IMP-SPECT with 3D-SSP. The mean Fractional Anisotropy (FA) values were calculated by averaging all FA values in voxels where FSL-TBSS study of FA map proved significantly decreased by comparing disease group (PDWoCD, PD-MCI, PDD and DLB) and control group.

Results: The mean FA values were significantly decreased in diffuse area of cerebral white matter in PDWoCI, PD-MCI, PDD and DLB compared with control subjects. In occipital lobe, the mean FA values were 0.353(PDWoCI), 0.350(PD-MCI), 0.328(PDD), 0.335(DLB) and 0.372(control). The volume of gray matter was decreased in the limited area in PDD, but in diffuse area in DLB. Perfusion SPECT study showed hypoperfusion of occipital lobe in DLB.

Conclusions: These findings suggest that there is both white matter disruption and gray matter atrophy in accordance with progressing cognitive impairment in PD, while there is not only white matter disruption but also more pronounced gray matter atrophy in DLB. Moreover, hypoperfusion of occipital lobe in DLB is caused by, at least in part, white matter disruption.

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How do the basal ganglia generate resting tremor in Parkinson's disease

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Objective: To reveal the contribution of basal ganglia dysfunction to resting tremor in Parkinson's disease (PD).

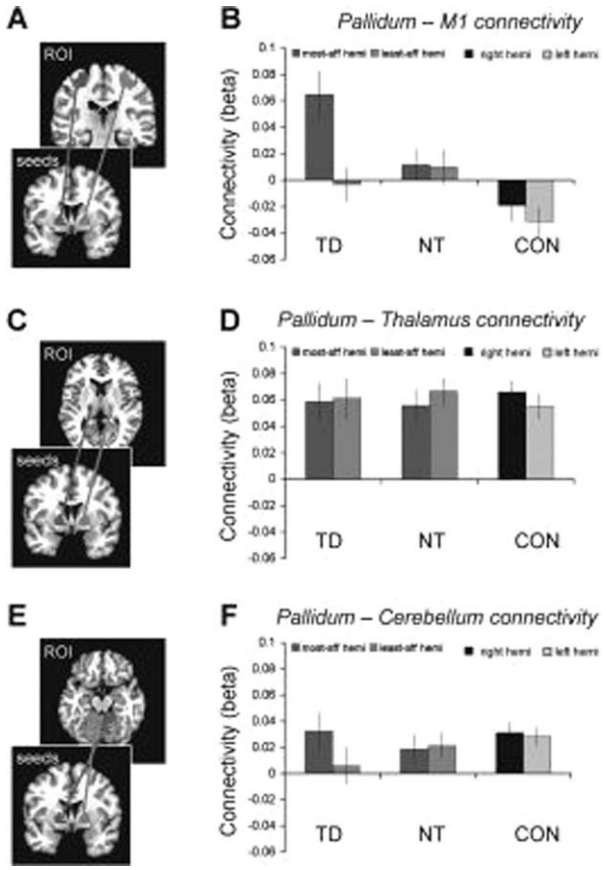

FIG. 1 (593).

Background: Tremor in PD and other disorders has been related to increased activity in a cerebello-thalamic "tremor circuit". However, in PD an intervention in both this tremor circuit (i.e. in the ventral intermediate nucleus of the thalamus; VIM) and in the basal ganglia loop (i.e. in the pallidum or subthalamic nucleus) can arrest tremor. Thus, we hypothesized that resting tremor in PD results from a perturbation of the tremor circuit by altered modulatory influences from the basal ganglia.

Methods: We compared three groups of healthy subjects (n=36), tremor-dominant PD (n=21) and non-tremor PD (n=23). In these groups, we quantified functional connectivity between the basal ganglia and the tremor circuit, using resting state fMRI. We took the output nucleus of the basal ganglia (pallidum) as the seed region for our connectivity analysis. The areas of the tremor circuit (primary motor cortex, VIM and cerebellum; previously identified) were used as regions of interest. During scanning, we measured spontaneous variations in resting tremor amplitude with EMG.

Results: Tremor-dominant PD patients showed increased connectivity between the pallidum and the primary motor cortex (M1), as compared to non-tremor PD and controls (Fig. 1A-B). The strength of these interactions was sensitive to the side of predominant dopamine depletion (Fig. 1B), and increased with tremor severity (Fig. 2A). Conversely, there was no correlation with bradykinesia (Fig. 2 D-F). A similar trend was seen for connectivity between pallidum and the cerebellum (Fig. 1 E-F), but not the VIM (Fig. 1 C-D). Cerebral responses in the pallidum did not co-fluctuate with tremor amplitude, but they marked the on- and offsets of high-tremor episodes. Activity in the entire tremor circuit co-fluctuated with tremor amplitude.

Conclusions: Our results show that increased interactions between the pallidum and M1 mediate the occurrence of resting tremor in PD. These interactions may be caused by enhanced synchronization in the basal ganglia loop in PD ("loss of segregation"). We propose that this destabilizes the cerebello-thalamic tremor circuit, providing an important context in which transient pallidal fluctuations may trigger pathological activity in the cerebello-thalamic tremor circuit.

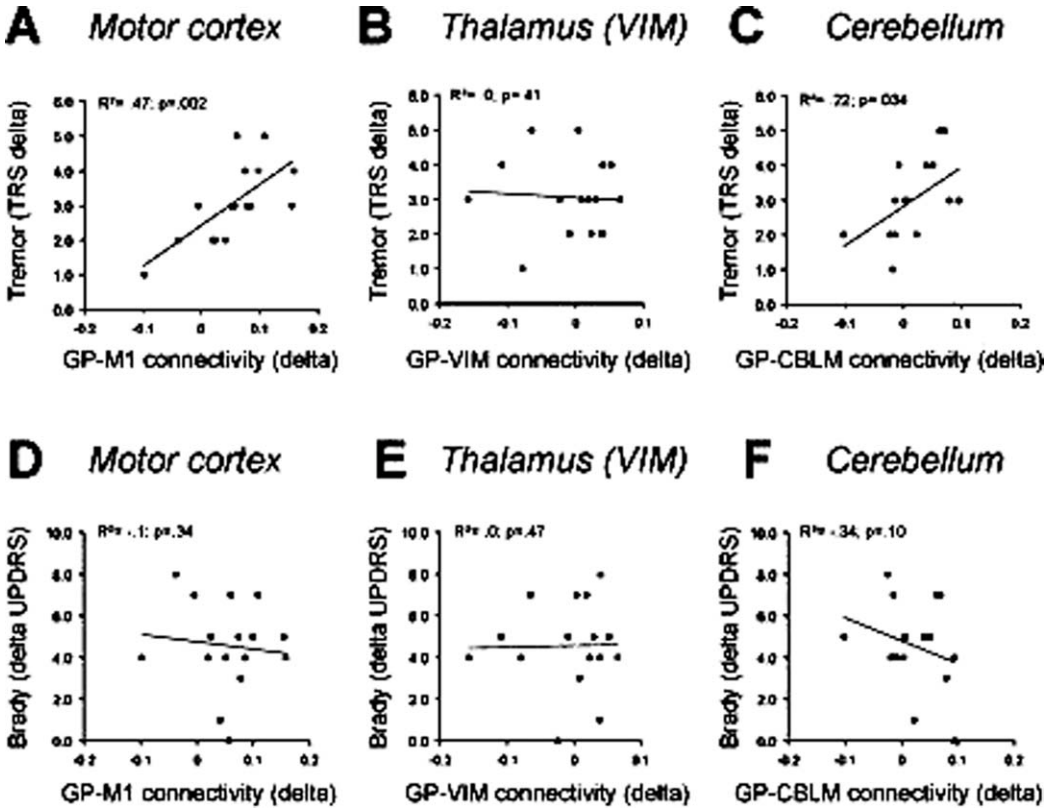

FIG. 2 (593).

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Can ^{123}I-FP-CIT SPECT detect preclinical nigrostriatal deficit in "de novo" Parkinson's disease patients

J. Hernandez-Vara, C. Lorenzo-Bosquet, G. Cuberas-Borros, O. De Fabregues-Boixar, A. Palasi-Franco, M. Barios-Profitos, J. Castell-Conesa, J. Alvarez-Sabin (Barcelona, Spain)

Objective: To assess wether ^{123} I-FP-CIT may be a useful tool to detect presymptomatic nigrostriatal degeneration in patients with early Parkinson's disease (PD).

Background: PD is a neurodegenerative condition characterized by a progressive loss of dopaminergic cells in the substantia nigra. Postmorten studies have shown that dopaminergic cells degeneration is associated with a decrease of presynaptic striatal dopamine transporter (DAT). Imaging of DAT binding assessed by SPECT can demonstrate the loss of dopaminergic nerve terminals in the striatum of PD patients. In patients with unilateral signs, a loss of dopaminergic innervation ipsilateral to affected side might be considered presymptomatic.

Methods: 50 PD patients, Hoehn-Yahr stage 1, were included [31 (62%) men; mean age 62±10.53 years]. All patients fulfilled clinical criteria, step 1 established by the Parkinson's Disease Society Brain Bank and were examined with the UPDRS to evaluate the severity of ilness. A FP-CIT SPECT was performed in all patients using a double-head gamma cammera. 20 patients, with essential tremor (ET) and SPECT considered as normal, were used as control group. SPECT images were analysed visually and by a volumetric semi-quantitative method by two nuclear medicine specialist. A two-tailed unpaired Student's t-tes was used to analyse differences in DAT uptake between groups. $P<0.05$ was considered statistically significant.

Results: Visual analyisis: In ET patients I-FP-CIT was symmetrically distributed in the striatal region, whereas PD patients showed reduced DAT uptake in the putamen contralateral to the affected side. Moreover, in 39 (78%) patients visual assessment revealed bilateral reduction of putamen uptake. **Quantitative analysis:** In PD patients, compared with the reference group, a significant decrease of DAT activity in both putaminal regions was found (PD: contralateral putamen 2.10±0.33; ipsilateral 2.32±0.28. ET: contralateral putamen 2.56±0.30; ipsilateral 2.72±0.31; $p< 0.0001$). No differences were found in the caudate.

Conclusions: ^{123} I-FP-CIT detects bilateral nigrostriatal degeneration in patients with unilateral symptoms and can be a valuable tool for identifying neuronal loss in the presymptomatic phase.

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Inter-rater reproducibility and accuracy of measurement of the substantia nigra using transcranial B-mode sonography (TCS)

H. Huber, J. Godau, A. Gaenslen, K. Brockmann, D. Berg (Tuebingen, Germany)

Objective: To i) test the inter-rater reproducibility when measuring the size of the substantia nigra (SN) within the mesencephalic plane, ii) investigate whether angulation of the ultrasound probe and/or mesencephalic brain stem size may have an effect on the measured size of the SN.

Background: TCS is increasingly used in the diagnosis of Parkinson's disease and other neurodegenerative disorders. However, subjectivity and dependence on the scanning procedure is still an issue.

Methods: Two investigators blinded for the results of each other investigated 443 neurodegeneratively healthy subjects by TCS (Examiner 1: n=195, Examiner 2: n=248), measuring the size of both pedunculi cerebri and the SN at its maximum extension within the mesencephalic scanning plane from both temporal bone windows using a Siemens Antares ultrasound machine.

Results: There was no difference in the distribution (Fig. 1) of measurements of the SN of both investigators. Angulation did not statistically affect the size of the SN of either side as calculated

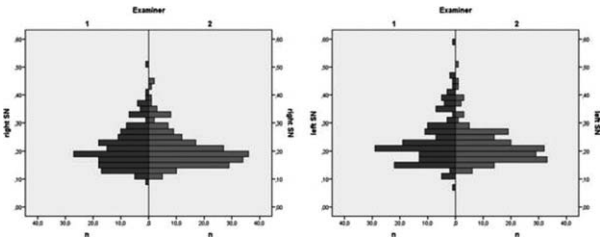

FIG. 1 (595).

using the ratio of the contralateral/ipsilateral crus cerebri. However, a significant positive correlation between the size of the SN and the size of the ipsilateral crus cerebri was found for each side (Right SN: rs=0,383, p<0,001; Left SN: rs=0,382, p<0,001; insufficient bone window in 74 subjects (16,7%)).

Conclusions: In this large cohort we could confirm a good inter-rater reproducibility concerning measurement of the SN. Moreover, we could show for the first time, that angulation of the ultrasound probe does not have a significant effect on the size of the SN when strictly staying within the mesencephalic plane. However, ipsilateral brainstem size does affect SN size and therefore needs to be considered when defining future cut off values for SN hyperechogenicity.

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Olfactory impairment in early Parkinson's disease and white matter abnormalities in central olfactory areas. A voxel-based diffusion tensor imaging study

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Objective: The present study aimed to investigate the relationship between olfactory dysfunction and white matter (WM) FA of central olfactory areas in a group of early PD patients.

Background: Olfactory dysfunction is known to occur before motor signs in Parkinson's disease (PD). Diffusion tensor imaging (DTI) studies in PD have reported fractional anisotropy (FA) reductions in the early stages of the disease.

Methods: Twenty-four PD patients at Hoehn and Yahr stages I and II and 24 healthy controls matched by age, gender and years of education participated in this study. DTI was acquired at a 3 Tesla scanner and odor identification was assessed using the University of Pennsylvania Smell Identification Test (UPSIT). We performed regions of interest of central olfactory system and voxelwise group comparisons using tract-based spatial statistics (TBSS). FA values of central olfactory areas were correlated with UPSIT scores.

Results: Both hyposmic and anosmic PD patients had lower FA values than controls and PD patients with normosmia in the WM adjacent to gyrus rectus. In addition, patients with anosmia had reduced FA in WM in the surrounding primary olfactory areas, specifically in the WM adjacent to the enthorrinal cortex. FA values of the WM adjacent to bilateral primary olfactory cortex and right gyrus rectus correlated with UPSIT scores in PD patients but not in controls.

Conclusions: Microstructural WM changes in the central olfactory system detected by MRI are associated with olfactory loss in early PD.

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From where begins? The degeneration of substantia nigra pars compacta in Parkinson's disease

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Objective: To visualize fibers from midbrain substantia nigra pars compacta (SNc) to striatum by diffusion-tensor imaging (DTI)-based

tractography and estimate the degree of involvement of divided areas in SNc by fiber density quantification.

Background: The loss of doparminergic neurons of SNc is characteristic in Parkinson's disease (PD) and the process had been reported to have an ordered pattern patologically. However, in aliving PD patients it is difficult to see such an ordered process.

Methods: From April 2005 to November 2009, 29 premedicated PD patients (22 women and 7 men, mean age 69.2±8.3 y/o, duration from onset 0.1 - 4.3 yrs and Hoehn-Yahr stage 1.7±0.6), 85 medicated patients with PD (50 women and 35 men, 70.3±7.1 y/o, duration of illness 8.9±4.7 yrs, Hoehn-Yahr stage 2.3±0.9), 88 non PD clients (51 women and 35 men, 68.6±14.3 y/o) as control were investigated. The data of DTI was obtained by GE Signa Twin Speed 1.5T and treated with Volume-One (http://volume-one.org/index-j.htm) and dTV (http://www.ut-radiology.umin.jp/people/masutani/PDF/dTV). Seeding points was placed at midbrain SNc and tracked fibers to striatum and thalamus. Midbrain SNc at orbit-meatal line was divided into medial, middle and lateral areas. The rate of cases based on drawn fibers from divided areas to striatum was evaluated and the rate of drawn fibers to tracked fibers was compared. The ratio of drawn fibers to tracked fibers between PD and control was analyzed by Student's *t*-test.

Results: Drawn fibers targeting to striatum were originated from medial to middle SNc and to thalamus were from lateral SNc. The ratios of cases of fibers from medial SNc to striatum were control 65.3%, more affected side of PD 55.3% and less affected side of PD 59.3%. The ratio of drawn fibers to tracked fibers from medial SNc to striatum was significantly different between control and PD, 0.19±0.11 and 0.15±0.11, respectively ($p<0.001$). There were no differences between areas other than medial area nor clinically predominant affected side.

Conclusions: The degenerative process in SNc was studied by DTI-based tractography and was found fibers from medial SNc to striatum was significantly decreased. Although there are problems to be solved in this technique, in addition to such study, it is expected to become a useful tool for PD diagnosis.

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Sonographical features in idiopathic Parkinson's disease and correlation with clinical parameters

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Objective: To describe ultrasonographical findings in 62 patients with Idiophatic Parkinson's Disease (iDP)and to analyze a possible correlation with clinical parameters.

Background: Substantia Nigra (SN) hyperechogenicity is characteristic of iPD. No relations between any sonographical finding and clinical features have been found.

Methods: 62 patients who met UKBBPD criteria were sonographically studied focusing on deep brain structures and were examined by an investigator blinded to echogenic parameters using Hoehn and Yahr (HY)stage and UPDRS.iPD family history, disease duration, motor complications and time until sonographical study, hallucinations, REM behaviour disorder, hyposmia or depression were also collected.

Results: 79% of patients showed a good bone window.93.8% had SN hyperechogenicity (56.5% bilateral) with mean areas of $0.33cm^2\pm0.09$ (right side) and 0.31±0.08 (left). Echogenicity of the raphe was increased in 14.5% patients; decreased in 27.4%. In 6.5% lentiform nucleus was hyperechogenic. Mean of width of ventricles':0.41cm±0.31 for third, and 2.48cm±8.83 for lateral. No correlations between SN hyperechogenic area or third ventricle's width and disease duration, HY, UPDRS, UPDRS separated items were found.A weak positive correlation between lateral ventricles' width and HY (r 0.586, $p=0.001$) and axial UPDRS items (r 0.533, $p=0.001$) was obtained. Patients with hallucinations had bigger third and lateral ventricle's width (0.68cm±0.38, 2.63±0.31 vs 0.38±0.29, 1.63±0.35, $p=0.002$). There were also significant differences in bilateral SN hyperechogenicity areas in patients with complications ($0.38cm^2\pm0.07$(right), 0.36±0.06 (left) vs $0.30cm^2\pm0.08$ (right), 0.29±0.09 (left), $p=0.01$. Patients with depression showed significantly more ventricular dilatation (77.7%vs34.9%, $p=0.032$). No differences were observed according to family history, hyposmia or REM behaviour disorder.

Conclusions: 93.8% of iPD patients showed SN hiperechogenicity;mean areas of $0.33cm^2\pm0.09$(right), 0.31±0.08(left). No correlations between sonographical features and clinical parameters was found;only a weak positive correlation between lateral ventricles'-width and HY and axial UPDRS items. Patients with hallucinations and depression showed bigger ventricles' widths, and those with complications had bigger SN hyperechogenicity areas,with no relation with disease duration.

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Baseline characteristics of the PARS study cohort

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Objective: The primary objective of the Parkinson Associated Risk Syndrome (PARS) study is to develop and test a strategy to identify a large-scale cohort 'at risk' for Parkinson's disease (PD) by combining olfactory testing with dopamine transporter (DAT) imaging.

Background: Prior to the onset of motor symptoms nigral and extra-nigral neurodegeneration identified as the pre-diagnostic phase of PD. Pathological changes in the anterior olfactory region may be the earliest site for neurodegeneration in PD. Loss of olfaction and development of changes in autonomic function, cognitive function and neuropscyhiatric symptoms often predate onset of PD by several years.

Methods: The ongoing PARS study has enrolled over 5,000 subjects >50 years old with and without a family history of PD. The University of Pennsylvania Smell Identification Test (UPSIT) was administered by mail and 400 subjects (300 hyposmic subjects and 100 normosmic subjects) have been invited to participate in longitudinal clinical and imaging evaluations. Hyposmia is defined as the lowest 15th percentile for age and gender. Clinical evaluations include neurological exam, cognitive testing, REM behavior disorder (RBD) questionnaire, mood evaluation, autonomic function questionnaires, biologics and dopamine transporter imaging with 123I b-CIT.

Results: In this ongoing study, 224 subjects (123 hyposmic, 101 normosmic) have undergone baseline clinical and imaging evaluation. Mean age 68.7 (range 60.4-90.9), 133 (59%) females and 91 (41%) males, 115 (51%) with a first-degree PD relative and 109 without (49%). RBD (endorsed by bed partner) in 14/123 (11.4%) hyposmics and 11/101 (10.8%) normosmics. Constipation (bowel movement <QOD) endorsed in 14/123 (11.4%) and hyposmics and 2/101 (2%) normosmics. DAT deficit detected in 27/123 (22.0%) hyposmics and 7/101 (6.9%) normosmics.

Conclusions: The PARS study is a multi-center observational study of individuals at-risk for Parkinson's disease. Baseline data suggests that hyposmic subjects are more likely to endorse non-motor symptoms and have mild DAT deficit on imaging. Longitudinal follow-up of this cohort will ultimately determine whether these subtle findings are early indicators of pre-diagnostic PD.

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Evaluation of mGluR5 in early Parkinson's disease using 18F-FPEB PET imaging

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Objective: To evaluate the role of the metabotrophic glutamate receptor type 5 (mGluR5) using 18F-FPEB and PET imaging in

patients with Parkinson's disease (PD) and compare with healthy controls (HC).

Background: mGluR5 is highly expressed in neocortical structures including striatal neurons. A reduction in mGluR5 expression may occur as a result of neurodegeneration of the striatum due to PD. Therefore, mGluR5 imaging may serve as a useful biomarker for early detection and PD progression. 18F-FPEB binds mGluR5 with high affinity and specificity and pre-clinical studies in non-human primates demonstrated 18F-FPEB uptake consistent with the known distribution of mGluR5 expression. The development of an imaging marker for mGluR5 provides the opportunity for dose occupancy studies for novel treatments for PD.

Methods: Early PD (n=4) and healthy controls HC (n=4) underwent 18F-FPEB PET imaging. Subjects received 5 mCi 18F-FPEB and serial dynamic PET projection data was acquired for 3 hours. Regional equilibrium tissue distribution volume measurements were assessed in striatal, neocortical, thalamic, and cerebellar regions. The standardized uptake value ratios (SUVr) of targets to a cerebellar reference region were compared in PD and HC. Analyses to evaluate correlation of 18F-FPEB SUVr with dopamine transporter uptake in most affected striatum were performed in the PD subjects.

Results: Mean age was 53.7 for HC and 66.3 for PD. For PD subjects mean UPDRS total score was 19.3 and mean Hoehn and Yahr score was 1.3, and duration of diagnosis was<2years for all subjects. There was a reduction in SUVr for PD subjects (ant cingulate=4.5, striatum=4.4, temporal lobe=4.4) compared to the HC subjects (ant cingulate 5.1, striatum 5.0, temporal lobe=5.6). 18F-FPEB SUVr correlated with 123Iβ-CIT uptake in the most affected striatum (r=0.35).

Conclusions: 18F-FPEB is a promising PET radiotracer for evaluating mGluR5 with excellent characteristics for human imaging. Preliminary data from this ongoing study indicates that 18F-FPEB PET shows reductions in striatal and neocortical mGluR5 in both early PD subjects. Additional studies are ongoing to evaluate 18F-FPEB in later stages of PD and the potential role of mGluR5 in PD related dyskinesias.

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Characterisation of resting oscillatory cortico-subthalamic connectivity in patients with Parkinson's disease

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Objective: To determine if loops between the subthalamic nucleus (STN) and different cortical areas have different spectral characteristics and sensitivities to dopaminergic input in patients with Parkinson's disease (PD).

Background: There is pronounced phenotypic variation in PD and in the degree of response of these patients to drugs and STN deep brain stimulation (DBS). This implies functionally distinct circuits which can be differentially modulated. PD patients undergoing DBS afford the opportunity to record electrical activity from the STN via implanted electrodes before leads are internalised. Such recordings have described excess beta range (13-35Hz) oscillatory activity which is suppressed by dopamine and DBS.

Methods: Resting recordings were acquired simultaneously from the cortex with magnetoencephalography (MEG) and from the STN with implanted electrodes in 11 PD patients. Recordings were done both after overnight withdrawal of dopaminergic medications and during the patient's usual medication regime, in an order couterbalanced across patients. Coherence, a measure of functional coupling, was calculated between the STN and all MEG channels. A beamformer was used to create frequency band specific images of coherence. These images were subjected to a 2x2 ANOVA, with drug and frequency band as factors, to create statistical parametric brain maps.

Results: 1) The topography of cortical activity coherent with STN activity was frequency dependent. Alpha (7-12 Hz) coherence was predominantly temporoparietal, whilst beta coherence was frontomedial. 2) Changes in beta coherence with dopaminergic medication correlated with changes in akinesia-rigidity.

Conclusions: The topography of cortical activity functionally coupled with STN is frequency dependent. Spatio-spectrally defined cortico-STN loops may differentially contribute to symptomatology.

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Study of the changes in the cerebral metabolic activity measured by 18F-FDG PET during the progression of dopaminergic depletion induced by unilateral lesion of the nigrostriatal pathway in rats

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Objective: To describe changes in 18F- Fluorodeoxyglucose (FDG) uptake by positron emission tomography (PET) during the progression of dopaminergic nigrostriatal neurodegeneration induced by unilateral lesion with 6-hydroxidopamine (6-OHDA) in rats.

Background: Parkinson's disease (PD) is characterised by dopaminergic depletion associated with metabolic and monoaminergic compensatory changes during disease evolution. There is scarce in vivo information published about such mechanisms during the progression of dopaminergic neuronal death in the model of unilateral 6-OHDA-induced parkinsonism in rats.

Methods: Eight male Sprague-Dawley rats were unilaterally lessoned using 6-OHDA in the nigrostriatal pathway. PET studies using monoaminergic (11C-Dihydrotetrabenazine (DTBZ)) and metabolic (FDG) radiotracers were conducted at different times during 6 weeks after the lesion. Analysis based on regions of interest was done for DTBZ PET and SPM2 analysis was conducted for FDG studies.

Results: The evolution of 6-OHDA lesion was associated with a progressive dopaminergic striatal depletion measured by DTBZ PET from 40% in the first week to 70%-80% depletion observed in the sixth week. A different metabolic pattern was evident during the progression of the dopaminergic depletion. Remarkably, the analysis revealed hypometabolism in the somatosensory cortex ipsilateral to lesion and a variable degree of hyper-metabolism bilaterally in motor regions, during the evolution.

Conclusions: 6-OHDA induced progressive dopaminergic depletion over the weeks after injection. Dynamic metabolic changes were observed during the evolution of the dopaminergic depletion. These findings could provide useful in vivo information about the compensatory changes occurring during the dopaminergic neuronal death in this model.

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Role of striatal interdependence in the compensation of dopaminergic depletion in early Parkinson's disease

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Objective: To asses the bilateral interdependence of striatal innervation in early Parkinson's disease (PD).

Background: Parkinson's disease is characterised by progressive dopaminergic depletion. Although numerous dopaminergic compensatory mechanisms have been proposed, the role of contralateral dopaminergic activity in the onset and progression of motor symptoms of PD remains elusive.

Methods: Fifteen clinically asymmetric (i.e. unilateral) PD patients were compared with 15 patients with bilateral motor features. A group of normal subjects was used as control. 6-(18)-fluoro-Ldopa (FDOPA) positron emisssion tomography (PET) studies were adquired. Region of interest (ROI) analysis was conducted to evaluate the constant of decarboxilation (Ki) and voxel based statistical analysis was done by SPM2. Images were realigned to compare primarily affected (PA) and secondarily affected (SA) striatum and asymmetry index (AI) between striata was calculated. Additionally, a nonprogressive lesion was done in the nigrostriatal pathway in one

monkey generating a 30% asymmetrical dopaminergic depletion measured by PET. Subsequently, systemic MPTP (0.25 mg/kg each 2 weeks) was progressively administered and 18FDOPA and 11C-DTBZ PET were adquired during progression.

Results: The mean putamen Ki was reduced bilateraly in PD patients compared to controls. No difference was detected between SA and the PA sides in both groups. Patients with AI over 35% and Ki (*1000) higher than 4 in the SA putamen were in the unilateral group, while those with AI in the lower range (AI⟨15%) were in the BL group. SPM analysis only showed differences between PD groups and control. In the monkey, MPTP treatment induced a progressive dopaminergic depletion preserving the striatal asymmetry without revealing motor abnormalities until advanced degree of dopaminergic depletion.

Conclusions: Our results suggest that the onset of motor symptoms related to dopaminergic depletion is related to dopaminergic status of contralateral striatum in humans and non human primates, providing an in vivo demosntration of the interdependence of both sides in the compensation of early PD. *Preliminary results presented in the Neurosciences Meeting, Chicago, USA. 2009.

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Neuromelanin-sensitive nigral volume is reduced in patients with multiple system atrophy and progressive supranuclear palsy

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Objective: To detect the neuromelanin-sensitive SNc volume for patients with several neurodengenerative disorders expressing extrapyramidal symptoms including multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) and to compare the results with those for patients with Parkinson's disease (PD) and controls.

Background: Neuromelanin-containing cells in the substantia nigra pars compacta (SNpc) may be detected in living person by neuromelanin MR imaging with 3-T scanning. In the previous study, we reported that neuromelanin-sensitive SNpc volume was reduced in patients with PD in parallel with disease progression.

Methods: We examined 19 patients with MSA, 10 with PSP and 8 with CBD and compared these results with those of 80 patients with PD and 54 controls. Axial T1-weighted images were obtained with a 3-T MRI scanner. The border of the neuromelanin-sensitive region in the SNpc was traced manually on these images with a pen tablet pointing device and calculated the approximate volume of neuromelanin-sensitive SNpc volume. The mean volume for the left and right substantia nigra was used for the statistical analysis.

Results: The mean neuromelanin-sensitive SNpc volumes were 74.4±36.2 mm^3 for MSA, 62.6±43.0 mm^3 for PSP and 85.0±16.7 mm^3 for CBD whereas they were 96.9±38.2 mm^3 for PD and 128.4±35.7 mm^3 for controls (Figure 1). The values for MSA, PSP and PD were significantly lower than those for controls.

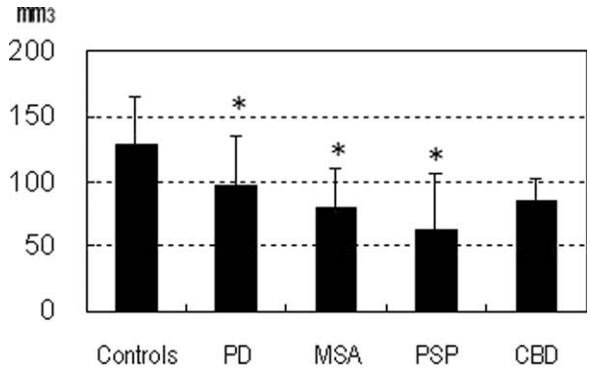

FIG. 1 (604). Neuromelanin-sensitive SNPc volume in patients with each disease. *: $p < 0.05$.

Conclusions: Neuromelanin MR imaging with 3-T scanning may detect degeneration of melanin-containing nigral cells in living patients with MSA and PSP as well as PD.

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Neuroimaging of dopaminergic function in a case of Perry syndrome

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Objective: To evaluate pre- and post-synaptic dopaminergic function in a case of Perry syndrome.

Background: Perry syndrome is an extremely rare rapidly progressive autosomal dominant parkinsonism with central hypoventilation, depression and weight loss due to mutation in the dynactin gene. No literature is available regarding imaging of dopaminergic system in this syndrome.

Methods: Our patient is a 57 year lady with a strong family history of dominantly inherited disease, who presented with depression and anxiety for 3 years. Over the past 2 years she developed bilaterally symmetric parkinsonian symptoms in the form of tremor, bradykinesia, frequent falls and mild rigidity, all of which responded to levodopa. There is also a history of progressive breathlessness on exertion as well as swallowing problems with weight loss, which improved following insertion of a PEG tube. On medication, there is a recent history of compulsive behaviors such as repetitive searching for weeds in the garden and scratching of the legs to the point of injury. Our patient underwent Positron Emission Tomography (PET) with ^{11}Cdihydrotetrabenazine (DTBZ), ^{18}F-fluorodopa (FDOPA) and ^{11}C-raclopride (RAC), 12 hours off levodopa.

Results: There were profound reductions in both FDOPA uptake and DTBZ binding in the striatum. There was no clear right to left asymmetry in the striatum, nor an anterior-posterior gradient of dopaminergic dysfunction typical of PD. Striatal dopamine D2 receptors were preserved based on normal raclopride binding.

Conclusions: Imaging of the dopamine system in our patient with Perry syndrome revealed profound reduction in presynaptic nigrostriatal dopaminergic function with preserved striatal dopamine receptors. This combination, which is similar to Idiopathic Parkinson's disease, explains the responsiveness of her symptoms to levodopa. However, the lack of anterior-posterior gradient and right-left asymmetry of dopaminergic dysfunction in striatum, as well as the profound involvement of the caudate nucleus is atypical for Idiopathic Parkinson's disease and may be relevant to the striking behavioural features in this case. Further imaging studies in patients with this syndrome will provide more insight into the pathophysiological mechanisms underlying its distinctive clinical features.

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Paramagnetic signals in Wilson's disease demonstrated by susceptibility-weighted magnetic resonance imaging

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Objective: To evaluate the patterns of paramagnetic signal abnormalities in Wilson's disease by susceptibility-weighted magnetic resonance imaging.

Background: Of the MRI abnormalities seen in patients with WD, the low signals in T2WI and conventional gradient echo sequences (T2*-weighted images) are believed to represent areas of increased metal ion accumulation, such as copper and iron. Currently available susceptibility-weighted imaging (SWI) has been shown to be superior in its ability to demonstrate paramagnetic signals than other conventional MR imaging.

Methods: A 32-year-old man was seen in our clinic with 3-year history of social withdrawal and bilateral clumsy hands with dystonia. The diagnosis of Wilson's disease was based on a combination of neurologic symptoms, the presence of the Kayser-Fleischer ring, low serum ceruloplasmin and copper, elevated urinary copper excretion, and genetic testing. Brain MRI including SWI were analyzed.

Results: Brain MRI showed bilateral symmetric high signal intensity in lateral margin of putamen and midbrain on T2-weighted images. SWI showed markedly dark paramagnetic signals in dentate nucleus, substantial nigra, striatum, globus pallidus, and cortical gyri. In lentiform nucleus, paramagnetic signals were most prominent with inhomogeneous and laminating pattern.

Conclusions: Since copper is paramagnetic, it is possible that the observed abnormalities in our patient reflect copper deposition. However, the contribution of copper to the degree of susceptibility effects in SWI is not determined yet. The signal abnormalities are also probably partly correlated with the paramagnetic effect of iron which accumulates commonly in areas which already have excessive copper accumulation. The ability to measure the amount of paramagnetic materials, such as copper or iron, in the brain of Wilson's disease will facilitate a better understanding of disease progression and will also help in predicting the treatment outcome with chelating agent.

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Effects of aging on [^{18}F]FP-CIT PET measures in normal subjects and PD patients

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Objective: To assess aging effects of [^{18}F]FP-CIT PET measures in the striatum of patients with Parkinson's disease (PD), comparing with those of normal subjects.

Background: Recently, [^{18}F]FP-CIT, a PET tracer for dopamine transporter (DAT), becomes available for clinical practice. While DAT ligands have consistently shown significant aging effects in the striatum of normal subjects, little is known whether [^{18}F]FP-CIT binding shows similar aging effects in PD patients. Current data indicate that DAT is highly subject to regulatory changes.

Methods: We analyzed [^{18}F]FP-CIT PET data of 30 normal subjects (age: 50.3±17.7 years, mean±SD; range 24∼82) and 28 patients with drug-naïve de novo PD (age: 54.2±14.7 years; range 31∼87 years). Parkinsonism was assessed by UPDRS III after overnight off-medications. [^{18}F]FP-CIT PET images were acquired using fusion PET scanner (Biograph TruePoint 40; Siemens/CTI, Knoxville, TN, USA). Binding ratios of [^{18}F]FP-CIT were obtained in the ventral striatum, the caudate and putamen in 3D images using occipital cortex as a reference region.

Results: [^{18}F]FP-CIT binding ratios of PD group were 85.0%, 81.5%, 69.8%, 45.7% and 35.9% of normal in the ventral striatum, caudate, anterior, middle and posterior putamen, respectively. UPDRS III scores in the PD group (mean: 16.2±9.3,±SD) correlated significantly with [^{18}F]FP-CIT binding ratios of the posterior putamen (r=-0.451, p=0.018), but not with those of the ventral striatum or caudate. [^{18}F]FP-CIT binding ratios of the posterior putamen also showed a significant correlation with age in the PD group (y=-0.032*age+5.073, r=-0.439, p=0.019), the slope of which was in parallel to that in the normal group (y=-0.034*age+11.012, r=-0.440, p=0.015).

Conclusions: Our data showed significant aging effects in the striatal binding of [^{18}F]FP-CIT in patients with de novo PD, which was similar to those in normal subjects despite substantial differences in the [^{18}F]FP-CIT binding between the two groups. To the extent that the severity of PD is comparable across newly-developed PD at the symptomatic threshold, our data suggest that aging effects of striatal [^{18}F]FP-CIT binding in PD patients are similar to those in normal subjects.

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A multimodal assessment of the brainstem using 3T MRI in PSP and PD

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Objective: We performed a multimodal MRI study including diffusion tensor imaging (DTI), measurement of R2 and the magnetization transfer ratio (MTR) at 3T in 17 controls, 19 patients with PSP and 10 with Parkinson's disease (PD) in order to investigate brainstem MRI metrics in both PD and progressive supranuclear palsy (PSP).

Background: Recent studies suggest that MR changes in diffusion tensor imaging (DTI) and the transverse relaxation rate (R2*) in the substantia nigra (SN) are significantly different in PD and controls. This has not been studied in PSP.

Methods: Echo-planar imaging DTI data were processed using FSL (FMRIB, Oxford, UK). Dual echo T2 relaxometry and MTR data were processed using in-house software. All images were registered to each individual's structural space and regions of interest (ROIs) were placed manually using ImageJ (NIH, Bethseda). ROIs were defined in the SN, the superior and middle cerebellar peduncles (SCP, MCP) and subthalamic nuclei (STN). ROIs were defined on T2-w images and transferred to the co-registered MD, FA, MTR and R2 maps. SPSS 16.0 for Mac was used for Statistical analysis.

Results: Groups were not different in demographics. H&Y, UPDRS and Frontal assessment battery ($p<0.05$) but not MMSE (NS) were greater in PSP. There were no significant differences in fractional anisotropy (FA) or mean diffusivity (MD) in the SN, STN or MCP. In the right and left SCP there were significant differences in FA ($P<0.01$) and MD ($p<0.005$). Post-hoc analysis revealed significant differences in both SCPs (MD and FA) between PSP and controls, and PSP and PD ($p<0.05$ except in FA in the left SCP in PSP vs PD NS). There were differences in MTR in the left SCP between PSP and control and PSP and PD, and a significant R2 difference in the lateral SN on the left in PD vs. control (all $p<0.05$). Using a cut off value of 0.895 x 10-3 mm/s, MD in the left SCP has 53% sensitivity and 90% specificity for PSP when compared to PD.

Conclusions: We were unable to reproduce the high sensitivity and specificity of previous studies in the SN in PD or PSP but found significant differences in the SCP in PSP compared to controls and PD using DTI and MTR. In addition to SCP atrophy, and SCP signal hyperintensity on FLAIR sequences, DTI and MTR measures may increase diagnostic sensitivity.

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Blinded analysis of conventional MR images in a cohort of pathologically confirmed parkinsonian illnesses at the QSBB

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Objective: To report the radiological diagnostic accuracy, and the sensitivity, specificity, positive (PPV) and negative (NPV) predictive

TABLE (609). *PSP: Sensitivity, Specificity, PPV and NPV (%)*

	Sensitivity	Specificity	PPV	NPV
Hummingbird	68	100	100	83
Morning Glory Flower	50	97	92	75
Dilation of the 4th ventricle	55	71	55	71
Midbrain atrophy (axial)	86	65	61	88
SCP Atrophy	57	85	71	76

PSP vs Control/MSA/PD/CBD

TABLE (609). *MSA: Sensitivity, Specificity, PPV and NPV*

	Sensitivity	Specificity	PPV	NPV
Hot Cross Bun	62	100	100	89
MCP hyperintensity	54	98	88	87
MCP Atrophy	38	93	63	83
Pontine Atrophy	38	86	45	82
Hyperintense putaminal rim	69	83	56	89

MSA vs Control/PSP/PD/CBD

values of cMRI abnormalities reported in the literature in a pathologically confirmed cohort including Parkinson's disease (PD), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).

Background: The accurate diagnosis of the cause of atypical parkinsonism remains challenging in clinical practice. Conventional MRI (cMRI) has been reported to show specific if not sensitive abnormalities in MSA and PSP. However, very few of these in vivo studies have pathological confirmation of the diagnosis.

Methods: Donors to the Queen Square Brain Bank were screened for the availability of MRI images which were reviewed by two neuroradiologists experienced in the MR scan interpretation of parkinsonian syndromes (CM, HRJ) and who were blinded to clinical information. MR images were systematically reviewed for the presence of specific abnormalities reported in the literature to enable calculation of sensitivity, specificity, PPV and NPV.

Results: We studied 48 pathologically confirmed cases (23 PSP, 6 PD, 13 MSA and 6 CBD) and 9 healthy controls. There were no significant differences in disease duration at time of MRI. There were more male than female cases in the PSP and PD groups. The MSA cohort were younger than those with PSP, CBD or controls but not PD. The final clinical diagnosis was supported in 68% and the radiological diagnosis in 61% (CM) and 59% (HRJ). Using cMRI 89% of controls, 55% of PSP, 67% of PD (no specific abnormalities) and 0% of CBD cases were correctly identified. 2 cases of PSP were classified as MSA, and 1 MSA as PSP. 2 CBD were classified as PSP. The sensitivity, specificity, PPV and NPV for key cMRI findings can are reported.

Conclusions: We report radiological accuracy in a pathologically confirmed cohort of PSP, PD, MSA and CBD using cMRI and the sensitivity, specificity, PPV and NPV of individual abnormalities. Using cMRI key diagnostic features with very high specificity and PPV have low sensitivity. This endorses the development of newer MR techniques (e.g. high field diffusion tensor imaging) as useful biomarkers early in disease.

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Differences in effective connectivity between tremor-predominant (PDT) and akinetic-rigid (PDAR) variants of Parkinson's disease (PD)

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Objective: To determine if PDAR and PDT variants can be distinguished based on their connectivity patterns.

Background: The standard basal ganglia (BG) model of PD does not adequately explain the existence of tremor, and the more benign prognosis of PDT relative to PDAR. A possible explanation is that the Cerebellar Thalamo-Cortical (CTC) loop may better compensate for deficiencies in the strato-thalamo-cortical (STC) loops in PDT subjects, but at the price of the emergence of tremor.

Methods: We examined 7 PDT subjects and 8 PDAR subjects both OFF and ON medication, as well as 10 age-matched healthy controls. Each subject performed a motor task consisting of right-handed sinusoidal squeezing at 1Hz and rest in 100s blocks. fMRI data were were acquired with a 3T Philips scanner. Regions of interest (ROI) were segmented on an individual basis, and we assessed effective connectivity between ROIs with a False Discovery Rate of 5%, using the PDfdr algorithm that we have previously validated in PD subjects (Li et al. 2008).

Results: In control subjects, significant connectivity was seen within structures associated with the contralateral STC loop and CTC loop. In PDAR subjects, like controls, the CTC loops and STC loops were coupled via a significant connection between the left cerebellum and right putamen, but the CTC loop was not recruited in PDAR subjects as implied by impaired connectivity. In PDT subjects, the connection between CTC loops and STC loops from the left cerebellum to right putamen was lost but there was a connection from the left cerebellum to the left putamen.

Conclusions: Our results suggest that PDT subjects "disconnect" their STC and CTC loops, which may be important for the genesis of tremor. However, this may allow the CTC loop to act more independently, allowing for more effective compensatory recruitment of the CTC pathway for tasks it may not normally subserve. J. Li, Z. Jane Wang, and M. J. McKeown, "Learning Brain Connectivity with the False-Discovery- Rate-Controlled PC-Algorithm", Proc. of EMBC2008.

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Region-specific cerebral atrophy in Parkinson's disease without dementia, identified with 3T MRI and voxel-based morphometry

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Objective: To investigate possible gray matter changes underlying previously found functional deficits in Parkinson's disease (PD) patients with visual hallucinations (VH) and to investigate grey matter changes in PD patients in general, when compared to healthy controls.

Background: Classically, PD is not characterized by anatomical changes of the brain. On the other hand, functional changes, as shown by PET and fMRI, have been extensively described in PD. In our previous fMRI study, PD patients with visual hallucinations (VH) (PDwithVH) showed reduced activations in ventral/lateral visual association cortices preceding image recognition, compared to both PD patients without VH (PDnonVH) and healthy controls.

Methods: Eleven non-demented PDwithVH, 13 non-demented PDnonVH en 14 healthy controls were scanned on a 3T MRI-scanner. Voxel-based morphometry was performed on whole brain structural T1-weighted images. Images were normalised, segmented and smoothed. Resulting grey matter images were 'modulated' and analysed with SPM5, using total grey matter as a covariate to remove variance due to differences in head size.

Results: No differences were seen between PDnonVH and PDwithVH. Both PDnonVH and PDwithVH (=PDtotal) showed grey matter reductions in bilateral prefrontal and parietal cortex, left anterior superior temporal and left middle occipital gyrus. A strong dominance of left parietal cortex grey matter reduction was seen in PDtotal, even after using side of PD symptoms as a covariate in the analysis.

Conclusions: Grey matter reductions were seen in PD patients in general, while no differences were seen between PD patients with or without VH, indicating that previously found functional deficits in PDwithVH were not caused by atrophy. The strongly significant left parietal reductions were hemisphere-specific and independent of side of PD symptoms. The left parietal cortex plays a role in self referenced movement and the initiation of new motor programs. While training-induced left parietal grey matter increases have been described in healthy volunteers, we hypothesize that the observed decrease in PD may reflect 'de-learning' of skilled movements with reduced internally guided behavior, typically described in PD.

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Transcranial brain parenchyma sonography in Parkinson's disease

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Objective: The aim of our study was to investigate the prevalence of the SN hyperechogenicity in PD patients, as well as its possible clinical correlates.

Background: Modern ultrasound systems allow high-resolution transcranial sonography (TCS) of the brain structures. Hyperechogenicity of the substantia nigra (SN) has been reported as a highly characteristic finding in more than 90% of patients with idiopathic Parkinson's disease (PD). This finding is stable during follow-up period and does not correlate with the disease stage.

Methods: The study comprised 103 consecutive PD patients and 50 healthy age-matched controls. For TCS examination a color-coded, phased array ultrasound system equipped with a 2.5 MHz transducer was used (Aloka Prosound Alpha 10, Aloka, Japan). The examination was performed through a preauricular acoustic bone window with a penetration depth of 16 cm and a dynamic range of 45-50 dB. The SN was identified within the butterfly shaped structure of the mesencephalic brainstem, with scanning from both temporal windows.

Results: The SN hyperechogenicity was identified in 95 out of 103 examined PD patients (92%), which was marked in 60 (63%), and moderate in 35 patients (37%). Median SN echogenic size was larger contralateral to the clinically more affected side of the body. Unilateral SN hyperechogenicity was also found in 5 out of 50 healthy controls (10%). No ventricular enlargements were notified in our study.

Conclusions: Our study demonstrated SN hyperechogenicity in more than 90% of PD patients. In adult subjects without neurological symptoms, the TCS finding of at least unilaterally marked SN hyperechogenicity indicates a subclinical functional impairment of the nigrostriatal dopaminergic system.

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Mapping neurodegeneration in Parkinson's disease: A pilot functional MRI study

F.B. Nahab, P. Kundu, H.M. Islam, A.M. Mittel, D. Severino, B. Levin, P.M. Pattany (Miami, Florida, USA)

Objective: To assess the utility of a novel functional MRI based brainstem connectivity method for mapping neurodegeneration in subjects with Parkinson's disease and controls.

Background: PD is a neurodegenerative disorder characterized by motor and non-motor features. Recent work by Braak and colleagues (2003) postulates that neurodegeneration takes place in a specific spatial pattern, starting in the caudal medulla and olfactory bulbs (stage 1) and proceeding up through the pons (stage 2) and midbrain (stage 3) to the neocortex (stages 4-6) in late stages. These patterns can only be identified currently at autopsy and no objective dopamine-independent biomarker of PD progression currently exists. We proposed to develop a non-invasive in vivo method that could serve as a correlate to Braak staging of neurodegeneration based on the hypothesized reduction in neuronal functional connectivity that may precede cell death.

Methods: Subjects underwent neurological examination and ratings by a movement disorder specialist (FN) to characterize PD severity, or lack thereof. Three PD subjects and two controls underwent a 5-minute resting-state (awake, eyes closed) BOLD-fMRI EPI scan (TR: 2-sec), and high-resolution structural scan on a Siemens 3T Trio MRI. No subjects or data were excluded from the analysis. We applied our Context Differential Autocorrelation Mapping (CDAM) method to fMRI data of the brainstem to obtain the preliminary results. Equally thresholded CDAM maps were overlayed on the 3D T1 MRI anatomical scans.

TABLE (613). *Subject Clinical Profiles*

Subject	Disease State	Age	PD Severity (Hoehn & Yahr)	Symptoms	Medication State
S1 (A)	Healthy	47	0	N/A	N/A
S2 (B)	Healthy	82	0	N/A	N/A
S3 (C)	PD	57	2	Sensory disturbance, slight tremor, and bradykinesia	Treated
S4 (D)	PD	61	2	Tremor and rigidity	Treated
S5 (E)	PD	66	3	Rigidity, tremor, sensory disturbance, depression, and imbalance	Treated

Results: Two healthy controls (S1-S2; mean age 64.5) were recruited along with 3 patients (S3-5; mean age 61.3) fulfilling UK Brain Bank PD criteria (See Table 1 for clinical profiles).

A review of the control CDAM maps showed similar CDAM profiles of widespread brainstem connectivity. The CDAM connectivity maps for our patients showed reduced connectivity in the caudal medulla in all PD subjects and an ascending decrease in connectivity associated with disease severity (See Figure 1).

Conclusions: These preliminary findings suggest an association between brainstem connectivity and PD disease severity. Further work is needed to assess the reliability of this method and an assessment of the impact of factors such as age, gender, iron deposits and vascular disease on these connectivity maps.

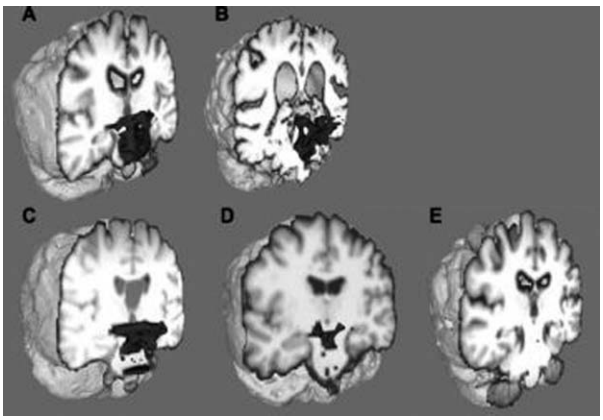

FIG. 1 (613). Summary autocorrelation maps of brainstem function for two controls and three subjects with PD. (All autocorrelation maps are displayed at equal statistical thresholds at the level of the brainstem). A) Control subject showing normal activity in the entire brainstem region. B) Control subject showing normal activity in the entire brainstem region. C) PD subject with loss of activity in the medulla and certain portions of the ???. D) PD subject with loss of activity in the medulla, residual of activity in the ??? and reduced activity in the midbrain. E) PD subject with widespread less of activity in the entire brainstem.

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Characterizing brainstem functional connectivity in essential tremor

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TABLE (614). *Subjects' Postural and Kinetic Tremor Responses (Pre- vs Post-Ethanol)*

Postural Tremor - Pre-Ethanol		Postural Tremor - Post-Ethanol		Kinetic Tremor - Pre-Ethanol		Kinetic Tremor - Post-Ethanol	
Frequency (Hz)	Power	Frequency (Hz)	Power	Frequency (Hz)	Power	Frequency (Hz)	Power
5.44	0.67	5.49	0.72	3.56	55.46	6.13	28.99
7.13	0.61	6.98	0.63	4.96	92.26	5.32	105.62
6.18	78.49	6.99	22.99	5.42	542.43	5.86	239.14
6.38	8.12	**	**	5.28	69.50	5.45	66.98
5.79	93.81	5.96	44.59	4.59	286.71	4.79	248.00
7.07	64.66	8.27	81.53	5.16	918.14	5.48	1192.86
2.52	10.5	2.16	14.4	5.25	71	4.91	58
5.89	273	**	**	5.78	1024	**	**

** Indicates a tremor peak frequency could not be identified.

Reductions in CDAM-based functional connectivity post-ethanol were broadly distributed. In particular, the connectivity of the red nucleus, olive and cerebellum differed based on the task, though each structure showed a reduction in CDAM connectivity with ethanol.

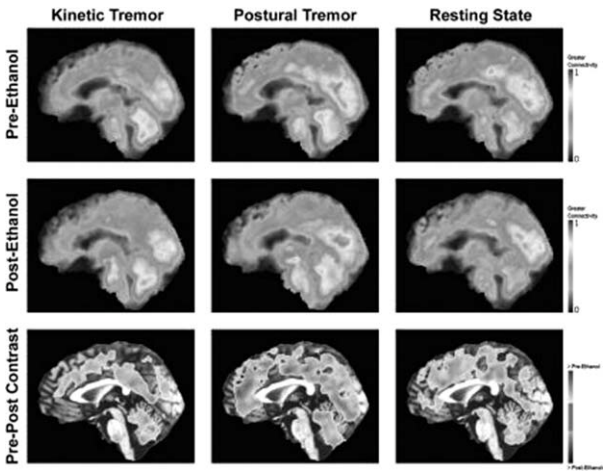

FIG. 1 (614).

Objective: To characterize the neural network in ET and identify differences in fMRI-based context differential autocorrelation mapping (CDAM) during tremor-inducing tasks and rest performed pre- and post-ethanol ingestion.

Background: Essential Tremor (ET) is a common and potentially disabling disorder involving the hands, arms, head, and voice. Various brain regions have been implicated in this disorder, including a disturbance of the Guillain-Mollaret triangle (red nucleus, olive, and cerebellum).

Methods: Eight subjects (3-females; mean age: 58) fulfilling ET TRG criteria were evaluated using the Tremor Rating Scale and digital spirography. Subjects received training to ensure consistent performance. Subject heads were stabilized to minimize motion artifacts. Subjects performed one of three tasks in random order during a 5-minute run: (1) continuous resting state [eyes closed, awake], (2) postural tremor [right arm elevated to manifest tremor], (3) kinetic tremor [spirography]. The postural and kinetic tasks were block design, with 20-s task and rest periods. On completing the 3 tasks, subjects were taken out of the Siemens 3T-MRI, consumed 50ml of 40% ethanol (80-proof liquor), and returned to the MRI to undergo a high-resolution T1 scan for spatial normalization while ethanol took effect. The tasks were repeated in the same order. A tri-axial accelerometer was placed on the hand to record movement and tremor during the study. The fMRI data was pre-processed using standard methods before using our CDAM method to generate the global connectivity maps for each subject. Group CDAMs were generated using AFNI's 3DANOVA tool (Cox 1997).

Results: Reduction in postural and kinetic tremor power following ethanol was observed in 50% and 75% of subjects, respectively.

Conclusions: Improvements in ET may be mediated by changes in functional connectivity of Mollaret's triangle. Furthermore, the connectivity patterns of each region varied based on the type of tremor manifesting.

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Nigro-striatal signature from MRI markers in Parkinson's disease

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Objective: To characterize the PD physiopathological modifications in 6 subcortical structures by simultaneously measuring quantitative magnetic resonance parameters sensitive to complementary tissue characteristics (volume atrophy, iron deposition, microstructural damage).

Background: Most of previous works investigating brain alterations in PD patients used a single MR parameter. However, our recent work (Cherubini et al., Neuroimage 2009) showed the potential improvements brought by the combination of MR predictors such as the mean relaxation rate (R2*) or mean diffusivity of the subcortical structures.

Methods: 30 PD patients (age: 61,89±11.91 y; Disease duration: 4,4±2.4 y; UPRDS motor score: 12±5.9; Levodopa equivalent daily doses (LEDD): 886±400/mg/day) and 22 control subjects (age: 57,41±9.7 y) underwent a 3 Tesla MRI including whole-brain T1-weighted, T2* weighted and and DTI scans. We compared PD patients and controls for mean R2* value, mean diffusivity (MD) and fractional anisotropy (FA) in pallidum, putamen, caudate nucleus, thalamus, subtantia nigra (SN) and red nucleus. The comparison was also performed using voxel-based analysis (VBA) for R2*, MD and FA maps to identify, for each parameter, the most sensitive subregions. The average values within each sub-region were used in a logistic regression.

Results: PD patients showed significant higher R2* values in the SN, lower FA values in SN and thalamus and higher MD in thalamus than control subjects. The VBA confirmed these results and identified also differences for MD in the striatum. The combination of three different markers was sufficient to obtain 95 % of area under the ROC curve in the comparison between PD patients and controls. The markers used in discriminant combinations were: R2* in SN + FA in SN + MD in putamen or in caudate nucleus.

Conclusions: The first remarkable result was that the predictive markers involved the nigro-striatal structures characterizing the PD physiopathology. The second interesting point is that the combinations highly discriminant are composed by markers from three different MR parameters (R2*,MD and FA). These findings demonstrate that multimodal MRI can be a new useful tool in subcortical pathologies.

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Serotonin and fatigue in Parkinson's disease. An exploratory PET study

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Objective: Using PET to assess in vivo the relationship between loss of brain serotonin function and severity of fatigue in Parkinson's disease (PD).

Background: Pathological and imaging studies in PD have demonstrated depletion of brain serotonin innervation. The contribution

of serotonin dysfunction to the occurrence of PD non-motor symptoms, however, remains to be clarified. In this study we aim to assess whether fatigue, a disabling non-motor symptom with occur in up 1/3 of PD patients, is related to serotonin dysfunction of non-motor sub-regions of the basal ganglia and the limbic system.

Methods: 15 PD patients (mean age 64.9±9.9 years; mean disease duration 4.9±2.4 years; mean UPDRS motor score 20.9±5.1) underwent 11C-DASB PET, a marker of serotonin transporter (SERT) binding. Fatigue was measured by the Parkinson Fatigue Scale (PFS-16; worst score 16). We used voxel-based whole brain analysis (SPM2 software) to identify clusters showing significant correlation between tracer binding and fatigue scores introduced in the analysis as covariate.

Results: Mean PFS-16 score was 8.2±4.9 (range 0-16) Whole brain voxel-based analysis showed that higher scores in fatigue scores significantly correlated with lower SERT binding in caudate, putamen, ventral striatum and thalamus ($p<0.01$).

Conclusions: In our cohort of PD patients, severity of fatigue was inversely correlated with SERT densities in the basal ganglia and limbic system suggesting that serotonergic mechanisms are implicated in the occurrence of this disabling symptom. A better understanding of this neurobiological deficit in PD may be useful in the development of treatments and prevention strategies for fatigue in PD.

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Withdrawn by Author

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Dopamine transporter SPECT in autopsy-confirmed MSA and Parkinson's disease

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Objective: To compare DAT SPECT results in patients with post-mortem definitive diagnoses.

Background: DAT SPECT reliably visualizes the dopaminergic degeneration in multiple system atrophy (MSA) and Parkinson's disease (PD). Some studies suggest that DAT SPECT could assist as well in the differentiation of these disorders based on more diffuse, more symmetric striatal DAT binding loss in MSA as compared to PD. However, these studies included patients fulfilling standard clinical diagnostic criteria and are not validated by autopsy findings.

Methods: Patients with a post mortem diagnosis of MSA (n=6) or PD (n=8), who had undergone DAT SPECT with β-CIT during life time were included. SPECT imaging according to a standardized protocol had been performed after a mean disease duration of 3.6 (MSA) and 4.2 yrs (PD), respectively.

Results: Visual analysis of SPECT scans showed bilaterally reduced DAT binding in all patients with MSA and PD. Overall striatal binding was reduced by 53% (mean) in both, MSA and PD. There was a trend for higher asymmetry of striatal binding in MSA as compared to PD (23±15% vs. 11±7%, $p=0.081$) with 3 MSA patients showing conspicuously high asymmetry of striatal binding above the level of PD. Putamen/caudate binding ratios did not differ between MSA and PD (mean 0.66 vs. 0.67).

Conclusions: To our knowledge, this is the first study comparing DAT SPECT findings in patients with autopsy-confirmed MSA and PD. DAT SPECT reliably documents the dopaminergic degeneration in both disorders. Contrary to our expectations and findings from studies including patients with clinical diagnoses, we found a trend for a higher asymmetry of striatal DAT binding in MSA as compared to PD. In clinical practice, MSA and PD cannot be differentiated by subregional analysis of striatal DAT binding.

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Metabolic and network correlates of disease severity in multiple system atrophy

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Objective: Using FDG PET, we investigated regional metabolism and network activity as a marker of disease severity in MSA patients.

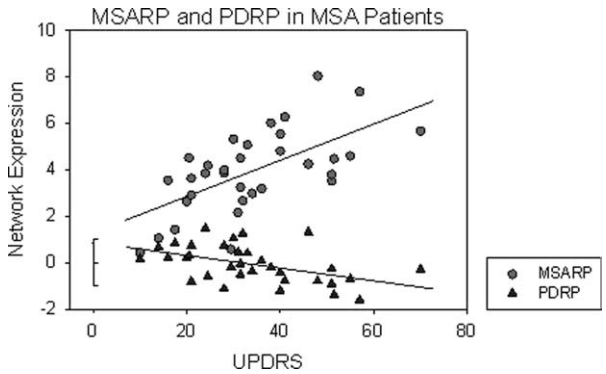

FIG. 1 (619).

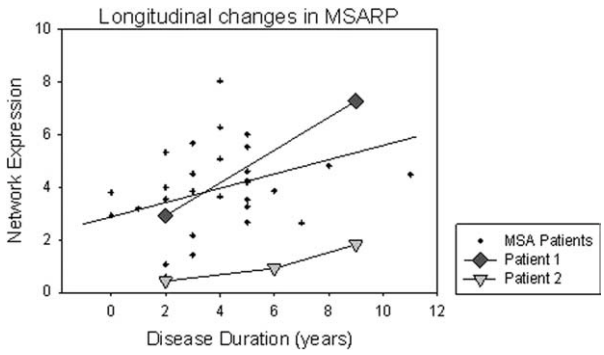

FIG. 2 (619).

Background: In early MSA, characteristic reductions in basal ganglia metabolic activity are present on FDG PET scans. Using network analysis, we have recently identified and validated a specific MSA-related spatial covariance pattern (MSARP). MSA patients exhibit elevated MSARP expression with normal expression of the PD-related covariance pattern (PDRP). However, little is known about the evolution of these metabolic abnormalities as MSA progresses.

Methods: Using FDG PET we studied 33 MSA patients, a comparison group of 20 PD patients matched for age (MSA 60.6±8.4yrs, PD 60.1±8.7yrs) and clinical severity, as measured by the UPDRSIII (MSA 34.2±13.8, PD 33.1±13.1) and H&Y stage (MSA 3.3±1.2, PD 2.8±0.9) at the time of PET, and 15 age matched controls. Patient diagnosis was uncertain at the time of PET; final MSA or PD diagnosis was determined after clinical follow up (3.9±2.9yrs). In all subjects, we prospectively computed regional putamen and cerebellar metabolism, MSARP expression, and PDRP expression. We then correlated regional metabolism and pattern expression with UPDRSIII and disease duration.

Results: MSARP expression increased and putamen metabolism decreased in MSA compared to control ($p<0.001$, $p<0.001$, respectively) and PD groups ($p<0.001$, $p<0.001$, respectively). Cerebellar metabolism decreased in MSA compared to PD ($p=0.005$), but not the control group. In MSA patients, there was a positive correlation between MSARP and UPDRSIII ($r=0.63$, $p<0.001$). Disease duration positively correlated with MSARP expression ($r=0.38$, $p=0.03$), but not with putamen or cerebellar metabolism. In two longitudinal patients with repeat imaging after 4 and 7 years we validated progressive increases in MSARP expression over time. MSA diagnosis was confirmed in all 3 subjects who had post-mortem exams.

Conclusions: Early MSA is associated with decreased basal ganglia metabolism and increased MSARP expression. However, increasing disease severity more accurately correlates with progressive changes in MSARP. Indeed, MSARP is a sensitive imaging biomarker with elevated pattern expression occurring before clinical diagnosis and increasing pattern expression with disease progression.

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Equivocal DAT–SPECT scan and clinical outcome over 4 years

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Objective: To ascertain local prevalence of borderline DAT–SPECT scan and clinical outcome of repeat scans in these patients over a period of 5 years.

Background: DAT–SPECT scan is an useful tool for clinicians dealing with tremor predominant movement disorder patients, to differentiate central, Essential, postural and action tremor particularly where there is doubt about associated parkinsonism. Various studies have shown over 97% sensitivity in PD and 100% specificity in ET. However there are a small but significant group of patients whose first scan has been visually normal but clinician felt strong evidence of parkinsonism.

Methods: All patients who had a DAT–SPECT scan over a period of 6 years (2003-9) registered in a Movement disorder clinic were analysed retrospectively. Patients with borderline normal or abnormal Scan (as decided by Radiologist, Nuclear Physicist and Clinician in a joint meeting) were studied in details about their Clinical course and diagnosis. A sub analysis of patients who had second scan was done.

Results: 130 DAT-SPECT scans (8 repeats) were performed on 122 patients. 40 scans were completely normal (30%), 20 scans were borderline normal or borderline abnormal (15%) and 8 of them were repeated (6.5%). 20 patients with borderline scans; had mean age 72 yr (range 45-88 yrs); 12 male, 8 females. Mean duration of Symptom at DAT scan was 60 months (6 -360 months). Mean follow up duration was 40 months (7-75months). After Review meeting 6 borderline scans became normal and another 6 became abnormal. 4 scans remained borderline normal, 2 borderline abnormal and 2 inconclusive. 8 patients had Scans repeated after a mean period of 16 months, 4 of these scans changed from borderline normal to clearly abnormal and another 4 from borderline normal to clearly normal. 4 scans which changed from borderline normal to abnormal, 3 were tremor predominant and one was atypical presentation (non motor, axial). 11 (55%) patients had change in their management while 5 (25%) had change in Diagnosis.

Conclusions: DAT –SPECT scan is an useful investigative tool in the management of selected patients in a movement disorder clinic. Repeat scans where there is disagreement in diagnosis is helpful in influencing diagnosis and management. Regular joint meeting with clinician, radiologist and physicist can improve diagnostic acumen of clinician as well as Radiologist.

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Evaluation of novel radiotracers targeting non-dopaminergic striatal biomarkers in HD: [18F]FPEB and PET imaging for metabotrophic glutamate receptor type 5 (mGluR5) in healthy subjects and subjects with Huntington's disease (HD)

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Objective: To evaluate ^{18}F-FPEB and PET for imaging mGluR5 in subjects with HD compared with healthy controls.

Background: Quantitative evaluation of striatal markers reflecting distinct functional, molecular, or transcriptional processes in diseases involving striatal pathology should be a valuable tool in understanding and treating these diseases. mGluR5 is highly expressed in striatum and in other neocortical structures. mGluR5 expression may be reduced due to neuron loss or alteration of gene expression. mGluR5 may be a useful biomarker for early brain changes in HD, HD progression, or for drug development in HD. ^{18}F-FPEB binds mGluR5 with high affinity and specificity. Studies in non-human primates demonstrated ^{18}F-FPEB uptake consistent with the known distribution of mGluR5 expression.

Methods: Early HD patients ($n=2$) and healthy controls (CO, $n=2$) underwent imaging. Subjects received 5 mCi ^{18}F-FPEB i.v. and serial dynamic PET projection data was acquired for 3 to 6 hours. Regional equilibrium tissue distribution volume measurements were assessed in striatal, neocortical, thalamic, and cerebellar regions. The standardized uptake value ratios (SUVr) of targets to a cerebellar reference region were compared in HD and CO.

Results: Both HD subjects were female with Htt expanded repeats and relatively mild motor signs, ages 54 and 44. COs were male, ages 57 and 43. For COs, ^{18}F-FPEB binding potentials for regions were caudate,temporal lobe>anterior cingulate>putamen>thalamus >>cerebellum, with ratios to cerebellum ranging from 4 to 6.5. The HD subjects revealed substantial mean reductions in ^{18}F-FPEB uptake in striatal regions and limbic cortical areas.

Conclusions: ^{18}F-FPEB is a promising radiotracer for mGluR5 with excellent characteristics for human imaging. This first-in-human study in HD indicates that ^{18}F-FPEB PET may detect early reductions in striatal and neocortical mGluR5 in relatively early symptomatic HD subjects. Future studies are ongoing to evaluate these objectives and other non-dopaminergic striatal markers further. Presented at HSG '09.

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Microstructural white matter differences between dementia with Lewy bodies and Parkinson's disease with dementia

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Objective: To investigate the power of diffusion tensor imaging (DTI) to differentiate the patterns of white matter impairment between DLB and PDD patients.

Background: DTI has been recognized as the most sensitive technique to detect subtle white matter changes. It provides information about the integrity of the white matter tracts by measuring the diffusional motion of water molecules[1]. Compared to control subjects, patients with Dementia with Lewy bodies (DLB) and Parkinson's disease patients with dementia (PDD) have reductions of the fractionary anisotropy (FA). However there are no studies comparing DLB with PDD.

Methods: DTI study to 15 DLB patients, 12 patients with PDD and 10 healthy control subjects. Both groups of patients had similar level of dementia (GDS, $p=0.4$). Images were acquired in a 3 Tesla Siemens Trio scan using an echo-planar imaging sequence of 30 directions, FNIRT Diffusion Toolbox from FSL v 4.1 software[2] was used to obtain the FA maps. The voxel-wise statistical analysis of the FA was carried out using tract-based spatial statistics methods (TBSS v1.2).

Results: DLB patients had reduced FA values compared to healthy control subjects in several associative fasciculi including the *corpus callosum* and the superior and inferior longitudinal fasciculus. Corrected levels of significance for different areas are represented in yellow to red colours ($p<0.05$ corrected for multiple comparisons). FA mean skeleton mask is represented in green colour. DLB patients also have reduced FA compared to PDD in these fasciculi ($p<0.1$ corrected). PDD did not show any region with decreased FA compared to controls or DLB.

Conclusions: DTI is a technique with high capacity to differentiate the patterns of cortical microstructural white matter impairments between DLB and PDD. Patients with DLB have alterations in the long term fibers connecting complex associative regions. **References:** 1. Mori, S.; Zhang, J. *Principles of diffusion tensor imaging and its applications to basic neuroscience research*. Neuron, 2006; 51 (5): 527-539. 2. Smith, S.M.; Jenkinson, M; Johansen-Berg, H; Rueckert, D; Nichols, T.E.; Mackay, C.E. Tract-based spatial statistics: *Voxel-wise analysis of multi-subject diffusion data*. Neuroimage, 2006; 31: 1487-1505.

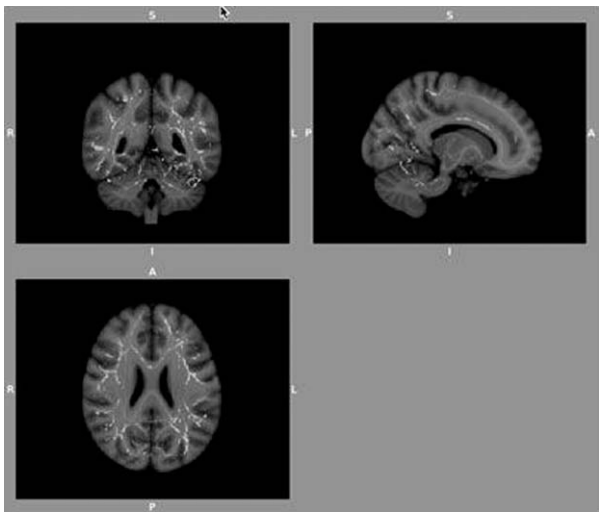

FIG. 1 (622).

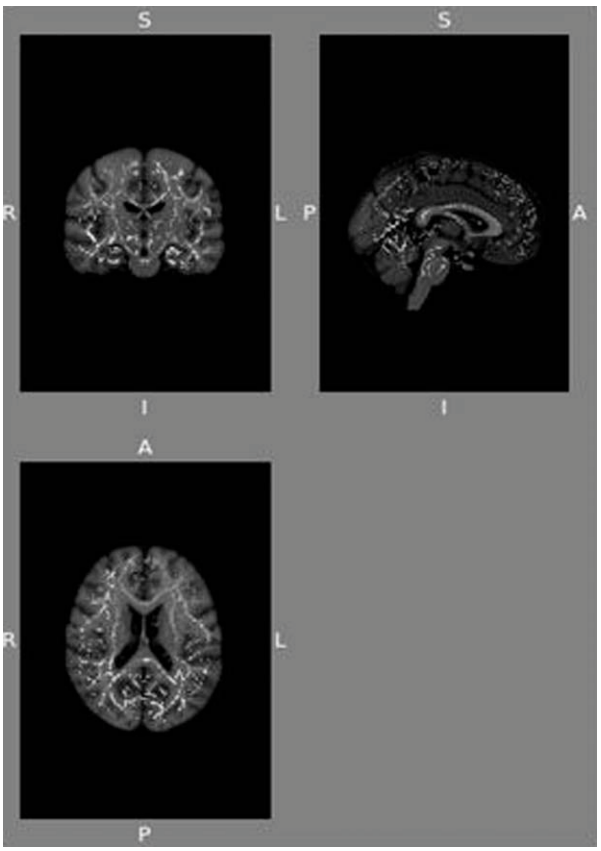

FIG. 2 (622).

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Optimal MRI methods for direct stereotactic targeting of the subthalamic nucleus and globus pallidus

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Objective: To quantitatively compare the visibility of the subthalamic nucleus (STN) and globus pallidus interna (GPi) for a variety of MRI methods and to assess the suitability of each technique for stereotactic targeting.

Background: Reliable identification of the STN and GPi is critical for clinically effective deep brain stimulation (DBS) of these structures. However, direct targeting of these nuclei is hindered by their limited contrast and relatively low visibility on standard MRI.

Methods: MR images were acquired from a group of nine healthy volunteers using seven different imaging sequences, and contrast to noise ratios (CNR) for the STN and GPi were measured for all sequences. (O'Gorman et al 2009) The sequences demonstrating the best contrast for the DBS target structures (T2* maps and susceptibility weighted images (SWI), generated by combining gradient echo

magnitude images with a scaled version of the phase data) were then applied pre-operatively to a group of ten movement disorder patients referred for DBS. Quantitative susceptibility maps were used to evaluate the extent of potential targeting errors on SWI. The CNR for these techniques was compared to those of the current standard T_2 and PD FSE.

Results: SWI offers the optimal contrast for visualisation of the STN, but the standard PD- weighted images remain optimal for visualisation of the pallidum. Susceptibility maps indicated that the GPi margins may be shifted slightly on SWI, although no shifts were seen for the STN.

Conclusions: SWI may offer improved visibility of the subthalamic nucleus on pre-operative MRI, potentially improving the accuracy of direct stereotactic targeting.

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Fahr syndrome in a patient with hipoacusia as the only clinical manifestation

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Objective: The description of the findings in our case (the association between Fahr syndrome and hypoacusia). - To show the complementarity of CT and MR.

Background: Case Report:

Methods: A 30- year-old- woman had been diagnosed with progressive hearing loss since 5. She was admitted to our Division because of abnormal findings in the cerebral MRI study. Neurologic examination revealed only hypoacusia.

Results: Evoked potentials auditory revealed disorganized answers. The laboratory studies were normal, including levels of calcium, copper, ceruloplasmin, lactate, piruvato, phosphorus. The endocrinology study rejected hypoparathyroidism. The cranial CT scans showed the presence of "calcifications" in both basal ganglia and pulvinar nuclei, with symmetrical distribution. The cranial MR scans showed asymmetrical- high hyperintensity in T1-weighted images in both caudate and putamen nuclei, and symmetrical-low hyperintensity in T1-weighted images in both pallido and pulvinar nuclei. Asymmetrical-low hyperintensity in T2-weighted images in putamen and caudate nuclei.

FIG. 1 (624).

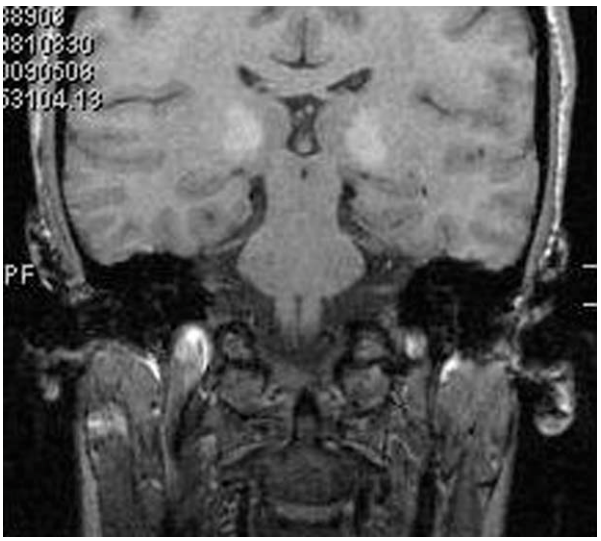

FIG. 2 (624).

Conclusions: We report a case of basal ganglia and pulvinar nuclei "calcifications", without movement disorders as clinical manifestation. Fahr disease corresponds to the idiopathic, non arteriosclerotic cerebral bilateral calcification of the strio-pallido-dentate system. The differential diagnosis of Fahr syndrome include: hereditary factors (5%), history of cerebral anoxia or encephalitis (16%), hypoparathyroidism (37%), neurofibromatosis (13%), not evidence of etiology (37%)... There are some reports in the literature about mitochondrial encephalopathy associated with Fahr disease. The syndrome is manifested by a variable combination of dystonia, parkinsonism, ataxia, cognitive empairment. Hypoacusia is an unusual clinical manifestation. De Natale et al. report 2 cases of Fahr syndrome associated with familial deafness. In our patient hypoacusia could be the initial symptom. CT has proved to be highly sensitive in detecting calcifications and is currently the reference technique. In cases of high attenuation deposits in CT with a pattern consistent with Fahr disease, MR can be very informative.

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Transcranial brain sonography in differential diagnosis of Parkinson's disease and progressive supranuclear palsy

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Objective: To evaluate the value of the TCS in differentiating PD from PSP in a group of consecutive patients with PD and PSP.

Background: Clinically differentiating Parkinson's disease (PD) from various degenerative forms of atypical parkinsonism (ATP), especially progressive supranuclear palsy, (PSP) may be quite challenging. The use of transcranial brain sonography (TCS) has been proved as sensitive and reliable in detecting basal ganglia (BG) alterations as well as the third and lateral ventricles changes which may be helpful in differentiating PD from PSP.

Methods: The study comprised 182 patients with sporadic parkinsonism and 50 healthy age-matched controls. TCS was performed in a previously described manner, by an examiner who was blinded to the clinical data.

Results: Moderate or marked substantia nigra (SN) hyperechogenicity on one or both sides was found in 89.5% PD and 18.75% PSP patients, and in 8.3% of normal healthy subjects. Third-ventricle (TV) dilatation of more than 10 mm was found in 87.5% of PSP patients, and was less frequent in controls and PD. Estimates of this

parameter as a discriminative measure showed that PSP might be discriminated from controls and PD (PPV of 87%, 68% respectively). Hyperechogenicity of the lenticular nucleus (LN) was found in 19% PD and 72% of PSP patients. Echogenicity of thalami and caudate nuclei were not significantly different between groups and did not contribute to discrimination between them. The TV dilatation in combination with LN hyperechogenicity differentiated PSP from PD, with a PPV of 91%.

Conclusions: TCS is an easy to implement, non-invasive, and inexpensive technique that could help in the differential diagnosis of parkinsonian syndromes. The routine use of TCS in the clinic could enable disease-specific therapy to be started earlier.

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Impaired prefrontal-striatal connectivity during executive processing in Parkinson's disease

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Objective: The aim of this study was to identify, *in vivo,* in PD patients changes in the prefrontal - striatal activation associated with executive performance and related connectivity abnormalities.

Background: Executive dysfunctions are part of the cognitive decline observed in Parkinson's disease (PD). Animal studies suggest that these symptoms may be linked to the disruption of dopaminergic functioning in the dorsal striatum and prefrontal cortex.

Methods: We used fMRI and a set-shifting paradigm to study activation changes related to executive processing in 9 idiopathic PD patients (off medication) compared to age-matched healthy subjects. Activation clusters in the dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC) were used as seed regions to perform probabilistic tractography using diffusion tensor imaging (DTI).

Results: PD patients presented a reduced activation in the right DLPFC, bilateral VLPFC and dorsal striatum during the set-shifting task compared to healthy controls. Probabilistic tractography with a seed applied to the DLPFC revealed an impaired connectivity with VLPFC and dorsal striatum. In contrast, probabilistic tractography with a seed applied to the VLPFC showed a normal connectivity.

Conclusions: These results suggest that the "executive" network is significantly impaired in PD and that functional and connectivity abnormalities in the prefrontal-striatal network are responsible for the executive impairment.

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Resting brain networks in patients with Parkinson's disease and freezing of gait

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Objective: To evaluate the functional integrity of resting-state neuronal networks (RSNs) using BOLD resting-state fMRI in patients with Parkinson's disease (PD) with and without "on-state" Freezing Of Gait (FOG).

Background: FOG is a disabling symptom of PD. It occurs both during "off" and "on" states with the latter being unresponsive to dopaminergic therapy. The pathophysiology of FOG remains unknown; however, some recent data suggest that "on-state" FOG might be related to a cognitive frontal dysfunction.

Methods: Sixteen PD patients (mean age: 66.9±6.09 y.o; H&Y<2.5) with "on-state" FOG (FOG+), and 13 age-, H&Y score-, and disease-duration-matched PD patients without FOG (FOG-) were enrolled in the study. PD was defined according to the UKBB clinical criteria; FOG was assessed through the FOG questionnaire. Whole brain functional imaging was performed on a 3T GE MR scanner. Statistical analysis of functional data was completed using BrainVoyager QX software.

Results: Eight functionally linked RSNs were extracted from the resting-state data of all patients. Within-network voxel-level group comparisons revealed significantly decreased activity in the right fronto-parietal network with maxima located in the lateral and middle frontal cortex (BA 9, BA 6) and in the occipito-temporal network (BA 37) in FOG+ compared to FOG- PD patients ($P<0.05$, small volume corrected) There were no significant differences in the default-mode network between the two groups.

Conclusions: Our findings of decreased resting-state activity in the right fronto-parietal and in the occipito-temporal cortical networks are consistent with previous FDG-PET studies that showed frontal hypometabolism in FOG+ PD patients and a positive correlation between improvement of FOG scores and the metabolic activity of the occipital and temporal cortices. Moreover, our data further corroborate the hypothesis that a prefrontal cortex dysfunction might be relevant to the pathogenesis of "on-state" FOG in PD.

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Typical cerebral metabolic patterns in neurodegenerative brain diseases

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Objective: To identify distinctive cerebral metabolic patterns at early disease stage, in patients with retrospectively confirmed diagnosis of different neurodegenerative brain diseases.

Background: The differential diagnosis of neurodegenerative brain diseases on clinical grounds is difficult, especially at an early disease stage. Several studies have found specific regional differences of brain metabolism applying [^{18}F]-fluoro- deoxyglucose positron emission tomography (FDG-PET), suggesting that this method can assist in early differential diagnosis of neurodegenerative brain diseases.

Methods: We have studied patients who had an FDG-PET scan on clinical grounds at an early disease stage and included those with a retrospectively confirmed diagnosis according to strictly defined

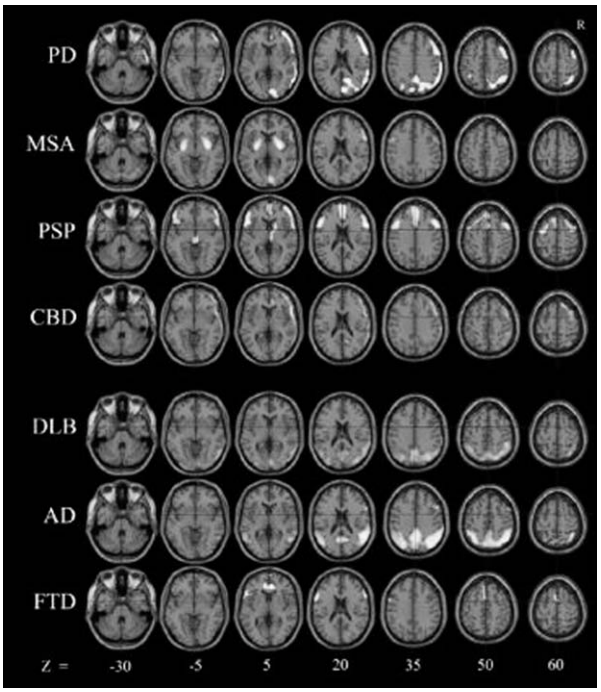

FIG. 1 (628).

clinical research criteria. 96 patients could be included of which 20 patients with Parkinson's disease (PD), 21 multiple system atrophy (MSA), 17 progressive supranuclear palsy (PSP), 10 corticobasal degeneration (CBD), 6 dementia with lewy bodies (DLB), 15 Alzheimer's disease (AD) and 7 frontotemporal dementia (FTD). FDG PET images of each patient group were analysed and compared to18 healthy controls using Statistical Parametric Mapping (SPM5).

Results: Disease-specific patterns of relatively decreased metabolic activity were found in PD (contralateral parieto-occipital and frontal regions), MSA (bilateral putamen and cerebellar hemispheres), PSP (prefrontal cortex and nucleus caudatus, thalamus and mesencephalon), CBD (contralateral cortical regions), DLB (occipital and parieto-temporal regions), AD (parieto-temporal regions), and FTD (fronto-temporal regions) (see figure 1).

Conclusions: The integrated method addressing a spectrum of various neurodegenerative brain diseases provided means to discriminate patient groups also at early disease stages. Clinical follow up enabled appropriate patient inclusion. This implies that an early diagnosis in individual patients can be made by comparing each subject's metabolic findings with a complete database of specific disease related patterns.

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Differential neural activation during cognitive tasks in asymptomatic carriers of the Parkinson's disease related *LRRK2* G2019S mutation

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Objective: To probe via fMRI the neural markers of pre-symptomatic cognitive deficits in carriers of the *LRRK2* G2019S mutation among first degree relatives of Parkinson's disease (PD) patients.

Background: The *LRRK2* G2019S mutation is an important determinant of PD in Ashkenazi Jews (AJ). It has been suggested that healthy first degree relatives of AJ PD patients with G2019S mutation are at increased risk for developing PD. Cognitive decline has been reported previously in PD patients and is often an early symptom of the disease. Hence, it was assumed that early neural markers of cognitive decline may precede the onset of motor symptoms among carriers of the G2019S mutation.

Methods: 10 asymptomatic first-degree relatives of PD patients (mean age 50.2±7.8) participated in a cognitive fMRI protocol. Five of the subjects were found to be *LRRK2* G2019S carriers. As this is an ongoing study, the genetic status of each individual has not yet been revealed. Brain scanning was performed during memory and response inhibition tasks. Initial whole brain analysis was based on general linear model using Brain Voyager.

Results: In the working memory task there was no difference between groups in reaction times (RT) or error rates (ER). Nevertheless greater activation was found in the superior and medial frontal gyri and in the pre-SMA in one group compared to the other. In contrast, in the response-inhibition task, there was a significant group effect in RT but not ER. The group with longer RT also demonstrated greater activations in the right caudate, the superior and medial frontal gyri and the cingulate gyrus.

Conclusions: Our preliminary analysis showed that it is possible to probe pre-symptomatic differences in cognitive neural activation between carriers and non-carriers of *LRRK2* G2019S mutation. Increased activation in correspondence to slower RT might reflect an inefficient compensatory neural mechanism. Together these findings support a notion that the *LRRK2* G2019S mutation is involved in early cognitive decline in PD, possibly prior to the onset of movement symptoms.

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Retrospective monocentric study of the unrestricted clinical use of [^{123}I]FP-CIT SPECT in 618 consecutive patients

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Objective: To analyse the unrestricted use of [^{123}I]FP-CIT SPECT in clinical practice.

Background: [^{123}I]FP-CIT is licensed for differentiating essential tremor from parkinsonian tremor and probable Lewy body disease from Alzheimer's disease. [^{123}I]FP-CIT may be useful for the diagnosis of other clinical conditions although some misuse of the tracer is sometimes encountered.

Methods: We reviewed the charts of 618 consecutive patients who had a [^{123}I]FP-CIT SPECT over 7 years in a single center. Symptoms of the patients, indications, SPECT results and consequences on diagnosis and treatment were studied. Among the prescribers, 72% were general neurologists and 23% were movement disorders' specialists.

Results: 102 had a SPECT for a research protocol and were excluded from analysis. Among the 516 other examinations, the most frequent indications were the confirmation of a degenerative parkinsonian syndrome (33%), the differentiation between essential and parkinsonian tremor (16%) and between iatrogenic and degenerative parkinsonian syndrome (11%), the evaluation of dopaminergic cell loss (8%), and the exploration of an atypical parkinsonism (7%). All other indications were observed with a frequency lower than 6%. The SPECT examinations were in agreement with the license label for 24% of the prescriptions of movement disorders' specialists vs. 16% for general neurologists ($p=0.03$).The SPECT was considered as helpful for the diagnosis in 66% and followed by a change of treatment in 30% of cases. When the SPECT does not help for the final diagnosis, it is most often related to an inappropriate use of the examination. This inappropriate use was observed in 45% of the prescriptions from the general neurologists vs. 19% of the prescriptions of movement disorders specialists ($p<0.0001$).

Conclusions: [^{123}I]FP-CIT SPECT is often helpful for the clinical diagnosis or treatment of movement disorders, although more than 80% of the indications laid outside the licensing limits. The use of [^{123}I]FP-CIT was considered as appropriate in 64% of the 516 cases, although this appropriate use was observed with a significantly higher rate in movement disorders specialists than in general neurologists.

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123I-Ioflupane (DaTSCAN^{TM}) dopaminergic brain SPECT: Establishing semiquantification reference values in a normal Greek population

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Objective: Establish reference values of 123I-ioflupane brain SPECT image semiquantification in a Greek population.

Background: Brain SPECT by 123I-ioflupane (DaTSCAN^{TM}, General Electric Healthcare) is an established imaging modality to diagnose nigrostriatal dopaminergic degenerative disorders. Qualitative visual image interpretation yields high diagnostic accuracy, yet

TABLE 1 (631).

	Studied normal Greek population (77)	Males (35)	Females (42)	German normal database
Tracer Uptake Ratio	Mean±SD	Mean±SD	Mean±SD	Mean±SD
STR/BKG	3.65±0.55	3.62±0.59	3.67±0.52	3.23±0.50
CAUD/BKG	3.80±0.59	3.74±0.62	3.84±0.56	3.64±0.53
PUT/BKG	3.50±0.53	3.50±0.57	3.49±0.49	3.02±0.56
PUT/CAUD	0.92±0.05	0.94±0.05	0.91±0.05	0.83±0.07

tracer uptake semiquantification offers a non-subjective adjunct to visual reading.

Methods: We evaluated 77 individuals (35 males, 42 females) referred to our Department for 123I-ioflupane brain SPECT with normal visual study interpretation. All studies were performed on the same γ-camera (General Electric Millennium VG), following a standardized data acquisition and reconstruction protocol. We performed semiautomatic semiquantitative tracer uptake analysis by choosing 3 consecutive transversal SPECT slices with maximal striatal uptake and manually defining regions-of-interest (ROI) over the left (L) and right (R) caudate nucleus (CAUD) and putamen (PUT) and a ROI in the occipital cortex as background (BKG). By measuring the mean counts in each ROI, we calculated the following ratios: STR(L+R)/BKG (STR: total striatal activity, defined as CAUD+PUT activity); CAUD(L+R)/BKG; PUT(L+R)/BKG; PUT(L+R)/CAUD(L+R). We compared our results with a German normal database that came with our hardware.

Results: The results are summarized in table 1.

As compared to the German reference, all our normal ratios tended to be relatively higher, with similar standard deviations in both populations denoting comparable levels of uncertainty. With the exception of the PUT/CAUD ratio, females displayed a slight tendency towards higher tracer uptake ratios, particularly the CAUD/BKG.

Conclusions: Marked differences in 123I-ioflupane uptake ratios have been described between different SPECT systems, so every department should establish its own reference values. These will probably differ from the normal values coming with the hardware or in the literature, since they directly reflect on the specific data acquisition and image reconstruction parameters used within each department.

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Freezing in Parkinson's disease: A pilot fMRI study

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Objective: To measure for the first time brain activity changes during upper limb freezing episodes in PD-patients using fMRI.

Background: Neural mechanisms of Freezing Of Gait (FOG) are currently unknown and difficult to address by functional magnetic resonance imaging (fMRI) studies. Our group recently demonstrated that motor blocks during rhythmic upper limb movement had highly similar spatio-temporal characteristics and were well correlated with the occurrence of FOG (Rs=0.81). The present study was designed to determine for the first time brain activity changes during normal movement and actual upper limb freezing (FO-UL) episodes in an MRI-environment.

Methods: Using a 3T-MR scanner, we conducted a pilot study on 9 PD-patients with FOG in the OFF-phase of their medication cycle. Using a block design, patients were presented with rest periods alternated with one of 4 randomly presented conditions requiring cyclical in-phase or anti-phase movements with both index fingers. Movement conditions were designed to be either freezing-provoking (small amplitude, fast movement frequency) or not (large, slow). Index finger movements were recorded during scanning (200Hz sampling rate) and classified into distinct events: (1) normal self-paced movement and (2) freezing episodes, i.e 'periods of involuntary stop or clear absence of effective cyclic movements lasting longer than 75% of normal cycle duration'. Analyses were conducted using SPM5-software.

Results: 6 out of 9 patients demonstrated FO-UL, resulting in a total of 217 freezing episodes with a mean duration of 4.98s. Whole-brain analysis revealed a clear hyperactivation relative to normal movement of the primary motor cortex, premotor area, supplementary motor area and the anterior cingulate. In contrast, activity in the globus pallidus, was significantly reduced during freezing ($p<.001$).

Conclusions: These pilot data demonstrate feasibility of measuring brain activity during actual upper limb freezing episodes and support the hypothesis that specific disturbances in the basal ganglia circuitry and striatofrontal pathways play a role in this movement breakdown.

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Does dopamine transporter SPECT (single photon emission computerised tomography) imaging alter patient management?

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Objective: To determine the utility of Dopamine transporter SPECT scanning in a movement disorder clinic setting and to assess its impact on patient management.

Background: Diagnosing parkinsonian syndromes is challenging, especially in the earlier stages. Dopamine transporter SPECT imaging supports clinicians in the differential diagnosis of parkinsonian syndromes and essential tremor.

Methods: Scans were performed in the setting of a specialist university hospital clinic with over 850 patients.We undertook a retrospective audit of consecutive scans done over a 12 month period. The scans were reported by a specialist radiologist and clinic notes were reviewed along with scan reports for correlation.

Results: 50 scans were requested out of 533 patients seen in a 12-month period: 32 males and 18 females with mean age of 77.7 years (range 58-88). Suspected clinical diagnosis was Idopathic Parkinsons Disease (IPD -21), Essential Tremor (10), Uncertain tremor syndrome (14) and others (5). Clinical diagnosis was confirmed in 18/21 in IPD and 7/10 in Essential tremor group.Imaging also contributed to clarity of diagnosis in 10/14 in the uncertain tremor group. The scan led to management change in 14 cases (28%). Clinician accuracy for clinical diagnosis was 90.4% for IPD and 70% for essential tremor. Only 1 patient failed to tolerate the procedure.

Conclusions: SPECT scanning used judiciously contributes significantly to patient management and clinical diagnostic accuracy. The scan appears to be well tolerated in almost all patients.

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Ultrasonographical findings in movement disorders: Our experience

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Objective: To describe ultrasonographical findings in 157 patients with movement disorders and to evaluate a possible correlation with clinical parameters.

Background: Hyperechogenicity of the Substantia Nigra (SN) in idiopathic Parkinson's disease (iPD) and other sonographic findings are useful for the differential diagnosis of movement disorders.

Methods: 157 patients who met diagnostic criteria for iPD, MSA, PSP, Dystonia and Essencial Tremor (ET) were ultrasonographically studied to describe echogenic features of deep brain structures. Investigators were blinded to the clinical diagnosis.

Results: 62 patients (39.5%) met diagnostic criteria for iPD, 60 (38.2%) for aPS, 25 (15.3%) ET, 3 (1.9%) MSA, 4 (2.5%) PSP and 3 (1.9%) Dystonia. 109 patients (69.4 %) showed a good bone window. SN hyperechogenicity was found in 41.4% of patients, being significantly more frequent (74.2%) in iPD ($p=0.0001$). Mean hyperechogenic areas were 0.26+/-0.11 for right midbrain and 0.25+/-0.09 for left side, being significantly bigger in iPD (right 0.33+/-0.09, left 0.3114+/-0.08). Echogenicity of raphe was decreased in 17.8%, significantly more frequently decreased in iPD and PSP ($p=0.0.34$). Echogenicity of lentiform nucleus was increased in 8.9% patients and significantly more frequent in Dystonia ($p=0.0001$). Width of ventricles showed a mean of 0.51+/-0.42 for the third and 1.78+/-5.83 for the lateral, with significant bigger measures in PSP (third 1.58cm+/-0.08, lateral 2.03+/-0.01) and MSA (third 1.34+/-0.25, lateral 2.08+/-0.07). For the SN hyperechogenic area, ROC

curves showed a cutoff value of 25.50cm2 in right side and 24.50cm2 in left one as the most sensitive (83.7%rigth, 78.9%left) and specific to predict the diagnosis of iPD. As for the third ventricle, we obtained a cutoff value of 1.49cm (100%S, 97.4%E) in PSP and 1.19cm (100%S, 92.3%E) in MSA.

Conclusions: In our sample, bilateral assimetric SN hyperechogenicity is more frequent and show bigger areas in iPD. Hypoechogenicity of raphe nucleus is more frequent in iPD and PSP. PSP and MSA showed significantly bigger width of ventricles. ROC curves showed useful cutoff values to predict iPD, PSP and MSA diagnosis. Prospective studies are needed to confirm these findings.

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An fMRI study of visual processing and hallucinations in Parkinson's disease: Preliminary data

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Objective: To identify functional neuroanatomical correlates of visual hallucinations in Parkinson's disease.

Background: Visual deficits have been identified as a correlate of visual hallucinations in PD. However, the relative contribution of peripheral (bottom-up) visual deficit and higher-level (top-down) deficits is unclear. The present study examined performance on visual processing tasks mediated by intermediate-level visual processes, during fMRI imaging, with the lateral occipital cortex (LOC) as the specified area of interest.

Methods: 9 PD patients with hallucinations and 9 without hallucinations (mean age 69.0 vs 65.1 years; mean disease duration 8.9 vs 6.1 years) underwent structural and functional MRI imaging. Two of the visual processing paradigms carried out during functional scans examined local and global visual processing: the Navon task and illusory figure completion (Kanisza task).

Results: Hallucinators showed a significantly greater number of local visual processing errors on both the Navon ($p<.05$) and Kanisza tasks ($p<.01$) with a failure to detect local targets in the Navon task and decreased sensitivity to distortions of the illusory Kanizsa triangle. Both tasks reliably activated bilateral LOC regions during fMRI (corrected for multiple comparisons, FWE $p<.05$). Group comparisons of fMRI regional activation during the tasks revealed clusters of significantly reduced activation within left LOC in hallucinators compared to non-hallucinators during the Navon ($p=.006$) and Kanizsa tasks ($p=.004$).

Conclusions: The Navon and Kanisza tasks were sensitive in detecting the types of visual processing errors made by PD patients with visual hallucinations. Underactivation of the left LOC was a consistent correlate of poorer performance on these tasks, and suggests a role for impairment of local feature visual processing in the generation of visual hallucinations in PD. The LOC region is modulated by cholinergic pathways, and therefore may account for the efficacy of cholinesterase inhibitors in treating visual hallucinations in PD.

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DTI study of brainstem white matter tract degeneration and voxel-based morphometry patterns of atrophy in PSP

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Objective: To assess patterns of grey and white matter atrophy, and degeneration of descending and ascending brainstem white matter tracts in progressive supranuclear palsy (PSP).

Background: PSP is a neurodegenerative disorder characterized by vertical supranuclear gaze palsy and early falls. Previous pathological studies have demonstrated involvement of brainstem white matter tracts. Diffusion tensor imaging (DTI) measures microscopic random motion of water in the brain and allows the assessment of white matter tract integrity by measuring directional diffusion (fractional anisotropy, FA).

Methods: Fourteen subjects that met published criteria for PSP were recruited (mean age=67 years, 50% female). All subjects had 3T head MRI including a T1-weighted volumetric MPRAGE and a DTI sequence. Voxel-based morphometry (VBM) was used to assess patterns of grey and white matter loss in the PSP patients compared to controls. White matter tract integrity was assessed by placing regions-of-interest on DTI color-coded FA maps. Regions were placed on the superior and middle cerebellar peduncles (SCP and MCP), the decussation of the SCP, the corticobulbar tract in the genu of the internal capsule, and the corticospinal tracts on the middle third of the cerebral peduncle and posterior limb of the internal capsule. Mean FA was calculated for all ROIs.

Results: On VBM, white matter loss was observed throughout the brainstem compared to controls, including the SCP and midbrain, with sparing of the pons. Both grey and white matter loss was observed in premotor cortex extending into prefrontal cortex, with grey matter loss also found in the supplemental motor area. Significant reductions in FA were identified in the SCP ($p=0.02$) in PSP, but not in the MCP ($p=0.89$). A trend for decreased FA was also identified in the decussation of the SCP ($p=0.12$) and in the corticobulbar tracts ($p=0.16$). No differences in FA were identified in the corticospinal tract ROIs.

Conclusions: PSP is associated with significant white matter tract degeneration and volume loss in the brainstem, with the disease preferentially affecting the SCP consistent with pathological findings. The corticobulbar tracts, premotor cortex and supplemental motor cortices are also involved in PSP.

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Stereological evaluation of basal ganglia and substantia nigra in Parkinson's disease

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Objective: To evaluate whether the patients with Parkinson's disease (PD) show nucleus caudatus, nucleus lentiformis, and substantia nigra (SN) asymmetry and atrophy or not and intend to depict out the probable volumetric asymmetry by using the stereological technique.

Methods: The study evaluated the volumetric measurements of each SN, nucleus caudatus and nucleus lentiformis. It included age and gender matched study and control groups of which were composed of twenty patients with PD and nineteen healthy subjects respectively. MR images were analyzed by using the point-counting approach holding the Cavalieri's principle.

Results: There were no significant differences among the subjects with respect to age (PD subjects: 69.00 ± 10.03 years, controls:64.47 ± 10.67 years,$p=0.181$). In PD and controls, there was significant difference between the volumes of left and right SN of PD patients and controls ($p=0.026$,$p=0.005$; respectively). There were no significant difference between the left and right nucleus caudatus ($p=0.602$, $p=0.632$; respectively) and nucleus lentiformis ($p=0.832$, $p=0.473$; respectively) of PD patients and controls. Significant asymmetries were found between left and right SN, nucleus caudatus, and nucleus lentiformis volumes both for PD subjects ($p=0.001$, $p<0.001$,$p=0.044$; respectively) and controls ($p<0.001$, $p=0.003$, $p<0.001$; respectively). There was a negative correlation between right SN volume and UPDRS score ($r=-0.466$, $p=0.038$).

Conclusions: There was significant atrophy in SN between the PD patients and control subjects. The Cavalieri theorem of systematic sampling in combination with point counting is found to be a reliable, simple, inexpensive and efficient method for estimating volumes in MRI and can provide valuable information in evaluation of morphological changes of PD in vivo.

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Distinct anatomical circuits underlie simple and complex tics, and repetitive behaviors in Gilles de la Tourette syndrome

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Objective: The aim of this study was to determine the neural correlates that are associated with the diversity of symptoms observed in Gilles de la Tourette syndrome (GTS) patients using voxel-based morphometry (VBM).

Background: GTS is a neurodevelopmental disorder characterized by motor and vocal tics, and is often associated with repetitive behaviors. Simple tics have been already related to dysfunction of the motor cortico-basal ganglia circuit. We suggest that dysfunction of the associative and limbic circuits underlie complex tics and repetitive behaviors, respectively.

Methods: 61 adult GTS patients and 30 age-matched controls were studied. GTS patients were clinically assessed (Yale Global Tics Severity Scale - YGTSS) and categorised in three groups: GTS-1, simple tics (n=21); GTS-2, simple and complex tics (n=23); GTS-3, tics and repetitive behaviors (n=17). Images were acquired using a 3T Siemens TRIO system. VBM was performed using SPM 5 and standard procedure. Clusters were considered significant at $P<0.05$ corrected for multiple comparisons.

Results: Compared to controls, all GTS patients showed decreased grey matter (GM) volume in the premotor and motor cortex, parietal, occipital, and anterior temporal cortices and white matter (WM) volume around the right putamen. YGTSS score was negatively correlated with GM volumes in the right premotor and motor cortex. In GTS-1 group, there was reduced volume of WM underlying the premotor and motor cortices. In GTS-2 group, there was additional reduction in GM volume in the premotor, prefrontal dorsolateral and orbitofrontal regions and in WM volume around the globus pallidus and thalamus. In GTS-3 group, decreased volumes were restricted to the GM of the right orbitofrontal and anterior temporal cortex and the WM around the right anterior putamen.

Conclusions: The results support the hypothesis that distinct neuronal circuits underlie the different symptoms of GTS.

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A magnetic resonance spectroscopy study of patients with early PD and PD with depression

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Objective: To examine the changes in the brain of patients with Parkinson's disease,and patients with or without depression, using magnetic resonance spectroscopy.

Background: Currently the early diagnosis of PD and PD with depression rely on the clinical manifestations, lack of objective diagnostic markers. The study focused on the application value of ^{1}H-MRS on the early diagnosis of PD and the diagnosis of PD with depression.

Methods: 62 patients with early PD patients and 30 healthy controls were admitted. The PD patients were assessed using Unified Parkinson's Disease Rating Scale (UPDRS), Activity of Daily Living Scale (ADL), mini-mental state examination (MMSE), Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA). According to criteria for depression, PD group were divided into PD with depression group and PD without depression group. The PD group and the control group underwent the multvoxel ^{1}H-MRS in the areas of the thalamus, striatum, substantia nigra, comparing NAA/Cr, Cho/Cr ratio in the thalamus, striatum, substantia nigra of the two groups. NAA/Cr, Cho/Cr ratio in the thalamus, striatum, substantia nigra were compared between PD with depression group, PD without depression group and controls.

Results: 1. PD group and the control group ^{1}H-MRS comparison Patients with PD showed lower NAA/Cr compared with controls,but a higher Cho/Cr in the thalamus, striatum and substantia nigra.

TABLE 1 (639). *Comparison of the MRS changes of the PD patients and the health controls*

	Substantia nigra		Thalamus		Striatum	
Groups	NAA/Cr	Cho/Cr	NAA/Cr	Cho/Cr	NAA/Cr	Cho/Cr
Control	1.82± 0.25	0.92± 0.28	1.76± 0.23	0.96± 0.25	1.68± 0.29	0.98± 0.16
PD	1.38± 0.12*	1.33± 0.24*	1.56± 0.54*	1.20± 0.21*	1.42± 0.14*	1.28± 0.18*

* $p<0.05$ compared with the health controls.

2. PD with depression group, PD without depression group, the control group ^{1}H-MRS comparison Comparisons of MRS ratios among the study groups are presented in Table 2. The comparison of controls versus PD with depression patients demonstrated significantly lower NAA/Cr and higher Cho/Cr in the PD with depression patients.Similarly, the comparison of PD with depression patients and PD without depression patients demonstrated significantly lower NAA/Cr and higher Cho/Cr in the PD with depression patients.

Conclusions: The findings suggest that reduced NAA/Cr and increased Cho/Cr of the substantia nigra,Thalamus and Striatum could be used as a marker for the early diagnosis in patients with PD and in PD with depression.

TABLE 2 (639). *MRS Ratios of PD with/without depression and control Groups*

	Substantia nigra		Thalamus		Striatum	
Group	NAA/Cr	Cho/Cr	NAA/Cr	Cho/Cr	NAA/Cr	Cho/Cr
PD with depression	1.52± 0.25Δ	1.21± 0.28&Δ	1.35± 0.24Δ*	1.09± 0.14Δ	1.32± 0.17Δ*	1.07± 0.24Δ
PD without depression	1.56± 0.24Δ	1.18± 0.18Δ	1.49± 0.12Δ	1.06± 0.20Δ	1.51± 0.14Δ	1.09± 0.16Δ
control	1.82± 0.25	0.92± 0.28	1.76± 0.23	0.96± 0.25	1.68± 0.29	0.98± 0.16

&△ $p<0.05$ compared with the health controls;* $p<0.05$ PD with depression compared with PD without depression patients.

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A prospective study of SPECT DAT imaging with [123I]PE2I in patients with movement disorders

M. Ziebell, B.B. Andersen, S.G. Hasselbalch, L.H. Pinborg, G. Thomsen, M. Karlsborg, G.M. Knudsen (Copenhagen, Denmark)

Objective: To assess the diagnostic predictive value of a [123I]PE2I SPECT scan in patients admitted for a diagnostic investigation.

Background: Single photon emission computed tomography (SPECT) imaging of the dopamine transporter (DAT) is able to detect loss of striatal DAT binding in patients with degeneration in the nigrostriatal pathway. Particularly in patients with light symptoms it can be difficult to discriminate those with striatal neurodegeneration from those without. Retrospective studies assessing diagnostic accuracy of SPECT scan with DAT radioligands such as [123I]PE2I have previously been done in selected patients. However, in order to represent the actual patient population a prospective study with a large group of unselected patients is required.

Methods: From 2003 until 2008, 205 patients were prospectively enrolled as they were admitted for a SPECT scan with [123I]PE2I because of diagnostic uncertainty. The binding of [123I]PE2I SPECT images were quantified as the binding potential of non-displaceable radiotracer (BPND). Twenty-three age-matched healthy volunteers served as a control group. With a mean of 21.1±14.1 months after the [123I]PE2I SPECT scan, based on medical records, a clinical diagnosis was established by two trained neurologists specialized in neurodegenerative diseases, blinded to the SPECT results.

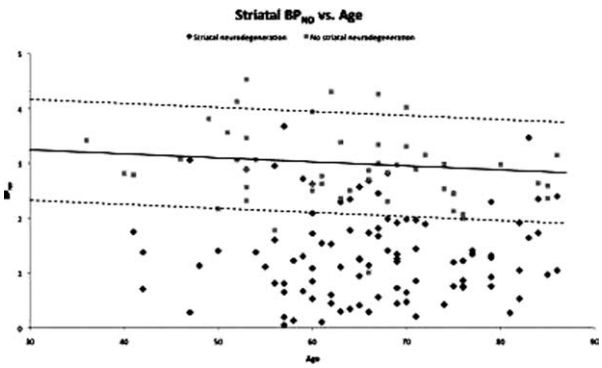

FIG. 1 (640).

Results: In 145 of 205 cases a clinical diagnosis could be established. Of the 145 patients 11 received a possible diagnosis and the remaining 134 a probable. Mean H&Y stage at the time of [123I]PE2I scan was 2±1. Ninety-four patients had a diagnosis consistent with striatal neurodegeneration the remaining 49 had a diagnosis not associated with striatal neurodegeneration. The figure shows the BPND of the most affected striatum in each of the 145 individuals. The solid line represent the mean age related striatal BPND of the 23 healthy controls±2 standard deviations (dashed line). The calculated negative predictive value was (45/60)=75 % and the positive predictive value (79/83)=95 %.

Conclusions: In a mixed group of patients with light signs of parkinsonism, SPECT scan with [123I]PE2I demonstrate a high positive predictive value in which patients suffer from a disease associated with striatal neurodegeneration.

POSTER SESSION 3

WEDNESDAY, JUNE 16, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

NEUROPHARMACOLOGY

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Lower limb spasticity treatment in the EU: Dysport® (botulinum toxin type A) dosing and reconstitution techniques

C. Coleman, J. Schwab, J. Mendoza, B. Zakine, C. Hubert (Brisbane, California, USA)

Objective: To compare dosing, reconstitution techniques, and injectors' perceptions of potential adverse events (AEs) when Dysport is used to treat lower limb spasticity in different EU countries.

Background: Dysport is a neuromuscular blocking agent approved to treat lower limb spasticity in the EU. This survey evaluated EU injectors' knowledge and experience with this intervention.

Methods: Phone interviews were conducted with Dysport-experienced injectors from five countries (France, Germany, Greece, Sweden and the UK) to assess their knowledge and experience with Dysport. Physicians were asked about the reconstitution dilution volumes, the average total dose and maximum dose they use in patients with lower limb spasticity as well as AEs.

Results: The reconstitution dilution volume was typically reported as 2.5 mL/500 U (Table 1). The average total dose and maximum dose used in lower limb spasticity by country, as reported by the physicians during the interviews, are shown in Table 1.

When using Dysport to treat lower limb spasticity, 38% to 65% of the surveyed physicians in the different countries specified potential AEs. Leg muscle weakness/hypotonia was the AE specified the most often (12-79% of physicians), followed by local injection site effects.

Conclusions: Most surveyed physicians reported using a reconstitution dilution volume of 2.5 mL/500 U (ie, 200 U/mL) in their patients with lower limb spasticity. A range of average total Dysport doses were reported for the treatment of lower limb spasticity in the different countries (range, 600-832 U). Leg muscle weakness/hypotonia and local injection site effects were the potential AEs specified most often by EU physicians.

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Hyposmia and dopaminergic therapy in Parkinson's disease: Case report

L. Correia Guedes, J.J. Ferreira (Lisbon, Portugal)

Objective: To describe the clinical case of a patient with improved hyposmia after the introduction of dopaminergic therapy illustrating the need for controled studies.

Background: Hyposmia is a well known pre-motor symptom of Parkinson's disease (PD) that affects approximately 80 to 90% of patients at the time of diagnosis. Odor detection and discrimination is impaired and is unrelated to the degree of motor symptoms. Dopaminergic modulation is known to influence odor detection thresholds and odor discrimination in animal studies. Smell is considered to be unaffected by anti-PD medications.

Methods: Medical history collection, clinical observation of the patient and longitudinal study of smell function using the University of Pennsylvania Smell Identification Test (UPSIT).

Results: Case report: We report the case of a 46 year old woman whose first complain possibly related to PD was hyposmia. The patient had a positive family history of PD (no *parkin* mutations) and noticed hyposmia months before the appearance of rest tremor. She was diagnosed PD 7 months later and medicated with ropinirole 2 mg/day. Two months later she noticed a clear subjective improvement in the discrimination and detection of odors. At that time, the UPSIT test scored 27/

TABLE 1 (641). *Reconstitution dilution volumes, average total dose and maximum dose by EU country*

	France (n=30)	Germany (n=35)	Greece (n=15)	Sweden (n=16)	UK (n=31)
Reconstitution dilution volume, % of physicians	2.5 mL: 63%, 1.0 mL: 17%, NS: 7%, Other: 13%	2.5 mL: 34%, 1.0 mL: 9%, NS: 57%	5.0 mL: 13%, 2.5 mL: 40%, 2.0 mL: 13%, 1.0 mL: 27%, Depends: 7%	2.5 mL: 38%, 1.0 mL: 19%, NS: 44%	5.0 mL: 19%, 2.5 mL: 61%, 2.0 mL: 10%, 1.0 mL: 10%
Average Total Dose, mean (min, max)	683 U (100, 1250)	832 U (100, 1500)	786 U (100, 1500)	650 U (200, 1000)	600 U (200, 1500)
Maximum Dose, mean (min, max)	1083 U (300, 2500)	1459 U (500, 2500)	1129 U (100, 3000)	1034 U (500, 1500)	1068 U (200, 2000)

NS = not specified.

40 and she had no motor fluctuations (UPDRS III=11, Hoehn and Yahr stage=2). One year later the UPSIT test scored 31, while she was on ropinirole 2mg/day, selegiline 10 mg/day and amantadine 200 mg/day. The patient smokes 20 cigarettes/day since her 19 years of age.

Conclusions: Our patient subjectively noticed that hyposmia was less severe after 2 months of therapy with ropinirole and UPSIT scores improved within only one year after diagnosis and after a further increase in therapy. Assuming that the improvement in hyposmia is not related with local nasal cavity factors, it may be speculated that the decrease in dopaminergic neurons in the bulbs associated with the progression of PD or a beneficial effect of dopaminergic therapy in olfactory functions are possible theoretical explanations. Control studies are needed to address the potential beneficial effect of antiparkinsonian drugs on hyposmia.

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Neurotoxic effect of aluminium exploratory behaviors and spatial learning in mice

N. Djebli, O. Rebai (Mostaganem, Algeria)

Objective: To evaluated to assess anxiety (1), responses to stress (2) and learning memory of animals (3).

Background: The fact that aluminium (Al) is toxic metal to living organisms, including human beings, was discovered a long time ago. Even when Al can reach and accumulate in almost every organ in the human body, the central nervous system is a particular target of the deleterious effects of this metal.

Methods: Albino mice were administered with drinking distilled water containing AlCl(3) (50 mg/kg/day) and control group with drinking double distilled water only for 3 months. After cessation of treatment, locomotor activity, hole-board test, forced swimming, black and white Test box and Morris water maze were evaluated to assess anxiety, responses to stress and learning memory of animals.

Results: In anxiety-related behaviors, Al exposed mice were more active in the locomotor activity and holeboard tests and they did not become hyperactive in the porsolt's swimming test. They were less affected by the light conditions in the central area of black and white test box. Al-treated mice had impaired spatial working memory, with lower performance at Morris water maze. The brains of experimental animals, studied by optical microscopy, have revealed damage in the hippocampus and cortex, including neurofibrillary degeneration, which can be due to the accumulation of Aluminium in these regions.

Conclusions: the present study provides further evidence for the neurotoxic action of Al in the mouse brain. Administration of Al chloride in the drinking water of mice resulted in distinct morphological alterations in the brain and behavioral results indicate cognitive impairment and enhanced anxiety of mice in an unfamiliar environment. The mouse behavior in the water maze demonstrates that the impairment in spatial working memory of Al-exposed mice was caused by inefficient use of a spatial mapping strategy, however, mice showed intact spatial reference memory. This may be induced by the deterioration of hippocampal function after Al exposure.

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The tolerability of rasagiline when used concurrently with serotonin reuptake inhibitors in Parkinson's disease: A retrospective analysis

P. Ghosh, J. Winslow, C. Musleh, C. Gandhy, L. Bahroo, F. Pagan (Washington, District of Columbia, USA)

Objective: To evaluate the incidence of symptoms of serotonin excess (SE) in patients with Parkinson's disease (PD) who take rasagiline concomitantly with a serotonin reuptake inhibitor (SRI).

Background: Rasagiline is indicated for treatment of the motor symptoms in PD. Serotonin reuptake inhibitors (SRI) are indicated for use in depression, a common non-motor symptom of PD. Non-selective monoamine oxidase (MAO) inhibitors are known to interact with SRIs by accumulating excess serotonin. We sought to evaluate the tolerability of a selective MAO-B inhibitor, rasagiline, when used concomitantly with an SRI.

Methods: We conducted a retrospective chart review of patients with PD on rasagiline and an SRI concurrently between 2006-2009. Evidence of SE was defined as tachycardia, hypertension, diaphoresis, tremor, rigidity, diarrhea, akathesia or changes in mental status. These reactions were graded on a 0 to 3 point response scale (0=no signs of SE; 1=symptoms of SE that overlap with PD such as rigidity or tremor; 2=symptoms of SE that do not overlap with PD; 3=signs of fulminant serotonin syndrome.)

Results: We screened 475 charts and identified 97 PD patients (67% male, mean age 68 years) on both rasagiline and an SRI. The mean duration of concurrent therapy was 13 months (range 1-36 months). 65% of patients (n=63) scored 0 on the response scale. 13% (n=13) scored 1. 22% (n=21) scored 2. No one scored a 3. Suspected drug interactions caused 6 patients (6%) to discontinue rasagiline after a mean of 1 month and 7 patients (7%) to discontinue the SRI after a mean of 3.6 months. Reasons for discontinuing rasagiline were agitation (5%) and diaphoresis (1%). Reasons for discontinuing the SRI included diaphoresis (3%), confusion (2%), agitation (1%) and diarrhea (1%).

Conclusions: Rasagiline, when used together with an SRI, was well tolerated (score 0-1) by 78% of patients; 22% had some signs of SE (score 2); no one had fulminant serotonin syndrome (score 3). These results indicate that symptoms of SE can occur with use of rasagiline and an SRI, but are well tolerated by the majority of patients. We are currently analyzing the group of higher scoring patients (score >1) and processing data for the interaction of specific SRIs with rasagiline.

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Reconstitution dilution volumes and botulinum toxin type A doses used to treat pediatric cerebral palsy in five EU countries

S. Hall, J. Schwab, J. Mendoza, B. Zakine, C. Hubert (Brisbane, California, USA)

TABLE 1 (645). *Reconstitution Dilution Volumes, Average Total Dose and Maximum Dose by EU Country*

	France (n=18)	Germany (n=20)	Greece (n=6)	Sweden (n=4)	UK (n=26)
Reconstitution Dilution Volume, % of physicians	2.5 mL: 61%, 2.0 mL: 17%, 1.0 mL: 17%, NS: 6%	2.5 mL: 25%, 1.0 mL: 15%, NS: 60%	2.5 mL: 83%, Don't know: 17%	Don't know: 50%, Other: 50%	2.5 mL: 46%, 2.0 mL: 12%, NS: 35%, Other: 8%
Average Total Dose, Mean (min, max)	375 U (150, 750)	544 U (100, 1200)	700 U (500, 800)	400 U (150, 800)	600 U (250, 1500)
Maximum Dose, Mean (min, max)	637 U (300, 1000)	906 U (300, 1500)	600 U (300, 1000)	467 U (100, 1000)	1148 U (300, 3000)

NS = not specified.

Objective: To assess reconstitution techniques, dosing, and injectors' perceptions of potential adverse events (AEs) when using botulinum toxin type A to treat pediatric cerebral palsy in the EU.

Background: Botulinum toxin type A blocks acetylcholine release and is a neuromuscular blocking agent that has been approved to treat pediatric cerebral palsy in the EU. This survey evaluated EU injectors' experience and knowledge of this intervention.

Methods: Phone interviews were conducted with botulinum toxin type A experienced injectors from five EU countries (France, Germany, Greece, Sweden and the UK) about their experience and knowledge of this intervention. The survey included questions about the reconstitution dilution volumes, average total dose and maximum dose used by the physicians as well as AEs in patients with pediatric cerebral palsy.

Results: The reconstitution dilution volume was typically reported as 2.5 mL/500 U. The average total Dysport dose and maximum dose used in the different EU countries, as reported by the physicians during the interviews, are shown in Table 1.

When treating pediatric cerebral palsy with Dysport, 17% to 40% of the surveyed physicians in the different countries specified potential AEs. The most common AE noted for patients with pediatric cerebral palsy was leg muscle weakness (29-100% of physicians).

Conclusions: Most surveyed physicians reported using a reconstitution dilution volume of 2.5 mL/500 U (ie, 200 U/mL) for pediatric cerebral palsy, but a range of average total Dysport doses were reported by physicians in the different EU countries (range, 375-700 U). Leg muscle weakness was the most common potential AE specified by physicians for Dysport-treated patients with pediatric cerebral palsy.

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Reconstitution dilution volumes and botulinum toxin type A doses used to treat blepharospasm/hemifacial spasm in the EU

T.S. Ichishta, J. Schwab, J. Mendoza, B. Zakine, C. Hubert (Brisbane, California, USA)

Objective: To evaluate the reconstitution techniques, dosing, and injectors' perceptions of potential adverse events (AEs) with botulinum toxin type A treatment in the EU.

Background: Botulinum toxin type A is a neuromuscular blocking agent that is approved in the EU to treat blepharospasm/hemifacial spasm. This survey assessed EU injectors' experience and knowledge of this treatment.

Methods: A phone survey was conducted with botulinum toxin type A experienced injectors from five countries (France, Germany, Greece, Sweden and the UK) about their experience and knowledge of this intervention. The topics included the dilution volumes used for reconstitution, the average total dose and maximum dose used by the physicians, and AEs.

Results: The reconstitution dilution volume was usually reported as 2.5 mL/500 U. The average total dose and maximum dose used in the five countries, as reported by the physicians during the interviews, are shown in Table 1.

When treating these patients with Dysport, 19% to 80% of the surveyed physicians in the different countries specified potential AEs. The most common AEs specified for blepharospasm were ptosis (56-83% of physicians) and diplopia (22-57%). The most common AE noted for hemifacial spasm was also ptosis (25-70%), followed by diplopia and facial nerve paresis.

Conclusions: Most surveyed physicians reported using a reconstitution dilution volume of 2.5 mL/500 U (ie, 200 U/mL) for blepharospasm/hemifacial spasm. A range of average total Dysport doses were reported for the treatment of blepharospasm/hemifacial spasm in the different EU countries (range, 54-213 U). Ptosis and diplopia were the two most common potential AEs specified by physicians for both blepharospasm and hemifacial spasm.

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Reconstitution dilution volumes and Dysport® (botulinum toxin type A) doses used to treat cervical dystonia (CD) in five EU countries

S. Illsley, J. Schwab, J. Mendoza, B. Zakine, C. Hubert (Brisbane, California, USA)

Objective: To evaluate reconstitution techniques, dosing, and injectors' perceptions of potential adverse events (AEs) when using Dysport to treat CD in the EU.

Background: Dysport is an acetylcholine release inhibitor and a neuromuscular blocking agent that has been available for use to treat CD for several years in the EU. This survey assessed EU injectors' experience and knowledge of this intervention.

Methods: Dysport-experienced injectors in five EU countries (France, Germany, Greece, Sweden and the UK) were surveyed via telephone about their experience and knowledge of Dysport including the reconstitution dilution volumes used, the average total dose and maximum dose used, and AEs in patients with CD.

Results: The reconstitution dilution volume was usually reported as 2.5 mL/500 U, although the dilution volumes as well as the average total Dysport dose and the maximum dose reported by the physicians during the interviews varied by country (Table 1).

When treating CD with Dysport, 33% to 72% of the surveyed physicians in the different countries specified potential AEs. Dysphagia (21-91% of physicians) and neck muscle weakness (14-49%) were the two most common AEs indicated as potentially occurring with Dysport treatment in patients with CD.

Conclusions: Most surveyed physicians reported using a reconstitution dilution volume of 2.5 mL/500 U (ie, 200 U/mL) for CD, but the average total dose varied by country (range, 387-586 U). The two most common potential AEs specified by the surveyed physicians were dysphagia and neck muscle weakness.

TABLE 1 (646). *Reconstitution Dilution Volumes, Average Total Dose and Maximum Dose by Country*

	France (n=24)	Germany (n=36)	Greece (n=8)	Sweden (n=10)	UK (n=31)
Reconstitution Dilution Volume, % of physicians	3 mL: 12%, 2.5 mL: 73%, NS: 8%, Other: 8%	2.5 mL: 67%, 1.0 mL: 11%, NS: 22%	2.5 mL: 63%, Other: 25%, Don't know: 13%	2.5 mL: 30%, NS: 60%, Other: 10%	2.5 mL: 45%, 2.0 mL: 6%, 1.0 mL: 16%, NS: 13%, Other: 19%
Average Total Dose, Mean (range)	123 U (20, 250)	134 U (20, 999)	104 U (8, 500)	54 U (8, 300)	213 U (20, 500)
Maximum Dose, Mean (range)	220 U (100, 500)	245 U (90, 999)	126 U (10, 500)	86 U (10, 400)	265 U (15, 1000)

NS = not specified.

TABLE 1 (647). *Reconstitution Dilution Volume, Total and Maximum Dose by Country*

	France (n=27)	Germany (n=38)	Greece (n=14)	Sweden (n=15)	UK (n=33)
Reconstitution Dilution Volume, % of physicians	2.5 mL: 54%, 1.0 mL: 25%, 0.7 mL: 7%, 0.6 mL: 11%, Other: 4%	2.5 mL: 71%, 2.0 mL: 8%, 1.0 mL: 21%, NS: 3%	2.5 mL: 57%, NS: 21%, Other: 21%	3.0 mL: 13%, 2.5 mL: 40%, 1.0 mL: 27%, NS: 7 %, Other: 13%	2.5 mL: 55%, 2.0 mL: 9%, 1.0 mL: 9%, NS: 15%, Other: 12%
Average Total Dose, Mean (min, max)	448 U (150, 800)	586 U (100, 1000)	387 U (100, 700)	530 U (150, 2500)	488 U (100, 1000)
Maximum Dose, Mean (min, max)	790 U (100, 1800)	1143 U (100, 2000)	600 U (100, 1000)	844 U (250, 2500)	845 U (100, 3000)

NS = not specified.

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Levels of reduced and oxidized coenzymeQ-10 and 8-hydroxy-2'-deoxyguanosine in the cerebrospinal fluid of the patients with living Parkinson's disease demonstrate that mitochondrial oxidative damage and/or oxidative DNA damage contributes to the neurodegenerative process

C. Isobe, T. Abe, N. Hattori, Y. Terayama (Chitose-shi, Hokkaido, Japan)

Objective: To investigate the possibility that mitochondrial oxidative damage oxidative DNA damage or both contribute to the neurodegenerative process of Parkinson's disease (PD).

Background: Sporadic PD, which accounts for 95% of total PD, underlying cause of dopaminergic neuron degeneration remains unknown. Although various factors, including oxidative stress, mitochondrial dysfunction have been implicated, a primary etiology has not been identified.

Methods: Subjects are 20 patients with PD and in 20 age-matched controls with no neurological disease. we employed high-performance liquid chromatography (HPLC) using an electrochemical detector to measure the concentrations of the reduced and oxidized forms of coenzymeQ-10 (CoQ-10) and 8-hydroxy-2'-deoxyguanosine (8-OHdG) in the cerebrospinal fluid (CSF).

Results: The percentage of oxidized/total CoQ-10 (%CoQ-10) in the CSF of the PD group (80.3±17.9%) was significantly higher than in the control group (68.2±20.4%) ($P<0.05$). The concentration of 8-OHdG in the CSF of PD patients (5.8±4.5 pg/ml) was greater than in the CSF of controls (1.8±0.6 pg/ml) ($p<0.0001$) and was positively correlated with the duration of illness ($r_s=0.87$, $P<0.001$). The %CoQ-10 was correlated with concentrations of 8-OHdG in the CSF of PD patients ($r_s=0.56$, $P<0.01$).

Conclusions: The present study suggests that both mitochondrial oxidative damage and oxidative DNA damage play important roles in the pathogenesis of early PD development.

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MAO-B inhibitors and dopamine agonists as initial treatment in Parkinson's disease: A naturalistic survey

T. Keränen, T. Mattila, H. Kuusisto (Kuopio, Finland)

Objective: To assess the outcome of monotherapy with either a MAO-B inhibitor or a dopamine agonist in early treatment of Parkinson's disease.

Background: MAO-B inhibitors have been shown to improve motor symptoms of early Parkinson's disease (PD) and delay the need of levodopa. Also dopamine agonists (DA) have symptomatic efficacy in early PD and they furthermore reduce the risk of dyskinesia and motor fluctuations related to levodopa therapy. Clinical trials suggest that a substantial proportion of patients remain on monotherapy with either MAO-B inhibitors or DA for 2–5 years.

Methods: We conducted a retrospective survey of all PD patients diagnosed at the Department of Neurology, Tampere University Hospital during 1.1.1995–31.12.2005. All patients diagnosed as having PD and treated initially with either MAO-B inhibitor or DA monotherapy, were included. The probability of reaching the end point (permanent discontinuation of the drug, a switch to another PD drug, or start of a combination treatment with other PD drugs) was assessed by the Kaplan-Maier method.

Results: During the study period a MAO-B inhibitor (rasagiline or selegiline) as the initial monotherapy was started in 121 patients and one of the available DA (bromocriptine, cabergoline, pramipexole or ropinirole) in 64 patients. The mean age of patients at the start of treatment was 63 years in both drug treatment groups was 63 years. The median duration of PD symptoms prior to treatment was 1 year in the MAO-B group and 1.4 years in the DA group. The median time to the end point was 1.8 years in the MAO-B group and 0.8 years in the DA group. The median time from the start of monotherapy to the initiation of levodopa was 3 years in both of the groups.

Conclusions: Our results suggest that benefits of MAO-B inhibitor and DA monotherapy in early treatment of PD in every day clinical practice may not be as long-lasting as shown by clinical trials.

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Synergistic anti-dyskinetic effect of topiramate and amantadine in the MPTP-lesioned non-human primate model of Parkinson's disease

C. Kobylecki, A.R. Crossman, R. Paula (Manchester, Lancashire, United Kingdom)

Objective: To evaluate the effects of combination treatment with topiramate and amantadine on L-DOPA-induced dyskinesia.

Background: L-DOPA-induced dyskinesia (LID) commonly complicates dopamine replacement therapy of Parkinson's disease (PD). Amantadine, an N-methyl-D-aspartate glutamate receptor antagonist, is the main pharmacological treatment for LID. The antiepileptic drug topiramate reduces LID in animal models via blockade of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Subthreshold doses of NMDA and AMPA receptor antagonists in combination have been reported to be effective in animal models of LID.

Methods: Dose-finding studies of amantadine (0.1-1.0 mg/kg, p.o.) and topiramate (5-20 mg/kg, p.o.) were performed in 1-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine (MPTP)-lesioned marmosets (n=7) previously primed for LID with L-DOPA. The effect of combination treatments with subthreshold doses of topiramate and amantadine was then assessed. Parkinsonian disability and dyskinesia were scored using a validated rating scale, and 'on-time' was calculated using automated locomotor activity counts.

Results: Topiramate and amantadine dose-dependently attenuated LID without worsening of parkinsonian disability. Doses of topiramate (5, 10 mg/kg) and amantadine (0.1, 0.3 mg/kg) that were ineffective individually, markedly reduced peak-dose dyskinesia in combination, without worsening parkinsonian disability. In addition, the duration of anti-dyskinetic action was extended. There was no reduction in 'on-time' with combination treatment.

Conclusions: These experiments suggest a synergistic anti-dyskinetic effect of topiramate and amantadine. Combination treatment with subthreshold doses may allow optimal treatment of dyskinesia, while minimising adverse effects.

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Neuroprotection of pramipexole in UPS impairment induced animal model of Parkinson's disease

C. Li, W. Xie, J. Jankovic, W. Le (Houston, Texas, United States)

Objective: This study is aimed at testing whether pramipexole has neuroprotective effects against ubiquitine proteasome impairment induced Parkinson's disease (PD) animal model of dopamine neuron degeneration in C57BL/6 mice.

Background: Pramipexole, a dopamine receptor D3 preferring agonist, is used to treat PD by acting directly on the dopamine receptors with significant improvement and mild side effects. Several studies have showed that promipexole possessed neuroprotective properties in acute MPTP or 6-OHDA lesioned animal model of PD. Recently, we have developed a new animal model of ubiquitine proteasome system (UPS) impairment that mimic a progressive neurodegeneration in nigro-striatal pathway and display some cordial features of PD. Using this model we tested the neuroprotective effects of pramipexole against nigral neurodegeneration and determine the possible underlying mechanisms.

Methods: Male C57BL/6 mice at the age of 10-12 weeks were pretreated with low dose (0.1 mg/kg) or high dose (0.5 mg/kg) pramipexole i.p for one week before micro-injection of proteasome inhibitor lactacystin (1.25 ug) in a stereotaxic frame bilaterally into MFB. All the mice were examined the rotarod performance once a week for 4 weeks. At the end the animals were decapitated and the brains were removed for histological examinations and biochemical assays of nigral dopamine neuron degeneration. All animal procedures were approved by the Laboratory Animal Care and Use Committee of Baylor College of Medicine.

Results: We found that administration with pramipexole significantly improves rotarod performances in lactacystin-lesioned animals, attenuate dopamine neuron loss and striatal dopamine reduction, alleviate proteasomal inhibition and microglial activation in substantia nigra. We also documented that pramipexole can increase the levels of brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF). In addition, we demonstrated an activation of autophagy in pramipexole treated mice.

Conclusions: These results suggest that pramipexole possesses a strong neuroprotection against UPS impairment induced dopamine neuron degeneration, and multiple molecular pathways may be attributed to the neuroprotective effect of pramipexole in the animal model of PD.

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Dysport® (botulinum toxin type A) dosing and reconstitution techniques used to treat upper limb spasticity in the EU

K. McClendon, J. Schwab, J. Mendoza, B. Zakine, C. Hubert (Brisbane, California, USA)

Objective: To assess dosing, reconstitution techniques, and injectors' perceptions of potential adverse events (AEs) when Dysport is used to treat upper limb spasticity in the EU.

Background: Dysport is an acetylcholine release inhibitor and a neuromuscular blocking agent that is approved in the EU to treat upper limb spasticity. This survey assessed injectors' knowledge and experience with this drug.

Methods: Dysport-experienced injectors from five countries (France, Germany, Greece, Sweden and the UK) were interviewed by phone about their knowledge and experience with this drug. The topics included reconstitution, the average total dose and maximum dose administered, and AEs.

Results: The reconstitution dilution volume was typically reported as 2.5 mL/500 U. The average total dose and maximum dose used in upper limb spasticity for the different countries, as reported by the physicians during the interviews, are shown in Table 1.

When using Dysport to treat upper limb spasticity, 48% to 76% of the surveyed physicians in the different countries specified potential AEs. Arm muscle weakness was noted the most often (35-80% of physicians), followed by injection site hematoma/irritation.

Conclusions: Most surveyed physicians reported using a reconstitution dilution volume of 2.5 mL/500 U (ie, 200 U/mL) for upper limb spasticity. The average total Dysport dose varied by country; German physicians reported using higher average total doses than the other countries (773 U versus 508-579 U, respectively). Arm muscle weakness and injection site hematoma/irritation were the potential AEs specified most often by EU physicians.

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Pardoprunox: Effects on motor and non-motor symptoms of Parkinson's disease

A.C. McCreary, M. Jackson, C. Ashby, Jr, S. Rose, P. Jenner (Weesp, Netherlands)

Objective: Parkinson's disease (PD) is characterized by both motor and non-motor symptomatology that requires improved therapy. Ideally, this might be achieved through the administration of a single medication with multiple pharmacological activities. We therefore present a review of the non-clinical data pertinent to the treatment of the motor and non-motor symptoms of PD through the use of pardoprunox (SLV308).

Background: Pardoprunox (SLV308) is a dopamine D_2 /D_3 partial receptor agonist with 5-HT_{1A} receptor agonist activity. This suggests potential efficacy in improving motor symptoms, reducing dyskinesia expression and potentially the treatment of depression and anxiety. We now present an overview of information in the public domain that supports a role for the compound in treating motor and non-motor components of PD.

Methods: The effects of pardoprunox in the 6-hydroxydopamine (6-OHDA) lesioned rat and MPTP treated primate models of parkinsonism, the forced swim test model of depression and social interaction model of anxiety are reviewed.

Results: Pardoprunox (SLV308) induced contralateral rotation in the unilateral 6-OHDA lesioned rat, reduced motor disability and increased locomotor activity in MPTP-treated common marmosets.

TABLE 1 (652). *Dilution Volume, Total Dose and Maximum Dose by EU Country*

	France (n=30)	Germany (n=39)	Greece (n=18)	Sweden (n=18)	UK (n=35)
Dilution Volume Used for Reconstitution, % of physicians	2.5 mL: 62%, 1.0 mL: 17%, 0.6 mL: 7%, NS: 7%, Other: 7%	5.0 mL: 8%, 2.5 mL: 44%, 2.0 mL: 5%, 1.0 mL: 8%, NS: 36%, Other: 5%	5.0 mL: 11%, 2.5 mL: 56%, 1.0 mL: 22%, Other: 11%	2.5 mL: 50%, 1.0 mL: 11%, NS: 39%	5.0 mL: 6%, 3.0 mL: 3%, 2.5 mL: 57%, 2.0 mL: 23%, 1.0 mL: 9%, NS: 3%
Average Total Dose, Mean (min, max)	508 U (150, 1000)	773 U (150, 3000)	542 U (100, 1500)	579 U (200, 1000)	566 U (100, 1000)
Maximum Dose, Mean (min, max)	822 U (200, 1500)	1319 U (200, 4000)	817 U (100, 2000)	979 U (300, 1500)	934 U (150, 2000)

NS = not specified.

Moreover, pardoprunox, unlike L-dopa or ropinirole, did not initiate dyskinesia in otherwise drug naïve MPTP treated primates and reduced dyskinesia expression in animals previously exposed to L-dopa. In the forced-swim test and social interaction models of depressive and anxiety-like behavior in the rat, pardoprunox produced effects consistent with antidepressant and anxiolytic-like activity.

Conclusions: These data demonstrate that pardoprunox ameliorates parkinsonian motor symptoms, does not prime for dyskinesia and may be used to reduce established dyskinesia. Moreover, pardoprunox reduced symptoms of depression and anxiety. This profile of pharmacological effects suggests that pardoprunox has potential for the treatment of both the motor and non-motor symptoms of PD.

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Mildronate attenuates reactive gliosis in the corpus striatum in 6-hydroxydopamine model of Parkinson's disease

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Objective: The purpose of this study was to evaluate Mildronate, a mitochondria targeted drug, in the rat model of 6-hydroxydopamine (6-OHDA) toxicity.

Background: Mitochodrial dysfunction and its link to neurodegeneration and neuroinflammation have a growing evidence to be essential in Parkinson's disease (Van Laar & Berman, 2009). Moreover, astroglial cells may play an essential role in these processes. Glial fibrillary acidic protein (GFAP) is an astrocytic marker in glia. Astrocytes are considered as the essential part of neuronal-glial-vascular unit (Allen and Barres, 2009).

Methods: Male Wistar rats were adapted to the experiment. Mildronate (50 mg/kg) or saline (at volume 1 ml/kg) were administered intraperitoneally for two weeks. On the day 15th rats were anesthetized and surgery was performed to inject 6-OHDA or artificial cerebrospinal fluid into corpus striatum. On the day 28th after surgery brains were removed and fixed at -80°C. The 10 μm thick brain tissue was cut in 24 cryostat sections each from corpus striatum and substantia nigra. The slides were then incubated with primary polyclonal rabbit antibody anti-GFAP.

Results: In the corpus striatum, 6-OHDA significantly increased (about four-fold) the number of GFAP positive glial cells compared to control group, indicating reactive gliosis. Mildronate administration per se did not influence the number of glial cells in corpus striatum, whereas its co-administration with 6-OHDA decreased the number of GFAP positive glial cells as compared to 6-OHDA group. Also in the substantia nigra, 6-OHDA administration significantly increased the number of GFAP positive glial cells, indicating reactive gliosis. Mildronate administration per se did not influence the number of glial cells, however its co-administrated with 6-OHDA showed tendency to decrease the number of GFAP positive glial cells compared to 6-OHDA group.

Conclusions: Data obtained suggest that Mildronate can be considered as a complementary drug in the therapy of several neurodegenerative diseases including Parkinson's disease.

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Botulinum neurotoxin type A complex proteins bind to neuronal as well as non-neuronal cells

Y. Sun, L. Wang, B.R. Singh (North Dartmouth, Massachusetts, USA)

Objective: To study the binding properties of botulinum neurotoxin type A or the respective Botulinum neurotoxin type A complex proteins to neuronal and various non-neuronal human cell types.

Background: For therapy with botulinum neurotoxin products, neurons are the primary target cells. Whereas Xeomin® is free from other clostridial proteins, the botulinum neurotoxin type A complex (e.g. Onabotulinum Toxin type A, Botox®) contains a set of complexing proteins or neurotoxin associated proteins (NAPs), which by themselves have no known role in the intracellular biochemical process involved in the blockage of the neurotransmitter release. Since the fate and possible interactions of NAPs with patient tissues after intramuscular injection are not known, we tested binding of neurotoxin and NAPs to cells derived from several different human neuronal and non-neuronal tissues.

Methods: Fluorescence-labeled (Alexafluor 488) type A botulinum neurotoxin, botulinum neurotoxin type A complex, NAPs and, for control, bovine serum albumine (BSA) were incubated with neuroblastoma SH-SY5Y, skeletal muscle RMS13, lymphoblast TIB-152 Jurkat and skin fibroblast Detroit 551 cells. After incubation and washing off unbound labeled proteins, the protein binding patterns on the four cell types were examined by fluorescence microscopy.

Results: Type A botulinum neurotoxin, its complex and its NAPs all bind to neuronal SH-SY5Y cells. Complex and NAPs additionally bind to RMS13 skeletal muscle cells, TIB-152 lymphoblasts, Detroit 551 fibroblasts as well as to the neuronal SH-SY5Y cells. No binding to these three non-neuronal cell lines was observed with pure botulinum neurotoxin type A BSA did not bind to any of the cell types.

Conclusions: While botulinum neurotoxin type A binds specifically to neuronal cells, the NAPs also bind to targeted neuronal cells and, in addition, even to other non-neuronal cell types suggesting that NAPs may not be passive but at least exert binding on cells in injected tissues. This raises the question whether NAPs also trigger reactions not relevant or even undesired for the therapeutic effects, e.g. immune responses.

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Risk of cardiac valve fibrosis and other fibroses with dopamine agonist use in Parkinson's disease

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Objective: To explore the association between dopamine agonists (DAs) and cardiac valve regurgitation (CVR) or pleural/pulmonary/pericardial/retroperitoneal fibroses in patients with Parkinson's disease (PD).

Background: There is increasing evidence on ergot DA-induced cardiac valve fibrosis (i.e. regurgitation) in PD patients while the association between DA use and other fibroses is still unclear.

Methods: A nested case control study was conducted in a cohort of PD patients who were newly treated with DAs or Levodopa. Study patients were identified from over 6 million persons in THIN (UK), Health Search-Thales (Italy), and IPCI (NL) general practice databases. Cases of CVR and fibroses were validated by manual review of medical records and specialist letters. Controls were matched to cases on age, gender, index date and database. Relative risks and 95% confidence intervals (CI) of CVR and fibroses were calculated for different DAs, compared to levodopa.

Results: In the study cohort of 19,656 PD patients (7,890 DA users, 11,766 levodopa users), 85 incident cases of CVR were identified during follow-up. Compared to levodopa, only cabergoline was associated with significantly increased risk of CVR (OR:4.6; 95%CI:2.4-8.8). The risk was statistically significant after 6 months of therapy (OR:7.4; 95%CI:3.7-15.0) and was highest in those patients switching from pergolide (OR:60.7; 95%CI:12-308) and after the first specific safety warning in 2004 (OR:5.1; 95%CI:2.5-10.5). There was no association between any DA and other fibroses (N. cases=13).

Conclusions: Increased risk of CVR was observed only in PD patients using cabergoline for more than 6 months. Detection bias

and previous exposure to pergolide may partly account for this risk. No increase in the risk of other fibroses for any DA was found.

POSTER SESSION 3
WEDNESDAY, JUNE 16, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

NON-MOTOR ASPECTS OF MOVEMENT DISORDERS (NOT PD): DYSAUTONOMIA

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Progression of autonomic failure in MSA assessed by the UMSARS-I subscale–a prospective 2-year follow-up survey by the EMSA-SG

S. Duerr, M. Koellensperger, F. Geser, W. Poewe, G.K. Wenning, on Behalf of the EMSA-SG (Innsbruck, Austria)

Objective: To assess progression of autonomic failure (AF) and predictors for progression of AF in multiple system atrophy (MSA) using the UMSARS-I subscale.

Background: MSA is a sporadic, rapid progressive disorder presenting with Parkinson and/or cerebellar symptoms in combination with AF. Although AF is one of the most characteristic features of MSA, quantified rates of progression have not been established so far.

Methods: We included 40 MSA patients at 10 EMSA-SG centres. Patients were followed up for 2 years with a complete neurological investigation every 6 months. Progression of AF and motor impairment was assessed using the UMSARS-I subscale (orthostatic symptoms, urinary/sexual/bowel function) and UMSARS-II (motor examination).

Results: All patients fulfilled the consensus criteria (67.5% MSA-P, 32.5% MSA-C; male 52.5%, female 47.5%). Mean age at baseline was 60.8±7.5 years, mean disease duration at baseline 4.1±1.6 years. Compared to baseline, there was significant progression of urinary dysfunction (30.8% in 1y, 35.9% in 2y, p=0.01), sexual dysfunction (27.9% in 1y, 33.7% in 2y, p=0.008) and bowel dysfunction (17.1% in 1y, 34.3% in 2y, p=0.006). Orthostatic symptoms increased by 22.6% within the first year and 28.3% after 2 years (n.s.). UMSARS motor scores progressed to baseline by 27% in the first year and by 49.5% in 2 years (p=0.0001). Urinary, sexual and bowel function significantly correlated with motor impairment (p=0.009/p=0.03/p=0.01); strong correlation was also found with orthostatic symptoms (n.s.). Regression analysis entering age, gender, disease duration, total motor score and motor subtype was assessed to determine predictors for AF progression. Male gender was a predictor for more pronounced progression of orthostatic symptoms (p=0.02); no significant baseline predictors for AF progression could be defined.

Conclusions: We could demonstrate marked progression of autonomic failure in MSA during a 2-year period; progression of orthostatic, urinary, sexual and bowel dysfunction strongly correlated with advancing motor impairment. Male gender was a predictor for more pronounced progression of orthostatic symptoms. Our data support recent findings that AF should be a key target for therapeutic intervention in MSA.

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A comparison of prevalence of non-motor symptoms in movement disorders

S.E. Malik, M.S. Siddiqui, M.S. Cartwright, V. Abbott, I. Ul Haq (Edison, New Jersey, USA)

Objective: To evaluate and compare the prevalence of non-motor symptoms (NMS) in Parkinson's disease (PD) with atypical parkinsonism (AP) and other movement disorders (essential tremor, dystonia, myoclonus among others).

Background: There is increasing awareness of presence of non-motor symptoms (NMS) in Parkinson's disease (PD). However, there are limited studies which have evaluated and compared the prevalence of NMS in Parkinson's disease (PD), atypical parkinsonism (AP) syndromes, and other movement disorders.

Methods: A retrospective chart review revealed 402 subjects met the inclusion criteria 1) diagnosis of movement disorder by a movement disorder neurologist at our institution 2) completion of Parkinson's Disease Non-Motor Symptom (PD-NMS). Out of 402 subjects, 271 had PD, 37 had AP, and 94 had other movement disorders. Simple and multivariate logistic regression were used to exam the prevalence rates of NMSs in the different movement disorders group. The three groups had significant age differences (mean age for PD was 68.3, AP 71.1, and other movement disorders 60.3, p <0.0001) but were similar in gender (p=0.85).

Results: When the NMS of PD subjects were compared with AP it was found that falls (p<.0001), orthostatic hypotension (p=.007), sadness (p=.002), leg edema (p<.0001), panic attacks (p=.018) were significantly more common in AP. When PD subjects were compared to other movement disorders, dribbling of saliva (p<.0001), smell/taste dysfunction (p<.0001), nocturia (p=.0006), constipation (p<.0001), urinary urgency (p=.001), hallucinations (p=.0004), falls (p=.01), somnolence (p=.004), vivid dreams (p=.02) and talking/moving in sleep (p=.015) were significantly more common in PD subjects.

Conclusions: We report a higher prevalence of symptoms of falls, orthostatic hypotension, leg edema, anxiety and sadness in AP as compared to PD. Most NMS were significantly more prevalent in PD as compared to other movement disorders.

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Safety and efficacy of droxidopa (Northera™) for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with Parkinson's disease (PD)

C.J. Mathias, H. Kaufmann (London, United Kingdom)

Objective: To assess the safety and efficacy of droxidopa for the treatment of symptoms and functional disability from NOH in patients with PD.

Background: Droxidopa is an oral pro-drug that increases central and peripheral nervous system levels of norepinephrine (NE). NOH is believed to result from inadequate stores/release of NE at the effector junction resulting in clinical manifestations including syncope and falls. The safety and efficacy of droxidopa was evaluated in a study of patients with NOH resulting from a variety of neurological conditions (N=101). We describe here results from this study for a subset of patients with NOH and PD (N=44).

Methods: The optimal dose of droxidopa for each patient was determined in an open-label titration protocol (100 - 600 mg t.i.d.). Those patients who responded to droxidopa continued with open-label treatment for one week and were then randomized (1:1, double-blind) to receive either droxidopa or placebo for two additional weeks. Symptomatic and functional improvement over time was assessed using the orthostatic hypotension questionnaire (OHQ). The OHQ consists of 10 questions which assess patient symptoms and function (activities of daily living, ADL), from which are derived a composite symptom score (OHSA), a composite ADL score (OHDAS) and a composite global score (OHQ). Safety data including vital signs, laboratory measurements and AEs were also collected.

Results: Standing systolic blood pressure at the end of study was elevated in the droxidopa treated group by an average of 14.7 mmHg

compared to baseline even though all patients were on concomitant dopa decarboxylase inhibitor therapy. Improvements were observed in ability to perform activities requiring standing for a short time ($p<0.05$), standing for a long time ($p<0.01$), walking for a short time ($p<0.05$), in the composite OHDAS ($p<0.005$) and the composite global OHQ ($p=0.005$) scores. Droxidopa was not associated with any increase in frequency or severity of adverse events relative to placebo.

Conclusions: Droxidopa appears to be a safe and effective treatment for symptomatic NOH in patients with PD. Note: Some data previously reported at WCPD, Miami, 2009.

POSTER SESSION 3

WEDNESDAY, JUNE 16, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

NON-MOTOR ASPECTS OF MOVEMENT DISORDERS (NOT PD): BEHAVIOR

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Non-motor manifestations in essential tremor: A literature review and description of neuropsychiatric profiles in 15 cases

R. Ventura, I. Amorin, R. Buzo (Montevideo, Uruguay)

Objective: To describe the presence of cognitive-behavioral alterations in essential tremor as well as different profiles.

Background: Classically, essential tremor has been considered an extrapyramidal disease exclusively showing motor manifestations. Our patients show characteristic profiles of cognitive disorders (Benito Leon and Louis, 2006) as well as personality disorders (Chatterjee and Jurewicz, 2004). Our work intends to research the presence of those alterations in patients suffering from essential tremor.

Methods: 15 patients fulfilling the diagnostic criteria of essential tremor (according to Mardsen) were studied. A clinical motor assessment was made by means of video recordings, Archimedes' spiral and stadification according to motor score and disability scales of tremor. Each of them underwent a tomography or skull magnetic resonance imaging (MRI), brain spect, neuropsychological study and complete psychiatric assessment. The literature review was performed through a search of the papers on the subject indexed in the Pubmed/Medline database.

Results: The statistical processing of the data is being performed. The preliminary results of our study show that most patients suffer from cognitive-behavioral disorders such as those reported by literature.

Conclusions: Our data would support the fact that Essential Tremor is a degenerative disease presenting non-motor manifestations as well as a clinical overlap of the profile of cognitive-behavioral alterations with those of other disorders such as Dementia with Lewy Bodies or Idiopathic Parkinson's disease.

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Home polysomnography in sleep related movement disorders

M. Anca-Herschkovitsch (Holon, Israel)

Objective: To show the wide utility of home PSG in diagnostic of sleep related movement disorders.

Background: Over one-third of adults are at risk of developing sleep disorders. The gold standard for diagnosis is polysomnography (PSG). Monitoring at home is an effective tool in sleep medicine by allowing people to undergo sleep studies without overnight hospital stays. In movement disorders the PSG use allows recognizing periodic limb movement of sleep (PLMS), restless leg syndrome (RLS), obstructive sleep apnea (OSAS) and REM Sleep Behavior Disorder (RSBD). In general population the prevalence for RLS is reported 4%-12% and for PLMS 4-9%.

Methods: 11.191 patients were examined by home PSG between 1999-2009. All patients were referred to sleep study from ambulatory service with diagnosis of EDS, insomnia, cognitive deficits, headache, painful limbs. The PD/HD patients have been assessed by movement neurologist. 228 patients (2%) diagnosed as PD (mean age 59.5, H&Ystage 1-3), 10 patients (mean age 51.5) as HD were currently treated with drugs. A portable EMBLA device with 16 channels for full PSG was used. The Epworth scale score (ESS) and device setting were made by PSG technician at patient's home before sleep. The sleep scoring was done following Rechtschaffen and Kales protocol using double checking with a sleep center.

Results: All patients completed a whole night home PSG without complains. The male group (6060): age 13-78 years, weight 45-143 kg, 56% with moderate, 20% severe SAS. 49% CPAP responders. The female group (4773) : age 13-78 years, weight 38-121 kg, 39% with moderate, 13% severe SAS .23% CPAP responders. 12% of all patients (71% males) were diagnosed with sleep related movement disorders: RLS 3.69 %, (60% males), PLMS 6.92 % (75% males), Bruxism 0.75 % (73%males), RSBD 1.06 % (76.4% males). Females are mostly affected by RLS in the age group 51-78 (84%), males in this age are predominantly affected by PLM and RSBD. The sleep architecture in HD, compared to normal and PD age-matched subjects revealed significantly prolonged NREM1/NREM2 but very small amount of REM sleep. Errors and repeated PSG were reported in 2.5% of cases.

Conclusions: The home sleep study could be a useful valid alternative for diagnosis in all field of sleep medicine including movement disorders and also a comfortable examination for elderly and disabled patients. Further controlled studies are desirable.

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Executive functions in primary focal dystonia and in Parkinson's disease

F.M.V. Dias, A. Kummer, F.C.P. Doyle, F. Cardoso, A.L. Teixeira (Belo Horizonte, Minas Gerais, Brazil)

Objective: To compare the performance of patients with primary focal dystonia (FD) and patients with Parkinson's disease (PD) in the Frontal Assessment Battery (FAB).

Background: PD and FD are defined by their motor symptoms, but non-motor symptoms are also frequent and disabling in both conditions. Presence of cognitive impairment is well established in PD and affects different domains (executive functions, processing speed, attention, memory, visuospatial functioning) even in the initial stages of PD when patients are not demented. On the other hand, existence of cognitive deficits in FD are still controversial, with a few studies demonstrating deficits in the somatosensory and visual perception, complex visuospatial tasks and executive functions. As executive functions are frequently impaired after damage of frontostriatal circuitry, the finding of this dysfunction in FD patients supports the current model of its pathophysiology.

Methods: FAB is an easily administered bedside test developed to assess executive function. FAB was administered to 30 patients with PD (M/F:10/20) and 30 with FD (M/F:10/20), paired by age and gender. Participants were not demented, according to Mini Mental State Examination (MMSE) and DSM-IV criteria, nor had delirium.

Results: Mean age of participants was 59.3 ($\pm$11.0) years. Patients of both groups did not differ in educational level ($p=0.23$), marital status ($p=0.50$) and duration of disease ($p=0.11$). The mean score in FAB of the PD patients was 10.2 ($\pm$4.2) and of patients with FD was 11.9 ($\pm$4.6) ($p=0.13$). Fifteen patients with FD (50%) and seventeen with PD (56.6%) scored under 11 in the FAB, a cut-off point for significant dysexecutive syndrome, but the differences did not reach statistical significance ($p=0.60$).

Conclusions: Patients with FD and PD did not differ in the performance on FAB, a measure of executive functioning. Our findings suggest

that executive functions of FD patients are also impaired. Further studies with more comprehensive neuropsychological batteries, larger sample sizes, and with a healthy control group should confirm these findings.

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Social cognition impairments in early stages of corticobasal degeneration

A.R. Chade, M. Roca, T. Torralva, O.S. Gershanik, G.J. Gomez Arevalo, B.F. Boeve, F. Manes (Capital Federal, Buenos Aires, Argentina)

Objective: To demonstrate impairment in social cognition in a case of early Corticobasal Degeneration.

Background: Theory of mind refers to the ability to infer other's mental states, including intentions and feelings. Patient JW, 65 years old, started with gait instability and festination with frequent falls, upper left limb apraxia and bradikinesia. A levodopa test was negative. Medical history, neurological exam, biomarkers and fluorodeoxyglucose-Positron Emission Tomography were supportive with the diagnosis of Corticobasal Degeneration.

Methods: the patient was evaluated with a neuropsychological battery and theory of mind tests especially designed to capture subtle deficits in cognitive and affective aspects of this function. His performance was compared with normative scores for age and level of education.

Results: JW presented an intellectual performance superior to media (IQ estimate: 114) showing in the cognitive evaluation only low scores in speed of cognitive processing of information tests and in verbal phonological fluency. We observed important deficits in both tests of Theory of mind indicating difficulties in the capacity to infer feelings or thoughts of others (Theory of mind).

Conclusions: Deficits in theory of mind tasks can be present in early stages of Corticobasal syndrome.

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Neuropsychiatric symptoms in Wilson's disease

N. Dragasevic, A. Potrebic, T. Pekmezovic, A. Tomic, N. Kresojevic, R. Jesic, V.S. Kostic (Belgrade, Serbia)

Objective: The objective of the current cross-sectional study was to use standardized psychiatric interviews in order to better characterize psychiatric symptoms in patients with Wilson's disease (WD).

Background: It has been shown that even among stable, long-term treated patients with WD significant percent of patients experience psychiatric symptoms.

Methods: The current cross-sectional study used standardized psychiatric interviews (i.e. the Structured Clinical Interview for DSM-IV Axis I Disorders and the Neuropsychiatric Inventory - NPI) in order to better characterize psychiatric symptoms in 50 consecutive, treated and clinically stable patients with Wilson's disease (WD).

Results: After psychiatric interviews it has been found that 9 patients (18%) had one, 7 patients (14%) had two, and 20 (or 40%) had 3 or more neuropsychiatric symptoms present. The most often endosed symptoms were anxiety (in 62%), depression (36%), irritability (26%), as well as disinhibition and apathy (24% of each). Twenty two patients, or 44%, had a score 4 or more on at least one of the NPI items: again, most frequently anxiety (17 patients or 34%), depression (13 patients-26%) and apathy (9 patients-18%).

Conclusions: Therefore, based on findings, even among stable, long-term treated patients with WD approximately 70% of patients experienced psychiatric symptoms.

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Withdrawn by Author

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Psychogenic movement disorders in children

D. Ghosh, L. Chahine (Cleveland, Ohio, USA)

Objective: To describe the demographics, history, phenomenology, and prognosis of children with psychogenic movement disorders (PMD).

Background: PMD may account for up to 25% of all disorders seen in pediatric neurology populations. Up to 6.4% of children with abnormal movements are diagnosed with a psychogenic movement disorder. In spite of the apparent commonness of this condition there is paucity of literature regarding PMD in children. Understanding the epidemiology, risk factors, and prognosis of children with PMD is important in identifying and treating these patients.

Methods: Electronic medical record of all consecutive patients presenting to the pediatric Spasticity and Movement Disorders clinic from July 2006 to December 2009 were reviewed. The cases with PMD were analyzed in respect to history, phenomenology through direct and video observation, investigations to rule out relevant differential diagnoses, and prognosis.

Results: 24 children with PMD were recorded. There were 5 males and 19 females. Mean age was 15.4 [SD 2.6] years (Range: 7-22 years). Mean duration of symptoms was 8.5 months (Range: 24 hours-3 years). Phenomenology included: myoclonus in 11 (42%), tremor in 9 (35%), dystonia in 5 (19%), and chorea in 1 (4%). Stressors that predated the onset of symptoms could not be identified in 8 (33%), and included trauma to the affected limb in 4 (17%), systemic illness in 4 (17%), family problems in 3 (12.5%), change in school in 3 (12.5%), sexual abuse in 1 (4%), and start of school in 1 (4%). 38% had multiple somatic complaints. Regarding prognosis, symptoms resolved in 7 (29%), partially improved in 4 (17%), and 13 (54%) were lost to follow up.

Conclusions: PMD in children are not uncommon. In contrast to previously reported case series, myoclonus was the most common psychogenic phenomenology seen in our series, followed by tremor. Prognosis in those with follow-up was good, with those that had shorter duration of symptoms did even better, supporting the need for early diagnosis and treatment.

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Complex neuropsychiatric symptoms in adolescent Wilson's disease: The need for multidisciplinary care

T. Hedderly, C. Hinnell, J. Moriarty, J. Jarosz, P. Hindley, A. Dhawan, R. Sherwood, M. Samuel (London, United Kingdom)

Objective: To describe the case of a young adult with Wilson's disease (WD) with severe neuropsychiatric illness significantly impairing her quality of life. To advocate for early detection of these symptoms and multi-disciplinary care.

Background: WD is an autosomal recessive disorder of copper transport and metabolism affecting 1 in 30000 people. Children and young adults predominantly present to paediatric services due to hepatic dysfunction. A large number of these patients will have unrecognized and unreported co-morbid neuropsychiatric symptoms. Our centre has developed a multidisciplinary team for the management of WD. This is one case highlighting the importance of this approach.

Methods: Description of the case history, MR imaging, course of treatment and clinical outcome.

Results: A 19 year-old female with a 9 year history of genetically-proven WD treated with penicillamine was seen in our multidisciplinary WD clinic. Although she had stable liver disease on penicillamine, direct questioning revealed a significant two year history of social anxiety and low mood. Psychiatric evaluation detected paranoia. She had a mild tremor. Worsening depression led to hospital admission for psychiatric symptoms and antidepressant therapy with venlafaxine was commenced. During her inpatient stay, she developed parkinsonism and was started on levo-dopa. This has improved her movement disorder but she continues to require intense psychiatric support. A multidisciplinary WD team, including hepatologists, neurologists and psychiatrists, has allowed for detection, appropriate

diagnosis and prompt management of the patient's marked neuropsychiatric symptoms.

Conclusions: Neuropsychiatric symptoms in children and young adults with WD are not rare. All clinician's who manage children or young people presenting with liver disease and diagnosed with WD need to screen for neuropsychiatric symptoms at diagnosis and during the ongoing management. Using a multidisciplinary approach, we are more able to identify previously undiagnosed co-morbidity requiring urgent intervention.

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Unilateral subthalamotomy in Parkinson's disease and response inhibition

M. Jahanshahi, I. Obeso, L. Wilkinson, E. Casabona, M.L. Bringas, M. Alvarez, M.C. Rodríguez-Oroz, N. Pavon, L. Alvarez, R. Macias, J. Obeso (London, United Kingdom)

Objective: To investigate if unilateral subthalamotomy in Parkinson's disease (PD) has dissociable effects on response initiation, response inhibition and response initiation under conflict in a conditional stop signal RT task.

Background: Evidence suggests that the subthalamic nucleus (STN) plays a key role in inhibition and in response selection/initiation under conflict. The conditional stop signal task requires response inhibition when a stop signal is presented on 'critical' trials but not on 'non-critical' trials, respectively allowing measurement of the SSRT and CIS.

Methods: 14 PD patients (12 male, mean age=53.64, mean duration=12.4yrs, mean 6.9mths after surgery) operated (8 right, 6 left subthalamotomy) at the CIREN, 12 unoperated PD patients (7 male, mean age=58.54, mean duration=9.4yrs) and 29 healthy controls (HC, 14 male, mean age=56.97yrs) were assessed. Patients were on medication. Participants performed 3 blocks of 128 trials of the conditional stop signal task (25% stop trials). For operated patients data from contralesional hand is reported.

Results: Unilateral subthalamotomy resulted in significant improvement of PD motor symptoms. Relative to unoperated PD, unilateral subthalamotomy was associated with significant speeding of all RT measures, which were similar to those of HCs. In contrast, SSRTs were not different for operated and unoperated PD and remained significantly prolonged relative to HCs. However, the operated group achieved inhibition with a significantly shorter mean stop signal delay (SSD). Operated patients made significantly more discrimination errors than unoperated PD and HCs. Significant speeding of critical StopRepond RTs (fail to inhibit trials) was observed for left but not right subthalamotomy, while CIS improvement was significant for right but not left subthalamotomy.

Conclusions: Unilateral subthalamotomy 'normalized' all RTs in PD except SSRT which remained prolonged relative to HCs. The operated group only achieved successful inhibition with shorter SSDs and made more errors, suggesting impulsivity. Thus STN lesioning influenced speed-accuracy thresholds and response inhibition at longer SSDs. The effect of left and right subthalamotomy was largely similar.

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Variation of muscle activity in REM sleep in patients with REM sleep behaviour disorder (RBD) and controls (Co) during 6 consecutive nights

G. Mayer, K. Kesper, W. Oertel (Schwalmstadt-Treysa, Hessen, Germany)

Objective: The aim of the study was to compare PSG recordings of RBD patients and Co during six consecutive nights.

Background: The polysomnographic (PSG) definitions of muscle tone in patients with RBD are based on single recordings. It is not known if muscle activity in REM sleep is continuously disinhibited or just in a few nights, nor if it is equally distributed throughout the cycles during consecutive nights.

Methods: So far 2 male patients (57, 68 years) with idiopathic RBD according to ICSD2 and one Co (61 years) underwent continuous PSG recordings. The recordings were performed with a Somnowatch device (Somnomedics) which allows to detect NREM and REM sleep, but does not differentiate between the NREM stages. The evaluation was performed with an automatic analysis of muscle tone according to Mayer et al. (2007).

Results: No RBD episodes were reported during the recordings. REM episodes could be clearly distinguished and were fragmented in all persons. Number of short movements (SM <0.5 sec) and long movements (LM >0.5 sec) were considerably higher in the RBD patients than in the Co (SM 55, 37 vs. 17; LM: 58, 41 vs 16). Times for SM and LM were much longer in the RBD patients, however the LM- and SM index (per s) were only higher in one patient. The distribution of LM- and SM indices showed small standard deviations in patient 1 (SM I: 36±6, LMI 32±7), bigger ones in patient 2 (SMI 22±11, LMI 19±9) and the Co (SMI 22±14, LMI 22±12).

Conclusions: The study confirms previous findings of increased frequency of SM and LM in RBD patients. The frequency was very stable in patient 1. Patient 2 and the Co had each one night with low frequency causing a high standard deviation. None of the patients had exceedingly high increase of frequency possibly indicating occurrence of manifest RBD. The data suggest that automatic EMG analysis of two nights allows to discriminate RBD from controls due to rather stable distribution of individual muscle activity of mentalis muscle. The results have to be confirmed by more consecutive recordings, which may allow to detect cut off scores. Mayer G et al. Quantification of tonic and phasic muscle activity in REM sleep behavior disorder. J Clin Neurophysiol 2008;25(1):48-55.

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The effect of levodopa on inhibition and response initiation under conflict in Parkinson's disease

I. Obeso, M. Jahanshahi (London, United Kingdom)

Objective: Our aim was to determine if levodopa medication produces similar or dissociable effects on response initiation (Go RTs), response inhibition (stop signal RT, SSRT) and response initiation under conflict (conflict-induced slowing, CIS) in a conditional stop signal RT task in Parkinson's disease (PD).

Background: The conditional stop signal RT task (De Jong, Coles et al. 1995) requires inhibition of response when a stop signal is presented on 'critical' trials but not on 'non-critical' trials. Evidence from animal, clinical and imaging studies supports a role for noradrenaline in response inhibition on the stop signal task, but the contribution of dopamine remains unclear (Eagle and Baunez 2009).

Methods: 10 male non-demented and non-depressed PD patients (mean age=69.30, SD=6.7; mean duration=11.8 years, SD=2.1) were assessed. All participants performed 3 blocks of 128 trials of the conditional stop signal RT task (25% stop trials) twice, on vs off medication with order counterbalanced.

Results: Levodopa medication significantly improved PD motor symptoms (mean UPDRS on: 15.3, SD=6.2; mean UPDRS off: 39.1, SD=11.1; p=.02). Mean SSRTs off (394.67ms, SD=89.0) and on medication (387.05ms, SD=74.1) were not significantly different (p=.85). The CIS showed a marginally significant (p=0.067) improvement in the "off" state (125.67ms, SD=117.7) compared to on medicaiton (199.02ms, SD=95.5). Medication improved Go RTs, with the change being non-significant in the critical direction (on: 540.96ms, SD=56.5; off: 591.88ms, SD=82.4; p =.22), but signifi-

cant in the non-critical direction (on: 567.45ms, SD=75.6ms; off: 500.98, SD=50.4; p =.03).

Conclusions: Our results suggest dissociable effects of levodopa: while levodopa improved the motor symptoms of PD and Go RTs, it had no effect on SSRT, the measure of response inhibition, and made conflict-induced slowing worse compared to when the patients were tested off medication. If these dissociations are replicated with an increased sample size, they have implications for the role of dopamine in response initiation, response inhibition and response initiation under conflict.

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Subthalamic activity in impulse control disorders in Parkinson's disease

M. Rodriguez-Oroz, J. Lopez-Azcarate, D. Garcia, M. Alegre, J. Artieda, J. Obeso (Pamplona, Navarra, Spain)

Objective: To study the role of the subthalamic nucleus (STN) in the impulse control disorders (ICD) induced by the dopaminergic (DA) treatment in Parkinson's disease (PD).

Background: Deep brain stimulation (DBS) of the STN in PD can be associated with abnormal impulsivity. The STN region has been implicated in the control of the impulsivity. The activity of the STN shows dopamine-dependent changes related to the motor state in PD. There are no studies of the non-motor effects (ICD) of the DA treatment and the activity of the STN.

Methods: We studied 28 PD patients treated with DBS-STN: 10 with ICD without levodopa induced dyskinesias (LID), 9 with LID without ICD and 9 without either ICD or LID. EEG and STN local field potentials were recorded through the implanted electrodes during the "off" and the "on" DA states. The power spectrum and the STN-EEG coherence were analysed using Fourier Transform based techniques. The position of every contact of the electrodes was determined in the postoperative MRI to identify where the oscillatory activity was generated in each patient.

Results: The 3 groups of patients had similar oscillatory activity in the "Off" state. In the "on" state, the ICD and LID patients had a theta-alpha activity peak (6-10 Hz) with different mean frequencies (6.7±1 Hz in the ICD and 8.4±0.9 Hz in the LID patients) not present in the patients without ICD or LID. The origin of the activity at ~6.5 Hz (ICD) was recorded between 2 and 7 mm and at ~8 Hz (LID) between 0 and 2 mm below the intercommisural line. STN-EEG coherence was stronger in ICD patients in the 4-7.5 Hz range and in frontal electrodes, while in LID patients it was in central leads and in the 7.5 -10 Hz range.

Conclusions: DA side effects in PD are associated with oscillatory activity in the theta-alpha band, but at different frequencies for the motor (LID) and the behavioural (ICD) aspects. The activity in the ICD is recorded in the associative-limbic area (ventral STN) and is coherent with the frontal cortex while in the LID it is recorded in the motor area (dorsal STN) and is coherent with the primary motor cortex. The STN is implicated in the motor and non motor complications of the DA treatment in PD trough a specific activity taking place in its different anatomo-functional territories.

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Biomarker identification in CSF in patients with Parkinson's disease and major depression

P. Svenningsson, J. Walinder, A.-K. Granerus, S.E. Palhagen (Stockholm, Sweden)

Objective: To increase our understanding of MD in PD patients and to identify biomarkers of this condition. In an ongoing effort the levels of monoamines and their metabolites, BDNF, CRH, NPY, orexin-A, IL-6 and corticosterone are examined in cerebrospinal fluid.

Background: Depressive symptoms are common in Parkinson's disease (PD), ranging between 10 and 70% mainly depending on criteria used for defining depression (Leentjens, 2004, J Ger Psychiatry Neurol 17:120-126). The biochemical basis of major depression (MD) in PD is largely unknown. MD is associated with changes in many different biochemical parameters not only involving monoamines, but also stress hormones, immune responses, neurotrophic factors and neuropeptides.

Methods: RIA, mass spectrometric and ELISA analyses were used for biochemical analyses. The analyses were performed in CSF from MD patients with (n=11) and without (n=12) PD at baseline and after 12 weeks of treatment with the antidepressant citalopram, and in patients with solely PD (n=14) at baseline and after 12 weeks.

Results: PD patients with MD have significantly lower baseline levels of MHPG, corticosterone and IL-6 when compared to patients with solely MD. In response to citalopram treatment, patients with solely MD exhibits an expected decrease in 5-HIAA and MHPG levels which was not found in PD patients with MD. Moreover, the levels of BDNF and IL-6 were lower in PD patients with MD compared with patients with solely MD after treatment with citalopram.

Conclusions: It appears that the biochemical basis and responsivity towards citalopram differs between PD patients with MD and MD patients without PD, maybe due to a more widespread neurodegeneration. Further studies examining levels of additional neurotrophic factors and neuropeptides to define improved biomarkers are ongoing and may be ready for presentation at the meeting.

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Depression and psychosis in patients with Parkinson's disease; association with vitamin B12 and vitamin D deficiency

M. Wasay, A. Yousuf, I. Azam (Karachi, Pakistan)

Objective: To identify frequency of vitamin B12 and 25- Hydroxy vitamin D deficiency in patients with known PD and its possible relation ship with depression and psychosis among these patients.

Background: Depression and psychosis are common in Parkinson's disease. Few studies have reported higher prevalence of vitamin D Deficiency in PD patients as compared to control. It is not clear that depression and psychosis in PD has any relationship to Vitamin B12 or Vitamin D deficiency.

Methods: Vitamin B12 and D levels were checked in consecutive patients with established PD. The levels were defined as mild Vitamin D Deficiency; 15-20 ng/ml, moderate Vitamin D Deficiency; 10-14 ng/ml and severe Vitamin D Deficiency; less than 10 ng/ml. Vitamin B12 was defined as levels less than 194pg/ ml. Depression and psychosis was diagnosed based on DSM-IV criteria or patients taking anti depressants or antipsychotic medications. Other variables included in analysis were activity level of patients (normal, assisted ambulation and bed ridden or wheel chair bound) and use of medications (Dopamine agonist monotherapy or Levadopa monotherapy and or combination therapy including other medications).

Results: We analyzed 42 patients. Age range was 39-79 years (mean 56 years). There were 19 women. Mean duration of PD was 6.5 years (range 4-13 years).Vitamin D levels were normal in 11 (26%) patients, mild deficiency 12 (29%), moderately deficient in 12 (29%) and severe deficiency in 7 (17%) patients. Vitamin B12 deficiency was present in 10 (24%) patients. Depression was identified in 7 (17%) patients. Psychosis was identified in 14 (33%) patients. Depression was independently associated with B12 deficiency (p=0.014) but no significant association with vitamin D deficiency (p=0.19). Psychosis was not associated with either B12 deficiency (p=0.09) and vitamin d deficiency (p=0.63). Patients with depression and psychosis were more likely to be bed ridden or wheel chair bound and taking combination therapy.

Conclusions: Vitamin D and B12 deficiencies are not uncommon in PD patients. Depression was independently associated with B12 deficiency in our study. We did not find any association between psychosis and B12 and vitamin D deficiency. Large prospective studies are needed to analyze this correlation.

POSTER SESSION 3

WEDNESDAY, JUNE 16, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

PARKINSON'S DISEASE: NEUROPHARMACOLOGY

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A specific inhibitor of RhO kinase 1 exerts a neuroprotective role on dopaminergic neurons in an experimental model of Parkinson's disease

C. Barcia, V. Annese, C.M. Ros, A. Gomez, F. Ros, E. Fernandez-Vilalba, M.-T. Herrero (Murcia, Spain)

Objective: Test the neuroprotective role of RhO Kinase inhibitor in a mouse model of Parkinson's disease.

Background: Microglial cells are thought to be the macrophages of the central nervous system. They are constantly patrolling the brain parenchyma in order to clear pathological elements. Activated microglial cells can be observed surrounding dopaminergic neurons in the brain of Parkinson's disease patients and but can also be found in the brain of human and non-human primates intoxicated with MPTP years after the neurotoxic insult. These evidences have suggested that some sort of microglial activation may be deleterious for dopaminergic neurons. In order to be effective, microglial cells need a rapid polarization and rearrangement of their cell body which is mediated by proteins involved in the reorganization of the cytoskeleton. Rho kinase is one of the key proteins implicated in the polarization and movement of the cell and may be crucial for the cytokine-secreting and phagocyting function of microglia.

Methods: In the present work, we have used the specific inhibitor of RhO Kinase 1 HA-1077 in order to block the activation of microglial cells in a model of PD in mice. We induced neuronal degeneration with a single dose of 30 mg/Kg of MPTP i.p. and sacrificed the animals 24, 48 and 72 h after MPTP.

Results: We observe that HA-1077-treated animals are protected against MPTP-induced dopaminergic neurodegeneration.

Conclusions: These results suggest that blocking Rho Kinase may have beneficial effects for the treatment of Parkison's disease.

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Neuroinflammation and blood-brain barrier P-glycoprotein function after striatal 6-hydroxydopamine lesion and COX-2 inhibition

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Objective: We studied an animal 6-hydroxydopamine (6-OHDA) PD model and hypothesized that COX-2 inhibition would reduce neuroinflammation and subsequently might improve expression and function of P-gp.

Background: Blood-brain barrier (BBB) P-glycoprotein (P-gp) function protects the brain from accumulation of toxic substances and toxic protein. P-gp and neuroinflammation are proposed to be involved in the progression of Parkinson's disease (PD). Mitigation of inflammation may improve P-gp function and may slow the progression of PD.

Methods: Using striatal 6-OHDA lesions in rats followed by either three weeks celecoxib or vehicle treatment, we have measured the resulting microglia reaction in the substantia nigra (SN) by histological quantification and uptake of [^{11}C]-PK11195 using microPET. Furthermore, we used [^{11}C]-verapamil and microPET for *in vivo* measurement of P-gp function, together with histological quantification of P-gp expression.

Results: 6-OHDA lesion caused increased microglia activity in striatum and SN as well as an increase in P-gp-expressing vasculature. [^{11}C]-PK11195-microPET was able to visualize microglia activation in the striatum only. Histology and PET did not confirm decreased microglia activity with COX-2 inhibition. COX-2 inhibition, on the other hand, prevented up-regulation of P-gp-expressing vasculature after lesioning.

Conclusions: COX-2 inhibition does not mitigate microglia activation after 6-OHDA lesion. On the other hand, COX-2 inhibition decreases the up-regulation of P-gp expressing vasculature which normally occurs after the induction of dopaminergic lesioning by 6-OHDA.

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Increase of α-synuclein oligomer in cerebrospinal fluid of the drug-naïve patients with Parkinson's disease

M.J. Park, H.-J. Bae, S.-M. Cheon, J.W. Kim (Busan, Republic of Korea)

Objective: To examine the possibility of α-synuclein as a biological marker for the Parkinson's disease.

Background: Detection of α-synuclein in the body fluid of patients with synucleinopathy showed promising but inconclusive results, partly due to the conformational changes of α-synuclein depending on environmental conditions.

Methods: Twenty-three, drug-naïve patients with Parkinson's disease (aged 62.4±12.7 years, 11 males) and age- and sex-matched 29 neurological control subjects (aged 60.1±16.2 years, 16 males) were recruited. The level of oligomeric and total α-synuclein in the cerebrospinal fluid (CSF) and plasma was measured using different enzyme-linked immunosorbent assay (ELISA) method.

Results: The level of α-synuclein oligomer in the CSF of Parkinson's disease patients was significantly increased, but other findings (plasma α-synuclein oligomer and total α-synuclein in CSF and plasma) showed no difference. When the control subjects were divided into symptomatic control group (11 patients complained parkinsonian symptoms, diagnosed as hydrocephalus and drug-induced or vascular parkinsonism) and neurological control group (10 normal subjects and 8 patients with diabetic opthalmoplegia), the level of α-synuclein oligomer in the CSF of Parkinson's disease patients still significantly increased compared to those of both control subgroups.

Conclusions: These findings can provide another evidence of the pathogenic role of α-synuclein oligomer and suggest that CSF α-synuclein oligomer can be a reliable marker for Parkinson's disease.

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COMT Val(158)Met polymorphism determines entacapone efficacy on L-DOPA pharmacodynamics and pharmacokinetics in Parkinson's disease

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Objective: To determine the consequences of COMT Val158Met polymorphism on entacapone efficacy in Parkinson's disease (PD) patients.

Background: L-DOPA metabolism is switched to the C-O-methyltransferase enzyme (COMT) when co-administered with dopa-decarboxylase inhibitors. COMT-activity is determined by a functional Val158Met polymorphism leading to a trimodal distribution of high (Val/Val), intermediate (Val/Met) or low (Met/Met) enzyme activity. Entacapone is a selective COMT inhibitor used in PD to increase L-DOPA bioavailability.

Methods: 33 consecutive PD patients, homozygous for the high-activity (Val/Val, n=17) or the low-activity (Met/Met, n=16) allele were included in a double-blinded cross-over trial testing 200 mg entacapone versus placebo during an acute L-DOPA/benserazide challenge. Serial measurements of motor score (UPDRS) and plasma L-DOPA concentrations were assessed up to 4 hours after dosing. Heterozygous patients were not evaluated. Primary criterion was genotype effects on entacapone-induced prolongation of ON time.

Results: Entacapone prolonged ON time by 35±46 min (p=0.006) in patients with the high-activity genotype (Val/Val) compared to only 9±37 min (p=0.35) in patients with the Met/Met genotype (p=0.04 for genotype). Basal COMT activity was higher in patients with Val/Val (1.3±0.1 vs. 0.8±0.1 pmol/mg protein, p=0.008). COMT inhibition by entacapone was higher in Val/Val compared to Met/Met patients (-0.5±0.3 vs. -0.3±0.3 pmol/min/mg protein, p=0.02). The area under curve of L-DOPA plasma concentration was increased after entacapone by 44% in patients with Val/Val genotype and by 22% in patients with Met/Met genotype (p=0.02 between genotype). Maximal dyskinesia score during L-DOPA challenge was increased in Val/val patients with entacapone compared to placebo (+0.7±0.7, p=0.02) whereas it remained unchanged in Met/Met patients (+0±0.7, ns).

Conclusions: Response to entacapone for both pharmacodynamics and pharmacokinetics of L-DOPA is higher in patients with Val/Val genotype compared to patients with Met/Met genotype. Entacapone response in heterozygous patients remain to be determined.

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PARIS, a parkin substrate, transcriptionally represses PGC-1α leading to neurodegeneration in Parkinson's disease

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Objective: Although mitochondrial dysfunction is thought to play an important role in the pathogenesis of PD, it has remained elusive how PD-associated genes lead to mitochondrial abnormalities. We have found a new parkin interacting substrate, (PARIS), whose levels are regulated by the ubiquitin proteasome system (UPS) via binding to, and ubiquitination by, the E3 ubiquitin ligase, parkin.

Results: PARIS is a novel KRAB and zinc finger protein that accumulates in models of parkin inactivation and in human PD brain. PARIS inhibits the transcriptional activity of PGC-1α, which regulates mitochondrial function, by binding to insulin response sequences in the PGC-1α promoter. Overexpression of PARIS both in vitro and in vivo leads to reduced mRNA and protein levels of PGC-1α, a substantial decrease of the PGC-1α target gene, NRF-1. Similar observations are made in human postmortem PD brain. Elevated PARIS levels also lead to a reduction in mitochondrial DNA, mitochondrial number and complexity and increased mitochondrial size. Moreover overexpression of PARIS leads to the selective loss of dopaminergic neurons in SNpc, which is reversed by either parkin or PGC-1α co-expression.

Conclusions: The identification of PARIS provides a link between parkin and mitochondrial dysfunction through regulation of PGC-1α.

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Cytotoxicity of *N*-methylated salsolinol derivatives in SH-SY5Y human dopaminergic neuroblastoma cells

M. DeCuypere, Y. Zhao, S. Anjaiah, D.D. Miller, M.S. LeDoux (Memphis, Tennessee, USA)

Objective: To quantify mitochondrial dysfunction and cytotoxicity produced by *N*-methyl-(*R*/*S*)salsolinol (*N*-methyl-SAL) and *N*-methyl-norsalsolinol (*N*-methyl-norSAL), putative dopaminergic neurotoxins which may contribute to neurodegeneration in Parkinson's disease (PD).

Background: The tetrahydroisoquinoline (TIQ) family of compounds are structurally similar to MPTP and are found naturally in many fruits and vegetables. Furthermore, certain TIQs, namely the salsolinol derivatives, can be synthesized endogenously from dopamine and have been detected in rodent and human brain. Although several studies suggest that TIQ derivatives are neurotoxins potentially relevant to dopaminergic cell death in PD, a paucity of data exists regarding the toxicity of the *N*-methylated derivatives of salsolinol which are concentrated in dopaminergic regions of human brain.

Methods: SH-SY5Y (5Y) cells were exposed to either *N*-methyl-SAL or *N*-methyl-norSAL for 24 and 48 hrs. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was used as a measure of overall cell viability, while the JC-1 assay was used to evaluate mitochondrial transmembrane potential. The pesticide and known mitochondrial complex I inhibitor rotenone served as a positive control.

Results: Treatment of 5Y cells with *N*-methyl-SAL and *N*-methyl-norSAL resulted in significant cytotoxicity at 24 and 48 hrs. Compared to non-treated cells, *N*-methyl-SAL (IC_{50}=0.376 mM) and *N*-methyl-norSAL (IC_{50}=0.305 mM) significantly reduced cell viability and mitochondrial transmembrane potential in a dose-dependent manner. The effect of exposure duration (24 vs. 48 hrs) only reached significance at higher concentrations of *N*-methyl-SAL and *N*-methyl-norSAL. Rotenone (IC_{50}=0.013 mM) was found to be a more potent neurotoxin at both time points.

Conclusions: Our data demonstrates that *N*-methyl-SAL and *N*-methyl-norSAL reduce mitochondrial transmembrane potential and are toxic to dopaminergic cells in a dose dependent manner. The difference in cell viability after exposure to *N*-methyl-SAL and *N*-methyl-norSAL indicates that methylation at the one-carbon position exerts only a small effect on relative neurotoxicity. Intraneuronal accumulation of *N*-methyl-SAL and *N*-methyl-norSAL may contribute to mitochondrial dysfunction and dopaminergic cell death in PD.

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Safinamide reduces levodopa-induced dyskinesia in MPTP-lesioned primates while prolonging anti-parkinsonian efficacy

L. Gregoire, A. Roach, T. Di Paolo (Quebec, PQ, Canada)

Objective: To understand the effects of the investigational drug safinamide in a model of L-dopa-induced dyskinesia.

Background: Safinamide is an α-aminoamide derivative with dopaminergic and non-dopaminergic activities currently in phase 3 development for use in combination with L-dopa or dopamine agonists for patients with Parkinson's disease (PD). Safinamide's non-dopaminergic activities include state-dependent sodium channel blockade and inhibition of induced glutamate release *in vitro*. Both dopaminergic (L-dopa enhanced dopamine levels) and non-dopaminergic components (including but not limited to glutamate transmission imbal-

ance) are implicated in L-dopa-induced dyskinesia (LID), a common treatment complication in patients with PD for which there is no currently approved therapeutic option.

Methods: Safinamide was tested in an animal model of LID, the MPTP lesioned dyskinetic macaque monkey (Grégoire et al, Park. Rel. Disorders 15:445-452, 2009). Dyskinesia and primary parkinsonian symptoms in response to individually tailored doses of L-dopa, and safinamide plasma levels, were measured in a group of dyskinetic animals, pretreated with either vehicle or safinamide administered by oral gavage one hour before L-dopa.

Results: In all animals, L-dopa induced dyskinetic motions over a period of 2-3 hours after oral administration. Safinamide pretreatment reduced dyskinesia scores in all cases, compared to vehicle, in two independent experiments. Both peak intensity and duration of the dyskinetic motions were reduced. The duration of the beneficial antiparkinsonian effect of L-dopa was prolonged with all doses of safinamide.

Conclusions: In this study safinamide reduced the dyskinesia that appears in parkinsonian primates in response to L-dopa administration. Safinamide did not reduce dyskinesia by simply antagonizing the dopaminergic action of L-dopa since it simultaneously prolonged the antiparkinsonian efficacy of L-dopa. The possible translation of this profile to patients with PD is currently being examined in clinical trials.

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Dopaminergic drug-induced modulation of the expression of dopamine transporter in peripheral blood lymphocytes from Parkinson's disease patients

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Objective: : to measure the effects of dopaminergic drugs on the expression of dopamine transporter (DaT) in peripheral blood lymphocytes (PBL), as a model to investigate drug-induced modulation of DaT expression in Parkinson's disease (PD).

Background: DaT is a presynaptic membrane protein through which dopamine neurons reuptake dopamine. In the pre-symptomatic stages of PD, DaT down-regulation contributes to the compensatory mechanisms to dopaminergic deficit. In symptomatic stages, the reduction of DaT binding due to nigrostriatal terminal degeneration can be identified by functional neuroimaging. These latter methods have been also applied in clinical trials as markers of disease progression in PD. The results showed more pronounced reduction of DaT binding following levodopa (LD) with respect to dopamine agonist (DA) treatment, thus rising the hypothesis of neuroprotection by DA in PD. However, there is still controversy as to whether dopaminergic drug-induced modulation of the expression of DaT might contribute to these latter results. To further define this issue, we thought of interest to investigate in vivo the modulation of DaT expression in PBL in PD.

Methods: PD patients aged 45-75 years (n=16) were enrolled at the time of clinical diagnosis. For each patient, DAT expression in PBL was measured by flow cytometry using an anti-DaT monoclonal antibody on 2 blood samples, drawn before (drug-naive state) and 8 weeks after the beginning of treatment with either LD or DA (pramipexole or ropinirole), respectively.

Results: : treatment with LD did not modify DaT expression in PBL. Treatment with DA was accompanied by a significant reduction of DaT expression in PBL, more pronounced with pramipexole with respect to ropinirole.

Conclusions: : the results indicate that DaT expression in PBL is down-regulated by DA but not by LD. The down-regulation of DaT expression in PBL by DA, if confirmed on larger number of patients, suggests that the previously reported difference between LD and DA on striatal DAT binding might underestimate the potential neuroprotective effects of DA.

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Mu-selective, but not non-selective, opioid receptor antagonism reduces L-DOPA induced dyskinesia in the MPTP macaque model of Parkinson's disease

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Objective: To compare the ability of a mu-selective opioid receptor antagonist with a non-selective antagonist in reducing L-DOPA induced dyskinesia (LID) in an MPTP macaque model of Parkinson's disease (PD).

Background: Over time, treatment of the motor symptoms of PD with L-DOPA produces debilitating side effects, including dyskinesia. Given the prominent role of the opioid system in basal ganglia function, non-selective opioid receptor antagonists (including naltrexone and naloxone) have been tested for anti-dyskinetic efficacy in the clinic, although without success. In the current study, ADL5510, a novel, orally-active opioid antagonist with mu-selectivity, was examined in L-DOPA treated MPTP macaques. Antidyskinetic effects were compared to those of the non-selective opioid antagonist naltrexone.

Methods: Cynomolgus monkeys, rendered parkinsonian by repeated administration of MPTP and with established LID, received acute challenges with L-DOPA (s.c.) in combination with either vehicle, ADL5510 (0.1, 1, 3 and 10 mg/kg, p.o.) or with naltrexone (1, 3 and 10 mg/kg, s.c.). Immediately following treatments, behavior was monitored for 6 h. Parameters assessed were total activity, parkinsonism and dyskinesia.

Results: ADL5510 (1, 3 and 10 mg/kg) reduced activity and LID (both chorea and dystonia) without affecting the anti-parkinsonian benefits of L-DOPA. The anti-dyskinetic effect of ADL5510 showed a U-shaped dose-response. It was inactive at 0.1 mg/kg, highly efficacious at 1 and 3 mg/kg (72% and 40% reductions, respectively), and then less effective at 10 mg/kg. The quality of on-time produced by L-DOPA was improved as indicated by a reduction in the percentage of on-time spent experiencing disabling dyskinesia (70 and 61% reductions, with 1 and 3 mg/kg respectively, compared to L-DOPA alone). Naltrexone, in contrast, did not alleviate LID or affect the anti-parkinsonian actions of L-DOPA.

Conclusions: Mu-selective opioid antagonists have the potential to form the basis of novel anti-dyskinetic therapies for PD.

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Suppression of neuroinflammatory signaling cascade by licofelone, a dual COX/LOX-inhibitor attenuates MPTP-induced neurotoxicity in mice

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Objective: The present study aimed to evaluate the possible role of licofelone, a dual COX/LOX-inhibitor in attenuating MPTP-induced dopaminergic neurodegeneration in mice.

Background: Recent advances in the underlying mechanisms and pathogenesis of Parkinson's disease (PD) have indicated the crucial role of neuroinflammation and oxidative stress. Various anti-inflammatory drugs also have shown beneficial effects in attenuating the progression of PD in experimental models. But, novel class of dual inhibitors of cyclooxygenase (COX) and lipooxygenase (LOX) is still remained unexplored.

Methods: Animals were challenged with MPTP 40 mg/kg (four injections of 10 mg/kg, i.p. at an interval of 1 hr). Alteration in behavioral (locomotor activity, catatonia), biochemical and cellular functions was evaluated.

Results: Systemic administration of MPTP induced Parkinson-like symptoms in mice as seen by decreased locomotor activity and catatonia. MPTP also produced significant oxidative damage (elevated levels of lipid peroxidation and nitrite, decreased levels of non-pro-

tein thiols) and mitochondrial dysfunction (decreased complex-I activity and mitochondrial viability) as well as increase in the levels of caspase-3 and NF-κB/p65. TTC staining of the brain slices also revealed significant striatal damage. Treatment with licofelone (5 or 10 mg/kg) for 7 days significantly improved the behavioral alterations (locomotor activity, catatonia), oxidative defense, restored mitochondrial enzyme complex activity and striatal damage as compared to MPTP-treated group.

Conclusions: Present findings of the study suggest that dual inhibition of COX/LOX by licofelone represents a new class of anti-inflammatory agents which may provide a novel therapeutic alternative for attenuation of neuroinflammatory signaling cascade as well as oxidative stress in PD.

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The glucocorticoid receptor in dopaminergic neurons mediates the neuroprotective role of glucocorticoids in parkinsonism

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Objective: In this work, we analyze the protective role of glucocorticoid receptor (GR) in different experimental models of Parkinson's disease (PD) and try to elucidate whether the effect of glucocorticoids (GCs) may be direct over dopaminergic (DA) neurons without the participation of other cell types.

Background: Increasing evidences from experimental and epidemiological studies, suggest that inflammation may play an important role in the pathogenesis of PD. GCs are known to regulate several phases of the inflammatory responses, through the binding and activation of GR, controlling the expression of anti-inflammatory or pro-inflammatory cytokines. However, their precise action in the central nervous system and their role in neuronal survival in pathogenesis of PD are not well characterized.

Methods: We used three experimental models of PD in order to elucidate the mechanisms of neuroprotection of GCs on DA neurons: a) rat mesencephalic cell cultures exposed to MPP+ and treated with GCs; b) C57/BL6 mice and DATcre mice intoxicated with MPTP and treated with GCs; and c) chronic parkinsonian non-human primates.

Results: We observed a neuroprotective effect against the neurotoxin on DA neurons after treatment with GCs in vivo as well as in vitro. Importantly, the neuroprotective effect of GCs persists in cultures without glial cells (treated with Ara-C), and DATcre-mice (without GR expression in DA neurons) do not show such protective effect. In addition, the postmortem analysis of the MPTP-treated monkeys, strikingly, showed that the proportion of surviving TH positive neurons expressing GR in the Substantia Nigra pars compacta was significantly higher in monkeys that presented higher DA cells loss.

Conclusions: These results demonstrate that GR could have a neuroprotective effect directly on DA neurons and may be involved in neuronal survival in parkinsonism, suggesting new potential therapies for PD.

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Does erythropoetin (EPO) induced under severe anemia improve parkinsonism

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Objective: To present a potential effect of erythropoietin (EPO) induced under acute severe iron deficiency anemia in Parkinson's disease.

Background: According to previous reports, EPO acts on dopaminergic neurons in the brain, that is, peripheral EPO permeates into the brain through the blood-brain barrier, and potentially activates dopamine (DA) synthesis and DA release from nerve terminals.

Methods: We report here that patients with Parkinson's disease (PD) who had acute severe iron deficiency anemia developed dyskinesia or showed worsening of their dyskinesia. Under their current medications, four patients whose duration of illness was from five to 16 years showed wearing off phenomenon and peak-dose dyskinesia. Another patient whose duration of illness was two years exhibited no motor complications. The causes of their anemia were gastric cancer, hemorrhoid and gastric ulcer.

Results: The level of blood hemoglobin on admission was 3.4∼6.9 g/dl. Anemia in these patients were suspected to develop within two or 3 months after the latest visit to our clinic. In four of the five patients whose EPO was quantified, EPO levels were high ranging from 64.2 to 1704.2 mIU/ml. The patients except one who have a two-year duration of the disease developed or showed worsened dyskinesia. After treating anemia by blood transfusion and iron supplementation, their dyskinesia was attenuated or disappeared without any changes in their medications.

Conclusions: Our present experience seems to suggest that highly elevated EPO levels in the plasma acts as a dopaminergic neuron activator in the brain. EPO or its nonblood forming analogs for PD therapy have potential therapeutic applications.

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Effective use of levodopa in Parkinson's disease patients in a regional hospital in Hong Kong

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Objective: To see the toleratbility of Parkinson's disease patients switching from levodopa-benserazide (LB) to levodopa-carbidopa (LC).

Background: There are 2 levodopa with dopa decarboxylase formulations available in Hong Kong, namely LB and LC. LB contains 200 mg levodopa and 50 mg benserazide, whereas LC contains either 100 mg levodopa and 25 mg carbidopa (25/100), or 250 mg levodopa and 25 mg carbidopa (25/250). It may be more convenient for Parkinson's disease patients to use LC if they need small doses, as they do not need to cut the tablet (e.g 100 mg levodopa means 1 tablet LC 25/100 and 0.5 tablet LB). It also applies for titrating up or down the doses (e.g. 150 mg levodopa means 1.5 tablet LC 25/100 and 3/4 tablet LB). Moreover, the price is lower for LC when the same levodopa equivalents are compared in these 2 drugs.

Methods: Parkinson's disease patients currently taking LB attending movement clinic in a regional hospital in Hong Kong from June 2009 to September 2009 would be asked to change to LC after discussion. They would be monitored for at least 3 months to see whether they tolerated the change in drug.

Results: 104 Parkinson's disease patients ween seen by the same neurologist in those 4 months' time. 4 patients did not take any levodopa. For the remaining 100 patients, 35 took LB and 65 took LC. 29 patients (out of 35) agreed to change LB to LC. They included 17 male and 12 female. Age ranged from 51 to 82. 27 pateints (93.1%) tolerated the change in drug in at least 3 months' time afterwards. 2 patients needed to change back to LB subseqently. Both of them were male, aged 57 and 64. The first one claimed his condition got worse with LC, and the latter could not tolerate the LC preparation.

Conclusions: The usage of LC when treating Parkinson's disease patients with levodopa is more cost-effective. It is also more conveninet for them in titrating the doses and avoid splitting the tablet if smaller doses are needed, which is beneficial as Parkinson's disease patients may have difficulties in these fine motor functions. Besides, the tolerability is good, with 93.1 % patients tolerated the change from using LB to LC.

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5-HT_{2A} receptor levels are increased in dyskinetic, MPTP-lesioned macaques

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Objective: To evaluate the levels of serotonergic type 2A (5-HT_{2A}) receptors in 3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesia in the MPTP-lesioned macaque.

Background: Long-term L-DOPA treatment in Parkinson's disease (PD) is associated with motor complications such as dyskinesia. Antagonists at 5-HT_{2A} receptors such as clozapine may be effective at alleviating dyskinesia. We hypothesised that enhanced 5-HT_{2A}-mediated neurotransmission is involved in the genesis of L-DOPA-induced dyskinesia.

Methods: Autoradiographic binding using [^{3}H]-ketanserin, a 5-HT_{2A} antagonist, was performed in brain sections from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned cynomolgus macaques (*Macaca fascicularis*): 6 normal macaques (vehicle-treated), 5 parkinsonian macaques without exposure to L-DOPA (MPTP-vehicle group), 6 parkinsonian macaques exposed to a single acute challenge of L-DOPA (single dose group), and 6 dyskinetic parkinsonian macaques chronically treated with L-DOPA (dyskinetic group). The cerebral regions studied included the motor and premotor cortex, striatum, globus pallidus, subthalamic nucleus, and substantia nigra.

Results: In the putamen of dyskinetic macaques, 5-HT_{2A} receptor levels were 43.25±5.67 fmol/mg. This represents a significant increase, compared to vehicle-treated, MPTP-vehicle, and single dose macaques (respectively 26.19±4.73 fmol/mg, 26.55±4.84 fmol/mg, and 34.55±3.71 fmol/mg; all $P<0.05$). In the caudate nucleus of dyskinetic macaques, 5-HT_{2A} receptor levels were 48.75±5.70 fmol/mg, which significantly differs from vehicle-treated animals (29.96±5.16 fmol/mg; $P<0.05$), but not from MPTP-vehicle or single dose macaques. In the middle layers of the motor cortex, 5-HT_{2A} receptor levels reached 116.12±7.54 fmol/mg in dyskinetic macaques, and 116.22±11.22 fmol/mg in single dose macaques. These two values represent a significant increase compared to vehicle-treated macaques (79.13±9.29 fmol/mg; both $P<0.05$).

Conclusions: Our results provide new insights into the pathophysiology of dyskinesia in PD, and provide a strong anatomical basis to explain why 5-HT_{2A} receptor antagonists might be effective at alleviating dyskinesia.

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5-HT_{1A} receptor levels are altered in both the dopamine-depleted and dyskinetic states in the MPTP-lesioned macaque model of Parkinson's disease

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Objective: To evaluate the levels of serotonergic type 1A (5-HT_{1A}) receptors in parkinsonian and dyskinetic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned macaques.

Background: Long-term L-3,4-dihydroxyphenylalanine (L-DOPA) treatment in Parkinson's disease (PD) is associated with the emergence of motor complications including dyskinesia. 5-HT_{1A} receptor agonists such as sarizotan and tandospirone may be effective at alleviating dyskinesia, but may also worsen parkinsonism suggesting a role for the 5-HT_{1A} receptors in both PD and dyskinesia.

Methods: Autoradiographic binding utilising the 5-HT_{1A} antagonist [^{3}H]-WAY 100,635 was performed in cynomolgus macaque (*Macaca fascicularis*) brain sections. Levels of specific binding were compared between groups of MPTP-lesioned L-DOPA naive (n=5, MPTP-vehicle), acute L-DOPA treated (n=6, MPTP-single L-DOPA dose), and chronically L-DOPA treated (n=6, MPTP-dyskinetic) macaques. An additional group of normal untreated non-MPTP-lesioned macaques (n=6) was also included.

Results: 5-HT_{1A} binding levels in the external layers of the motor cortex of MPTP-vehicle (168.49±13.55 fmol/mg) and single L-DOPA groups (168.85±11.86 fmol/mg), were significantly reduced (both by 14%, $P<0.05$) compared to normal macaques (195.74±11.99 fmol/mg). In the middle layers of the motor cortex, 5-HT_{1A} binding levels were significantly increased (by 99, 74 and 116% respectively, all $P<0.05$) in MPTP-vehicle (30.50±2.13 fmol/mg), single L-DOPA dose (26.68±3.01 fmol/mg) and chronically treated dyskinetic groups (33.14±5.50 fmol/mg) compared to vehicle-treated macaques (15.32±3.95 fmol/mg). In the matrix of the caudate nucleus, 5-HT_{1A} binding levels were increased (by 219%, $P<0.05$) in dyskinetic macaques compared to single L-DOPA dose macaques (14.88±4.75 vs. 4.66±0.97 fmol/mg).

Conclusions: Our results show that 5-HT_{1A}-mediated neurotransmission is altered in both parkinsonian and dyskinetic states. These data may also provide an anatomical basis to explain why 5-HT_{1A} receptor agonists, if effective at relieving dyskinesia, might also worsen parkinsonism.

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Long-term study on clinical benefits and quality-of-life of intraduodenal levodopa in routine care for a cohort of treatment-naïve patients with advanced Parkinson's disease

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Objective: We report as an interim analysis, the 12-month data of Duodopa treatment-naïve subjects with advanced Parkinson's disease (PD) regarding their functional levels assessed as UPDRS total and sub-scores and disease-specific quality-of-life measured by PDQ-39.

Background: Continuous dopaminergic stimulation (CDS) via intraduodenal application of a levodopa/carbidopa gel (Duodopa) has shown clinical efficacy by reducing 'off'-time and motor fluctuations (Nyholm D et al 2008) and improving quality-of-life (Antonini A et al 2008). It is of great clinical importance to demonstrate that these benefits are achieved not only in strictly selected patients but also in routine care. We present an encouraging long-term treatment effect in PD patients selected for treatment with Duodopa in Sweden and Norway.

Methods: The reported data are taken from an open and observational, prospective 48-month study (12 months recruitment, 36 months treatment) on health outcomes and cost impact of Duodopa treatment in subjects with advanced PD. Of 75 such subjects, 27 were Duodopa naïve at start. All 27 fulfilled the SPC criteria for changing from conventional PD medication to treatment with Duodopa. UPDRS was the primary efficacy parameter for measuring disease progression. PDQ-39 was used to assess the health-related quality-of-life experienced by the subjects. The Duodopa naïve subjects were assessed by UPDRS and PDQ-39 at baseline and then once every 3 months during the first 12 months.

Results: Primary results from the 12-month interim efficacy analysis show significant and sustainable decreases from baseline in UPDRS total score in the Duodopa naïve treatment group. Furthermore, these effects were seen soon after treatment began. PDQ-39 also showed marked efficacy, which was significant at the first three quarterly assessments, but not at the 12-month evaluation.

Conclusions: Our results support the feasibility of CDS by Duodopa with a direct and sustainable benefit on functionality and quality-of-life.

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Can inhibition of fatty acid amide hydrolase (FAAH) provide a useful approach to reduce impulse control disorder and dopamine dysregulation syndrome in Parkinson's disease?

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Objective: To examine the role of FAAH, a key enzyme responsible for endocannabinoid catabolism, in modulating L-DOPA-mediated hyperactivity, a correlate of psychomotor pathologies including impulse control disorder (ICD) and dopamine dysregulation syndrome (DDS), in parkinsonian primates.

Background: Dopaminergic therapies for Parkinson's disease (PD) are associated with motor and non-motor complications, the latter including psychosis, ICD and DDS. Non-dopaminergic neurotransmitter systems, including the endocannabinoid system may contribute to the mechanisms underlying such complications.

Methods: Pharmacodynamic effects of orally administered vehicle or the selective FAAH inhibitor, URB597 (3-60 mg/kg), on plasma levels of fatty acid amides were assessed in MPTP-lesioned marmosets via LC-MS/MS. The effects of URB597 (10 mg/kg, *p.o.*) on L-DOPA-induced hyperactivity, reversal of parkinsonian disability, dyskinesia and psychosis were then assessed.

Results: URB597 (3, 10, 30, or 60 mg/kg, *p.o.*) increased plasma levels of the FAAH substrates N-arachidonoyl-ethanolamide (AEA, anandamide), N-oleoyl-ethanolamide (OEA) and N-palmitoyl-ethanolamide (PEA) by 10.3±0.3, 7.8±0.2 and 1.8±0.1 fold (mean of URB597 groups±SEM), respectively *cf.* vehicle (all $p<0.001$). L-DOPA (20 mg/kg, *s.c.*) alleviated parkinsonism but elicited dyskinesia, psychosis-like behaviours and hyperactivity, a correlate of ICD and DDS in human PD patients. Treatment with URB597 (10 mg/kg, *p.o.*) did not modify the anti-parkinsonian actions of L-DOPA, L-DOPA-induced dyskinesia or psychosis. However, URB597 reduced L-DOPA-induced hyperactivity to levels equivalent to those seen in normal, non-MPTP-lesioned animals. Specifically, URB597 reduced total L-DOPA-induced activity, as well as magnitude and duration of hyperactivity by 32%, 48% and 52%, respectively, to levels equivalent to those seen in normal animals. URB597 did not alter plasma L-DOPA levels and was devoid of behavioural effect when administered alone.

Conclusions: Inhibition of FAAH may represent a therapeutic approach to reducing L-DOPA-induced side effects such as ICD and DDS, while maintaining the anti-parkinsonian benefits of L-DOPA treatment.

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Neurorestorative efficacy of PYM50028 (Cogane™) in rodent and primate models of Parkinson's disease: Translation to dosing in humans

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Objective: To assess plasma and brain levels of PYM50028 associated with neurorestoration in animal models of Parkinson's disease (PD) and to determine how to achieve equivalent plasma levels in humans.

Background: PYM50028 (Cogane™) elevates central glial- and brain-derived neurotrophic factors (GDNF and BDNF) and restores MPTP-induced dopaminergic losses in mice and motor function in primates.

Methods: MPTP-lesioned mice were administered PYM50028 (10 mg/kg/day *p.o.*) for 60 days. PYM50028 levels in plasma and brain, and the extent of the dopaminergic lesion were assessed. Seven stable MPTP-lesioned macaques were administered PYM50028 (20 mg/kg/day *p.o.*) for 18 weeks. Plasma and brain levels of PYM50028 and parkinsonism were assessed.Twelve healthy volunteers (HV) and six PD patients were administered PYM50028 (150, 450 and 150 mg/day, *p.o.,* respectively n=6/group) for 28 days and plasma levels assessed. A compartmental pharmacokinetic model was used to predict C_{max} at steady state for different doses.

Results: In MPTP mice, PYM50028 (10 mg/kg) produced plasma and brain levels of 439±23 ng/ml and 3894±179 ng/g and restored dopaminergic parameters. In MPTP macaques PYM50028 (20 mg/kg) produced a plasma C_{max} and $AUC_{0\text{-}24h}$ of 400±40 ng/ml and 6790±633 ng.h/ml and a brain level of 4260±417 ng/g and significantly reduced the median parkinsonian disability by 43%. In PD patients PYM50028 (150 mg) was well tolerated and produced a plasma C_{max} and $AUC_{0\text{-}24h}$ of 546±135 ng/ml and 6182±1319 ng.h/ml, which was similar to HVs (587±47 ng/ml and 6487±616 ng.h/ml). Exposure to PYM50028 increased dose proportionally. Modelling predicts that a plasma C_{max} of ~400 ng/ml would be reached with a dose of 125 mg. Plasma half life and plasma protein binding levels of PYM50028 are similar in animals and humans.

Conclusions: Neurorestorative efficacy of PYM50028 is associated with plasma levels >400 ng/ml. In PD patients, this level is surpassed by oral dosing of 150 mg PYM50028 and is predicted to be reached with ~125 mg oral dose.

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Improvement of fast tapping movements under rasagiline in Parkinson's disease–indication of a non-dopaminergic effect

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Objective: We analyzed whether adding rasagiline to dopaminergic treatment in parkinsonian patients (PD) could improve fast tapping movements (FTM).

Background: In a recent study we showed that FTM are impaired already in 411 de-novo PD, without benefit, however, from dopaminergic therapy alone under optimized conditions over 4 years. In addition, from all clinical ratings, only gait correlated significantly with tapping results [Kraus PH et al. (2005) Analysis of the course of Parkinson's disease under dopaminergic therapy: performance of "fast tapping" is not a suitable parameter. Mov Disord 20:348-354].

Methods: We used a fast single-handed stylus tapping task to control changes in motor performance. In addition, patients' clinical states were rated with the Short Parkinson Rating Scale (SPES). Our investigator initiated open prospective study was a multicenter study with observational follow up. During the first visit, after acquisition of all data, rasagiline therapy was started with commercially available medication at 1 mg per day. Visit 2 followed 6 to 8 weeks later with identical examinations. We included 24 PD patients with at least 4 weeks' constant dopaminergic therapy prior to the start of the study. None of the patients had MAO-inhibitor therapy before.

Results: We found a significant (p=0.0117) and relevant (effect size=0.474) improvement of FTM of the initially more affected hand when adding rasagiline to the dopaminergic treatment.

Conclusions: Since FTM impairment in PD does not improve even under long-term dopaminergic therapy the present significant improvement of FTM we found under rasagiline is evidence to postulate a non-dopaminergic effect of rasagiline. On the basis of our findings, we believe that FTM as a very simple tapping test could be used as an indicator of the scope for this non-dopaminergic effect on locomotion.

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Dynein dysfunction and autophagic stress in cell injury: Implications for Parkinson's disease

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Objective: To investigate whether dynein dysfunction impaired the formation of aggresomes, fusion of autophagosome-lysosome and caused aggregation of α-synuclein in vivo and vitro, leading to autophagic stress and finally neurodeneration.

Background: Autophagy is a highly regulated process involved in bulk degradation of cytoplasmic organelles and long-lived proteins in lysosomes. However, recent evidence suggests that autophagic stress induced by pathologic alterations in autophagy-related pathways contributes to autophagic cell death and neurodegeneration with the significant accumulation of autophagosomes and autolysosomes, which have been described in Parkinson's disease and other neurodenerative diseases.

Methods: pDsRed2-N1-dynein plasmid and RNAi-mediated knockdown of dynein was used to determine the role of dynein in degradation of α-synuclein; The expression of α-synuclein, microtubule-associated protein light chain 3(LC3), lysosomal-associated membrane protein 1 (lamp1) and dynein were detected through western blot and their co-localization by immunofluorescence microscopy. SD rats were treated with neurotoxin rotenone to observe the alterations of dynein, α-synuclein and the formation of autophagosome.

Results: After treated with MPP^+ for 24h, α-synuclein ($P<0.01$)and LC3-II proteins ($P<0.05$)were increased in PC12 cells, while dynein was decreased ($P<0.01$). The immunofluorescent signals for α-synuclein, LC3-II and their co-localization increased in MPP^+-treated cells, on the contrary, it was decreased for aggresomes, and also the co-localization of dynein and Lamp1 with α-synuclein and LC3-II respectively. Besides, aggregation of α-synuclein occured after RNAi-dyenin, but α-synuclein ($P<0.001$) reduced when induced autophagy by overexpression of dyenin. In the meantime, we detected significantly decreased dynein, and aggregated α-synuclein and accumulated autophagosomes in rotenone-induced rat models.

Conclusions: These data demonstrated that dysfunction of dynein impaired the aggresome formation, fusion of autophagosome-lysosome and α-synuclein degradation, and finally caused autophagic stress and neurodegeneration with accumulated α-synuclein and autophagosomes. So more attentions should be attached to upregulate dynein for clearance of α-synuclein, implicating its protective role in Parkinson's disease.

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Systemic L-DOPA deplete the striatal serotonin release in rats with nigro-striatal dopaminergic denervation

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Objective: To investigate the striatal serotonin release derived from L-DOPA systemically administered to rats with nigro-striatal dopaminergic denervation.

Background: In the nigro-striatal dopaminergic denervated striatum, the raphe-striatal serotonergic neurons can convert exogenous L-DOPA into dopamine with intrinsic aromatic L-amino acid decarboxylase in rats, which is released from the striatal serotonergic terminals and can contribute to the dopaminergic neurotransmission. However, little is known concerning the effects of systemic L-DOPA on the striatal serotonin release.

Methods: Male Splague-Dawley rats (250 g) were used. The nigro-striatal dopaminergic denervation was induced by 8 μg/4 μl 6-hydroxydopamine into the right medial forebrain bundle and was confirmed by 0.05 mg/kg of apomorphine. L-DOPA was intraperitoneally injected to the intact or the dopaminergic denervated rats 30 minutes after 30 mg/kg of benserazide. L-DOPA doses were arranged to 50, 100 and 200 mg/kg. The striatal dopamine and serotonin release were quantitatively measured per 5 minutes in freely-moving rats using with in vivo microdialysis method coupled to high performance liquid chromatography. Serotonin immuno-staining was also performed in dopaminergic denervated rats with 200 mg/kg of L-DOPA. Brains fixed with 4% paraformaldehyde were cut on a cryostat into 30 μm sections, which were immuno-stained with anti-serotonin antibody. The immuno-positive area was measured and compared between the intact and lesioned side of the striatum.

Results: Basal releases (mean±SEM fmol/sample) of dopamine and serotonin were 23.60±1.81 and 0.83±0.02 in the intact rats, and were 2.93±0.37 and 1.07±0.05 in the dopaminergic denervated rats. Serotonin release decreased to 60% after L-DOPA in both rats. In 200 mg/kg of L-DOPA, the striatal serotonin release transiently increased to 150% in the intact rats and 130% in the dopaminergic denervated rats, and then decreased to 60%. Immunohistochemistry showed a decrease of serotonin immuno-positive area after L-DOPA in the dopaminergic denervated striatum, which was comparable to an increase of immuno-positive area induced by serotonergic hyperinnervation.

Conclusions: Our results suggests that the raphe-striatal serotonergic neurons can compensate for dopamine release when exogenous L-DOPA is systemically administered in rats.

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Efficacy of amantadine for freezing of gait in Parkinson's disease

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Objective: To explore efficacy of amantadine for the treatment of Freezing Of Gait (FOG) in patients with Parkinson's disease (PD).

Background: FOG is one of the most debilitating symptoms of PD. FOG is associated with high risk of falls and morbidity. FOG frequently does not respond to dopaminergic therapy or deep brain stimulation. Treatment choices are limited to physical therapy which does not provide long term benefit. The mechanism of FOG is not well understood but it is believed to be largely driven by non-dopaminergic deficits explaining resistance to standard PD medications. Amantadine is one of PD medications used predominantly for management of tremor and drug-induced dyskinesia. Mechanism of action of amantadine in PD is attributed to dopamine uptake inhibition and NMDA antagonist properties. There is limited clinical observation that this drug may be effective for FOG but no controlled studies have been published up to date.

Methods: A retrospective chart review study was conducted. We identified patients diagnosed with PD and other parkinsonian gait disorders at the Northwestern University Movement Disorders Center who were prescribed amantadine specifically for gait disorder. Response to treatment was graded as worse, no change, or improvement as judged by the patient report.

Results: We identified 13 patients (mean age 70.5 +/- 7.2 years, disease duration 4.4 +/- 2.8 years, H&Y stage 2.7 +/- 0.8) who were prescribed amantadine for gait disorder and had a follow up encounter. Eleven patients had PD and two had primary Freezing Of Gait. Median dose of amantadine was 100 mg twice daily. Treatment effect was assessed on average 3 months after initiation of amantadine. Twelve patients reported improvement in gait, and one patient reported worsening of gait. Average duration of follow up was 19 months. Four patients reported wearing off of amantadine benefit within 6 (range 2-9) months. Amantadine was discontinued in four patients due to adverse events.

Conclusions: Based on the results of this open label retrospective pilot data amantadine may be useful for management of FOG. Limitations of such study design are well recognized. Further investigation in a double blind placebo controlled study with well defined outcome measures is warranted.

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Trehalose ameliorates dopaminergic and tau pathology in parkin deleted/tau overexpressing mice through autophagy activation

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Objective: To study if 1 % trehalose in the drinking water could revert the phenotype of a mouse model of tauopathy with parkinsonism.

Background: We had developed and characterized a mouse model of tauopathy with parkinsonism, over-expressing human mutated tau protein with deletion of parkin gene (PK−/−/TauVLW). These mice present abnormal dopamine-related behavior, severe drop out of dopamine neurons in the ventral midbrain, lower dopamine levels in the striatum and abundant phosphorylated tau positive neuritic plaques, neuro-fibrillary tangles, astrogliosis, and plaques of murine b-amyloid in the hippocampus (Menendez J et al 2006; Rodriguez-Navarro et al 2008). Trehalose is a natural disaccharide that inhibits

amyloid formation, alleviate polyQ-induced pathology in a mouse model of Huntington's disease and stimulates autophagy.

Methods: We added 1 % trehalose in the drinking water of PK−/−/TauVLW mice for 2.5 months and studied dopaminergic and tau pathology.

Results: The number of dopamine neurons in the ventral midbrain and the dopamine related protein levels in the midbrain and striatum are elevated after 2.5 months of trehalose treatment. The number of phosphorylated tau positive neuritic plaques and the levels of phosphorylated tau are decreased, as well as astrogliosis in the different brain regions. The levels of autophagy markers in the brain and also in the autophagic vacuoles isolated from liver indicate that these effects of trehalose are mediated by autophagy induction.

Conclusions: Trehalose is protective in a mouse model of tauopathies and parkinsonism. It is safe at high concentration and during 2.5 month treatment and could be used in clinical trials for Parkinson's disease and tauopathies.

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Trehalose induces autophagy and protects from epoxomicin-induced neurotoxic effects in human neuroblastoma cells

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Objective: To investigated the effect of trehalose in NB69 cells, treated with epoxomicin, a proteasome inhibitor.

Background: Trehalose, a disaccharide present in many non-mammalian species, protects cells against environmental stress.

Results: Here we report that trehalose induces autophagy and protects from the epoxomicin-induced neurotoxic effects in NB69 human neuroblastoma cells. Trehalose has a dose- and time-dependent effect increasing the autophagy-lysosomal pathway in NB69 cells. In addition, trehalose (50 mM x 24 h) protects from increased polyubiquitinated, α-synuclein and p-tau proteins levels induced by epoxomicin (10 nM x 24 h). Furthermore, trehalose reversed the epoxomicin inhibitory effects on the autophagy system and increases the proteasome activities.

Conclusions: Trehalose may be a promising neuroprotector for Parkinson's disease.

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Effects of amyloid (1-42)-ß peptide on cortical cultures from parkin null mice

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Objective: To examined the effects of amyloid (1-42)-ß peptide (Aß1-42) on the survival, cell types and signalling pathways affected on cortical mixed neuron-glia and glial cultures from WT and PK-KO mice.

Background: Parkin mutations accont for the most frequent and best characterized cause of Parkinson's disease (PD) in humans. PD is a multifactorial disease which has been often related to oxidative stress. Suppression of parkin in mice produces dopamine cell death attributed to abnormally high free radical production mediated by an enhanced, mono amino oxidase related, intracellular metabolism of dopamine. The production and aggregation of amyloid b peptides has been linked to the development and progression of Alzheimer's disease.

Methods: We used cortical mixed neuron-glia and glial cultures from WT and PK-KO mice.

Results: The results shown that the treatment of glial cells with Aß1-42 at 4.4 μM for 48 h induced significant cell death by necrosis (trypan blue) and apoptosis (TUNEL). PK-KO glial cells were more resistant than WT to both mechanisms of cell death. Our study shown that the total number of cells was reduced in WT as well as the number of astrocytes, expressed as the area of $GFAP^+$ cells. However, the percentage of microglial cells was more significantly increased in Aß1-42-treated PK-KO cultures than in WT. The study, by Western blot, of the temporal profile of activation of ERK 1/2 and AKT proteins at 10, 30, and 90 min of treatment with Aß1-42, revealed that PK-KO glial cells had a higher increase of phosphoproteins after 10 min than WT cultures. The results obtained in mixed neuron-glia cultures also shown that PK-KO cultures were more resistant to the Aß1-42 treatment. The percentage of microglial cells was more significantly increased in Aß1-42-treated PK-KO cultures than in WT, however, the incubation of the mixed cultures with Aß1-42 (4.4 μM) for 48 h increased the area of $GFAP^+$ cells, more in WT than PK-KO neuron-glia cultures.

Conclusions: Neuronal ang glial PK-KO cultures are more resistant to Aß-induced toxicity than WT cultures.

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Evolution of the "short duration" response to L-DOPA in the MPTP-lesioned non-human primate model of Parkinson's disease

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Objective: To determine the effects of priming with L-DOPA on its short duration response in MPTP-parkinsonism.

Background: Long-term treatment of PD with dopaminergic drugs is associated with changes in the anti-parkinsonian response to L-DOPA, like wearing-off and dyskinesia. Though the evolution of the response to L-DOPA has been studied in humans, the contribution of disease progression and the chronic use of L-dopa to these motor complications is difficult to discriminate.

Methods: Parkinsonism was induced in six *cynomolgus* monkeys by treatment with MPTP. After stabilisation of parkinsonism, animals were submitted to acute challenges of L-DOPA methyl ester/benserazide, 4:1, s.c. (15, 25, 30, 40, 60 mg/kg) and vehicle. 6 hour video recordings of the behaviour were performed (pre-priming). Parkinsonian disability and dyskinesia were assessed blindly with validated rating scales. Animals were then treated with L-DOPA (as Madopar) 25 mg/kg p.o twice daily for 3 months, resulting in stable dyskinesia (after-priming), after which received the same acute L-DOPA challenges as per pre-priming. Non-parametric methods were used to compare the effect of L-DOPA dose on the anti-parkinsonian effect (time to ON-state, threshold to switch-ON, duration of ON-state) and dyskinesia (severity, duration, threshold) during pre-priming and after-priming phases (Friedman test and *post hoc* Dunn test) and between priming phases for each dose of L-dopa (Wilcoxon matched pairs test).

Results: The median threshold to switch-ON was 25 mg/kg in both pre- and after-priming phases. After-priming, time to ON-state decreased for the median threshold dose (197 vs 9 mins; $p=0.13$). The median threshold for dyskinesia decreased from 25 mg/kg to 15 mg/kg with priming. An increase in the duration of disabling peak-dose dyskinesia was found (9.1% to 68.8 % of ON-time) though only significant for disabling dyskinesia (L-DOPA 60 mg/kg, 5.4 % vs 30.2% of total peak-dose dyskinesia, $p=0{,}031$). There was no change in maximum dyskinesia severity with priming.

Conclusions: The repeated use of L-DOPA is associated with specific changes in the acute response to L-dopa independent of the progressive dopaminergic neuron loss. The reduction in threshold underlying the sensitization of the dyskinetic response suggests a contribution of pharmacodynamic factors.

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Pulsatile and continuous infusion of L-dopa induce abnormal involuntary movements in 6-OHDA-lesioned rats

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Objective: To compare the ability of pulsatile L-Dopa/carbidopa (ip) administration or daily infusion of L-Dopa/carbidopa (id) to

induce abnormal involuntary movements (AIMs) in 6-OHDA-lesioned rats and the effect of these treatments on the expression of established AIMs.

Background: Pulsatile plasma levels of L-Dopa characterise the oral therapy of Parkinson's disease and are linked to dyskinesia induction. By contrast, continuous intra-duodenal (id) delivery of L-dopa/carbidopa (Duodopa®) gradually decreases the intensity of established dyskinesia in advanced Parkinson's disease. It is not known, however, whether Duodopa® would prevent dyskinesia induction in early Parkinson's disease.

Methods: Male 6-OHDA-lesioned Wistar rats with duodenal and jugular vein cannulae were initially treated (Phase 1) with L-Dopa/carbidopa (7.85/12.5mg/kg ip b.i.d), L-Dopa/carbidopa (20/5mg/ml; infusion rate: 0.04ml/h) or vehicle (ip or id) for 14 days.Treatments were then switched (Phase 2) from pulsatile to continuous or from continuous to pulsatile and administered for another 14 days. AIMs were assessed twice weekly. Serial blood samples were taken once a week and plasma analysed for L-dopa and 3-OMD content by HPLC-ECD.

Results: In Phase 1, pulsatile L-Dopa/carbidopa treatment induced moderate to severe AIMs for up to 3h after each injection with severity gradually increasing over the 14 days. After 4 days of L-Dopa/carbidopa infusion, peak AIMs was of similar severity to that produced by pulsatile L-Dopa/carbidopa treatment. In Phase 2, switching from continuous to pulsatile L-Dopa/carbidopa resulted in severe AIMs expression as occurred in Phase I. Switching from pulsatile to continuous L-Dopa/carbidopa administration did not alter the severity of AIMs but reduced the duration over the 14 days. Plasma levels of L-Dopa and 3-OMD did not differ between treatments over the two phases.

Conclusions: In conclusion, these data suggest that treatment with continuous duodenal L-Dopa infusions in early PD may not reduce the risk of developing dyskinesia, but will reduce the duration of established dyskinesia in later stage patients previously treated with pulsatile oral L-dopa.

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Does L-dopa have toxic effects in Parkinson's disease brain?

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Objective: To examine the relationship of cumulative life-time doses of L-dopa with 1) the nigral dopaminergic cell count and 2) the regional distribution and extent of aS pathology in a post mortem Parkinson's disease (PD) cohort.

Background: Several *in vitro* studies have proposed that L-dopa may exert a toxic effect on dopaminergic neurons and modulate the aggregation process of a-synuclein (aS) but applicability of these data to the patients with PD is debatable.

Methods: Eligible cases (n=96) with well-documented clinical reports on pharmacological treatments were identified from the archives of Queen Square Brain Bank. The density (neurons/mm^2) of pigmented neurons was measured unilaterally in a single section of substantia nigra (SN) at the level of the IIIrd cranial nerve. Semi-quantitative assessment of aS pathology was carried out as recommended by Braak PD staging and Dementia with Lewy bodies consensus criteria. Cortical Lewy body (LB) densities were also determined using a morphometric approach.

Results: The mean cumulative life time dose of L-dopa was 3.4±3.4kg (ranging from 0-21.2kg). Significant negative correlation was found between the L-dopa and the neuronal density in SN. Results from the multivariate model show that yearly average dose of L-dopa remained significantly associated with the rate of neuronal loss in SN after adjustments for gender, age at onset and age at death. Regarding the distribution of aS pathology, we found no difference in the life-time cumulative dose of L-dopa between the Braak PD stages. No relationship was detected between the L-dopa and cortical LB load, whereas there was a significant negative correlation between L-dopa and number of LBs in SN and in locus coeruleus.

Conclusions: Our results suggest an association between increasing cumulative life-time dose of L-dopa and decreasing neuron density in SN, but we cannot be certain whether this is independent of disease duration. Future action is to try to divide our cases into two groups (low vs. high dose of L-dopa) matched for duration and examine the SN neuronal densities in these subgroups. However, life-time cumulative dose of L-dopa was not associated with increased distribution of aS pathology or load of cortical LBs, and the negative correlation found in SN and LC could be a reflection of neuronal loss.

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Prevalence and factors related to impulse-control disorders in Parkinson's disease patients

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Objective: To assess the prevalence of ICD in a sample of PD patients and factors related to their occurrence.

Background: Impulse-control disorders (ICD) have been recently described as an adverse drug reaction in Parkinson's disease (PD). They have been linked to dopamine agonists, younger age, younger age at disease onset and cognitive factors.

Methods: Non-demented, non-operated PD out-patients were recruited at the Toulouse Movement Disorder Clinic. Subjects were systematically questioned about compulsive behaviors related to punding (i.e. an intense inappropriate and unproductive fascination for common objects with repetitive meaningless movements), hypersexuality (i.e. a preoccupation with sexual feelings and thoughts, nymphomania or satyriasis), compulsive shopping (i.e. poorly controlled preoccupations or behaviours regarding shopping), pathological gambling (PG: a failure to resist gambling impulses despite severe consequences) or binge eating (BE: eating an amount of food that is definitely larger than most people would eat or a lack of control over eating). Full medical history and UPDRS were performed.

Results: 98 subjects were recruited (mean age was 67±10 years; 61% were males; UPDRS II and III in ON-state were 13±7 and 24±9; 7% were on antimuscarinics, 10% on MAOb-I, 15% on amantadine, 21% on COMT-I 80% on agonists or 90% on levodopa) Twenty-seven subjects (28%) had at least one ICD (punding: 6%, hypersexuality: 9%, PG: 2%, comp.shopping: 7%, BE: 15%). Subjects with an ICD were younger (61±1 vs 69±1 years, $p<0.001$), younger at disease onset (52±2 vs 59±1, $p<0.001$), were more frequently on agonists (96% vs 75%, $p<0.003$), had higher levodopa equivalent dose (1380±133 vs 1017±81, $p<0.05$) and higher IMAOb frequency (22% vs 7%, $p<0.04$). A logistic regression analysis disclosed that age > 69 years was the only significant factor related to ICD (Odds Ratio, IC95%: 0.3, 0.1-0.7, $p<0.01$). Agonists administration (pramipexole in particular) showed an almost significant relationship to ICD (OR: 7.2, 0.9-59.3, $p=0.066$).

Conclusions: Prevalence of ICD in our sample was high. Age was the only significant independent factor related to ICD. Agonist administration may also be related to ICD, but a larger sample size is needed to further explore this issue.

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Adverse drug reactions to dopaminergic agonists: A study in the French pharmacovigilance database

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Objective: To compare the frequency of ADR reports between the different DA.

Background: Dopamine agonists (DA) are mainly used in Parkinson's disease, (apomorphine, bromocriptine, lisuride, pergolide, piribedil, pramipexole, ropinirole) but also in hyperprolactinemia (bro-

mocriptine, cabergoline, lisuride, quinagolide) or Restless Leg Syndrome (pramipexole or ropinirole). Differences in pharmacokinetics and in affinities to dopamine alpha or serotonin receptors, could suggest possible differences in their adverse drug reactions (ADRs) profile.

Methods: We used the French Pharmacovigilance Database to select ADRs reports from 1st January 1984 to 31st December 2008, in which at least one DA was suspected. The numbers of specific ADRs were compared between the different DA. Odds Ratios (OR) with their 99.3% confidence interval (to compensate for alpha-error inflation) were calculated for each ADR using ropinirole as reference.

Results: 2189 suspected reports were analyzed (bromocriptine: 39%, piribedil: 28%, ropinirole: 13%, other: 20%). Diurnal somnolence was less frequently reported with all DA as compared to ropinirole (6% vs 23%, $p<0.001$). Impulse Control Disorders were more frequently reported with pramipexole [OR=6.20 (1.61-23.86)]. Although a significant difference could be noticed among DA in the frequency of confusion or disorientation ($p<0.001$), nausea and vomiting ($p<0.05$) or edemas ($p<0.001$), no single comparison yielded significant differences with ropinirole. No difference among DA was observed in the frequency of hallucination or arterial hypotension ADR reports ($p=0.3$ and $p=0.1$ respectively). Cardiac valvulopathy was significantly more frequently reported with pergolide as compared to ropinirole (45% vs 5%, $p<0.001$).

Conclusions: Our data show significant differences in the kind of ADR reported for each DA. Pergolide appeared as the leading cause of cardiac disorders, while ropinirole was associated with the highest frequency of diurnal somnolence reports and pramipexole with more frequent neuropsychiatric ADR reports, including impulse control disorders.

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Improvement of Parkinson's disease symptoms with zolpidem

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Objective: It is said that drugs enhancing the GABAergic transmission may improve parkinsonian symptoms. We present 3 patients (p) with Parkinson's disease (PD) that showed a significant improvement of motor and non motor symptoms with zolpidem (ZP), an imidazopyridine short-acting hypnotic drug used to treat insomnia.

Background: The highest density of ZP-binding sites is in the output structures of the basal ganglia: the ventral globus pallidus and the substantia nigra pars reticulata. For this reason ZP may induce selective inhibition of GABAergic inhibitory neurons in this level. This mechanism could activate both, the thalamus with the supplementary motor area, and the pedunculopontine nucleus with the reticulospinal and vestibulospinal pathways.

Methods: Case 1: 50 y/o man, disease duration: 3 years, HY: 3. He has wearing off (WO) and dyskinesias (DK). Foot dystonia and severe lower limbs pain in off. Case 2: 76 y/o man, disease duration: 12 years, HY: 3. He has WO, and a severe off state with akinesia, foot and oromandibular dystonia and lower limbs pain. Case 3: 61 y/o woman, disease duration: 8 years, HY: 3. She has WO and DK. Severe trunk and cervical dystonia associated with lower limbs pain in off state. The UPDRS III was performed before and after an oral dose of 7.5 mg of ZP.

Results: Motors symptoms significantly improved and dystonia disappeared in all 3 p. Other symptoms such as pain and dysphagia also improved. The total UPDRS III score post ZP decreased approximately 30% or more (similar to L-dopa in 2 p and superior in 1 p). Clinical effects appeared about 15-20 min after ZP administration and lasted about 1-2 h. None of them showed drowsiness.

Conclusions: ZP could be useful in a subpopulation with advanced and fluctuating PD. Adverse effects in these patients seemed to be insignificant in the short term. This drug and possibly other selective Gabaergic agonists may represent another therapeutic approach in patients who have complications with the long-term L-dopa treatment. The duration of the effects and other potential adverse events are still issues to work on.

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Neuroprotective efficacy of mildronate in 6-hydroxydopamine neurotoxicity model in rats

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Objective: The aim of this study was to evaluate the effects of mildronate, an aza-butyrobetaine drug, in 6-hydroxydopamine (6-OHDA) neurotoxicity model, since previously we have found its regulatory effects on mitochondrial functions (Pupure et al., 2008).

Background: Present evidence suggests that inhibition of mitochondrial complex I may be the main cause of sporadic Parkinson's disease (PD) and derangements in complex I cause alpha-synuclein aggregation (Dawson & Dawson, 2003). Besides, oxidative stress contributes to the cascades leading to dopamine cell degeneration in PD (Jenner, 2003). Recently, the novel strategy to protect pathological events in the nigro-striatal system of PD patients by drugs capable of regulating/ improving mitochondrial processes has been put forward (DiMauro & Mancuso, 2007).

Methods: Male Wistar rats received i.p. mildronate (50 mg/kg) or saline (for control animals) for two weeks. Afterwards rats were anesthetized and neurotoxin 6-OHDA was injected into the corpus striatum. Apomorphine (APO, 0.2 mg/kg s.c.) was injected in days 14, 21 and 28 after surgery to evaluate contralateral rotations. 10 micron thick sections from the corpus striatum and the substantia nigra were cut and stained for visualization of tyrosine hydroxylase (TH) positive cells immunohistochemically.

Results: Results show that in rat brain mildronate decreased (by 46%) the rate of APO-induced rotations in comparison to 6-OHDA group. Mildronate completely protected cells against 6-OHDA-induced death in the corpus striatum by increasing (by about 82%, $p<0.0001$) the number of TH-positive cells. Less effect was seen in the substantia nigra, were mildronate had a tendency to increase TH expression.

Conclusions: In conclusion, this study shows that mildronate acts as a neuroprotective agent in PD neurotoxicity model probably through its mitochondria-targeted action and may serve as a prototype in the new drug design, which is pointed to the treatment of different mitochondrial pathologies, including PD. Acknowledgements. ESF 1DP/1.1.1.2.0/09/APIA/VIAA/031, L'ORÉAL Latvian "For Women In Science" fellowship.

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Nicotinic alpha4beta2 agonist promotes turning behaviour in 6-hydroxydopamine lesioned rats

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Objective: To investigate whether a small molecule partial agonist of alpha4beta2 nicotinic receptors (nAChR), NS3956 has effect on rotational behaviour in 6-hydroxydopamine (6-OHDA) lesioned rats.

Background: Nicotine has been implicated in Parkinsons disease (PD) as smokers have a lower prevalence for the disease. In animal PD models, nicotine has been shown to exert a neuroprotective effect and to improve motor deficits. In 6-OHDA lesioned rats, nicotine induces turning behaviour by eliciting release of striatal dopamine (DA), presumably via alpha6 and alpha4beta2 nAChRs. We therefore tested a nicotinic alpha4beta2 partial agonist, NS3956 in a rat model of rotational behaviour after 6-OHDA lesion and further studied the effect of the compound on DA-release from striatal homogenates *ex vivo*.

Methods: Female Sprague Dawley rats were unilaterally lesioned with 6-OHDA injected in the medial forebrain bundle (mfb). NS3956 was administered in doses of 0.1-3 mg/kg s.c. Thereafter rotational

behaviour was measured for at least 60 min. NS3956 was administered either alone or in combination with nomifensine (0.3mg/kg s.c.) or mecamylamine (0.75mg/kg i.p.).

Results: NS3956 induced rotations in 6-OHDA-lesioned rats in a dose-dependent manner with a minimal effective dose of 1 mg/kg. When rats were co-treated with the dopamine reuptake inhibitor, nomifensine, a more pronounced effect of NS3956 was observed. Under these conditions a significant increase in turning behaviour was evident at a NS3956-dose of 0.3 mg/kg. The effect of NS3956 was abolished by pretreating the rats with the non competitive nAChR-antagonist mecamylamine. Ex vivo, NS3956 induced DA-release from striatal homogenates.

Conclusions: The data demonstrate that the nAChR alpha4beta2 partial agonist NS3956 induces rotational behaviour in hemi-parkinsonian rats and that this effect is dependent on nAChR receptor function. The minimal effective dose of the compound was lower in the presence of a dopamine reuptake inhibitor which may suggest that NS3956 promote dopamine release. These observations provide support for nicotinic alpha4beta2 receptors as potential therapeutic targets and identify NS3956 as a useful pharmacological tool to study the involvement of nicotinic receptors in animal models related to PD.

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In vivo evaluation of adenosine a_{2A} receptor availability in Parkinson's disease patients with and without levodopa induced dyskinesias studied with [^{11}C]SCH442416 PET

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Objective: To investigate Adenosine$_{2A}$ (A_{2A}) receptor availability in Parkinson's disease (PD) patients with and without Levodopa induced Dyskinesias (LID).

Background: Dopamine replacement with levodopa represents the mainstay of treatment in PD. While providing effective relief from the motor symptoms of PD, levodopa use is associated with development of LID. The A_{2A} receptors are expressed on medium spiny striatal neurons of the indirect pathway and play a role in modulating dopamine transmission. A_{2A} receptor antagonists also have anti-parkinsonian activity boosting levodopa efficacy. The development of LID may be related to changes in the availability of A_{2A} receptors within the striatum of PD patients as they regulate traffic through the indirect pathway. We aimed to study A_{2A} receptor availability in PD patients with and without LID using Positron Emission Tomography (PET) and [^{11}C]SCH442416, a radioligand with nanomolar affinity for A_{2A} receptors.

Methods: Six PD patients with LID and 6 PD patients without LID were studied withdrawn from medication for 12 hours. Patient groups were matched for disability and results compared with three age matched controls. Using spectral analysis, [^{11}C]SCH442416 regional volumes of distribution (Vd) were computed. Striatal and thalamic [^{11}C]SCH442416 binding potentials (BP) reflecting the ratio of specific:non-specific uptake were compared between groups.

Results: The mean striatal BP of PD subjects with LID was significantly higher than that of PD subjects without LID (1.444 ± 0.548 vs 0.709 ± 0.311 $p=0.017$, $t=2.85$). These results were also reflected in striatal subdivisions (caudate $p=0.023$, $t=2.66$ and putamen $p=0.037$, $t=2.42$). Thalamic BP was similar between PD subjects with and without LID (0.135 ± 0.184 vs 0.132 ± 0.137 $p=0.98$, $t=0.03$). The striatal BPs of the three controls lay within the BP range of the PD subjects without LID.

Conclusions: PD patients with LID show increased A_{2A} receptor availability in the striatum. This finding suggests that altered adenosine transmission is associated with the occurrence of LID in PD. It provides a rationale for the development and use of A_{2A} receptor antagonists in the treatment of these motor complications on patients with PD.

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Abdominal pain–a wearing off symptom in Parkinson's disease

A.Q. Rana (Toronto, Ontario, Canada)

Objective: To report abdominal pain as a symptom of levodopa wearing off in Parkinson's disease.

Background: Levodopa induced end of dose wearing off symptoms are extremely diverse and may include psychological, emotional, autonomic, sensory and motor abnormalities. Abdominal pain has also been reported as a wearing off symptom. History taking and establishing a clear relationship of abdominal pain with the dosage of levodopa becomes critical in these patients. We describe two PD patients on levodopa who developed acute abdominal pain as a manifestation of end of dose wearing off.

Methods: Mr. N.V. was a 61-year-old male with PD who was on levodopa/carbidopa 100/25 mg three times daily for about four years when he began to experience end of dose wearing off about one and half hour prior to each scheduled dose of levodopa/carbidopa. He would suffer severe abdominal pain in the wearing off period. His abdominal pain would improve on taking levodopa. Mr. K.W. was a 71-year-old male with PD, who was on levodopa 200/50 four times daily and entacapone. He began to experience abdominal pain 3 AM, six hours after taking his last scheduled dose of levodopa/carbidopa, as his evening dose of levodopa /carbidopa wore off. The abdominal pain would continue till 5 AM when he would take his next dose of levodopa resulting in complete relief of abdominal pain. His neurologist determined that this was due to a wearing off effect of evening dose of levodopa.

Results: The first patient was seen in the emergency department few times, and no cause of his abdominal pain could be found. CT scan of abdomen, MRI spine, and chest X-ray were normal. Analgesics and spasmolytics were ineffective in addressing his abdominal discomfort. The adjustment of dosing schedule of levodopa in both patients ameliorated abdominal pain.

Conclusions: Abdominal pain may be a levodopa induced wearing off symptom in PD patients and careful history taking may help avoiding the other invasive investigation.

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Dopamine agonist induced compulsive eating in diabetic patient with Parkinson's disease

A.Q. Rana (Toronto, Ontario, Canada)

Objective: To discuss the importance of screening for dopamine agonist induced compulsive eating in diabetic patient with Parkinson's disease with a case report.

Background: Dopamine agonists used in Parkinson's disease may cause impulse control disorders in about five percent of the patients. ICD behaviors may include gambling, hypersexuality, hobbyism, compulsive shopping, and complex stereotyped behaviors such as punding. A small percentage of PD patients exhibit food-cravings, compulsive eating, and undesired weight gain in the setting of dopamine agonist therapy. This disorder can be especially harmful in the management of Parkinson's disease patients with diabetes mellitus type II as weight gain and obesity are associated with increased risk for insulin resistance. Here in, we present a diabetic patient who developed a compulsive eating disorder while on the dopamine agonist pramipexole.

Methods: Our patient was a 61-year old male with a history of diabetes mellitus type II, and idiopathic Parkinson's disease. He was on pramipexole for Parkinson's disease when he developed an insatiable craving for food. The patient described how he would eat 8-10 times a day and began binging in the middle of the night. He stated that after starting his drug therapy with pramipexole, it was as if he had lost all self-control and often found himself eating even when he was not hungry.

Results: Pramipexole was discontinued and these abnormal behavioral symptoms resolved completely.

Conclusions: Given the serious medical consequences that have been associated with overweight and obesity in diabetic patients, physicians should particularly inquire about possible compulsive eating behavior in patients on dopamine agonists.

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Do Parkinson's disease patients disclose adverse drug reactions spontaneously?

M.V. Rey, S. Perez-Lloret, N. Fabre, F. Ory, U. Spampinato, J.-L. Montastruc, O. Rascol (Toulouse, France)

Objective: To explore the gap in the frequency of ADRs to antiparkinsonians when explored by means of a full exhaustive questionnaire or by the patients' spontaneous disclosure.

Background: Underreporting of adverse drug reactions (ADRs) is generally >90%. Whether this may be related to physicians' failure to identify ADRs remains unknown. The lack of time during the medical visit may induce physicians to rely only on patients' spontaneous ADRs report and not in a systematic evaluation.

Methods: Non-demented, non-operated Parkinson's disease outpatients of the Toulouse Movement Disorder Clinic were initially asked to disclose any "unpleasant effect in connection with their medication" during the last week. Afterwards, they were systematically questioned about the presence of a predefined list of common ADRs to antiparkinsonians. Only ADRs starting within 6 months after causative agent introduction were further analyzed. ADR severity was assessed by the usual pharmacovigilance scale (mild/moderate/severe). Severity of somnolence or impulse-control disorders was also evaluated by a patient's auto-administered 10-cm VAS scale. A complete medical and medication history was conducted and a full UPDRS was performed.

Results: 98 subjects were recruited (mean age was 67±10 years; 61% were males; UPDRS II and III in ON-state were 13±7 and 24±9; 7% were on antimuscarinics, 10% on MAOB-I, 15% on amantadine, 21% on COMT-I, 80% on agonists or 90% on levodopa). Sixty-nine out of the 98 subjects (70%) had at least one ADR that started a short time after introduction of a causative agent, but only 25 of them (36%) disclosed it spontaneously. This figure was essentially similar for the majority of explored ADRs (for example, hypotension symptoms, dry mouth, colored urine, somnolence, vivid dreams, sleep disorders or impulse-control disorders). Nausea/vomiting was the only ADR reported spontaneously by >75% of the affected patients (7 out of 9 cases). Patients' failure to spontaneously disclose the ADRs was related to shorter disease duration ($p<0.05$) but not to ADRs' severity.

Conclusions: The gap between ADRs identified by the full questionnaire or by spontaneous report was 64%, thus suggesting that a pro-active attitude towards the search of ADRs during the medical visit should be adopted.

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Motor and non motor efficacy of subcutaneous apomorphine infusion in advanced PD compared to Parkinson's patients on conventional therapy. A "real life" study

P. Martinez-Martin, A. Todorova, P. Odin, T. Henriksen, Y. Naidu, S. Tluk, P. Reddy, A. Martin, R. Katzenschlager, A. Antonini, K. Ray Chaudhuri (London, United Kingdom)

Objective: To investigate the effect of Apomorphine infusion as compared to conventional therapy on motor and non motor symptoms (NMS) in patients with PD.

Background: Subcutaneous Apomorphine infusion is the most potent dopamine agonist and we recently reported the beneficial effect of Apomorphine infusion on NMS in PD. We report a real life pragmatic comparative study.

Methods: In some European countries prescribing Apomorphine is dependent on funding approval from recognised bodies and occasionally funding is not approved in spite of suitable patients. These 'Control' patients (C) were followed up using similar clinical protocol (UPDRS 3 and 4), NMS Scale (NMSS) and PD quality of life (PDQ-8) and compared to a group of patients started on Apomorphine infusion (Apo) for identical clinical needs. In C conventional treatment with modifications was continued. To our knowledge this is the first such comparative study.

Results: 17 patients with PD (Apo) (mean age 59.5±11.7 yrs, disease duration 12.05±4 yrs, median HY score 4 (IR:3,4)) were started on Apomorphine infusion and compared to 17 C patients (mean age 66.4±7.0 yrs, disease duration 13.23±4.7 yrs, median HY score 3(IR:3,5)) over a period of 12.5±11.5 months, with assessments of UPDRS, NMSS and PDQ-8 at baseline and follow up at approximately 6 months. There were no significant differences in the baseline characteristics between Apo and C and both were on comparable levodopa and dopamine agonist treatments. During follow up, C showed no change in UPDRS 3, PDQ-8, NMSS and unchanged dyskinesias in spite of modification of oral therapies, Apo showed significant improvements in UPDRS 3, UPDRS 4, PDQ-8, and NMSS total (all, $p=0.001$-0.0003).

Conclusions: This study illustrates the serious drawback for PD patients of non-availability of treatment with Apomorphine infusion and the effect of this therapy on motor and NMS of PD.

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The effect of continuous dopaminergic stimualtion with ropinirole on non-motor symptoms, quality of life and autonomic functions in Parkinson's disease patients

M. Trošt, A. Šubic, T. Steblovnik, M. Kirbiš (Ljubljana, Slovenia)

Objective: To compare effects of standard ropinirole (SR) and prolonged release ropinirole (PRR) on sleep quality, mood, overall quality of life and cardiovascular autonomic function in patients with parkinson's disease (PD).

Background: Non-motor dysfunction in PD has a great effect on patients' quality of life. Patients' disability is influenced by the disease itself and the side effcts of dopaminergic drugs. A treatment concept of continuous dopaminergic stimulation (CDS) was developed to provide a more physiologic dopaminergic replacement with supposedly a beneficial effect on all PD symptoms. PRR is one of the CDS treatments.

Methods: 15 PD patients (mean age 60.5±10.8 y, 10 male, disease duration 8.4±5.3 y, H&Y 2.2±1.1) treated with SR were enrolled. They were evaluated immediately before switching from SR to PRR and again three to six months after switch. At each evaluation they completed three questionnaires about non-motor PD symptoms: Parkinson's disease sleep scale (PDSS), Beck depression inventory (BDI) and Parkinson's disease quality of life questionnaire (PDQ-39). Participants also underwent a 24-hour ambulatory blood pressure (BP) and heart rate (HR) monitoring. In addition, they self-performed orthostatic tests and led a diary of orthostatic symptoms. Results on SR and PRR were compared using paired samples t-test or Wilcoxon singed ranks test, as appropriate.

Results: Questionnaire scores on SR and PRR were: 10.2±1.9 (mean±SE) and 8.1±1.5 ($p=0.049$) for BDI, 50.0±6.5 and 42.0±6.1 ($p=0.032$) for PDQ-39 and 98.8±8.0 and 101.5±2.1 (p=NS) for PDSS. Daytime BP did not change after switch to PRR. We observed borderline significant rise in nighttime PB without a change in nighttime HR. This resulted in less pronounced circadian BP fluctuation and increased number of patients with reversed circadian rhythm. We observed no difference in orthostatic BP changes.

Conclusions: CDS with PRR improves non-motor symptoms and overall quality of life in PD patients compared to SR. While we failed to detect an effect of PRR on daytime BP or on orthostatic tolerance, we observed a trend towards less favourable circadian BP rhythm with PRR. PRR may have an undesirable effect on nighttime activity of the autonomic nervous system.

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Transdermal nicotinotherapy: An ongoing study in patients with advanced Parkinson's disease

F. Grapin, G. Villafane, P. Cesaro, P. Maison, E. Itti (Creteil, France)

Objective: To evaluate efficacy on motor symptoms and safety of transdermal nicotinotherapy in parkinsonian patients.

Background: The use of nicotine in Parkinson's disease (PD) has been suggested due to a low prevalence of smokers among PD patients reported. A previous pilot study demonstrated positive results.

Methods: This is a controlled, randomised, single blind study startedJanuary 2009. The 40 patients are aged between 35 and 70 years old, both gender, diagnosed as suffering from advanced PD, having a maximum score of IV (OFF state, Hoehn and Yahr classification) and L-Dopa responders. Anticholinergics are forbidden, all other symptomatic medications are allowed and L-Dopa may be decreased since week 7. Patients are distributed in 2 parallel groups: Transdermal nicotinotherapy, and no additional therapy to compensate the lack of placebo patches. Treatment is increased step by step during 11 weeks to reach the target dose of 90 mg, or the maximal tolerated dose, that remains stable for 28 weeks. Afterwards nicotine is progressively tapered. Primary efficacy criteria is the improvement of the UPDRS III at week 39, assessed in standardized "OFF", video recorded and evaluated by a blind central review at the end of study. Secondary efficacy criteria are : UPDRS III motor score in "defined ON conditions", improvement of cognition (Mattis Dementia Rating Scale) and PDQ39 scale at week 20 and 50. Potential disease modifying effect is evaluated using the semi quantitative data of ^{123} I-FP-CIT imaging to assess changes of striatal dopaminergic innervation in. Cotinine levels in urine are regularly measured as biomarkers of adherence to treatment. Adverse events are collected throughout the study. In case of adverse event possibly attributed to nicotine, dose is decreased until complete disappearance. Clinical examinations, ECG and vital signs are performed at selection and during follow up visits.

Results: Our main goal is to demonstrate the safety and feasibility of chronic high dose nicotine treatment in advanced Parkinson's disease, and to assess the motor efficacy.

Conclusions: This study could be followed in the future by a double blind, randomized study in 2 parallel groups versus placebo in a larger cohort of patients.

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High-speed dopamine detection in the awake primate brain

K. Yoshimi, M. Inoue, S. Natori, N. Nishikawa, N. Mitani, Y. Einaga, Y. Shimo, N. Hattori, S. Kitazawa (Tokyo, Japan)

Objective: To observe actual phasic dopamine neurotransmission in the monkey striatum.

Background: Dopaminergic neurotransmission of phasic and tonic timescale are studied separately, and the contribution of each type of transmission on movement disorder has not been well understood. Recent voltammetric recordings with carbon-fiber microelectrode have successfully shown involvement of phasic dopamine release in cognitive functions of rodents. Similar high-speed recording of dopamine concentration in the striatum and prefrontal cortex of behaving primates has been awaited.

Methods: We applied novel 5% boron-doped diamond microelectrode (BDD) to secure the physical strength of the probe in the larger brain. To detect a phasic response with a short duration, constant-voltage at 0.6Vwas applied to diamond microelectrode and the electrochemical current was sampled by 25 Hz.

Results: The signal-to noise ratio of measurement with diamond microelectrode was equivalent to that of widely used carbon-fiber microelectrode in the striatum of C57BL/6 mice, during the stimulation of medial-forebrain bundle (MFB). MFB response is enhanced by nomifensine, a dopamine uptake blocker. In the caudate nucleus of awake Japanese monkey (Macaca fuscata), the current increased following deliveries of juice reward. When a prediction cue of flash light was presented 2.0 sec prior to the juice delivery, phasic current response was observed with a latency of about 100 msec.

Conclusions: These results were consistent to reported firing response of midbrain dopamine neurons to reward-prediction signal. Since presynaptic dopamine neurotransmission can be supressed by D2 agonists, it is not clear whether dopamine neurotransmission reflect the firing of midbrain dopamine neurons or not, especially in PD patients under the medication.The method can be applied in the future to evaluate dopamine neurotransmission using primates in intact and parkinsonian conditions.

POSTER SESSION 3

WEDNESDAY, JUNE 16, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

PARKINSON'S DISEASE: QUALITY OF LIFE/CAREGIVER BURDEN

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The effect of therapy in Parkinson's disease

B. Aguiar, R. Aljanati, M. Martinovich, V. Raggio, V. Pomar, R. Buzo, A. Ojeda, N. Gonzalez, G. Nogueira, L. Aguerre, G. Montado, F. Alfonso (Montevideo, Uruguay)

Objective: To evaluate the effectivenness of a interdisciplinary boarding in the Program of Education and Rehabilitation in the Parkinson's disease for patients, relatives and caregivers (PRENPAR).

Background: Although the incidente of voice and speech disorders in PD is high (80%-90%), only a small percentage of these patients receive speech therapy. Improvement in communication is important component of developing the highest levels of independence and quality of life.

Methods: Fifty patients with idiopathic Parkinson's disease (PD) were selected to receive an interdisciplinary boarding in the Program of Education and Rehabilitation in the Parkinson's disease for patients, relatives and caregivers (PRENPAR). Two groups were paired by age and sex. Demographic data, years of treatment, plus quality of life was evaluated with PDQ-39. UPDRS scale was used. Controlled parameters of the voice and the speech were applied in three opportunities, the evolution of the speech is analyzed before and after having carried out an interdisciplinary therapy as well as the scales. They are carried out 3 controls, first to the beginning, the second at the 10 weeks and the third to the 3 months. Between the second and the third control a group of patients receives therapy in an open group, the other group of patients doesn't converge to any therapy. The treatment programme included respiratory exercises and speech therapy, physical and psychological therapy for ten-week periods of intensive treatment.

Results: Results Patients in Group II were younger (63.6 vs 66.3 years,).There were no differences in the duration, the onset, type of the disease and the type of dopaminergic therapy. The TMF in Group I was significantly higher than in Group II (9 seg. Vs 11 seg. at de beginning, $p<0.001$). Each ten-week period of treatment resulted in highly significant ($P<0.001$) improvements of motor performance

and speech. No motor decline was detected over three months, indicating that patients maintained a constant level of functional, as well as quality of life.

Conclusions: Continuous rehabilitation treatments may positively influence the maintenance of functional and motor performance in patients with PD.

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An approach to improve Parkinson's disease (P.D.) quality of life

R.E. Aljanati, M. Martinovic, V. Raggio, B. Aguiar, N. Gonzalez, O.A. Julia, L. Aguerre, G. Montado, V. Pomar, G. Nogueira (Montevideo, Uruguay)

Objective: To report P.D. patients groups clinical findings, after 36 months approach with a new Specific National Program.

Background: Parkinson's disease (PD) is caused by complex genetic, patophysiological and environmental factors interaction. Mental illness symptoms are frequent. Prevalence of PD in Uruguay's population is 1.36/1000; age media is 72 years. Total Uruguay population, 3.3 millions. An interdisciplinary group with appropriate staff started a new national, educational and motor, mental, and social rehabilitation program for caregivers and P.D. patients. Quality life improvement goal was achieved satisfactorily.

Methods: Patients and caregivers program includes: genetic counselling and diagnosis, weekly specialized therapy (physical, psychological and speech therapy, swallowing difficulty management and sialorrhea); monthly group activity where various professionals expose about different areas such as occupational therapy, diet, nutrition and psychosocial interventions. Clinical evaluation and scales are used (Scopa psychosocial, HADS, PDQ 39, UPDRS). The project has worked with 138 patients and 137 relatives of these 58 patients where includded in the semanal program.

Results: Patients benefit from knowledge, information of their resources, group activities where they don't feel alone with their chronic disease. Family members, often primary caregivers, receive adequate support. Patients and caregivers separate groups psychotherapy work --limited time offer-- had very good results. Increase and optimization of their own resources, by identification or confrontation with their own fantasies, fears, from "reciprocal scaffolding" (apuntalamiento recíproco) perspective can be observed.

Conclusions: The Program has proved to be a useful support for PD patients and their families, trying to promote their positive health aspects (adaptative functioning, resilience, supports, and Quality of life).

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Moving towards patient-centered healthcare for patients with Parkinson's disease

M. van der Eijk, M. Munneke, M. Faber, B.R. Bloem (Nijmegen, Netherlands)

Objective: To describe the experiences of Parkinson's disease (PD) patients and informal caregivers concerning received healthcare. These experiences can be used to help health professionals in providing patient-centered care tailored to the specific preferences and needs of each individual PD patient.

Background: According to the Institute of Medicine patient centeredness is one of the most important pillars of quality of care (1). The Picker Institute (www.pickerinstitute.org) and the WHO each appointed prime aspects to subdivide patient-centred care, such as emotional support and freedom of choice (2). Thus far, regarding the treatment of PD little attention has been given to patient centeredness.

Methods: Eight focus groups involving 40 idiopathic PD patients (mean age 64 years, 75% men) and 20 informal caregivers (mean age 65 years, 26% men) were organized to explore the experiences in relation to the patient centeredness of care. The principles of the Picker Institute and the WHO were used as a framework for discussion and qualitative analysis.

Results: Both patients and informal caregivers expressed a desire to be actively involved in clinical decision making, but also identified a current lack of information to do so. Instruments to find specific expertise and provisions to support freedom of choice are missing. PD patients identified the lack of collaboration between healthcare providers as a major bottleneck. Patients and their partners also wanted to be instructed how to cope with the disease in light of their relationship, in order to prevent an overburden of informal caregivers.

Conclusions: Focus group discussions revealed numerous unmet needs among PD patients and their partners. This information will be used to design new patient-centered interventions for PD patients in the Netherlands, and to construct a validated patient centeredness questionnaire. This instrument will give insight in the quality of care from a patient perspective, by asking about actual experiences instead of merely patient satisfaction. **References** 1. Crossing the quality chasm: a new health system for the 21st century. Institute of medicine. 2001 2. Murray C, Evans D. Health System Performance Assessment. Debates, Methods and Empericisms. World Health Organization, Geneva. 2003, 598-602.

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Motor impairment and its impact on quality of life in Parkinson's disease: A Mexican hospital-based study

A. Cervantes-Arriaga, M. Rodríguez-Violante, T. Corona (Mexico City, Mexico)

Objective: To assess and correlate PD motor symptoms and motor fluctuations with quality of life in Mexican PD patients from a tertiary hospital.

Background: Parkinson's disease is a neurodegenerative disease in which the motor symptoms are tremor, rigidity, bradykinesia and postural instability. All of ths this features as well as motor fluctuations have an impact on the patient's quality of life. Hospital-based patientsmay show different features, known as referral bias, in comparison with population-based samples.

Methods: A cross-sectional study was carried out. 139 consecutive PD patients were recruited from the movement disorders outpatient clinic in Mexico City. Motor function was evaluated in the "on" state with UPDRS III. Hoehn and Yahr stage, presence of motor fluctuations and levodopa equivalent daily dose (LEDD) were registered. PDQ-39 was applied to assess quality of life.

Results: 139 patients were studied (56.8% men) with a mean age of 63±11.9 years. Mean age at PD diagnosis of 57.2±12.6 years. 68.3% had tremor as the initial symptom. Mean UPDRS III score was 21.5±12 (range of 2-67), mean Hoehn-Yahr stage was 2.2±0.8. Motor fluctuations were present in 31.2% of the sample while dyskinesia was present in 13.6%. Mean LEDD was 479.9±431.3 mg/day. Mean PDQ-39 simplified index (PDQ-SI) was 32.5±18.8. Score for individual dimensions was as follows: mobility 44.3±29.3, activities of daily living (ADL) 40±28.3, emotional wellbeing 39.3±26.4, social stigma 31.5±31.7, social support 15.2±22.7, cognition 25.5±20.4, communication 26.7±25 and bodily discomfort 39.7±25. A strong correlation was found between UPDRS III and PDQ-mobility ($rs=0.45$, $p=0.001$) and PDQ-ADL ($r=0.46$, $p<0.001$). When analyzing the presence of motor fluctuations a statistically significant difference was found in PDQ-mobility, ADL, cognition and simplified index ($p<0.05$). No associations were found with dyskinesias.

Conclusions: A higher UPDRS III score was associated with a lower quality of life. The PDQ dimension more affected was mobility and in a lesser degree activities of daily living and emotional wellness. Presence of motor fluctuations had a marked impact on quality of life. No correlation was found with the presence of levodopa-induced dyskinesias or with LEDD. Data is similar to population-based studies.

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Speaking range profiles in Argentine patients with Parkinson's disease

M.J. Codino, A. Barmat de Mines, G.A. Albanese (Buenos Aires, Argentina)

Objective: The present study aims to compare speech range profiles (SRP) of subjects with Parkinson's disease (PD) during treatment with control subjects matched in sex and age.

Background: Speech and voice disorders occur in 45% of patients with PD. These are a consequence of the laryngeal, articulatory and respiratory muscle dysfunction. PD speech has been characterized as hypophonic and with hypokinetic dysarthria. SRP displays the interactions between frequency and intensity during functional speech. In the past few years, it has become an alternative procedure for voice screening. Differences in age and sex in these ranges have been established in healthy speakers for several languages. However studies of SRP in patients with PD whose native language is other than English are scarce. One study done with Brazilian PD women revealed they had lower F0 range, and higher intensity than control subjects.

Methods: 13 subjects with PD recruited from the Neurology Department at Dr. Cosme Argerich Hospital, participated in this study. In addition 12 subjects with normal voices served as controls. Voice samples were obtained by recording each subject reading a sentence described in a previous article by Gurlekian et. al (2001), which contains all the phonemes and allophonic forms of Buenos Aires Spanish. The software used was ATR (LIS, CONICET). The analyzed F0 parameters were: Maximum F0, Minimum F0, F0 range (difference between maximum F0 and minimum F0) and Predominant F0 (the one which occurred most often when reading the sentence). Intensity range was also measured, and the area of the phonetogram resulting from the combination of all the frequencies and intensities, too (Vocal field).

Results: Predominant F0, Maximum F0 and Minimum F0 were higher in PD patients than in control subjects. In these PD patients, F0 range was found to be more variable and Intensity range, less variable.

Conclusions: In comparison with controls, in treatment PD patients have higher F0 parameters characterized by variable range of F0, and narrow Intensity range (which likely accounts for the characteristic hypophonia of parkinsonian speech).

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Non-motor symptoms in early Parkinson's disease are the key determinants of health-related quality of life

P. Martinez-Martin, C. Falup-Pecurariu, J.J. van Hilten, P. Odin, A. Antonini, C. Trenkwalder, D. Aarsland, D.J. Brooks, K.R. Chaudhuri (Brasov, Romania)

Objective: To explore the role of non-motor symptoms (NMS) as a predictor of health-related quality of life (HRQoL, Functioning and Psychosocial aspects) in early Parkinson's disease (PD).

Background: There is little information on the impact of NMS on HRQoL in early PD. Assessments are generally dominated by motor impairment. The NMS Scale (NMSS) allows a comprehensive assessment of NMS in real life.

Methods: Consecutive PD patients (UK PD brain bank criteria), across all stages of PD, were recruited from an international collaborative venture. Standard assessments (Hoehn and Yahr [HY], UPDRS/SCOPA-Motor, PDQ-8) were applied with the NMSS as the primary outcome measure. Descriptive statistics, non-parametric and multiple regression analysis were used.

Results: 750 patients were recruited, 58.5% males, mean age 65.9±0.3 years, and duration of PD 7.37±5.6 years. Most (78.9%) were receiving L-Dopa and/or dopamine agonists (59.5%) but 6% were drug-naïve. There were 16.6% patients in HY stage 1 and 36.9% in stage 2. NMS Scale scores for the two HY groups were 34.1±26.5 (range: 1-137) and 47.8±37.3 (range: 1-197) ($p<0.0006$). Only three patients were free of NMS, all of them in stage 2. Motor rating scores were significantly higher for patients in stage 2, as were motor complications (both, $p<0.0001$) and HRQoL ($p=0.001$). Association between NMSS and PDQ-8 scores reached 0.60 ($p<0.0001$). In the multiple regression model, including age, sex, motor impairment and complications, and NMSS scores as independent variables, the most important predictor of HRQoL was NMSS, followed by motor complications ($F=66.0$; adjusted R-squared, 0.47; $p<0.0001$).

Conclusions: Our data indicate that early PD patients have a considerable burden of NMS, a fact that may be frequently overlooked. In addition, this study suggests that NMS independently influence HRQoL, more so than motor impairment and complications and is the most important determinant of HRQoL in early PD.

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A study of the nutritional status of people with idiopathic Parkinson's disease: Comparison of urban and rural community-dwellers

A. Jaafar, B. Porter, W.K. Gray, E.J. Turnbull, R.W. Walker (North Shields, Tyne and Wear, United Kingdom)

Objective: To identify the prevalence, and nature, of under-nutrition in a representative population of people with PD.

Background: PD patients have an increased risk of under-nutrition. We are unaware of any previous population-based prevalence studies of under-nutrition in PD.

Methods: People diagnosed with idiopathic PD from two distinct geographical areas of north-east England, one predominantly urban and one predominantly rural, were asked to participate in this study. Those who participated were assessed using a number of standard assessment tools and rating scales including, the UPDRS, PDQ-39, MMSE, Hospital Anxiety and Depression scale (HAD) and Hoehn & Yahr stage. Body mass index (BMI), mid-arm circumference (MAC), triceps skin fold thickness (TSF), mid-arm muscle circumference (MAMC) and grip strength were recorded together with social and demographic data.

Results: There were 82 (34 male, 48 female) participants from the urban study area and 54 (25 male, 29 female) from the rural area. A BMI <20 identified 19.5% of the urban study group, but only 9.3% of the rural group, to have under-nutrition. In both study areas low BMI was associated with greater age, lower MAC, TSF, MAMC, reduced grip strength and a report of unintentional weight loss. By dichotomising all participants into those with BMI below 20 and those with BMI of 20 and above, female gender, older age and higher UPDRS score emerged as predictors of under-nutrition.

Conclusions: Under-nutrition is a problem for community-dwelling people with PD in both urban and rural areas, although a greater percentage of those in urban areas have under-nutrition. Problems increase with age and disease progression and are greatest in females. All PD patients should be screened for under-nutrition.

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Care requirements of a prevalent population of rural, community-dwelling people with idiopathic Parkinson's disease

R.W. Walker, J. Dunn, W.B. Sweeney, W.K. Gray (North Shields, Tyne and Wear, United Kingdom)

Objective: To establish the care requirements of rural-dwelling people with PD.

Background: We have recently reported on the care requirements of a prevalent population of urban-dwelling people with PD (Porter *et al.,* 2010). Providing care to people with PD living in rural areas can present different challenges when compared with care provision to those living in large towns and cities.

Methods: All people diagnosed with idiopathic PD from within a predominantly rural area of north-east England were asked to participate in this study. Those who agreed to participate were assessed

using a number of standard rating scales including Hoehn & Yahr stage, UPDRS, Hospital Anxiety and Depression Scale, PDQ-39 and MMSE. Social and demographic information (e.g. age, sex, place of abode) was also recorded. Mann-Whitney U test was used to establish significance of differences between those in institutional care and those living in these own homes.

Results: Seventy-eight people (41 males, 37 females) participated in the study. Of these, 10 (12.8%) were living in residential or nursing homes. Those in care were significantly ($p<0.05$) older, and had significantly lower MMSE scores and higher UPDRS scores, poorer patient perceived quality of life and were more depressed than those living in their own homes. The percentage of people with PD living in care homes in this rural study was similar to that found previously in an urban population. There was no significant difference in age, Hoehn and Yahr stage and UPDRS scores between those living in institutional care in rural and urban areas.

Conclusions: Within our study area, living in a more rural area does not appear to be a barrier to care home placement in people with PD. **Reference:** Porter B, Henry SR, Gray WK, Walker, RW. Care requirements of a prevalent population of people with idiopathic Parkinson's disease. Age Ageing 2010;39(1):57-61.

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Is motor phenotype important in predicting health status in Parkinson's disease?

C. Hinnell, C. Hurt, R. Brown, S. Landau, M. Samuel (London, United Kingdom)

Objective: To explore the relationship between motor phenotype and health status (HS) in Parkinson's disease (PD).

Background: The concept of motor phenotypes in PD is well-established.(1) When compared with tremor-dominant PD, patients with postural instability and gait difficulty (PIGD) have more disability and a more rapid progression of disease.(1) However, there are limited data on the impact of motor phenotype on HS in PD. Schrag et al.(2) suggested that patients with akinetic-rigid PD have worse PDQ-39 scores than those with tremor-dominant disease. However, the impact of motor phenotype on HS in PD remains uncertain.

Methods: PROMS-PD enrolled a large, heterogeneous sample ($n=513$) of patients with PD and collected detailed information on demographics, clinical characteristics and motor and non-motor symptoms through the use of a structured interview, clinical rating scales and clinical examination. Using multiple regression analyses we explored the relative contribution of motor phenotype to variance in health status (PDQ-8).

Results: $N=482$ patients were included in the analysis (101 tremor, 38 no clear subtype, 343 PIGD). Clinical and demographic variables accounted for 19.5% of variance in PDQ-8 scores. While UPDRS motor score was a strong predictor of HS ($\beta=0.332$, $p<0.001$) and explained an additional 9% of the variance in HS, motor phenotype explained less than 1% of the variance in HS ($\beta=0.098$ $p=0.021$). PIGD did not predict worse HS when compared to the tremor subgroup. PDQ-8 scores did not differ significantly between the tremor-dominant and PIGD phenotypes.

Conclusions: Although UPDRS motor score is a strong predictor of HS in PD, the subclass of motor phenotype has minimal impact, suggesting that both PIGD and tremor-dominant phenotypes suffer similarly decreased HS. Both groups are therefore likely to benefit from equally aggressive but individually tailored intervention. 1. Jankovic J, McDermott M, Carter J, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology. 1990;40:1529-1534. 2. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry. 2000;69:308-312.

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Coping with Parkinson's disease and its relationship to mood and cognition

C.S. Hurt, D. Burn, J. Hindle, S. Landau, M. Samuel, K. Wilson, R.G. Brown (London, United Kingdom)

Objective: The present study sought to investigate coping and its relationship to depression, anxiety and cognition in PD.

Background: PD brings with it a range of problems with which a patient must cope. The type of coping employed by patients with chronic illness can impact upon their psychological well-being. However findings from studies of coping and well-being in PD remain inconsistent. Furthermore, coping strategies such as problem-focused or task-oriented coping, often require higher level cognitive functioning. Cognitive impairment is common in PD with up to 90% of patients showing evidence of a cognitive disorder. It was hypothesised that coping styles would be associated with cognitive function in PD.

Methods: 513 patients with PD were recruited as part of the PROMS-PD study; a longitudinal investigation of mood states in PD. 471 participants completed the Coping Inventory for Stressful Situations (CISS), the Hospital Anxiety and Depression Scale (HADS), the UPDRS III and the Addenbrooke's Cognitive Examination-Revised (ACE-R). Correlations and multiple regression analyses were performed to explore the relationships between coping styles and depression, anxiety and cognition.

Results: Coping style significantly predicted depression and anxiety after controlling for clinical and demographic variables (Adjusted $R^2=.341$, .474 respectively). Use of emotion-focused coping was the strongest predictor of depression and anxiety. Use of task-oriented coping, avoidance and distraction were associated with less depression. Emotion-focused coping was used more by patients who were younger, had more severe motor symptoms and longer disease duration. Greater cognitive impairment significantly correlated with less use of task-oriented coping ($r=0.107$, $p=0.021$) and greater use of avoidance and distraction ($r=-0.121$, $p=0.009$, $r=-0.111$, $p=0.018$ respectively).

Conclusions: Coping style predicted depression and anxiety in PD. Cognitive impairment was associated with less use of task-oriented coping. Therapies designed to promote task-oriented coping and reduce emotion-focused coping may help to improve well-being in patients with PD. In particular therapies should target younger patients, those with severe motor symptoms and longer disease duration who reported greater use of coping strategies associated with poor well-being.

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Mismatch of non-motor symptoms among DBS-candidate Parkinson patients and their carepartners may be scale driven

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Objective: This study surveys patient and caregiver recognition of non-motor symptoms (NMS) among Parkinson's disease (PD) deep brain stimulation (DBS) candidates.

Background: Non-motor symptoms (NMS) of Parkinson's disease (PD) may be more debilitating than motor symptoms. While deep brain stimulation surgery (DBS) in PD is primarily performed to improve motor symptoms, NMS are universally present in this advanced population. This study surveys patient and caregiver recognition of NMS among DBS candidates.

Methods: The NMSQ (questionnaire) and NMSS (scale) were administered to PD patients and caregivers prior to DBS implantation in STN or GPi targets. Primary caregivers were either a spouse, parent, friend, proxy, or children.

Results: This study included 33 PD patients (23 males, 10 females) paired with a caregiver (26 spouses, 2 children, 3 friends, 1

parent, and 1 proxy). Mean patient age was 61.3 years +/−8.1. The most positive NMSQ responses for PD patients were gastrointestinal (87.9%), sleep (84.9%), and memory (75.8%). The least positive responses for PD patients were cardiovascular/falls (54.6%) and sexual (54.6%) items. The most positive answers in PD patients NMSS were sleep (90.9%) and GI (75.8%) items. The least positive answers in PD patients were with perceptual (delusion/hallucination, diplopia) (18.2%) and cardiovascular (45.5%) items. Patient and caregiver scoring correlations for NMSQ and NMSS were 0.662($p<0.0001$) and 0.527 ($p=0.002$), respectively. The highest NMSQ patient/caregiver correlations were with sleep (0.62, $p<0.0001$), urinary (0.62, $p<0.0001$), and memory (0.62, $p=0.0001$) items. The lowest correlations were with cardiovascular/falls (0.36, $p=0.04$) and miscellaneous (pain, anosmia, weight change, sweating) (0.41, $p=0.02$) items. The highest NMSS correlations were with attention/memory (0.62, $p<0.0001$), mood/cognition (0.55, $p=0.0009$), and sexual (0.5, $p=0.005$) items. The lowest correlations were in miscellaneous (0.38, $p=0.03$) cardiovascular/falls (0.39, $p=0.02$), and perceptual (0.40, $p=0.02$) items.

Conclusions: 1) The frequency and prevalence of NMS among DBS candidates and the agreement between patients and caregivers varied depending on which scale was used. 2) The overall correlation in this cohort between patient and caregivers was greater with the NMSQ than NMSS.

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Withdrawn by Author

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Non-motor symptoms in advanced Parkinson's disease are the key determinants of health-related quality of life

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Objective: To explore the role of non-motor symptoms (NMS) as predictors of health-related quality of life (HRQoL) in advanced Parkinson's disease (PD).

Background: NMS are common and have important clinical consequences in PD, but the impact of NMS on HRQoL in late PD is not known. The NMS Scale (NMSS) allows a comprehensive assessment of NMS in real life.

Methods: The NMSS was applied to an international cohort of PD patients (UK PD brain bank criteria) recruited consecutively across all stages of PD. Patients with clinically relevant dementia were excluded by investigators. HRQoL was assessed using the PDQ-8. Secondary measures included Hoehn and Yahr [HY] and UPDRS/SCOPA-Motor. Descriptive statistics, non-parametric tests, and multiple linear regression were used.

Results: Of the 750 patients recruited (58.5% males; mean age 65.9±0.3 years; PD duration 7.37±5.6 years), 13.5 % were in stages HY 4 (n=84) and 5 (n=17). Patients in stage 5 experienced more and more severe NMS than patients in stage 4. Mean NMSS scores were 93.0±48.4 for patients in stage 4 and 125.3±65.7 for those in stage 5 ($p=0.08$). HRQoL, as per the PDQ-8, was significantly worse in HY stage 5 ($p<0.005$). Association between NMSS and PDQ-8 scores was significant (Spearman $r=0.58$, $p<0.0001$). In the multiple regression model including age, sex, motor impairment, motor complications, and NMSS scores as independent variables, the only significant independent predictor of HRQoL was NMSS ($F=14.8$; adjusted R-squared, 0.43; $p<0.0001$). Of all NMSS domains, mood/apathy had the highest influence on HRQoL ($F=7.05$; adjusted R-squared, 0.35; $p<0.0001$).

Conclusions: Our study indicates that NMS, as a whole, increase as patients progress from HY stage 4 to 5. Similar to our findings in early PD, NMS are more important determinants of HRQoL than motor impairment. In late stages, mood alterations and apathy are the most relevant NMS predicting HRQoL.

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Constipation and Parkinson's disease: Stories from the bathroom

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Objective: Toileting difficulties not a glamorous research topic, yet these difficulties significantly decrease the quality of life of the individual. From the earliest descriptions of Parkinson's disease (PD), constipation is described as a significant symptom. Yet, very little is known about the type, incidence, and impact long term constipation has on those living with PD. This paper will share stories from people who report that they are constipated in an effort to draw attention to this much maligned clinical issue.

Background: The scientific evidence surrounding bowel management and PD is slim, even thought there is no doubt that symptoms such as constipation are strongly associated with PD. People with PD report that without laxatives they would not be able to go to the toilet to pass stool (faeces) comfortably, many have tried three or more different types of laxatives over the years. However, they report that none of these remedies have given them any long-term success and have often lead to some very embarrassing situations.

Methods: This mixed method research used a combination of standard PDQOL tool sets and open ended questions, designed to elicit detailed experiences of reported bowel dysfunction. In total 40 people with PD were interviewed their stories were thematically coded and set as a backdrop to their reported QOL. These QOL scores were further aligned alongside a Hoehn & Yahr matched control cohort of 40 people with PD who did not report any bowel dysfunction.

Results: The qualitative findings highlight some of the reasons why these participants do not access or ask for assistance. Over 60% of participants questioned stated that their initial concerns were dismissed as trivial by their medical practitioners. Their stories highlight a general professional disinterest in constipation that has for these people resulted in poor bowel management program choices and more negative QOL scores than those not reporting a bowel dysfunction.

Conclusions: Differing clinical opinions regarding the onset or cause of constipation is academically interesting and challenging, however it does not meet the immediate clinical needs of this group of people. This research moves a step closer to the compilation of a clinically efficacious long-term management strategy for constipation that is useable and accessible to people with PD as well as their health service providers such as Pharmacists, Doctors and Nurses alike.

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Health-related quality of life declines before depressive symptoms commence in Parkinson's disease

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Objective: The aim of this cross-sectional study was to explore the relationship between health-related quality of life (HRQoL) and the onset of depressive symptoms in Parkinson's disease (PD).

Background: Depression is well known as one main factor impacting on HRQoL in negative way in PD patients. However, when the HRQoL in PD patients begins to decline in the course of onset of depressive symptoms is nearly unknown.

Methods: We built a clinical database with a series of 151 consecutive PD patients. Patients were evaluated using the Hamilton Depression Rating Scale (HDRS), the 39-item Parkinson's Disease Questionnaire (PDQ-39), Unified Parkinson's Disease Rating Scale (UPDRS), Mini-Mental State Examination (MMSE), Hoehn-Yahr stages, Parkinson's disease sleep scale, and Activity of Daily Living Scale (ADL). Patients were divided into several subgroups according

to the total score on the HDRS. Multiple comparisons among these subgroups were performed with Fisher's Least Significant Difference (LSD) test. A multivariate analysis was carried out to determine the factors that best accounted for each dimension of PDQ-39 in order to observe how depressive symptoms affected the HRQoL in PD.

Results: Prevalence of depressive symptoms in PD (dPD) was 29.1%, and another 52.3% demonstrated possible depressive symptoms. The HRQoL worsened as depressive symptoms became more severe. Depressive symptoms affected the HRQoL mainly in emotional well-being, cognition, social support and communication dimensions.

Conclusions: Depressed patients, and those with possible dPD experience reduced HRQoL. The HRQoL starts to decline since possible dPD commence, and it gets worsened when depressive symptoms develop. Interventions such as emotional support, behavioral training, and antidepressants may improve the quality of life for patients with PD, especially the large portion with possible dPD. To our knowledge, large scale randomized controlled trials examining the efficacy and safety of antidepressants to improve depressed symptoms in PD patients are still inadequate, so we emphasize here the necessity and significance of such trials in the future.

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The burden of direct care tasks on the Parkinson's disease caregiver

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Objective: To guide the development of palliative interventions for late-stage PD by evaluating (1) specific tasks that contribute disproportionately to caregiver strain, and (2) the relationship of direct care strain to global strain, caregiver depression, and mutuality.

Background: With progression from mid to late-stage PD, family caregivers become increasingly vulnerable to caregiver strain, in large part due to a substantial burden of direct care tasks. To date, a profile of specific direct care tasks performed by PD caregivers has been lacking.

Methods: 144 caregivers of patients with mid (n=92) and late-stage PD (n=52) completed questionnaires assessing direct care tasks performed, associated strain from direct care, global strain, and quality of the marital relationship (mutuality). Tasks were grouped into categories by previous factor analysis. Caregiver depression was measured with the Center for Epidemiological Studies Depression Scale (CES-D). Descriptive statistics were calculated for all items. Two-sided t-tests were used for comparisons by disease stage. Bivariate correlations were used to analyze the relationships between direct care strain, global strain, caregiver depression and mutuality.

Results: Number of tasks performed by caregivers differed according to disease stage (t_{142}=5.40, 2-sided p-value=0.000), with late-stage caregivers performing an average of 11 additional tasks compared with mid-stage caregivers (95% CI: 6.73-14.19 tasks). This increase was not specific to task category. Direct care strain of all mobility tasks increased, as did many personal care and transportation tasks (43% each). Dementia-related tasks were rated at least somewhat hard regardless of disease stage. Caregivers who had higher levels of strain from direct care also reported more depression and global strain and lower levels of mutuality. This relationship was consistent across all task categories.

Conclusions: 1. Late-stage PD caregivers provided significantly more care in all categories of direct care tasks than mid-stage caregivers, and experienced more strain from care related to declining motor function. 2. Dementia-related tasks produce significant strain regardless of disease stage. 3. Efforts to reduce strain from direct care would in turn reduce global strain and depressive symptoms caregivers experience, and could lessen the negative influences on the spousal relationship.

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Video assisted swallowing therapy improved quality of life measures more than traditional swallowing therapy in patients with Parkinson's disease

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Objective: To assess the effect of video assisted swallowing therapy (VAST) compared to traditional swallowing therapy (TST) on SWAL-QOL, pleasure of eating (POE) and anxiety and depression among PD patients with SD.

Background: Swallowing disturbances (SD) are common among advanced Parkinson's disease (PD) patients. SD affect quality of life measures which are related to swallowing (SWAL-QOL) and PD patients with SD experience increased anxiety and depression compared to patients without SD.

Methods: Patients were divided randomly into TST and VAST groups. Five swallowing therapy sessions over 2 weeks practiced compensatory techniques. VAST patients practiced the adjusted swallowing therapy strategy assisted by a video feedback tool. All patients filled SWAL-QOL questionnaire, POE scale and anxiety and depress questionnaires pre and post therapy as well as 6 month post intervention.

Results: Forty-two (24 males) non-demented PD patients with clinically significant SD which was confirmed by fiberoptic endoscopic evaluation of swallowing (FEES) with a mean swallowing disturbance questionnaire (SDQ) of 14.65±5.81 were included. Their mean age was 67.6±8.26, mean duration of motor symptoms of 7.43±4.66 years and mean H&Y at ON 2.21±0.79. A significant ($p<0.05$) decrease in level of anxiety between pre to post therapy was observed in both groups. VAST treated group reported significantly greater improvement in SWAL-QOL ($p<0.01$) and POE ($p<0.05$) than TST group. The improvement in SWAL-QOL was maintained over 6 months post treatment in the VAST group and not in the TST group.

Conclusions: VAST and TST similarly decreased anxiety and depression of PD patients with SD. VAST had a greater effect on PD patients' SWAL-QOL and POE than TST with better carry over effect.

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Quality of life in Parkinson patients with duodopa treatment: A one year follow up

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Objective: The objective of the study was to evaluate the quality of life in patients with advanced Parkinson's disease before and after initiation of treatment with infusion of liquid levodopa, Duodopa, and monitor the changes in the quality of life one year after intiation of treatment.

Background: One of the treatment options in advanced Parkinson's disease is liquid levodopa administered directly into the duodenum, Duodopa. Duodopa which is proven to significantly reduce fluctuations and nonmotor symptoms. By improving motor ability patients autonomy increases and quality of life may also increase. How the patients impression of quality of life and spouse or family menbers experience the quality of life of patients covariate are not known.

Methods: 21 patients enrolled into the study. Both men and women participated. All patients were diagnosed as patients with advanced terapiresitent levodopa responsive Parkinson's disease were treatment changed from tablet regimen to infusion with liquid levodopa administered though af double barrel PEG tube to the duodenum, Duodopa. Patients used PDQ39 to evaluate their own quality of life as well as ratings were performed from the spouse or near relative. Ratings of effect of treatment using UPDRS were registrated at the same time and intervals. Ratings were made before treatment change and one year after.

Results: Patientes improved from treatment in motor skills, when using infusion of liquid levodopa administered directly into th duodenum. Self evaluated PDQ39 ratings by patients showed improvement in quality of life. Spouse or near relative also rated a positive change in quality of life of the patient using PDQ39 after instituated infusion treatment.

Conclusions: In advanced Parkison's disease treatment with advanced therapy using infusion of levodopa directely into the duodenum through a PEG tube improved motor skills in patients as well as self evaluated quality of life measurred with PDQ39. The evaluation of the quality of life in patients made from spouse or near relative using PDQ39 also indicated, that patients had a better quality of life with Duodopa treatment. Duodopa treatment therefore enhances quality of life and autonomy of patients and should be considered in patients with advanced terapiresistent Parkinson's disease.

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Impact of non-motor dysfunction in the quality of life of Mexican patients with Parkinson's disease

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Objective: To identify and describe the association between the presence of nonmotor dysfunction and quality of life in Mexican patients with Parkinson's disease.

Background: Parkinson's disease is the second most common neurodegenrative disease. Motor symptoms are well known to affect the quality of life. Recently it has been reported that nonmotor dysfunction has an important effect on patient's quality of life. Up to half the patients refers that nonmotor symptoms impacts their quality of life in an important way.

Methods: A cross-sectional study was carried out. 139 consecutive PD patients were recruited from the outpatient clinic of the National Institute of Neurology and Neurosurgery in Mexico City. Clinimetric data registered included the Hoehn-Yahr stage, UPDRS III score, Schwabb y England, PDQ-39 and the NMSQuest along with demographic data.

Results: 139 patients were studied (56.8% men) with a mean age of 63±11.9 years. Mean age at PD diagnosis of 57.2±12.6 years. Mean Hoehn-Yahr of 2.2±0.8. A strong correlation was found between NMSQuest total score and the PDQ-39 simplified index ($rs=0.628$, $p<0.001$). Cognition dimension of the PDQ-39 had the stronger correlation ($rs=0.65$, $p<0.001$). Moderate correlation (rs entre 0.4-0.6, $p<0.05$) was found between NMSQuest total score and the following dimensions: Bodily discomfort, communication, emotional wellness, mobility and activities of daily living. Social stigma showed a poor correlation ($rs=0.39$, $p<0.001$). Depression/Anxiety had the stronger correlation with a lower quality of life ($rs=0.58$, $p<0.001$) followed by apathy/attention/memory and sleep dominions. In the multiple regression analysis only the HY stage ($P<.0.05$) and NMSQuest predicted the quality of life even when UPDRS III and motor fluctuations were introduced to the model.

Conclusions: Non motor dysfunction had a major impact in the quality of life; taken as a whole nonmotor symptoms were more important than motor symptoms in the quality of life of our patients. NMSQuest scores had a strong correlation with the PDQ-39 cognitive dimension. Depression/anxiety is one of the main factors determining a low quality of life in our sample along with the HY stage. Non motor evaluation including neuropsychiatric aspects should be performed in all PD patients.

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Depressive symptoms among cognitively-intact, community dwelling Filipino patients with Parkinson's disease

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Objective: To determine the prevalence of depressive symptoms and its correlation with the quality of life among cognitively-intact, community dwelling Filipino patients with idiopathic Parkinson's disease (PD) seen at the Movement Disorders Clinic of a tertiary hospital.

Background: Parkinson's disease (PD) is a neurodegenerative disease primarily affecting the elderly that is exemplified by its chronic progressive course affecting the motor system. It was not until recently that non motor symptoms of PD have been recognized as among the most troublesome features of the disorder. Approximately 40 - 50% of all patients with PD present with depression. Rates of depression vary widely between different countries. This variability is the result of wide differences in diagnostic criteria, screening methods and populations studied. In the Philippines, no prospective study on depression and its relation to quality of life in patients with PD has yet been reported.

Methods: 76 Filipino outpatients fulfilling the United Kingdom Parkinson's disease Society Brain Bank Clinical Diagnostic Criteria for PD were included in the study. Demographic data were obtained including: age, sex, onset of disease, disease duration and medication intake. The Mini Mental State Examination (MMSE) was done to exclude significant cognitive impairment. The Montgomery Asberg Depression Rating scale (MADRS) was administered to quantify the degree of depressive symptoms. The degree of depressive symptoms was correlated with the quality of life instrument, Parkinson's disease Questionnaire (PDQ 39) and Short form health survey (SF 36); and the functional and motor severity using the Unified Parkinson's Disease Rating Scale (UPDRS).

Results: Our cohort of patients had a mean: age of 61 years (range: 42–81 years), and disease duration of 1.3 years (33 months). Out of the 76 patients, 46 (60.5%) probably had significant depressive symptoms based on the MADRS cut off score of >14. Depressive symptoms were associated with poorer scores on both UPDRS I-III, PDQ39 and SF 36.

Conclusions: The prevalence of significant depressive symptoms among this Filipino cohort of patients is 60.5% which is higher than commonly reported worldwide. The depressive symptoms were significantly correlated with poorer quality of life and level of functioning.

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Is mood phenotype important in predicting health status in Parkinson's disease?

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Objective: To explore the relationship between empirically defined mood phenotypes and health status (HS) in Parkinson's disease (PD).

Background: A recent prospective study of mood states in PD (PROMS-PD) identified 4 potential clinical phenotypes of mood disorder: 2 depressive phenotypes with and without anxiety, anxiety without depressive symptoms and a 'healthy' subgroup. Anxiety symptoms were prominent. Depression is known to significantly impact upon health status in PD[1], but little is known about the impact of anxiety on health status, alone or combined with depression, knowledge useful in optimizing management.

Methods: PROMS-PD enrolled a large, heterogeneous sample (n=513) of patients with PD and collected information on demographic, clinical characteristics and motor and non-motor symptoms through structured interviews, clinical rating scales and clinical examination. Using multiple regression analyses we explored the relative contribution of the following domains: mood phenotypes, motor symptom severity (UPDRS-III), cognition (ACE-R) and other non-motor symptoms (ONMS) to variance in health status (PDQ-8).

Results: N=462 patients were included in the analysis (37 depressed/anxious, 35 depressed, 104 anxious, 286 healthy). Clinical and demographic variables accounted for 19.6% of variance in PDQ-8 scores; younger age, number of physical comorbidities, disease du-

ration and levodopa equivalent dose each significantly predicted HS. Mood phenotype independently predicted HS. A regression model containing clinical and demographic variables and all four symptom domains explained 45% of the variance in HS. ONMS were the strongest determinants of HS ($\beta=0.330$, $p<0.001$) followed, in order, by depressed/anxious mood phenotype and motor symptoms ($\beta=0.202$ and 0.185 respectively, $p<0.001$).

Conclusions: Mood phenotypes predicted health status in PD. The depressed/anxious phenotype predicted poorest health status. Our results not only provide support for the utility of the mood phenotypes but also emphasize the importance of screening for, and managing different types of mood disturbance. **Acknowledgement:** Parkinson's Disease Society (UK). Reference 1. Schrag, A, Jahanshahi, M & Quinn, N. What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry 2000;**69**:308-312.

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A prospective review of admissions of Parkinson's disease (PD) patients

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Objective: The aim of this study was to establish patterns of admission of people with PD to determine if improved multidisciplinary care in the community could help keep people at home.

Background: Hospital admission of PD patients results in problems with patients getting medication on time[1], can precipitate confusion and hallucinations and is best avoided where possible. If admission is unavoidable, patients are best managed by or with input from PD specialists.

Methods: PD patients admitted to University Hospital, Coventry, UK were identified from coding data over a 6-month period; notes were then reviewed.

Results: 289 patients were admitted on 321 occasions utilising 4327 bed days with an average length of stay of 14.9 days. 74.5% were admitted from home and 25.5% from residential (RH) or nursing homes (NH). All patients from RH/NH were discharged back there and 14 of the 215 patients admitted from home (19%) were discharged to RH/NH. 79% admissions were cared for on non-specialist wards Commonest PD-related causes of admission were hallucinations, medication adjustment and need for rehabilitation. Heart disease and stroke were the commonest non-PD causes of admission. Delays in discharge (764 bed days) were caused by in-hospital complications (e.g. urinary tract infection, pneumonia, deteriorating PD, falls, constipation, incontinence), time to adjust PD medications, delays in finding RH/NH and delays waiting for social or therapy services.

Conclusions: The vast majority of PD admissions were cared for on non specialist wards. Almost 1:5 patients admitted from home were discharged to RH/NH resulting in an increase in care costs[2]. Improved access to PD specialists, nurses, therapists and psychiatric support services in the community may have the potential to reduce the number and duration of admissions and would be a better use of NHS resources than prolonged inpatient stays in addition to bringing care closer to home, a key priority for the department of health in the UK[3]. 1. 'Life with Parkinson's today-room for improvement'. Parkinson's Disease Society of the United Kingdom, 2008. 2. Findley L, et al. Direct economic impact of Parkinson's disease: A research survey in the United Kingdom. Mov Disord. 2003;18:1139-1145 3. Delivering Care Closer to Home: Meeting the Challenge. Department of Health 2008.

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Driving and Parkinson's disease

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Objective: The aim of this prospective longitudinal study was to determine the driving ability using a driving simulator and to compare the driving performance with physical and cognitive functions in patients with Parkinson's disease (PD).

Background: Driving is a complex form of activity and may be negatively influenced by motor symptoms, psychiatric complications, cognitive disturbances and increased daytime sleepiness in patients suffering from Parkinson's disease.

Methods: The study sample consisted of 53 patients with PD and healthy age-matched controls. All participants were still driving at the time of study and had at least 10 years of driving experience. Detail anamnese including a driving questionnaire was taken from all participants, clinical examination including Unified Parkinson's Disease Rating Scale, Hoehn-Yahr stage and Epworth Sleepiness Scale Scores was processed. Subjects were assesed for cognitive performance using the Mini-mental State Examination (MMSE) and Addenbrook's cognitive test (ACE). Driving ability was determined by a combination of reaction (using randomly moved point on the computer display) and driving simulator SKODA car.

Results: There was longer reaction time in the tracking experiment in PD patients, but no significant differences in driving simulator performance of PD patients and healthy controls. Most of non-demented individuals with PD (Hoehn Yahr stage II-III) were safe to drive, only few patients were classified as fail on the driving test and they were predicted to be unfit to drive. Their errors correlated with cognitive impairment and small driving exposure. Few correlations were found between measures of physical mobility with driving skills but cognitive impairments have impact on driving performance within the PD population.

Conclusions: A combination of clinical tests including cognitive screening tests and driving simulator seems to be a useful instrument judging driving ability. These results require confirmation in future studies.

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Economic burden of Parkinson's disease in Singapore

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Objective: To evaluate the economic burden of PD and factors independently associated with individual components of total cost (direct medical, direct non-medical and indirect cost) in Singapore.

Background: PD exerts a significant impact on the health care budget of any country. It has been reported that the total economic cost of PD to the United States amounted to US$23 billion annually, and would exceed US$50 billion by 2040. There is a paucity of published literature in Asia. To the best of our knowledge, there are only two published PD studies in Asia and only one adopted the societal perspective, which is generally considered to be the preferred perspective in economic analyses as it takes into account alternative uses for resources outside of the health care sector. Without the inclusion of productivity loss, we would not be able to evaluate the economic burden of chronic diseases such as PD in a meaningful manner.

Methods: A consecutive sample of 195 PD patients (mean age: 68.2, male: 51.8%) attending a tertiary neuroscience clinic were identified and interviewed using standardized questionnaires including a financial burden questionnaire, two HRQoL questionnaires and the Beck Depression Inventory questionnaire.

Results: Annual total cost of PD from a societal perspective was SGD 11,345 per patient, with direct cost accounted for 38.5% and indirect cost 61.5%. The main cost driver for direct medical, direct non-medical and indirect cost was pharmacotherapy (50.4%), home care (76.1%) and productivity loss (97.9%) respectively. In multiple linear regression analysis, higher education, younger age, and longer duration of PD were associated with higher total cost. Other factors such as living in private housing, larger household size, older age, higher UPDRS motor scores, and poorer HRQoL scores were inde-

pendently associated with individual components of total cost (direct medical, direct non-medical or indirect cost).

Conclusions: PD exerts a considerable burden on patients, the health care system and society at large with a total societal cost of approximately SGD 26-46 million per annum in Singapore. As productivity loss account for a large share of the economic burden imposed by PD, treatments and health care programmes with potential for returning patients' to higher productivity are urgently needed.

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The effect of the medicare part D on Parkinson's disease patients

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Objective: To evaluate the impact of the Medicare Part D (MPD) doughnut hole (DH) on Parkinson's disease (PD) patients medication usage and drug costs.

Background: The Medicare Modernization Act offers prescription drug coverage through MPD. The standard benefit includes a gap in coverage, commonly known as the DH. Additional information on the impact of the MPD program and the DH on prescription drug utilization and behavior is needed to inform policy.

Methods: Prescription claims data from January 1, 2008 to December 31, 2008 were obtained from the IMS LRx retail pharmacy database, which currently captures 62% of all prescriptions filled in the US. Subjects included in the analysis were PD patients 65 years of age and older classified as either a Standard Part D Benefit (SDB) study group or a Commercially Insured (CO) patient control group.

Results: 93,041 PD patients were identified; 28% were SBD and 72% were CO. Of the 26,377 SBD patients 51% of them hit the DH: with 51% reaching it by July. Of those that reached the DH; 74% remained in the DH for the entire year. Annual drug spend was categorized by the 2008 MDP guidelines; with patients either not reaching the DH ($\leq$\$2510); reaching the DH but not hitting catastrophic coverage (CC) level (>\$2510 and $\leq$\$5726); or hitting CC (>\$5726). The percentage of patients with spend $\leq$\$2510 was significantly greater in the CO group (65% vs 49%) ($p<.05$); while reaching the DH spend level but not the CC levels was significantly greater in the SBD group (38% vs 22%) ($p<.05$); the proportion reaching CC spend levels was the same in both groups (13%). For SBD and CO patients with drug spend in the DH level, 12% discontinued therapy and 9% switched therapy, while 2% of SBD and 1% of CO reduced therapy. Market level compliance was similar between the groups.

Conclusions: The MPD PD population has a higher drug spend than their CO counterparts. A much lower percentage of SBD PD patients than originally expected are making it through the DH to the CC level (13% vs 38%), which effectively reduces the projected savings from the MPD program. SBD patients do not seem to be responding to the cost pressure by switching to generics–but they are reducing their therapies more than CO patients.

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Initial diagnosis and treatment patterns in Parkinson's disease

M. Lage, M. Tarrants, J. Castelli-Haley (Kansas City, Missouri, USA)

Objective: To evaluate US diagnosis and treatment patterns of newly identified Parkinson's disease (PD) patients.

Background: To our knowledge, nationwide patterns of initial PD treatments were last described from 1999-2001 claims data and this analysis serves to update the current literature.

Methods: Data used for this analysis were derived from the MedStat® Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits Databases from January 2004 through June 2008. Patients were included in the analyses if they were diagnosed with PD (initial diagnosis is the index date) and had continuous insurance coverage from 6 months prior through 12 months post index date. All analyses are descriptive in nature.

Results: 25,444 patients were identified. 82% of the population identified was >65 years of age with an average age of 75 years and 55% were male. Patients had a mean Charlson comorbidity index of 1.49 with hypertension and psychoses being the most prevalent comorbidities. 35% of diagnoses were made in a neurology office, 30% by internal medicine and family practice and 17% in a hospital. 28% of patients with a PD diagnosis remained untreated with a PD prescription during the 1 year follow-up. Of those that were treated, 49% received a PD medication prior to a PD diagnosis, 12% at initial diagnosis and 39% within the 1 year follow-up period, with 88% of those treated within 6 months. Only 15% of initial PD prescriptions were provided at the neurologist office; 46% of initial prescriptions were received during a hospital admission. 75% received levodopa (LD) as part of their initial treatment regimen, 22% a dopamine agonist (DA) and 4% a MAO B Inhibitor. LD + DA was the most common adjunctive regimen.

Conclusions: PD treatment patterns are complex and involve treatment before diagnosis, at diagnosis and after diagnosis. Conversely, there are those with no treatment prior to diagnosis, no treatment at diagnosis, and no treatment in the 12 months post diagnosis. As PD treatment algorithms and therapeutic options are being continuously updated by the neurology community, this study provides a view of what the current nationwide PD diagnosis and treatment patterns are. This type of analysis continues to highlight the ongoing educational need to the larger community of healthcare practitioners and payers regarding updated PD guidelines.

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An interdisciplinary outpatient clinic for patients with Parkinson's disease

D. Tarsy, D.K. Simon, L.C. Shih, E. Gandelman, L.R. Kapust, L.E. Kraics, A.S. Silver, P. Rose (Boston, Massachusetts, USA)

Objective: To describe and evaluate an outpatient interdisciplinary clinic for the management of patients with PD.

Background: Interdisciplinary clinics appear to improve coordination of care for patients with multifaceted disorders. Improved outcomes include quality of life, caregiver satisfaction, medication compliance, and access to specialty care. Our interdisciplinary team of clinical subspecialists meets monthly to evaluate PD patients with motor and nonmotor problems.

Methods: Team members include movement disorders neurology, psychiatry, neuropsychology, sleep disorders, registered nurse, social worker, community outreach, physical therapy (PT), occupational therapy (OT), voice and swallowing therapy, and nutrition. Each month, 4-5 patients see up to three clinicians for 45-60 minutes each during a single morning for an initial or follow-up visit. At a team conference, recommendations are made for further evaluations, therapeutic interventions, and community referrals. Patients and family caregivers meet with a facilitator to discuss events of the morning. Each patient then meets with their neurologist to discuss team recommendations and reports are sent to the primary care physician and outside neurologist. Each patient completes a questionnaire to assess satisfaction with this process.

Results: 27 visits were made by 25 patients during 8 clinics; a mean 3.4 patient visits per clinic. Attendance was impacted by weather, length of clinic, and ability of patients to arrive early am. Two neurologists each referred 12 patients; 3 neurologists each referred one patient. PT/OT saw 24 patients, social work saw 15 patients, psychiatry saw 10 patients, voice therapy saw 7 patients, swallow therapy saw 6 patients, sleep neurology saw 2 patients, and neuropsychology saw 1 patient for 65 specialist visits during 8 clinics. Clinician satisfaction was high in that patient problems were usefully addressed from several viewpoints and plans for intervention promptly initiated.

Conclusions: Insights were gained during group discussions that may not have been readily evident during multiple traditional outpa-

tient visits. Patient satisfaction was also high. Results of the patient questionnaire will be presented. The PD Center at Beth Israel Deaconess Medical Center is a National Parkinson Foundation Center of Excellence.

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Effects of intraduodenal levodopa infusion therapy on Parkinson's disease

V. Tomantschger, G. Tautscher-Basnett, M. Freimueller (Hermagor, Austria)

Objective: To systematically observe the effects of continuous dopaminergic stimulation (CDS) on quality of life and activities of daily living (ADL) in patients with advanced Parkinson's disease (PD).

Background: In recent years CDS has become increasingly important in the management of all aspects of advanced Parkinson's disease (PD).

Methods: 16 patients are switched from oral medication to CDS (i.e. intraduodenal levodopa infusion therapy) during or shortly after their inpatient neurorehabilitation. The changes in medication and the consequences documented with the following scales and scores are reported: UPDRS, PDQ39, Barthel Index (BI). The data are analysed for all 16 patients at baseline and at 6 months, for 12 patients also at 12 months.

Results: During the observation periods the average change in daily dosage of intraduodenal levodopa is +5%, (range: from -9,5% to +76%) during the first 6 months, and an additional average of +1% in the next 6 months (range: 0% to +35%). In the PDQ39 the average reduction in score is 36% across all patients in the first 6 months, and an additional 6% in the patients observed for 12 months. The UPDRS scores shows an average reduction of 27,1% in the first 6 months and 26,8% over the 12 months period (i.e. on average the improvement could be maintained). In the BI an overall gain in ADLs of 14,9% could be seen in the first 6 months, over 12 months this gain in ADLs is still 11,56%.

Conclusions: After switching from oral medication to intraduodenal CDS this small sample of PD patients shows generally a high percentage of improvement in ADLs and QoL on PDQ39, UPDRS and BI scores during the first 6 months. Improvements can be maintained for another 6 months unless additional comorbidities occur. It is not clear whether improvement is due to the regular intake of levodopa through CDS and/or the increase in dosage or also in part due to other factors such as neurorehabilitation and close contact with/monitoring through professionals. Systematic long-term observations will show how long PD patients maintain level of functioning and QoL, how neurorehabilitation influences this gain and how the dosage of levodopa by intraduodenal infusion changes over long-term treatment.

743

Occurrence of diabetes and hypertension in overweight vs. normal weight veterans with Parkinson's disease

M. Trail, N.J. Petersen, E.C. Lai (Houston, Texas, USA)

Objective: Compare the occurrence of diabetes and hypertension in a sample of overweight vs. normal weight veterans with Parkinson's disease (PD).

Background: Studies of diabetes and hypertension associated with PD are inconclusive. Because PD patients tend to live sedentary lifestyles, we hypothesized that they might have a higher incidence of diabetes and hypertension, particularly those who are overweight.

Methods: We mailed a demographic and illness characteristics survey, gathering data on 100 veterans with PD. From patients' self-reported weight, we classified them as normal weight (BMI<24.9) and overweight (BMI >25) based upon the National Heart Lung and Blood Institute definition. We obtained diagnoses of diabetes and hypertension and disability status from patients' charts.

Results: The mean age was 72.8 years, and 98 patients were male, 2 female. Mean disease duration was 8.1 years and disability was mild to moderate (mean H&Y 2.68). Over half our (male) patient sample was overweight (55.7%) and a significantly higher percentage had diabetes than the normal weight group (20.7% versus 4.8%; p=0.0382). Although 65.5% of overweight patients had hypertension compared to 52.4% of normal weight patients, the difference was not statistically significant.

Conclusions: Based upon data from the National Health and Nutrition Examination Survey 2003-2004, the percentage of our overweight PD subjects (55.7%) is lower than that of the United States male population, especially for men over 60 (73.7%) but still cause for concern. The association between PD and diabetes, hypertension, and other co-morbidities merits exploration. We need to investigate the relationships between the sedentary lifestyles of patients with PD, weight, and types and levels activity. Providers treating this group might discuss nutrition, physical activity, and weight reduction when appropriate.

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Five year follow-up of newly diagnosed Parkinson's disease: Progression and prognostic factors of motor impairment, disability and quality of life

D.C. Velseboer, B. Post, N. van Geloven, R.J. de Haan, R.M.A. de Bie (Amsterdam, Netherlands)

Objective: To assess change over time and prognostic factors of motor impairment, disability and quality of life (QoL) in patients with newly diagnosed Parkinson's disease (PD).

Background: Though a large number of studies focusing on the progression of PD exist, the number of studies describing prognostic factors is relatively sparse. Furthermore, available prospective studies encompass only prevalent cases, introducing a selection of surviving PD patients and underestimating disease progression.

Methods: A group of 133 patients with newly diagnosed PD — recruited from outpatient clinics — participated in this five year prospective cohort study. At baseline, we measured patient's demographic and clinical characteristics in terms of initial symptoms, side of symptoms, duration of symptoms and types of therapy, as well as motor impairment (the Unified Parkinson's Disease Rating Scale Motor-Examination), disability (Schwab and England Activities of Daily Living Scale, the AMC Linear Disability Score), and QoL (Parkinson's disease Quality of Life questionnaire). Follow-up assessments were performed 1, 2, 3, and 5 years after inclusion. Health change over time and the impact of prognostic factors on these outcomes were analyzed using linear mixed models.

Results: The final assessments of the five year follow-up will be finished in the first half of January 2010. Of the original 133 PD patients, we expect that 101 participants will complete the study. Twenty-four patients have died since the beginning of the study and 8 were lost to follow-up. During the first three years of follow-up, there was a slight progression of disability and QoL. Motor impairment progressed with 3 UPDRS-ME points per year. Analysis of the data will be completed before June 2010 and will be ready to be presented at the MDS congress. We will then present the mid-long health outcomes during the 5-year follow-up and their most important prognostic factors.

Conclusions: Follow-up of this five year cohort study in patients with newly diagnosed Parkinson's disease will be ready in January 2010. Data will be analyzed and ready to be presented at the MDS congress.

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Impact of nonmotor symptoms in Parkinson's disease on quality of life: A veteran based study

A.A. Wagle Shukla, S. Ounpraseuth, V. Gray, J. Schwankhaus, S.W. Metzer (Little Rock, Arkansas, USA)

Objective: To determine nonmotor symptoms in a Parkinson's disease (PD) cohort using NMS-Quest scale, to examine the clinimetric

TABLE (745). *Correlation between NMS-Quest, PDQ-39 and PDQ-39 domains*

Domains	Correlation	Lower 95% CI	Upper 95%	p-value
Mobility	0.61	0.44	0.74	<0.0001
Daily Living	0.55	0.36	0.70	<0.0001
Well-Being	0.60	0.42	0.73	<0.0001
Stigma	0.44	0.23	0.62	<0.0001
Social Support	0.51	0.31	0.67	<0.0001
Cognition	0.65	0.49	0.77	<0.0001
Communication	0.65	0.49	0.77	<0.0001
Bodily Discomfort	0.56	0.37	0.70	<0.0001
PDQ-39 Total	0.72	0.58	0.82	<0.0001

properties and investigate its impact on quality of life evaluated by Parkinson's Disease Questionnaire (PDQ-39).

Background: Recently, NMS-Quest has been recommended as standardized screening instrument for evaluation of nonmotor symptoms in PD but its impact on quality of life in elderly veterans has not been studied.

Methods: Veterans with PD were prospectively enrolled from a movement disorders clinic in a VA hospital at Little Rock, Arkansas. Subjects with diabetes, prostate enlargement, cardiac arrhythmias and GERD were excluded. Demographics were documented. A structured evaluation using UPDRS, MMSE, Hoehn & Yahr (H&Y) and Schwab & England scales was performed. NMS-Quest and PDQ-39 questionnaires were administered. NMS-Quest has 30 items evaluating 10 domains: gastrointestinal, urinary, sexual and cardiovascular, cognitive, psychiatric, sleep, pain and miscellaneous. Each item response can be "yes" scoring 1 or "no" as 0, total score ranging 0 to 30. PDQ-39 is a well validated instrument frequently used for evaluation of quality of life.

Results: 68 subjects, all men were recruited. Mean age was 75.5±8.2 years, and mean disease duration was 8.6±5.9 years. NMS-Quest total score mean (median) was 14.4±5.6 (14.0) points. The NMS-Quest total correlated significantly with PDQ-39 and PDQ-39 domains (r=0.62 to 0.82, all p<0.0001).

Correlation between PDQ-39 and the domains of NMS-Quest were all significant except for miscellaneous (p=0.1174) and sexual (p=0.1317). NMS-Quest was free of floor or ceiling effects. Overall, Cronbach αwas 0.81 for item-total correlation, domains ranging 0.33 to 0.59. It also showed convergent validity with H&Y stage (r=0.26), UPDRS total (r=0.35), UPDRS III (r=0.26) and negatively correlated with Schwab & England (r=-0.33) values. PDQ-39 total was higher in the group where H&Y stages ≥3.

Conclusions: Quality of life in veterans with Parkinson's disease is significantly affected by nonmotor symptoms. Metric attributes of NMS-Quest as a screening instrument are satisfactory.

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Incidence of hip fracture in Parkinson's disease: A population-based study

M. Wieler, C.A. Jones, D. Voaklander, W.R.W. Martin (Edmonton, Alberta, Canada)

Objective: To examine the incidence of hip fracture in PD in seniors (65+ yrs) in the province of British Columbia, Canada and to compare PD hip fracture rates to those in the general population.

Background: PD is a significant risk factor for falls with the risk for falling being two-fold greater in PD compared to the general population. This places persons with PD at risk of hip fracture. Little information exists, however, as to the incidence rate of hip fracture in PD in comparison to the general population.

Methods: To identify PD cases, linked records of inpatient hospitalization and physician billing were examined for PD-specific diagnostic codes. PD prescriptions were captured through the provincial drug insurance plan which provides 100% coverage for those over age 65. Case ascertainment was based on hospitalization, physician billing and drug use from a base population of ~500,000. Hip fracture cases were identified using ICD9 codes. Data for the fiscal years 1991/92 to 2000/01 were stratified by year, age group, and sex. Incidence rates of hip fractures were calculated using prevalent PD cases in year as the denominator.

Results: The mean age of patients with PD and hip fracture was 81.3 years vs 81.0 years for the general population hip fractures. Hip fracture rates in PD were ~10 times greater compared to the general population. Males within the PD population had nearly double the rate of hip fractures compared to females. Rates increased with age for both sexes in PD.

Conclusions: Patients with PD have a greater risk for hip fracture compared to the general population over the age of 65. Given the economic and societal burden of hip fracture on both the individual and health system level, the PD population requires additional support to prevent and treat hip fractures. Presented in part at the World Congress on Parkinson's Disease and Related Disorders, Dec/09.

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Three months follow-up study about improvement of functional impairment in patients with Parkinson's disease treated with entacaponum

C. Zaharia, V. Tudorica, D. Pirscoveanu (Craiova, Romania)

Objective: The aim of this study was to assess changes in mobility in subjects with idiopathic Parkinson's disease treated with L-Dopa and COMT inhibitor.

Methods: Twenty-five patients (13 women and 12 men), aged between 65 and 75 years diagnosed with idiopathic Parkinson's disease in stage II Hoehn and Yahr were enrolled in this study. All the patients were treated with L-Dopa and Benserazidum in average dose of 605,9 mg L-Dopa/day. Our patients were evaluated using Columbia Rating Scale for Parkinson's disease (CRS) (subscale for tremor, rigidity and bradykinesia with range of results between 0 and 60 points) in the moment of admission in study. We started the treatment with entacaponum 200 mg with each dose of L-Dopa. The patients were evaluated three months later using the same CRS subscales. The results were analysed by Student test.

Results: In the moment of admission in the study the patients obtained an average score of 14,5 points on CRS subscales for tremor, rigidity and bradykinesia. After three months of treatment with entacaponum we have seen a significantly statistic improvement of tremor, rigidity and bradykinesia, the patients having a lower score on CRS.

Conclusions: We can conclude that treatment with entacaponum in addition to L-Dopa improves functional impairments of patients with idiopathic Parkinson's disease in a significantly statistic manner.

POSTER SESSION 3
WEDNESDAY, JUNE 16, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

PARKINSON'S DISEASE: SLEEP DISORDERS

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Sleep disorders in Parkinson's disease in Uruguay

B. Aguiar, R. Aljanati, M. Martinovich, R. Buzo, V. Raggio, V. Pomar, A. Ojeda, N. Gonzalez, G. Nogueira, F. Alfonso, L. Aguerre, G. Montado (Montevideo, Uruguay)

Objective: The objective of our study was to establish the clinical characteristics of patient with moderate phase of Parkinson's disease (PD) with complaints of sleep.

Background: Sleep disturbances are the most important non-motor symptoms of PD and may affect 50%–90% of PD patients. The alterations are: insomnia, parasomnia and excessive daytime sleepiness, with the exception of the REM sleep behaviour disorder (RBD) that can precede or to accompany to PD, the rest of the dysfunctions arises as the illness advances.

Methods: 53 PD patients (by the UKPDSBB Criteria) of Clinic's Hospital in Montevideo, Uruguay, to receive an interdisciplinary boarding in the Program of Education and Rehabilitation in the Parkinson's disease for patients, relatives and caregivers (PRENPAR). With moderate stage of the disease (by the Hoehn &Yahr staging: 2-3 stage, UPDRS part III–12-50 points) and without dementia (by the MMSE >23) were included into the study. Patients were included into two groups based on a positive (Group I) or negative (Group II) answer to the question: UPDRS IV number 41"Do you have sleep problems?" Group I consisted of 30 patients (16 men and 14 women) with subjective sleep disturbances and Group II consisted of 23 patients (14 men and 9 women) without sleep problems. A very detailed clinical history, neurological sleep history plus quality of life scale (PDQ-39)was performed and statistically analyzed.

Results: Patients in Group II were younger (63.6 vs 66.3 years,) and more depressed (BDI-18.5 vs 11.1 points, $p<0.001$). The presence of motor fluctuations and sleep fragmentation was much more common in Group I: 45.1% vs 21.5% ($p=0.036$) and 55.9% vs 36.4% ($p=0.043$), respectively. There were no differences in the duration, the onset, type of the disease and the type of dopaminergic therapy. The average L-dopa dose in Group I was significantly higher than in Group II (825.5 vs 550.2 mg/d, $p<0.001$).

Conclusions: The most important reasons of sleep disturbances in PD are: sleep fragmentation, depression, motor fluctuations and restless legs syndrome. Only the high dose of L-dopa has a significant negative impact on the sleep problems.

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Excessive daytime sleepiness in the MPTP non human primate model of Parkinson's disease

Q. Barraud, V. Lambrecq, S. McGuire, M. Hill, F. Tison, E. Bezard, I. Ghorayeb (Bordeaux, France)

Objective: Here, we took advantage of the MPTP-treated monkey model of Parkinson's disease (PD) to investigate the relationship between Excessive Daytime Sleepiness (EDS) and the occurrence of parkinsonian motor signs. In parallel, we assessed the modifications of monoamines and orexin levels after MPTP intoxication.

Background: EDS is among the most frequent and disabling sleep-disordered manifestations of PD. It sometimes precedes the motor features by years and may serve as early biomarker of the prodromal phase of PD. Although EDS pathophysiology remains far from being understood, the hypothalamic orexinergic system is thought to be involved in the EDS emergence.

Methods: Eight adult Maccaca mulata monkeys were implanted surgically with a 3 channels telemetry transmitter that allows long-term continuous electroencephalographic (EEG), electromyographic (EMG), electrooculographic (EEG) biopotentials and general locomotor activity monitoring. Sleep-wake activities were continuously monitored over a 2 weeks baseline period in all animals. Subsequently, 6 animals were injected with MPTP.

Results: In baseline condition, the percentage of time spent asleep during daytime (8 am to 8 pm) accounted for about 5% in all animals. Immediately after the first MPTP injection and before the emergence of motor symptoms, the percentage of time spent asleep during daytime dramatically increased (about 35%) indicating EDS. This was concomitant with a breakdown in the dopaminergic homeostasis, as evidenced by a decreased dopamine turnover whereas serotoninergic, noradrenergic and orexinergic levels remained unchanged. In the long run, EDS remained persistent but cannot be ascribed to a cellular loss of orexin neurons as stereological count of these neurons failed to document any cellular loss following parkinsonism inducing by MPTP.

Conclusions: By using the gold standard MPTP non-human primate model of PD, we here demonstrate that daytime awakening is deregulated right after the very first exposure to MPTP, despite lack of motor symptoms. This is reminiscent of the early alteration of the regulatory mechanisms of vigilance in the human PD. This suggests that EDS in the MPTP model might represent a potential biomarker of the prodomal phase of PD and serve to investigate potential vigilance promoting drugs.

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Hallucinations and sleep disorders in Parkinson's disease: Ten year prospective longitudinal study

C.G. Goetz, B. Ouyang, A. Negron, G.T. Stebbins (Chicago, Illinois, USA)

Objective: Prospectively assess the relationship of hallucinations to sleep disorders over a ten-year longitudinal study of PD patients.

Background: Short and moderate duration studies have assessed hallucinations and sleep in Parkinson's disease, but very little is known about long-term outcomes.

Methods: Eighty-nine PD patients were recruited to fill cells of normal sleep without hallucinations ($N=20$); sleep fragmentation only ($N=20$); vivid dreams/nightmares ($N=20$); hallucinations with insight ($N=20$); hallucinations without insight ($N=9$). At baseline, 0.5, 1.5, 4, 6 and 10 yrs, sleep disorders and hallucinations were assessed by standardized scales with the longitudinal data analyzed by generalized estimating equations with assumptions of linearity in time.

Results: At 10 years, we could account for all subjects (27 interviewed, 62 deceased or too ill for interview). Hallucination prevalence and severity significantly increased over time (adjusted $p=0.004$, adjusted $p=0.002$). In contrast, presence of vivid dreams/nightmares or sleep fragmentation did not increase over time. For all visits, the prevalence of sleep fragmentation did not differ between subjects with vs. without hallucinations ($OR=1.50$, $p=0.09$). However, severe sleep fragmentation was significantly associated with concurrent hallucinations (OR 2.01, $p=0.006$). The presence of vivid dreams/nightmares was also highly associated with the concurrent presence of hallucinations ($OR=2.60$, $p<0.001$) and the presence of severe hallucinations ($OR=1.88$, $p=0.025$). Sleep fragmentation and vivid dreams/nightmares among the subjects that were non-hallucinators at baseline did not predict future development of hallucinations.

Conclusions: Hallucinations and sleep abnormalities follow very different patterns of progression in PD over ten years. Whereas patients with hallucinations often have concurrent sleep aberrations, neither sleep fragmentation nor vivid dreams/nightmares are predictive of future hallucinations.

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A study of sleep problems in a community-dwelling cohort of people with PD

R.W. Walker, A.R. Howells, I.L. Cookey, W.K. Gray (North Shields, Tyne and Wear, United Kingdom)

Objective: To evaluate the extent and nature of sleep problems in a community dwelling cohort of people with PD.

Background: Sleep disturbance is a well recognised and common symptom of PD. There are, however, few studies of such problems within a prevalent population of community-dwelling people with PD.

Methods: All people diagnosed with idiopathic PD from within a predominantly rural area of north-east England were asked to participate in this study. Those who agreed to participate were assessed for excessive daytime sleepiness using the Epworth sleepiness scale

(ESS) and were also asked a series of questions related to their night-time sleep pattern. They were also assessed using a number of standard rating scales including Hoehn & Yahr stage, UPDRS, Hospital Anxiety and Depression Scale, PDQ-39 and MMSE. Mann-Whitney U test was used to test for significance of difference.

Results: Seventy-five people (38 males, 37 females) agreed to participate in this study, 31 (41.3%) reported the quality of their sleep to have deteriorated since being diagnosed with PD. Using the ESS scoring system, 20 (26.7%) had excessive daytime sleepiness, although only 3 (4.0%) had narcolepsy. Excessive daytime sleepiness was not associated with age or gender, but was significantly associated ($p<0.01$) with greater Hoehn and Yahr stage, reduced cognitive function, lower quality of life, greater depression and higher UPDRS score (sub-sections I, II, and III). Excessive daytime sleepiness was only weakly associated with a report of a deterioration in the quality of sleep (OR=2.14).

Conclusions: Sleep disturbance is a common problem in people with PD and is associated with a range of other motor and non-motor symptoms.

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Nighttime sleep and daytime sleepiness in idiopathic and genetic Parkinson's disease

M. Kasten, V. Tadic, N. Brueggemann, A. Schmidt, L. Kertelge, C. Wisse, L. Drude, K. Lohmann, J. Hagenah, C. Klein (Luebeck, Germany)

Objective: Characterization of daytime and nighttime sleep disturbances in IPD, GPD and controls and correlation with PD symptoms, depression, cognition, and hallucinations.

Background: Sleep disturbances are frequent in idiopathic Parkinson's disease (IPD). Its correlation with PD symptoms, disease duration and co-morbidities is debated and data on genetic PD (GPD) are scarce.

Methods: We examined 88 IPD patients (27 with an onset age <50 years (EOPD)), 40 *PINK1* and *Parkin* mutation carriers (21 manifesting (MC) and 19 nonmanifesting (NMC)), and 98 unrelated controls, who underwent a standardized neurological examination. The Parkinson's disease Sleep Survey (PDSS) and the Epworth Sleepiness Scale (ESS) were used as outcome measures. As possible predictors we evaluated: Hoehn and Yahr scale, UPDRS II-IV, falls, pain, hallucinations, Beck Depression Inventory (BDI) and Montreal Cognitive Assessment (MoCA).

Results: PDSS scores indicated decreased sleep quality in all PD groups compared to controls ($p<0.001$), more in EOPD than late onset PD (LOPD) ($p=0.030$), and higher in *PINK1* MC than NMC ($p<0.001$). ESS was higher in the IPD than in controls ($p<0.001$), and higher in *PINK1* MC than controls ($p=0.007$) and *PINK1* MC than NMC ($p=0.022$). Both PDSS and ESS were correlated with BDI scores ($r=0.656$ and $r=0.409$, $p<0.001$) and with each other ($r=0.326$, $p>0.001$). In linear regression models PDSS was associated with disease duration, UPDRS IV score, Hoehn and Yahr, falls, and BDI with combined explained variance of 58.5%. ESS was associated with age at examination, Hoehn and Yahr, and BDI scores with combined explained variance of 17.8%.

Conclusions: Both nighttime and daytime sleep problems are increased in PD, genetic and idiopathic and particularly EOPD. Although daytime and nighttime problems are correlated, BDI seems to have stronger impact particularly on nighttime sleep. Thus, appropriate treatment of depression may be a therapeutic option for PD patients with sleep problems. Poorly levodopa-responsive symptoms such as falls also correlated with sleep quality, as did fluctuations. Taken together, the association with disease duration, symptoms and affected status suggest sleep alterations to be an integral part of PD.

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The impact of depression on sleep quality and excessive daytime sleepiness in Parkinson's disease patients

N. Klepac, M. Titlic, D. Britvic, I. Lusic, L. Unusic (Zagreb, Croatia)

Objective: To evaluate the sleep disorders in Parkinson's disease (PD) patients and its relationship with depression.

Background: Sleep disorders occur commonly in PD, and may have a substantial impact on quality of life. Sleep-related problems in PD can be divided into disturbances of nighttime sleep and wakefulness manifesting as excessive daytime somnolence. Sleep disorders in PD may occur as a direct consequence of the disease process itself or it may be secondary to factors associated with the condition, such as mood disturbances and effects of medications.

Methods: A total of 195 outpatients, diagnosed as having idiopathic PD in accordance with the United Kingdom Parkinson's Disease Society Brain Bank criteria, were evaluated by Pittsburgh sleep quality index (PSQI), Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn &Yahr staging (H&Y), Epworth Sleepiness Scale (ESS) and Beck Depression Inventory (BDI). Patients were divided into two groups in terms of BDI score: depression and non-depression group. A 172 patient who fulfilled the criteria for major depression matched for age, gender and disease duration were included as control group.

Results: Sleep quality on PSQI was significantly poorer in the group of depressed patients as compared to general PD patients. Depressed PD patients had poorer sleep quality than non-depressed one but still better than patients with major depression. This was evident in several component of PSQI; sleep latency, sleep duration and frequency of nighttime problems. In PD patients sleep quality correlated with duration of the disease, disease severity and depression. Moreover, depression scores accounted for most of the variance in a stepwise regression analysis on sleep quality. Excessive daytime somnolence was more pronounced in the group of PD patients as compared to patients with major depression. There was no correlation between sleep quality and excessive daytime somnolence, but strong correlation was found with disease severity and dopamine agonist.

Conclusions: Depression was the most important factor associated with the sleep disorder among patients with PD. As contrary to sleep disorders during night daytime somnolence was independent of depression and was intrinsic to PD patients.

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Sleep related comfort in patients with Parkinson's disease

S.M. Nica, G. Mihailescu, I.E.-V. Davidescu, S.C. Nica (Bucharest, Romania)

Objective: To evaluate the frequency of sleep disorders in patients with PD and the improvement of quality of life by treating this symptom.

Background: Patients with Parkinson's disease (PD) complain of sleep disorders more often than patients with other chronic diseases. Sleep disorders and daytime fatigue associated with PD are common and under-recognised problems.

Methods: We tried to answer this question by evaluating 35 patients (22 male and 13 female), mean age 63.2 years, with a mean duration of PD of 4,5 years, followed up for 2 years on 6 weeks basis, using the Epworth Sleepiness Scale (ESS), Parkinson's Disease Sleep Scale (PDSS), EQ-5D Questionnaire, UPDRS II, PDQ 39, Hoehn & Yahr scale and CGI. They were treated the first year with a non-ergot dopamine agonist and the second year levodopa products and COMT inhibitors were added.

Results: 41% of patients had impaired sleep perception and were unaware of having daytime sleep episodes (big differences between personal and relatives rating). 18% of them had daytime sleepiness, but no sleep attack reported. Quality of life (QoL) deteriorated significantly with increasing disease severity, but also by the presence of sleep disorders. Sleep disorders were more often present in advanced

PD and was more frequent in patients treated with dopamine agonists.

Conclusions: Sleep disorders are frequent in PD and, due to the impact on daytime activities, are influencing QoL. Treatment of PD is primarily aimed to improve motor function. However, advanced PD is often complicated by additional problems such as sleep disorders. Males with higher Hoehn and Yahr stage, dysautonomia and longer disease duration had higher ESS scores. Dopamine agonists treatment controlling optimally the motor symptoms led to an increased quality of life despite the increase of 1.5 points on the ESS. Our data show that associating general lifestyle modifications (rest and exercise) and physical therapy to antiparkinsonian and simptomatic treatment may influence sleep disorders and increasing QoL.

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Does idiopathic restless legs syndrome protect against Parkinson's disease

D.M. Elizabeth, W.G. Ondo (Houston, Texas, USA)

Objective: To explore the hypothesis that restless legs syndrome (RLS) protects or mitigates Parkinson's disease (PD) onset and severity.

Background: Studies of PD populations show that about 20% of PD patients meet criteria for RLS, however, the vast majority of patients present with PD first. No study has yet evaluated patients who have idiopathic RLS and later develop PD. Despite similar treatments, the pathology of PD and RLS are contradictory in two regards–PD has reduced dopamine whereas RLS has increased dopamine turnover, also PD has increased CNS iron deposition whereas RLS has reduced CNS iron. It is therefore possible that idiopathic RLS could actually protect against PD.

Methods: Patients with idiopathic RLS preceding PD onset, as defined by onset of RLS greater than 5 years before motor symptoms of PD, or a family history of RLS in a first degree relative and onset of RLS anytime before PD, were collected from the Baylor College of Medicine Parkinson's Disease Center database. They were compared to a group of patients with idiopathic PD prospectively collected consecutively over two weeks. We compared demographics, age of onset, appearance of dyskinesia, L-dopa equivalent dose, and basic PD phenotype at onset.

Results: The RLS/PD group: N=31, 13 female, 18 positive family history of RLS, 6 with family history of PD. PD group: N=31, 9 females, 1 with family history of RLS, 9 with family history of PD. Age at onset of RLS/PD was 65.10±6.5yr vs. 56.67±11.47 for patients with idiopathic PD ($p<0.01$). Patients in idiopathic PD developed dyskinesia 14/31 vs 2/21 RLS/PD patients at last follow-up ($p<0.01$). PD phenotype and L-dopa dose were similar in both groups. Only 1 patient amongst those with RLS and PD was referred for RLS.

Conclusions: Idiopathic RLS may delay the onset of PD, reduce dyskinesias, and may reduce progression of PD.

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Cyclic alternating pattern (CAP) in *de novo* Parkinson's disease

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Objective: To analyze cyclic alternating pattern (CAP) parameters scoring in *de novo* PD patients.

Background: Sleep disturbances are a frequent problem in Parkinson's disease (PD) patients. Several studies have been carried out analyzing sleep macrostructure in PD. CAP has become a tool for the comprehensive analysis of sleep microstructure. CAP is a periodic electroencephalogram (EEG) activity of NREM sleep characterized by sequences of cycles composed by a phase A (transient eletrocortical event) and a phase B (recurring EEG background activity).

Methods: Seven untreated PD patients (57% male, mean age: 64.1±6.5 years) and eight non-PD volunteers (50% male, mean age: 66.6±6.5 years) were enrolled in the study. Subjects slept two nights in the sleep laboratory. Polysomnographic recording was carried out during the usual sleep time on a 64-channel Racia-Alvar digital system (Deltamed software, 256Hz and 16bit resolution). The recording protocol followed standard American Academy Sleep Medicine (AASM) guidelines. Sleep recordings were visually scored according to AASM criteria by a trained rater blinded to diagnosis condition. CAP was scored according to the published criteria.

Results: Conventionally scored sleep variables did not show any significant differences between control and PD groups. Considering total NREM sleep, d*e novo* PD patients showed lower CAP A phase duration and CAP A subtypes duration than control subjects (Mann-Whitney U test $p<0.02$). Percentage of CAP A2 was significantly lower in PD group (Mann-Whitney U test $p=0.037$). PD subjects showed statistically significant lower A3 duration in N1 and N2 stages. PD patients showed higher number of A3 occurrences in N2 stage (Mann-Whitney U test $p=0.021$). According Pittsburg Sleep Quality Index (PSQI) score, worse sleep quality was associated with higher number of the CAP A3 subtype ($r_s=0.58$; $p=0.023$).

Conclusions: PD patients have showed significant differences in CAP A phases. Considering these preliminary results, authors suggest that CAP analysis could be a useful tool for sleep research in PD.

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Sleep-related falling out of bed (SFOB) in Parkinson's disease: A clinical marker of RBD?

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Objective: To (1) describe sleep-related falling out bed (SFOB) in Parkinson's disease as a potential clinical surrogate for REM sleep behavior disorder (RBD) and (2) describe the REM Behavior Disorder Screening Questionnaire (RBDSQ) scores in a PD population.

Background: SFOB in Parkinson's disease has been mentioned in studies concerning self-injury during sleep and sleep-related violence but has not been the focus of previous investigations. The RBDSQ is a sensitive screening tool for RBD validated against sleep disorders patients and healthy sleepers (Stiasny-Kolster *et al*. Mov Disord 2007) but its discriminatory values for RBD in PD are unknown.

Methods: We performed a retrospective analysis of 50 consecutive PD patients seen at the University of Miami Movement Disorder Clinic, who completed an initial clinical examination and the RBDSQ amended with questions about SFOB and resulting injuries. A general sleep questionnaire to assess for RBD clinical mimickers was also completed. Diagnosis of RBD was based on criteria determined by the International Classification on Sleep Disorders-Revised Diagnostic and Coding Manual (2001).

Results: Mean age of the 50 PD patients (34 men, 16 women) was 68.0±11.6 years, the age of PD onset was 59.4±12.8 years with a PD duration of 8.5±4.3 years and Hoehn-Yahr stage mean of 2.1±0.4. Thirteen patients reported history of SFOB (26%). Seventeen patients (34%) fulfilled diagnostic criteria for RBD, 10 of which (58.8%) reported SFOB. Five patients reported injuries related to SFOB. As expected, RBD patients had significantly higher mean RBDSQ scores than those without (8.0±2.5 vs. 2.8±1.5, $p<0.001$). SFOB patients had higher RBDSQ scores than the remaining sample (non-SFOB) (8.2±3.0 vs. 3.3±2.0, $p<0.01$). Among those with RBD, patients with SFOB scored higher than the non-SFOB group (9.3±2.3 vs. 6.3±1.6, $p=0.014$).

Conclusions: (1)We propose that SFOB may be a clinical marker of severe RBD and should prompt rapid confirmatory polysomnography (PSG) and pharmacologic treatment to avoid imminent injury. (2) The RBDSQ is useful in detecting RBD in PD with similar score distribution for RBD in PD as reported for other RBD patients corroborated by PSG.

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Is there correlation between tear of the rotator cuff and REM sleep behavior disorder in patients with Parkinson's disease? A preliminary study of 20 patients

H.A.G. Teive, R.P. Munhoz, N. Becker, P.S. Santos, L.C. Werneck (Curitiba, Parana, Brazil)

Objective: To determine whether there is correlation between rotator cuff tear and presence of REM sleep behavior disorder (RBD) in 20 patients with Parkinson's disease (PD).

Background: Shoulder disorders are very common in patients with PD, including shoulder pain, frozen shoulder, adhesive capsulitis, myofacial pain syndrome and, particularly, rotator cuff tear. RBD has been reported in association with many neurodegenerative disorders, predominantly synucleinopathies, such as PD.

Methods: Twenty patients with PD and with shoulder pain, were evaluated in our study. All of them met the clinical diagnostic criteria for PD, as described by the UK PD Society Brain Bank. Patients underwent a neurological examination and an orthopaedic assessment. The Hoehn-Yahr stage was determined. Patients underwent an ultrasound or MRI exam of the shoulder searching rotator-cuff changes (partial or complete tear of the rotator cuff). RBD was defined as "Clinically probable RBD" and polysomnography was performed in four patients ("Definite RBD").

Results: There were 10 males and 10 females with a mean age of 72,8 years (range, 52-84 years) and mean Hoehn-Yahr stage=2,85. The mean duration of disease was 12,15 years (range, 5-22 years). Partial or complete rotator cuff tear was detected in 13 patients (65%) and "Clinically probable RBD" in 12 patients (60 %). Rotator cuff tear was associated to RBD in 76,93 % of the patients. In 23,07% of the patients we found rotator cuff tear without RBD. In the group of patients without rotator cuff tear (n=7) RBD was diagnosed in 28,57%.

Conclusions: In this preliminary study with 20 patients with PD and shoulder pain, we found a robust relationship between rotator cuff tear and clinically probable RBD.

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Effect of rotigotine on sleep and nocturnal symptoms in Parkinson's disease: RECOVER study

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Objective: To assess the effects of 24-hour transdermal delivery of the non-ergoline dopamine receptor agonist, rotigotine, on sleep and nocturnal symptom outcomes in subjects with idiopathic Parkinson's disease (PD).

Background: Few controlled studies have evaluated the treatment of sleep problems in PD as a primary outcome measure.

Methods: This was a multicenter, multinational, double-blind, placebo-controlled, parallel-group trial (NCT00474058) (partly presented at the XVIII WFN World Congress on Parkinson's Disease and Related Disorders; Miami Beach, FL, USA; December 2009). Subjects with idiopathic PD and unsatisfactory early-morning motor control were randomized 2:1 to receive rotigotine (2-16 mg/24h) (n=190) or placebo (n=97). Treatment was titrated to optimal dose over 1 to 8 weeks and maintained at that dose for a further 4 weeks. Subjects were hospitalized for 2 nights before assessment at baseline and again at end of maintenance. The coprimary endpoint was the mean change in modified Parkinson's Disease Sleep Scale (PDSS-2) total score from baseline to end of maintenance (Full Analysis Set, last observation carried forward). The PDSS-2 assesses sleep disturbance, early morning akinesia, and nocturnal motor and non-motor symptoms. Mean changes in PDSS-2 domain and individual item scores were additional exploratory endpoints. Treatment differences were estimated using an ANCOVA model.

Results: Baseline mean (SD) PDSS-2 total scores were similar between treatment groups (placebo, 20.3 [10.2]; rotigotine, 19.3 [9.2]). The rotigotine group (n=178) showed significantly greater improvement than the placebo group (n=89) in PDSS-2 total score and in all PDSS-2 domains of "disturbed sleep", "motor symptoms at night", and "PD symptoms at night" (Table). All PDSS-2 individual items except one ("distressing hallucinations") showed improvement during rotigotine treatment, with $p<0.05$ versus placebo on 10 items (Table).

Conclusions: In this study, once-daily rotigotine treatment is associated with beneficial effects on sleep and nocturnal symptoms in subjects with idiopathic PD.

TABLE (759).

PDSS-2	Least squares mean (95% CI) treatment difference	P-value
Total score	-4.26 (-6.08, -2.45)	<0.0001
Disturbed sleep	-1.40 (-2.22, -0.58)	0.0009
Poor sleep quality	-0.20 (-0.44, 0.05)	0.1229
Difficulty falling asleep	-0.46 (-0.72, -0.19)	0.0008
Difficulty staying asleep	-0.19 (-0.46, 0.08)	0.1673
Tired and sleepy in the morning	-0.40 (-0.67, -0.13)	0.0036
Got up to pass urine	-0.21 (-0.45, 0.04)	0.0982
Motor symptoms at night	-1.54 (-2.24, -0.84)	<0.0001
Restlessness of legs or arms	-0.36 (-0.59, -0.13)	0.0025
Urge to move legs or arms	-0.43 (-0.66, -0.20)	0.0003
Distressing dreams	-0.11 (-0.29, 0.08)	0.2543
Painful posturing in the morning	-0.34 (-0.56, -0.12)	0.0027
Tremor on waking	-0.33 (-0.59, -0.06)	0.0153
PD symptoms at night	-1.41 (-2.08, -0.74)	<0.0001
Distressing hallucinations	0.00 (-0.15, 0.14)	0.9464
Uncomfortable and immobile	-0.49 (-0.73, -0.25)	<0.0001
Pain in arms or legs	-0.36 (-0.59, -0.14)	0.0015
Muscle cramps in arms or legs	-0.31 (-0.53, -0.09)	0.0067
Breathing difficulties or snoring	-0.24 (-0.42, -0.07)	0.0064

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Clinical and polysomnographic features of sleep disorders in Mexican Parkinson's disease patients

A. Velez-Cedeño, V. Alatriste-Booth, M. Rodríguez-Violante, A. Cervantes-Arriaga, T. Corona (Mexico City, Mexico)

Objective: To assess the clinical and polysomnographic features of sleep disorders in a sample of Mexican patients with Parkinson's disease.

Background: Parkinson's disease (PD) is a neurodegenerative disease which has a recognized pre-motor phase. Up to 20% to 90% of the patients present sleep disorders like insomnia and REM behavior disorder. These sleep disorders may even precede the motor manifestations by years or may worsen with disease progression making early diagnosis of great importance.

Methods: A cross-sectional study was carried out. Patients referred from the movement disorders outpatient clinic for evaluation at the sleep disorders clinic from August to November 2009 were included. NMSQuest and Epworth sleepiness scale were applied as a screening tool. A night polysomnography was carried out.

Results: 30 patients were referred to our clinic in the study period. Two patients were excluded since PSG was not valorable. 28 PD patients (57.1% men) were analyzed. Mean age at PD diagnosis of 59.6±13 years. Mean UPDRS III score was 38.9±19.9. 71.4% had tremor as the initial symptom while the remaining were bradykinetic/rigid. The mean Hoehn-Yahr stage was 2.3±0.8. All patients referred at least one sleep disturbance in the NMSQuest. Mean percentage of sleep efficiency was 58.8±18.5%. REM sleep latency was 200.3±100.7 and mean total sleep time was 293.2±106.7 minutes. Percentage of each sleep phase was as follows: phase one19.6±11.2%, phase 2 60.5±18.3%, phase 3 15.6±11.1% and REM 11.2±7.4%. Obstructive sleep apnea was diagnosed in 42% of the patients. Periodic limb movement disorder was found in 21% and REM sleep behavior disorder (RBD) in 46% (38% were subclinical). No significant differences were found between genders.

Conclusions: Sleep dysfunction and sleep disorders are common in patients with PD. All patients referred to the clinic due to self-reported sleep disorders had an abnormal polysomnography. PSG architecture in our sample was similar to other reports. Caregivers should be aware that RBD is frequent but may be subclincal and a night PSG is recommended for a complete analysis of sleep architecture.

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Parkinson's disease patients: "Owls" or "larks"

A. Videnovic, C. Noble, A. Marconi, T. Kuhta, C. Zadikoff, T. Simuni, P. Zee (Chicago, Illinois, USA)

Objective: To examine different chronotypes, and their associations with demographics, sleep quality, and disease characteristics of patients with PD.

Background: Chronotype (circadian type) is an individual diurnal preference, often referred to as "morningness/eveningness". As intrinsic human attribute, chronotype has important influence on mental and physical performance. The Horne-Ostberg Morningness-Eveningness Questionnaire is a validated tool developed to measure the chronotype spectrum. Circadian types and their impact on PD have not been studied in the PD population.

Methods: The Horne-Ostberg Morningness-Eveningness Questionnaire (HOQ) and Epworth Sleepiness Scale (ESS) were administered to consecutive patients in a sub-specialty PD clinic. Additional data included demographics, disease duration, sleep duration, and medication regimen. Summary statistics were used to summarize data. Associations of HOQ with other variables were evaluated via Pearson rank correlations and ANOVA.

Results: 100 subjects (53M/46F), age (median, range) 65.5 (40-90) years, disease duration 4 (1-37) participated in this study. Employment status was: employed 30%, unemployed 4%, retired 65%. Sixty subjects (60%) had HOQ scores $\geq$59 and were qualified as morning types. Three subjects (3%) had HOQ scores $\leq$41 and were qualified as evening types. Thirty seven subjects (37%) had HOQ scores between 42 and 58 (neither type). Associations among chronotypes and age, disease duration, ESS score, and sleep duration were not statistically significant. Median ESS score was 9 (range 0-19). Fifty six subjects (56%) had ESS scores $\geq$10 (indicative of excessive sleepiness). Associations between ESS score and age, disease duration, and sleep duration were not statistically significant.

Conclusions: Dominant chronotype in our PD cohort was the "morning" type. Significant correlations were not found between chronotypes and age, disease duration, and daytime sleepiness. A larger study, including age matched controls, is underway to examine relationship between chronotypes and circadian misalignment in PD.

POSTER SESSION 3
WEDNESDAY, JUNE 16, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

RATING SCALES

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Influence of age and gender in motor performance in healthy subjects

F.J. Jiménez-Jiménez, M. Calleja, H. Alonso-Navarro, L. Rubio, F. Navacerrada, B. Pilo-de-la-Fuente, J.F. Plaza-Nieto, P.J. García-Ruiz, J.A.G. Agúndez (Arganda del Rey, Madrid, Spain)

Objective: With the aim of analyse the possible influence of age and gender in motor performance; we analyzed basic motor function in a large series of healthy sex-matched individuals aged >40 years.

Background: Slowing of motor performance in human aging is a well demonstrated clinical observation. Information on the influence of gender in motor performance is less well-established.

Methods: We studied 246 subjects (123 males and 123 females; mean age 63,67$\pm$10,79 and 63,61$\pm$11,04 years, respectively), stratified by age in 7 groups for each gender: A (41-50 years, n=19), B (51-55 years, n=12), C (56-60 years, n =12), D (61-65 years, n=24), E (66-70 years, n=17), F (71-75 years, n=23) and G (>75 years, n=16). Evaluation included four timed tests (pronation-supination, finger tapping and movement between two points, all with both hands, and walking test); and three tests performed on a personal computer (speed for pressing repetitively a key–frequency, visual reaction time and movement time, all with both hands). Statistical analysis included two-ways analysis of variance (ANOVA) for two factors (age and gender) and Pearson's or Spearman's correlation tests where appropriate.

Results: The analysis of motor performance between subgroups showed a clear influence of age on motor performance of all the tests, with the exception of the left visual reaction time. Moreover, the results of all the motor tests performed were inversely correlated with age. Gender showed a clear influence in the performance (the speed of motor performance was significantly better in males) of all the tasks with the exception of left pronation-supination, and left and right visual reaction time.

Conclusions: Our results confirm in a large series of healthy subjects that basic motor performance deteriorates with age and is influence by gender.

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A novel and systematic approach to evaluating lower limb apraxia in Parkinson's disease

L. King, Q. Almeida, E. Roy (Waterloo, Ontario, Canada)

Objective: To evaluate the presence of upper vs. lower limb apraxia in Parkinson's disease (PD) using a newly developed and systematic tool to assess lower limb apraxia.

Background: Gait apraxia is one of the most poorly understood symptoms in neurology. Upper limb apraxia is typically evaluated using a multimodal gesture approach, but due to the lack of similar lower limb assessment tools, the link between upper and lower limb apraxia has been largely unexplored. In stroke, greater cortical damage is associated with a higher co-existence of upper and lower limb apraxia (Ambrosoni et al, 2006). Basal ganglia damage is also believed to contribute to apraxia, although the relationship between PD severity and co-existence of upper and lower limb apraxia has yet to be studied. Thus, a systematic method of lower limb apraxia test was developed and contrasted to a well established method for upper limb apraxia assessment (Roy et al.,1994) in order to answer these questions.

Methods: Praxis was examined in 48 individuals with PD and 16 healthy controls using the Waterloo-Sunnybrook Apraxia Battery and a newly created battery for lower limb apraxia. As in the upper limb assessment, patients were asked to perform i) transitive gestures (eg. push a gas pedal), ii) intransitive gestures (eg. stomp your foot), and iii) meaningless gestures (eg. plant one foot forward, drag ipsilaterally) in the context of pantomime (i & ii) and imitation (i,ii, & iii) with each leg. Each participant's performance was evaluated on a detailed criteria that factored in movement location, joint posture, action characteristics, movement plane, and foot orientation. Z scores of the PD population were then computed relative to the control data in order to identify apraxic individuals ($Z \leq -2$). Apraxic patients were divided into high and low severity groups for PD symptoms as determined by the UPDRS.

Results: Apraxia was identified in both groups and all conditions. Interestingly, the low severity group (UPDRS=31.2) showed the

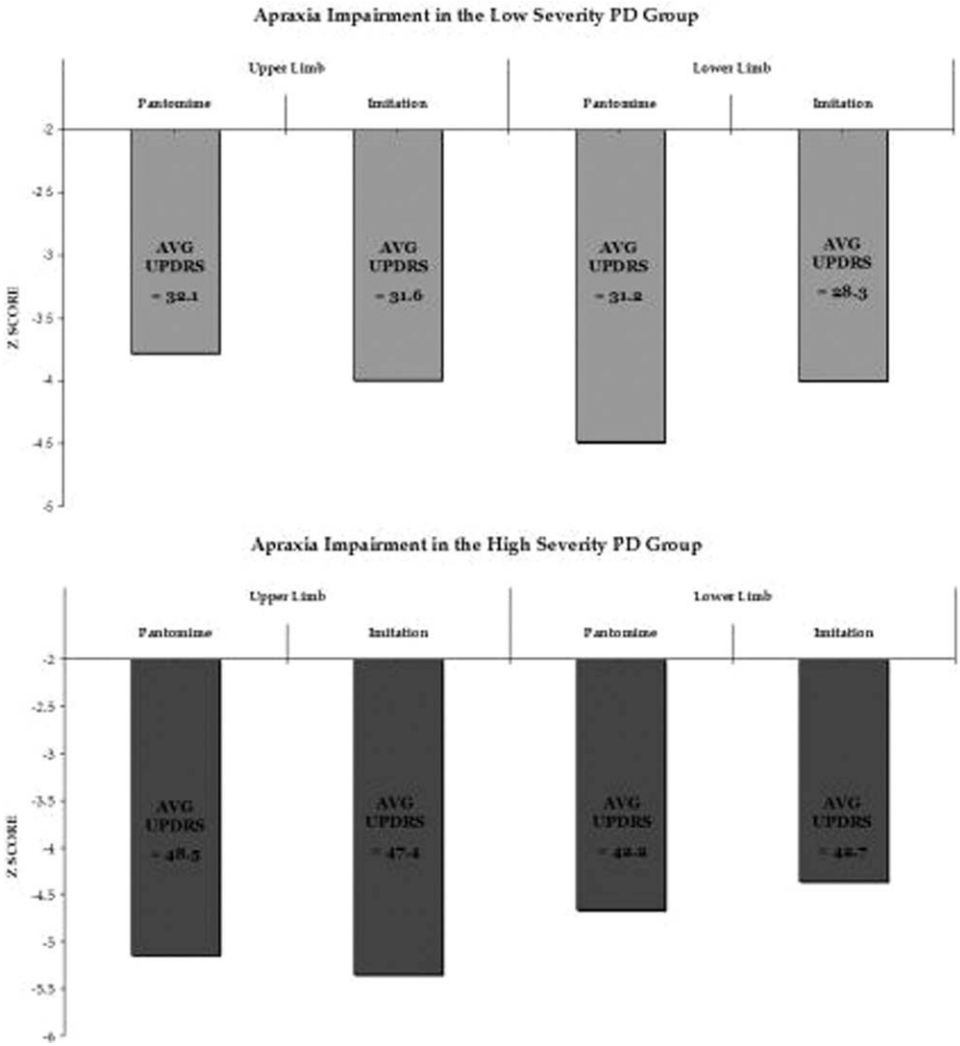

FIG. 1 (763).

greatest apraxia impairment in the lower limb pantomime task (Z=-4.48), while all other tasks resulted in similar performance.

Conclusions: The current study suggests that lower limb apraxia may be more readily identified (than upper limb) in less severe PD patients. Thus, assessment of lower limb apraxia may be important to include (and consider) in treatment and diagnosis of PD.

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Potential practical difficulties in the administration of the updated Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

M.A. Humphreys, B. Mohamed, E. Morgan, D. Sastry, C. Thomas (Cardiff, Wales, United Kingdom)

Objective: To assess ease of application of the MDS-UPDRS and identify problems with its use.

Background: Parkinson's disease (PD), is a neurodegenerative disorder which manifests with a wide spectrum of motor and non-motor symptoms. Treatment of PD may induce further motor and non-motor adverse effects. The Movement Disorder Society-sponsored revision of the Unified PD Rating Scale was developed to clinically rate PD symptoms and also to monitor disease progress and its management. This scale may be associated with some difficulties in interpretation of questions and in application of the scale overall.

Methods: Following a 4 patient pilot study, the main study involved 53 patients with PD seen in Cardiff outpatient/day hospital specialist movement disorder service. MDS-UPDRS was used (Part 1a by a medical student, Parts 1b and 2 by patient +/- carer). Total scores were recorded, and feedback obtained by means of questionnaire and interview regarding ease of use of the scale and its reflection of the patients' perceived condition.

Results: Mean MDS-UPDRS score=38 (14-69). A number of problems with the scale's use were identified relating to day-to-day variability in disease severity, motor fluctuation, interpretation of questions and confounding factors such as co-morbidities and their treatments. Greater intra-patient variation in self-assessment occurred when no carer participated in completion of the scale, and many problems related to questions being too specific to assess more complex clinical problems.

Conclusions: The MDS-UPDRS was well received by people with PD. The majority of problems identified were observed, not reported. Patients reported very few difficulties with the questionnaire. Carer participation in scale-completion appeared to enhance clarity of responses. Further research is needed to assess differences in objec-

tive and subjective completion of the scale between patients/carers and healthcare professionals.

POSTER SESSION 3
WEDNESDAY, JUNE 16, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

SURGICAL THERAPY: PARKINSON'S DISEASE

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Functional stereotopy of the subthalamic nucleus. Circuitry projections and somatotopy within the Schaltenbrand-Wahren Atlas virtual model

M.S. Alvarez, L.G. Alvarez (Havana City, Cuba)

Objective: Suggest circuitry projections and somatotopy of the Subthalamic nucleus on a Schaltenbrand-Wahren Atlas virtual model, which could serve as a guide in future approaches and registering descriptions.

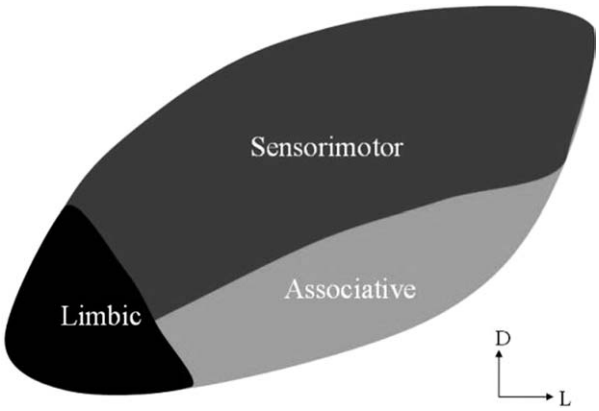

FIG. 1 (765).

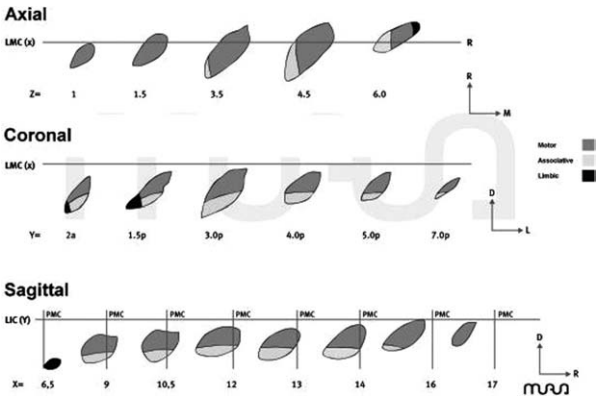

FIG. 2 (765).

Background: Functional territories of the subthalamic nucleus could be a key for successfully surgical approach. For this reason, its knowledge is every time more indispensable and it should be much more precise as to its functional parcelling.

Methods: We have taken as initial reference the classical distribution in which the most medial region corresponds with the limbic area, the dorsolateral region with the sensorimotor area and the ventral region with the associative area. The major axis was divided into six equal parts. The most medial part is called limbic portion and the most lateral one, motor portion. A perpendicular line was traced to the major axis at the point marked by its more medial 6th, which is called limbic line. A ventral line was traced from the limbic line's inferior division up to the ventral border of the motor line. In this way, the nucleus is divided into three areas corresponding with coronal cuts performed in monkeys. The motor area was redistributed in six equal parts through the major axis.

Results: Due to the fact that the major axis is not parallel to any of the three planes, none of the SW Atlas cuts include the three functional areas in all their extension. Coronal and axial cuts are the ones that include the major parts of the representation, as they are planes of a major parallelism with the nucleus' major axis in this atlas. On the contrary, sagittal cuts include small portions, as this plane is practically perpendicular to STN major axis, as represented in the sagittal cuts. No sagittal cut contains the three circuitries.

Conclusions: STN somatotopy distribution varies according to the dependency of selected microseries. In this way, the coronal cuts are more representative, the authors suggest that they be used in the registers' representations of future investigations. This adds the advantage of an easy comparison with the results in animal models. On the contrary, each cut of the sagittal plane has an incomplete representation of circuitries, a reason why they should not be used in the projection of registering results.

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Quality of life after DBS STN in Parkinson's disease is related to the stimulation amplitude

M. Baláz, M. Bocková, I. Rektor (Brno, Czech Republic)

Objective: To observe whether stimulation parameters can improve quality of life (QoL) of patients with Parkinson's disease beyond the usual improvement of motor functions.

Background: Deep brain stimulation of subthalamic nucleus (DBS STN) is an important surgical treatment of advanced Parkinson's disease improving the cardinal/major clinical symptoms. As this therapy is not curative, but symptomatic, it appears to be very important to assess and observe the quality of life. Certain group/part/subgroup of patients with PD has the QoL influenced more by the non-motor symptoms and thus the parameter selection for these patients can be insufficient if based only on the purely motor assessment.

Methods: We compared DBS amplitude and QoL in two groups of patients with PD 24 months after the DBS surgery. Each group consisted of 5 patients with similar clinical profile (duration of disease, timing of DBS surgery in course of PD, L DOPA dose, age, stimulation amplitude). Group A consisted of patients who required further increase of stimulation amplitude 2 years after DBS, despite clinically significant improvement of their motor functions as judged by experienced clinician (UPDRS III was used). Group B consisted of 5 matched patients who were satisfied with their DBS parameters and overall clinical state 2 years after the surgery. The QoL was assessed by PDQ - 39 questionnaire.

Results: The quality of life was significantly improved in both groups of patients correspondingly with their UPDRS III improvement. However, group A (patients demanding the stimulation increase) showed a less important improvement of QoL compared to group B, despite their good motor function. After the further increase of the amplitude stimulation in group A (mean increase of amplitude of 0.4 V), there was a tendency of additional improvement of PDQ-39 without any observable improvement of motor functions.

Conclusions: In certain subset of PD patients the increase of stimulation amplitude has a potential to improve some non-motor functions and thus have an additional effect on quality of life. The meticulous observation of QoL should be a routine part of assessments before and after the DBS STN surgery and can even aid during the parameter setting.

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Impulse control disorders in PD patients who have undergone DBS surgery

A. Bharmal, C. Lu, J. Quickfall, A. Haffenden, S. Kraft, Z. Kiss, O. Suchowersky (Calgary, Alberta, Canada)

Objective: To 1) determine the prevalence and 2) describe the treatment outcomes of impulse control disorders (ICD) in PD patients who have undergone deep brain stimulation surgery (DBS).

Background: DBS is thought to influence mood and behavior in PD patients. ICD is such a behavior that requires further investigation in this population. Here we describe our experience in managing such disorders in PD patients who have undergone DBS surgery.

Methods: Chart review of all patients who had undergone DBS surgery from 1999-2008 was performed. Patient demographics, PD duration, medications, ICD presence, and severity of ICD were queried as part of routine clinical care. ICD was defined using the criteria set forth by the Minnesota Impulse Disorder Interview.

Results: 43 patients had STN-DBS and 6 had GPi-DBS between 1999-2008. Full follow-up information was available for 26 of these patients. Five had an ICD of pathological gambling (4/5) or hypersexuality (1/5). Mean levodopa equivalent daily dose was significantly reduced following surgery at all time points, including in the 5 ICD patients ($p=0.036$). Two developed de novo ICD post-operatively (although both had gambled some pre-operatively). 3/5 patients described feeling more impulsive following surgery, and 2/3 patients with pre-DBS ICD described a worsening of their symptoms with continued financial losses after surgery. All patients experienced partial or full remission of their ICD symptoms through family taking control of their finances (2/5), switching (1/5), discontinuing (2/5), or decreasing dopamine agonist dose (4/5), and addictions programs (2/5). Four patients described significant marital strains: one couple divorced and another had relational strains from disinhibition and anger management.

Conclusions: Despite decreasing dopmaine agonist and levodopa equivalents following DBS surgery, patients with pre-existing ICD continue to exhibit hypersexuality or pathological gambling, and de novo ICD can develop. Given such behavior even with a decrease in dopamine use, information on any ICD should be elicited routinely from all patients being considered for DBS surgery. More information is needed to determine the effect of DBS on ICD.

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Short and long-term effects of DBS on gait and other symptoms of Parkinson's disease

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Objective: Aim of this study was to compare the short and long-term effects of subthalamic nucleus (STN) deep brain stimulation (DBS) on Parkinson's disease (PD) symptoms.

Background: Gradual gait deterioration in PD patients after DBS is usually put down to the natural progression of the disease. However, the cause may also lie in a selectively decreasing effect of stimulation on gait disorders, or in chronic DBS negative impact on stability and gait.

Methods: Two groups of patients were studied. The first group (DBS1, N=8) included patients implanted with STN DBS 1-2 years earlier (mean time since DBS implantation 15.8 month, mean age 58.8 years, PD duration 13 years); the second group (DBS5, N=10) included patients with at least 5 years of DBS therapy (mean time since DBS implantation was 67.6 month, mean age 61.7 years, PD duration 17.1 years). Both groups were examined during four clinical medication/stimulation states (On/Off; Off/Off; Off/On; On/On). Unified Parkinson's Disease Rating Scale (UPDRS) and Gait and Balance scale (GABS) were used for the evaluation. Data was analyzed using repeated measures ANOVA with time since implantation (years) between group and therapy or DBS effect (On, Off) within group.

Results: In group DBS1, active DBS improved all clinical subscores except tremor, similar to medications. In group DBS5, DBS improved all clinical subscores with the exception of gait and postural instability. However, the effect of levodopa on gait was partially preserved.

Conclusions: The effect of STN DBS on PD appears not to be constant in time. Short term stimulation has a positive effect on the majority of PD symptoms, including gait disorder; however, long-term stimulation loses its efficiency on gait while maintaining stable effectiveness for other symptoms. Levodopa effect on gait abnormalities also declined over time, but was still preserved in patients with long-term stimulation.

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Target specificity for post-DBS anger

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Objective: The purpose of the study was to see if deep brain stimulation of the subthalamic nucleus (STN), the globus pallidus internus (GPi), or the ventralis intermedius nucleus (Vim) was associated with increased anger states post-surgical intervention.

Background: The COMPARE DBS trial suggested that patients with STN DBS had a trend towards higher anger scores.

Methods: All patients at the University of Florida Movement Disorders Center who received DBS for Parkinson's disease or Essential Tremor with targets of STN, globus pallidus internus (GPi), or ventralis intermedius (Vim) were included. Patients operated on at other institutions were excluded. Pre- and 4-6 month postoperative Visual Analog Mood Scales (VAMS) scores for all groups were compared. A linear regression model analyzed relationship between the VAMS anger score and independent variables such as age, years with symptoms, MMSE score, handedness, ethnicity, gender, side of surgery, target of surgery, baseline DRS total, baseline BDI score, and education.

Results: A total of 322 operations were analyzed, with N=195 for STN, N=71 for Vim, and N=56 for GPi. The only subset of VAMS scores to show a statistically significant change between the three targets was the anger subset, with GPi having mean (standard) changes of 2.38 (9.53), STN 4.82 (14.52), and Vim -1.17 (11.51) ($p=0.012$). The linear regression model analyzing for independent variables revealed a relationship with the VAMS anger score which showed that surgical target and disease duration were significantly associated with VAMS anger score changes. On average, STN and GPi surgeries had a change of 11.95 ($p=0.001$) and 8.44 ($p=0.022$) units, respectively, compared to Vim. For every year of disease duration, the VAMS anger score change increased by 0.24 ($p=0.023$).

Conclusions: STN and GPi DBS are associated with significantly higher anger scores as measured by the VAMS scales. Vim did not reveal a relationship. The target specificity for this mood change may be revealing when considering lesional and stimulation induced effects. More study is needed.

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Active contact location and acute mood response to STN DBS stimulation in Parkinson's disease

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Objective: The purpose of this study was to 1) examine the effects of unilateral and bilateral STN DBS stimulation of the clinically

determined optimal electrode contact on acute mood response and 2) investigate the influence of contact location on stimulation-induced acute mood responses.

Background: Previous work has suggested that bilateral deep brain stimulation of the subthalamic nucleus (STN DBS) in Parkinson's disease (PD) not only improves motor functioning but affects mood as well. However, little is known about the effects of electrode contact location on acute mood response to STN DBS.

Methods: We identified the location of the clinically chosen contacts and measured acute mood response to stimulation with the Visual Analog Scale in 26 PD patients with bilateral, monopolar STN DBS. Patients were off PD medications overnight and were assessed with both stimulators off, both stimulators on, left stimulator on only and right stimulator on only in a counterbalanced and double-blind manner.

Results: Participants reported significantly improved positive mood as well as decreased anxiety and apathy with bilateral stimulation ($ps<.05$) and a similar pattern for unilateral stimulation. Only change in apathy ratings was related to change in UPDRS motor ratings for bilateral stimulation ($p<.05$). There was no relationship between left unilateral stimulation-induced changes in mood and location of active contact ($ps>.10$). Right unilateral stimulation-induced acute change in positive mood was significantly correlated with the right "Z" axis coordinate (both $p = .05$), such that a more positive mood response was associated with more dorsal right active contacts. There was no relationship between stimulation-induced change in UPDRS motor ratings and active contact location ($ps>.10$).

Conclusions: These data suggest that unilateral and bilateral STN DBS stimulation affect acute mood, with an overall improvement in mood ratings. For these clinically chosen contacts, mostly surrounding dorsal STN, there was a limited relationship between contact location and acute mood response. It remains possible that stimulation of other portions of the STN may produce different acute mood responses.

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The dominant-STN in Parkinson's disease: A new concept?

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Objective: To investigate the presence and the significance of a "dominant subthalamic nucleus (STN)" in Parkinson's disease (PD) patients with bilateral STN deep brain stimulation (DBS).

Background: Bilateral STN-DBS is effective in improving motor symptoms in PD. Unilateral STN-DBS is performed in patients with relevant hemiparkinson or with contraindications for bilateral surgery. We observed that in some PD patients the motor improvement from one STN alone (the "dominant STN") was equal to the benefit achieved with bilateral stimulation.

Methods: Twenty-two PD patients with bilateral STN-DBS were assessed in 4 randomized DBS conditions: bilateral off-stimulation, bilateral on-stimulation, unilateral right- and unilateral left-stimulation. We defined as "dominant STN" the STN that when stimulated could achieve >75% of improvement in the Unified Parkinson's Disease Rating Scale (UPDRS) total motor score obtained with bilateral stimulation.

Results: A dominant STN was found in 15 patients (68%). Stimulation of the dominant STN significantly improved the total motor UPDRS scores and subscores (ipsilateral and contralateral) and this benefit was similar to the bilateral stimulation benefit. In 4 patients the dominant STN was ipsilateral to the most affected side. Predictive factors of dominant-STN were younger age and greater PD asymmetry at surgery.

Conclusions: The dominant STN can be observed in patients with bilateral STN-DBS, suggesting that one STN might drive the entire clinical benefit. More studies are needed to explore bilateral interconnections of the basal ganglia that can elucidate and predict this phenomenon. Unilateral STN-DBS targeting the dominant STN could be the best surgical choice also in advanced PD.

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Family dysfunction after deep brain stimulation of the subthalamic nucleus for advanced Parkinson's disease

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Objective: Our aim was to study family dysfunction after DBS-STN.

Background: Deep brain stimulation of the subthalamic nucleus (DBS-STN) for advanced Parkinson's disease (PD) has been associated with neuropsychiatric and behavioural side effects.

Methods: Cross-sectional study of PD patients who underwent bilateral DBS-STN, and their family caregivers. Patients and caregivers were excluded if demented or aphasic. Assessment tools included a structured questionnaire, the Schwab & England scale, the MMSE, the Familiar APGAR scale, the Dyadic Relationship Scale, the WHOQoL-BREF, a depression scale validated for the Portuguese population (CES-D), and the Zarit Caregiver Burden scale. Answer to an open-question about the patient-caregiver relationship was audio-taped and written down. A descriptive analysis was performed.

Results: 30 patients and respective family caregivers were recruited. None was excluded. 22 patients were female; mean age 64.3 years and mean disease duration 16.7 years. Mean Schwab & England score after DBS was 80%. Family APGAR scale scores showed marked family dysfunction in 2 patients and 1 family caregiver, moderate dysfunction in 5 patients and 6 caregivers and highly functional family in 23 patients and 23 caregivers. Mean Dyadic Relationship Scale was 9.1 for patients and 13.7 for family caregivers. Mean WHOQoL-BREF Environment Domain score was 30.1 for patients and mean WHOQoL-BREF Physical Domain for family caregivers was 28.6. Mean CES-D was 19.9 for patients and 17.9 for caregivers. Mean Zarit Caregiver Burden score was 33.3.

Conclusions: Most patients were independent for the activities of daily living, and none was demented. The majority had no family dysfunction. These results suggest that DBS might not affect family dysfunction, but a prospective study is needed to test this hypothesis.

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Extensor bar for deep brain stimulation electrode insertion: Technical note

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Objective: To describe the use of a special plastic extensor bar created to give support for the deep brain electrode at the time of brain insertion and fixation.

Background: Deep brain stimulation (DBS) has been used in an increasing frequency over the last decades. There were several technical developments in the making of the stimulating electrodes themselves and the stereotactic techniques, aiming to improve safety, efficacy and easiness for implantation.

Methods: This plastic extensor bar was attached to the stereotactic electrode carrier during DBS procedures. The bar was a hollow cylinder, with an internal diameter compatible with the diameter of the stimulating electrode to be implanted. It had a lateral cleft through which the electrode could be removed without moving it from its original targeting position. The kit included one cannula that fit the internal diameter of the bar, and was used as an electrode insertion guide, and was also removable through the lateral cleft.

Results: The extension of the bar was calculated so that the tip of the electrode would be at the isocenter while its more bulky connector plate was lying over the top of it. By doing this, there was no need for any assistant or external device to hold the electrode while finalizing its fixation to the skull.

Conclusions: The use of this extension bar made DBS procedure easier, faster and potentially safer. We used this technical variation in all patients being submitted to DBS for Parkinson's disease and epilepsy.

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Effects of pedunculopontine nucleus area stimulation on speech production in Parkinson's disease

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Objective: To evaluate the effect of pedunculopontine nucleus (PPN) area stimulation on temporal speech parameters in Parkinson's disease (PD).

Background: Gait impairment, including freezing (FOG), is frequent in PD and responds poorly to classical pharmacological and surgical treatments. Freezing can also be seen for speech and since FOG may be improved by PPN stimulation, it is of great interest to examine the influence of PPN stimulation on speech.

Methods: Seven PD patients with severe Freezing Of Gait unresponsive to L-dopa and bilateral STN stimulation underwent bilateral electrode implantation within the PPN area. Speech recordings were carried out together with other clinical and gait evaluations (Ferraye et al., 2009, Brain), before and after surgery (5 times during the one-year follow-up). We analyzed the maximal phonation time (MPT) during vowel production, a pneumophonic coordination marker that is frequently reduced when speech is abnormal. A linear mixed model was used (R software) for group analyses with patient as a random term, and treatment (L-dopa, STN stimulation, PPN stimulation) and state (off, on) as fixed effects.

Results: There was no effect of PPN stimulation, nor any interaction between L-dopa and PPN stimulation treatments ($p=0.3$; $N=231$ measures), when comparing postoperative data off vs. on PPN stimulation (on STN stimulation, off/on dopa). However, dopaminergic administration had a significant deleterious effect ($p<0.001$; $N=231$), reducing the MPT up to 23%. Postoperatively, the effects of PPN stimulation did not change between the first and last evaluations ($p=0.3$; $N=126$). Comparison of preoperative and one-year follow-up data showed a negative synergestic effect of treatments: worst MPT were found on dopa/STN stimulation/PPN stimulation whereas the best situation was off dopa/on STN stimulation/pre-PPN surgery ($p<0.001$; $N=225$).

Conclusions: The MPT speech parameter was not altered by PPN area stimulation alone, but appeared to deteriorate under the.combination of L-Dopa and PPN treatments. Further analyses are underway to better understand the impact of stimulating the brainstem on dysarthric speech.

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Motor and cognitive outcome of Parkinson's disease patients eight years after STN-DBS implant

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Objective: To report the long-term prospective follow up of a cohort of patients with Parkinson's disease (PD) treated with deep brain stimulation (DBS) of subthalamic nucleus (STN) for 8 years.

Background: Numerous studies have demonstrated that STN-DBS is highly effective, however, postoperative long-term outcomes have been reported up to 5 years and longer-lasting observation are lacking despite being certainly needed.

Methods: We studied a series of 20 consecutive patients who received continuous stimulation for 8 consecutive years. Motor assessment was performed by means of UPDRS while cognition by means of an extensive neuropsychological battery.

Results: The motor efficacy of STN stimulation was 55.5% at 5 years ($p<0.001$) and 39% at 8 years ($p<0.001$, compared to baseline; $p<0.01$, comparing 8 to 5 years). Speech was not improved and postural stability had worsened ($p<0.05$). Considering individual motor items 5 and 8 years after implant, outcome was comparable for resting tremor, rigidity, speech and gait, but worsened at 8 years for all other the items. The efficacy of combined treatment (stimulation and medication) on motor symptoms was 64% after 5 years ($p<0.001$) and 54.8% after 8 years ($p<0.001$). At 8 years, UPDRS-ADL score was worsened by 56.6% ($p<0.01$). One patient had developed dementia at the 5 years with further progression at 8 years. Compared to baseline, at 5 years there was a significant decline on the letter verbal task and on the episodic memory task. At 8 years there was a significant decline on the same domains and on the Modified Wisconsin Card Sorting Test (MWCST). Comparisons of 8- and 5-year scores only revealed a significant decline on an episodic memory task. Eight years after surgery, no significant change was observed on scores for depression or anxiety compared to baseline. The mean preoperative LEDD was reduced by 61% 6 months after implant, by 58.2% at 5 years and by 60.3% at 8 years.

Conclusions: Eight years after surgery the efficacy of STN-DBS is partly decreased due to progression of PD and the appearance of levodopa-resistant symptoms. The 5-year cognitive and safety data were retained. These evidences may support the view that STN implants should be performed earlier in patients who are appropriate candidates for this procedure.

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Effects of low or high frequency stimulation of the PPN area in Parkinson's disease

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Objective: To study the effects of PPNa stimulation frequency on gait disorders, akinesia and alertness.

Background: Gait disorders are frequent in advanced PD. Pedunculopontine nucleus area (PPNa) stimulation was reported to improve Freezing Of Gait and falls in some patients. However, the appropriate stimulation frequency remains unclear as improvements were obtained under variable frequencies.

Methods: Seven PD patients (aged 63 ± 6 years) who developed severe gait disorders and freezing despite STN stimulation were bilaterally stimulated in the PPNa. One year after surgery, the effect of low (15-25 Hz) and high (60 or 80 Hz) stimulation frequency was double blindly assessed during 24 hour-periods of stimulation. Percent of freezing episodes occurring during a walking protocol, mean half and full turns durations, a subscore for akinesia and the score on the Epworth sleepiness scale were measured both off and on levodopa.

Results: Five out of 7 patients off levodopa and 4/7 on levodopa performed the half and full turns faster under low as compared to high PPNa stimulation frequency. Three out of 7 patients off levodopa and 2/7 patients on levodopa displayed less freezing under low as compared to high frequency stimulation. Three out of 7 patients showed less akinesia under the low frequency stimulation condition, both off and on levodopa. Alertness improved in 6/7 patients under low as compared to frequency stimulation. Only one patient was better improved under high stimulation frequency.

Conclusions: This study confirms the superiority of low as compared to high PPNa stimulation frequency for gait, akinesia and alertness. In accordance with animal studies, low PPNa stimulation frequency could have a beneficial excitatory effect on the neuronal structures involved in the control of gait. On the contrary, high frequency stimulation of the PPNa did not worsen akinesia.

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Deep brain stimulation impairs on-line executive control in Parkinson's disease patients

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Objective: To evaluate the effects of high frequency deep brain stimulation (DBS) on the faculty to detect, inhibit and correct erroneous responding in Parkinson's disease (PD) patients.

Background: High frequency DBS is generally considered to inactivate the subthalamic nuclei (STNs) and to restore the thalamo-cortical projections impaired by striatal dopamine depletion caused by PD. This therapy dramatically improves PD motor symptoms. Recent fMRI data collected in healthy volunteers suggest that the STNs are involved in the urgent inhibition of ongoing actions. We reasoned that a side effect of DBS could be to impair this ability in PD patients.

Methods: 16 PD patients treated by DBS for at least 6 months performed a between-hand conflict reaction time (RT) task involving thumb responses in 4 treatment conditions: Stimulator ON–Medication ON, Stimulator OFF–Medication ON, Stimulator ON–Medication OFF,. Stimulator OFF–Medication OFF. The electromyographic activity of the response agonists (flexor pollicis brevis) was recorded and analysed, allowing the detection of partial errors, that is of subliminal activations of the muscles involved in erroneous responses. Responses were thus classified in 3 categories: correct, partial errors and overt errors.

Results: The medication exerted no notable effect on the patients' performance. DBS shortened correct RT but increased the overt error rate and decreased the number of partial errors. Detailed analyses of the temporal distribution of the 3 response categories revealed that the increase in overt error rate observed when the stimulator was ON was specifically due to a failure to detect, inhibit and correct partial errors before they resulted in overt erroneous responses.

Conclusions: Our data suggest that while it improves motor performance by shortening RT, DBS impairs the patients' faculty to suppress erroneous response activations as revealed by their inability to counteract partial errors when the stimulator was ON. Previous studies provided evidence that the hyperdirect cortico-subthalamic pathway is involved in externally-triggered motor inhibition. The present findings demonstrate that this pathway also mediates the suppression of self-initiated inappropriate actions.

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Dysphagia in Parkinson's disease improves by subthalamic high frequency stimulation

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Objective: Dysphagia and hypersalivation are common axial symptoms of Parkinson's disease (PD). Complications are pharyngeal retentions and aspiration that can make oral nutrition impossible. Dysphagia in PD may persist in spite of improvement of motor symptoms by medication or surgical treatment with deep brain stimulation (DBS). However recent radiographic swallow studies could show an improvement of dysphagia by subthalamic nucleus DBS.

Background: All phases of swallowing have been shown to be impaired in PD. Laryngoscopic studies allow more detailed informations about the phanryngeal phase which is important regarding retention and aspiration. This study aimed in the evaluation of qualitative and quantitative variations of swallowing in PD by DBS.

Methods: Seven patients with PD underwent stereotactic surgery for treatment with subthalamic nucleus DBS. Patients were evaluated for dysphagia in medication off state before surgery and during DBS: The anatomy of orofacial structures was examined by an otolaryngologist. A videotaped laryngoskopy was performed including a qualitative and quantitative assessment of retention, penetration, aspiration and leaking regarding solid, mashed and liquid food.

Results: Before surgery as well as during DBS 5 patients complained dysphagia. All of them reported a feeling of tacked bolus, 2 patients additionally reported aspiration. Two patients were free of symptoms. Before surgery retentions of solid food were found in all 5 symptomatic patients and in one patient without complaints, leaking was detected in 4 patients. Aspiration was not observed. Penetration was normal in all patients. During DBS retention improved in 3 of 5 patients. All patients with leaking showed an improvement during DBS.

Conclusions: Based on laryngoscopic criteria dysphagia in parkinsonian patients improved to a variable extent during DBS of the subthalamic nucleus. The decrease of retentions is supposed to be related to a harmonisation of motor activity. It is not clear yet if leaking was caused by an impaired laryngeal sensitivity or an impaired fine motor tuning (diadochokinesis) or both. Since DBS seems to be effective on swallowing disturbances in PD the interaction of the motor and sensory parts in swallowing could give an explanation for the variability of improvement in individual patients.

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Decreased cost of antiparkinsonian medications after treatment with deep brain stimulation

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Objective: To compare rates of antiparkinsonian medication cost increase between Parkinson's disease (PD) patients treated with deep brain stimulation (DBS) and medications alone.

Background: PD patients treated with DBS typically reduce their dose of PD medication by 25-50% after implant. It remains unknown, however, whether these benefits are continued long term and what impact these patterns have on the economic burden of PD.

Methods: With IRB approval, a retrospective analysis was conducted of 18 patients with idiopathic PD implanted with bilateral subthalamic DBS and 18 controls treated with standard medications alone (MED). Exclusion criteria were less than two visits post-surgery, previous brain surgery or participation in a treatment trial. For each office visit, frequency of each dose of anti-PD medication was recorded. Costs were extracted from the 2008 Red Book. Rates of medication increase were compared between (1) all patients before surgery, (2) DBS group after, and (3) MED group after. A random coefficient model was used for mean trajectory for each group and a random component for how each patient's trajectory varied about the mean trajectory, including total daily cost as outcome, group, and group x time as fixed effects. Patient and time were included as random effects.

Results: Participants were 18 MED (10 male, 8 female, average age 64) and 18 DBS (10 male, 8 female, average age 62) with an average 26 visits. Before DBS, the rate of increase in total cost was similar in MED and DBS subjects ($p=0.97$), and at the time of DBS, patients in each group were receiving a comparable total total levodopa equivalent dose (772 mg for MED vs 961mg for DBS). Rates of increase compared pre- to post-DBS were significantly different ($p=0.02$) as well as compared between DBS and MED ($p=0.02$).

Conclusions: The rate of increase in PD medication cost was significantly lower after DBS, and when compared to patients treated with medical therapy alone. More investigation is need to determine if DBS-related decreases in PD medications may have additional implications for disease modification and delayed development of motor complications.

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A prevention success case of neuroleptic malignant-like syndrome after discontinuation of deep brain stimulation

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Objective: To describe a prevention success case of neuroleptic malignant-like syndrome (NMLS) by discontinuation of bilateral subthalamic nucleus deep brain stimulation (STN-DBS) in a patient with Parkinson's disease (PD).

Background: NMLS is an uncommon, however, potentially fatal complication of dopaminergic treatment. It is characterized by hyperthermia, muscle rigidity, tremor, perspiration, sialorrhea, and elevated creatinine kinase activity.NMLS has been described in patients with PD due to the abrupt discontinuation of L-dopa treatment. There are no reports about NMLS after discontinuation of STN-DBS and treatment.

Methods: Case report.

Results: A 59-year-old man with a 16-year history of PD underwent STN-DBS. After surgery, he could reduced dopaminergic medication and his motor function was very much improved. Two years after surgery, he showed manic state suddenly. Due to his manic state he was running in our examination room. We considered that this state was dangerous, so that we turned off the stimulation. A few days after discontinuation of STN-DBS, NMLS appeared. NMLS was improved by fluid therapy, then his manic state was improved. Soon thereafter we started again STN-DBS without medication. Four years and six years after surgery, he got manic state again. We discontinued the stimulation, however, NMLS appeared again. NMLS was similarly improved by fluid therapy. Seven years after surgery, the symptom repeated again. Based on that previous event, we maintained low stimulation amplitude level. Then creatinine kinase activity wasn't elevated so much. Manic state was similarly slight.

Conclusions: Our case is suggested that NMLS may appeare when STN-DBS was discontinued for several days or more. We prevented NMLS after discontinuation of DBS, because STN-DBS was continued with low stimulation amplitude level.

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Pre-operative quality of life (QOL) assessment in patients being submitted to stereotactic surgery for Parkinson's disease

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Objective: To evaluate preoperative quality of live in patients who were candidates to stereotactic surgery for Parkinson's disease.

Background: Stereotactic surgery is a useful palliative procedure in patients with Parkinson's disease. Reporting exclusively the outcome regarding motor symptoms might not reflect the overall surgical results and patient satisfaction. Quality of life evaluation might be an integral part of the pre- and postoperative work-up in this patient population.

Methods: Seventy-eight patients being submitted to stereotactic surgery for Parkinson's disease were preoperatively evaluated using the PDQ-39 tool. There were 58 men; age ranged from 39 to 75 years (mean=59 years). Eighty percent of the patients were retired, mainly due to disease-induced limitations, 82% of them were married, and 91% could read and write. Seventy percent of the patients were diagnosed as having Parkinson's disease between the age of 40 and 59 years. Patients with severe psychiatric disorders or dementia were excluded.

Results: Overall, patients presented the poorer results on the daily activities (mean=59) and mobility (mean=57) scores. These were followed by the corporal discomfort (mean=43), emotional well-being (mean=42), stigma (mean=36), communication (mean=35), cognition (mean=25) and social support (mean=16) scores. There was no relationship between QOL scores and duration of the disease. There was a significant impact on mobility, daily life and corporal discomfort scores in patients in whom rigidity predominated over tremor. There was a continuous decrease in mobility scores in older patients.

Conclusions: This preoperative QOL evaluation would serve as a baseline control for future evaluation of the surgical outcome in this patient population. It should be emphasized that these patients represent a selected group with advanced Parkinson's disease in whom surgical treatment was being considered as a palliative option. Their clinical and QOL findings did not meet the general Parkinson's disease population profiles.

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Neuropsychological effects of unilateral versus bilateral STN DBS surgery in Parkinson's disease

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Objective: To systematically examine the neuropsychological consequences of unilateral versus bilateral STN DBS surgery in PD patients.

Background: Recent research suggests that bilateral subthalamic (STN) deep brain stimulation (DBS) is associated with increased acute and long-term complications including speech difficulties and cognitive dysfunction in Parkinson's disease (PD) patients (Alberts et al 2008; Benabid et al 2009).

Methods: Results of presurgical and postsurgical standard neuropsychological tests of 10 patients with unilateral and 11 patients with bilateral implanted STN stimulators as well as 12 demographically matched PD control patients who were not candidates for DBS surgery were examined and statistically analyzed. There were no significant group differences in patients' age, years of education and length of disease. The patients underwent neuropsychological testing before surgery and 4-6 months following surgery.

Results: A significant reduction in phonemic fluency ($P<.05$) on the FAS test was found in the patient group who underwent bilateral but not unilateral STN stimulator implantation. In addition, a significant improvement in attention and working memory ($P<.01$) was found in the unilateral but not the bilateral surgery group.

Conclusions: The results of this, preliminary, study suggest that postoperative cognitive deficits tend to occur with increased frequency in patients undergoing bilateral STN DBS. We therefore suggest that unilateral or staged surgical procedure may be preferable over bilateral procedure, particularly in patients with asymmetric symptomatology, mild cognitive decline or in older patients. Individually tailored surgical procedure that maintains maximal motor improvement and minimal cognitive impairment is advised.

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Retrospective review of deep-brain stimulator settings and therapeutic impedances from patients with movement disorders

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Objective: To clarify time-dependent impedance changes and their effect on programming choices of deep brain stimulation devices.

Background: Deep-brain stimulation (DBS) has become a mainstay for treating Parkinson's disease and other movement disorders, yet our understanding of the interaction between DBS and the brain remains arcane. Experimentally observed changes in brain-electrode interface characteristics have pushed DBS manufacturers to include, in addition to voltage controlled stimulation (VCS) options, current controlled stimulation (CCS) settings in new devices.

Methods: A retrospective review of 89 DBS patient's electrode impedances and stimulation parameters was conducted, specific to implantation with Soletra impulse generators (Medtronic; Minneapolis, MN). Data from patients whose stimulation settings were not changed for at least 3 consecutive visits was analyzed. A total of 1009 data points spanning 4019 days were extracted for final analysis.

Results: Data was binned over 90 day periods and compared when the case was used as the anode (monopolar, MP) and no significant changes in impedance were observed. Significant differences ($p<.01$) were seen in impedances when the impulse generator case was not used as the anode (bipolar, BP). This difference was between the first 90 days compared to later time periods. A calculation of delivered current was performed and no significant change with time was observed for BP settings. Current was found to increase with time using MP settings ($p<.01$) and decrease beyond 4 years.

Conclusions: The results of this study suggest that VCS may be advantageous with MP settings, as demonstrated by the fluctuation of delivered current when these settings were used. CCS may be preferred with BP settings over the first 90 days due to impedance instability. In all other BP circumstances the results suggest that CCS and VCS may lead to equivalent outcomes, as steady impedance and calculated current were observed with VCS.

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Deep brain stimulation in a 'triple heterozygote' patient with Parkinson's disease

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Objective: To evaluate the effects of deep brain stimulation (DBS) in a patient with Parkinson's disease (PD) carrying mutations in three different 'parkinsonian' genes–parkin, LRRK2 and GBA.

Background: Genetic factors play an important role in etiology of PD, and most frequently mutated genes in both familial and sporadic cases are parkin, LRRK2 (leucine-reach repeat kinase 2) and GBA (glucocerebrosidase). Genetic cases of PD are usually characterized by some specific clinical features, such as young onset or predisposition to early levodopa-induced dyskinesias. Therefore, surgery in these patients may be considered as one of the most attractive treatment options.

Methods: In a large cohort of Russian patients with PD we carried out systematic mutation screening, including gene dosage analysis (real-time PCR), restriction analysis for common nucleotide substitutions, and direct sequencing of candidate genes. We identified a 'triple heterozygote', i.e. a patient carrying heterozygous mutations in three genes: 1) duplication of exon 5 in the parkin gene; 2) a common mutation G2019S in the LRRK2 gene; 3) a common mutation N370F in the GBA gene. Earlier this patient was described by us as having parkin and LRRK2 mutations (Eur. J. Neurol. 2007; 14: 413-417).

Results: The patient, a 45-year-old woman with negative familial history, noticed hand tremor, rigidity and gait abnormality at age 39. Levodopa (400 mg a day, gradually increased up to 800 mg) was administered from the very beginning with a good effect, and pramipexol 2 mg a day was added two years later. The disease was characterized by relatively rapid progression and early manifestation of very severe, disabling choreo-ballistic levodopa-induced dyskinesias. Because of dyskinesias (even on small dose of levodopa) she could not walk, stand or sit, and was virtually bedridden. Bilateral deep brain stimulation (DBS) of the GPi resulted in 'dramatic' improvement lasting, up to now, for 1 year.

Conclusions: We suggest that three mutations (parkin+LRRK2+GBA) had additive effect and led to early development of the severe phenotype of PD. In such complex genetic cases DBS may be as effective as in common 'non-genetic' forms of PD.

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Transcranial sonography for postoperative location of subthalamic stimulation electrodes in Parkinson's disease surgery

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Objective: We attempt to analyze the usefulness of transcranial duplex ultrasound (TCDx) as a complementary method for early postoperative comfirmation of electrodes location into the subthalamic nucleus in patients submitted to deep brain stimulation.

Background: The exact position of deep brain stimulation electrodes in Parkinson's disease (PD) surgery is usually inaccurately assessed employing clinical, neurophysiological and conventional neuroimaging parameters.

Methods: Fifteen consecutive patients with PD were studied by TCDx after surgery. The stimulation electrode was located in the X plane by calculating the distance between electrode and third ventricle midline. The electrode was also identified in the Z plane attending to its topographic relationship with the Substantia Nigra (SN). Data were compared with surgery's stereotactic and postoperative CT and MRI coordinates.

Results: The electrode position and its relationship with SN could be easily visualized by TCDx in all patients in the Z plane. Coordinates of electrodes into SN were different from coordinates of electrodes placed out (9 [9-9,80] vs 7,20 [6,15-8,40], $p<0.01$). A ROC curve showed a cutoff value of 8.85mm as the most sensitive (100%) and specific (90.5%) point to predict electrodes into SN, with an area under the curve of 0.98 (CI 95% 0.807-10.303), $p=0.001$. There was also a significant correlation between ultrasonographic data and stereotactic coordinates in the X plane ($\rho=0.714$, $p<0.01$).

Conclusions: Transcranial ultrasonography is a non-invasive, easily feasible technique useful to early and realiably identify the exact location of stimulation electrodes into the subthalamic nucleus in X and Z planes.

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Hiperammoniemic encephalopathy secondary to treatment with valproic acid for seizure prevention in deep brain stimulation

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Objective: To describe two patients in a cohort of 33 patients affected of Parkinson's disease who underwent bilateral subthalamic stimulation that were treated with valproic acid developing a subacute hiperammoniemic encephalopathy.

Background: There are no reports in the literature about encephalopathies secondary to treatment with anticonvulsivants in Parkinson's disease or the necessity of preventive treatment for seizures.

Methods: Case records of 33 patients who underwent deep brain stimulation were reviewed. The data collected included 19 men and 14 women, median age of 63 years-old and average disease evolution of 12 years. All of them were operated according to our protocols.

Results: Of the 33 patients, 2 (6,06%) suffered a encephalopathy consisting in obnubilation, dysarthria and global weakness some days after the surgery. Both were treated, like the others, with valproate acid at standard doses of 1500 mg per day. The surgical procedure had no major complications, immediate and posterior postoperative recovery was correct. In these two cases at emergency room ammonia serum levels were high despite normal levels of valproic acid. Liver and renal function were normal, stimulator operation was correct and no fever, infections or new drugs were administrated before and during the episode. In the hospital entrance, valproic acid was stopped and they recovered completely till the basal status. No recurrence till today.

Conclusions: These cases suggest that, in certain cases, the prophylaxis with valproic acid can develop metabolic complications in Parkinson's disease patients who undergo brain stimulation. Whether seizure preventive treatment is necessary or other antiepileptic drug might be used remains unclear.

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AAV2-GDNF-induced functional recovery and restoration of the dopaminergic system in MPTP monkeys

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Objective: To evaluate functional recovery and anatomical restoration of the dopaminergic system after GDNF gene delivery in a stable MPTP primate model of Parkinson's disease (PD).

Background: Clinical studies to date with GDNF or Neurturin have failed to meet efficacy endpoints. Failure of these studies has been largely attributed to technical delivery issues. In contrast to previous protection orientated studies, and consistent with the design of clinical trials, we investigated regeneration with GDNF gene transfer after stable lesioning of the dopaminergic neurons.

Methods: AAV2-GDNF was infused into the putamen of Rhesus macaques lesioned 3-6 months earlier with MPTP. Convention enhanced delivery (CED) was used to maximize distribution. Motor defects were monitored for 24 months after treatment using a clinical rating scale. PET imaging was used to evaluate dopamine function. Immunohistochemistry was performed to visualize GDNF expression, regeneration of the dopaminergic system and any immune responses.

Results: Functional recovery was observed throughout the 24-month assessment in AAV2-GDNF macaques without adverse effects. Enhanced PET imaging was correlated with the behavioral recovery. Increased tyrosine hydroxylase staining was found to match the pattern of GDNF expression. Importantly, the presence of GDNF in the substantia nigra indicated anterograde transport from the putamen independent of the nigrostriatal neurons, which were severely lesioned in the right hemisphere. No immune response or adverse pathologies were found after 24-months of GDNF expression.

Conclusions: Overall this study demonstrates that AAV2-GDNF can be safely delivered to the putamen with broad GDNF expression in both putamen and substantia nigra due to anterograde transport. This stimulated reinnervation of the lesioned putamen and an enhancement of dopaminergic function. Together with clinically significant functional recovery and an absence of any adverse effects, these findings support initiation of a Phase I study in PD using CED of AAV2-GDNF to the putamen alone.

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Reversible cognitive impairment induced by deep brain stimulation of subthalamic nucleus

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Objective: To describe a case of a patient with young onset Parkinson's disease (YOPD) who developed significant cognitive impairment after bilateral Subthalamic Nucleus deep brain stimulation (STN DBS) that was proven to be stimulation induced and was reversed by changes in the stimulation parameters.

Background: The effect of STN DBS on cognition had been studied extensively but still is not completely understood. The current consensus is that overall STN DBS does not affect cognition in patients with normal cognitive functioning. There is no sufficient data in regards to the effect of certain stimulation parameters on the various domains of cognitive functioning.

Methods: We present a case of a 46 year old woman with YOPD, characterized by tremor, rigidity, bradykinesia, bilateral foot dystonia, motor fluctuations and dyskinesias. The patient was an engineer working full time. Normal cognitive functioning was confirmed by neuropsychological test. She underwent bilateral STN DBS surgery. Her DBS programming initially was complicated, due to difficulties to control her foot dystonia. This eventually responded to high levels of stimulation. Three months after initial programming she reported problems with memory, concentration and attention. Neuropsychological test confirmed significant worsening. In order to determine if this was related to surgery or to stimulation, it was decided to temporarily stop her stimulation. Neuropsychological test repeated after 1

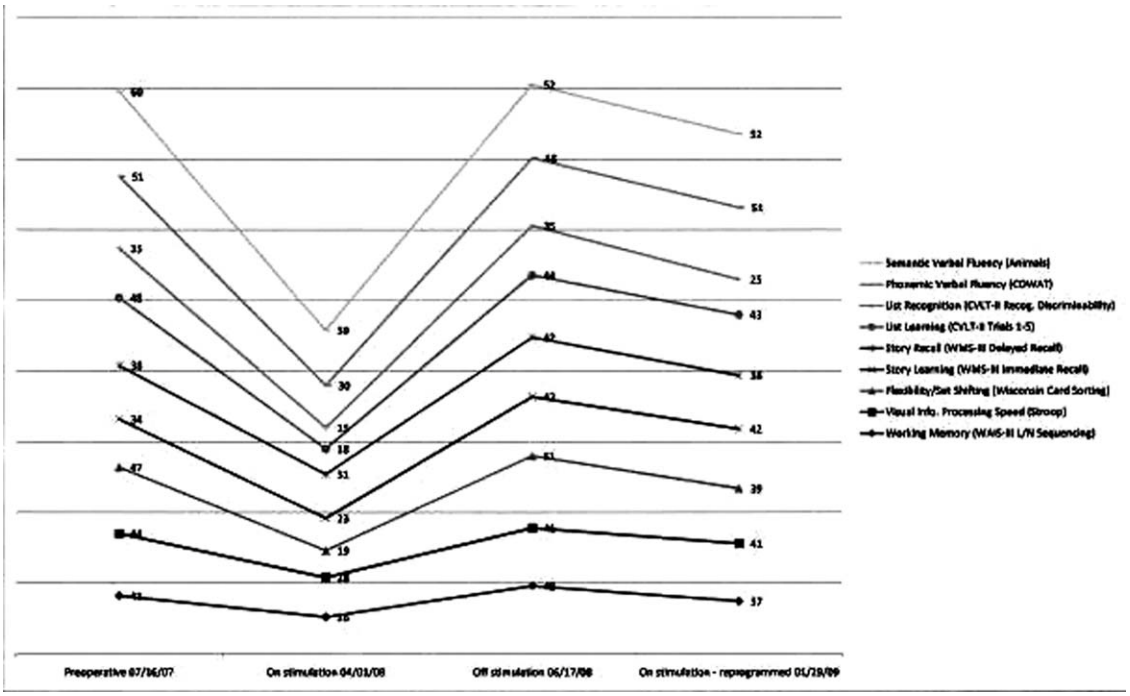

FIG. 1 (788).

TABLE (788). *Changes in treatment and neuropsychological test*

		Preoperative	On DBS	Off DBS	On DBS reprogrammined
DBS parameters					
Active contact	Left		case+, 1-, 2-, 3-		Case+. 1-
	Right		Case+, 7-		4+, 5-
Pulse Width (mcsec)	Left		90		60
	Right		90		60
Frequency (Hz)	Left		185		130
	Right		185		130
Amplitude (V)	Left		3.8		1.7
	Right		4.1		3.3
Medication					
Carbidopa/levodopa 25/100		1 tab 5 times/daily	0	1/2 tab 5 times/daily	0
Carbidopa/levodopa orally dysintegrated tab (Parkopa)		1/2 tab 2 times/daily	0	1/2 tab 2 times/daily	0
Ropinirole		5mg 3 times/daily	5mg 3 times daily	5 mg 3 times/daily	4mg 5 times/daily
Rasagiline 1mg		1	1	1	1
Amantadine 100 mg		1 tab 4 times/daily	1 tab 2 times/daily	1	2 tab 2 times/daily
Entacapone 200mg		1 tab 5 times daily	0	0	0
Levodopa equivalent		1155	495	845	726
Neuropsychological test domains					
Working memory (WAIS-III)		41	26	48	37
Visual information processing speed (Stoop)		44	28	41	41
Flexibility/set shifting (Wisconsin card sorting)		47	19	51	39
Story learning (WMS immediate recall)		34	23	42	42
Story recall (WMS delayed recall)		38	31	42	38
List learning (CVLT-II trials 1-5)		48	18	44	43
List recognition (CVLT-II discriminability)		35	15	35	25
Phonemic verbal fluency (COWAT)		51	30	48	51
Semantic verbal Fluency (Animals)		60	39	52	52

Levodopa Equivalent = (Levodopa + Controlled release levodopa × 0.7) × 1.1 if on COMT inhibitors + Pramipexole × 100 + Ropinirole × 33.

month off DBS revealed that her cognitive functioning normalized. Reprogramming was done with adequate control of her motor function by lower DBS parameters. Patient reported no negative effect on her cognition and was able to return to work. Neuropsychological test this time showed slight worsening in several domains compared to off DBS state, but significant improvement compared to the first on DBS state.

Results: In this patient reversible cognitive impairment was caused by high levels of stimulation.

Conclusions: Cognitive impairment after STN DBS can occur in previously cognitively intact patients, can be induced by high level of stimulation and reversed by changes in the stimulation parameters. Different domains of neuropsychological functioning can respond differently.

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Analysis of antiparkinsonian drug reduction after bilateral subthalamic deep brain stimulation

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Objective: To quantitatively analyze the reduction of antiparkinsonian drugs one year after subthalamic deep brain stimulator (DBS) implantation in patients with idiopathic Parkinson's disease (PD).

Background: Bilateral deep brain stimulation of the subthalamic nuclei (STN) is a well established and cost-effective treatment in advanced PD. Based on the multicentric randomized, controlled studies, one may expect approximately 50-60% dose reduction. Our primary aim was to analyze the achieved antiparkinsonian drug reduction in Hungary.

Methods: Eighteen consecutive patients with PD previously underwent bilateral STN DBS implantation were involved in the study. The stimulation achieved a stable and clear clinical benefit in all of the cases. One year after the implantation, we evaluated the drug usage of the patients and correlated it with the postoperative symptomatic improvement measured by the modified Hoehn-Yahr, Schwab and England, and Unified Parkinson's Disease Rating Scales. Because none of the investigated variables followed the normal distribution, non-parametric tests (Wilcoxon signed-rank, McNemar and Kendell's tau tests) were applied to test the statistical significance.

Results: Preoperatively, the patients used 12.7±4.57 tablets a day out of 3.19±0.97 different antiparkinsonian drugs, which was significantly reduced to the application of 7.00±2.96 tablets out of 1-3 (1.84±0.76) drugs ($p<0.001$). Meanwhile, the usage of amantadine, water soluble levodopa formulation, MAO-B and COMT inhibitors were also significantly decreased ($p<0.05$). The dosage od dopaminerg medication was significantly lowered from 1136 mg to 706 mg expressed in levodopa equivalent dosage ($p<0.001$).

Conclusions: Our clinical study confirms the previously published findings that antiparkinsonian medication can be significantly lowered after bilateral STN DBS. Because not only the dosage, but also the applied number of tablets can be decreased, it may result in a better compliance and quality of life.

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Comparison of the unipolar and bipolar subthalamic deep brain stimulation in idiopathic Parkinson's disease

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Objective: To compare the efficacy of unipolar subthalamic deep brain stimulation (DBS) with that of bilateral stimulation in patients with idiopathic Parkinson's disease (PD).

Background: Bilateral deep brain stimulation of the subthalamic nuclei (STN) is a well established and cost-effective treatment in advanced PD. Based on the clinical efficacy and side-effects, both unipolar and bipolar stimulation modes may be applied. Bipolar stimulation usually produces a more focused and therefore thinner stimulation-activated tissue volume than the unipolar stimulation does; however, in most cases it requires higher amplitude (Voltage) to achieve the same efficacy. The primary aim of our clinical study was to quantify the different clinical efficacy between the two stimulation modes.

Methods: Twenty patients with PD previously underwent bilateral STN DBS implantation were involved in the study. The stimulation achieved a stable and clear clinical benefit in all of the cases. Approximately one year after the implantation, we evaluated rigidity, tremor and bradykinesia according to the Unified Parkinson's Disease Rating Scale in a practically off condition due to an overnight dopaminerg drug withdrawal. Keeping the negative contact of the chronic stimulation setting constant, the amplitude of stimulation was changed between 0 and 4 Volts by 0.2V steps. Subsequently, the improvements in rigidity, tremor and bradykinesia were compared between unipolar and bipolar modes.

Results: In all of the examined cases, the unipolar stimulation had a higher clinical efficacy: the parkinsonian symptoms started to respond at lower voltage levels and the size of the improvement was higher within the limits of the examined stimulation settings. To achieve the same level of improvement in rigidity, tremor and bradykinesia during bipolar stimulation, 12%, 21% and 24% higher voltage was required respectively compared to that of the unipolar mode.

Conclusions: Our clinical study confirms the empirical data about the differences between unipolar and bipolar subthalamic deep brain stimulation. According to our results, during the switch from unipolar to bipolar stimulation mode one usually need to increase the stimulation amplitude by 10-25% depending on the clinically relevant symptoms.

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Effects of chronic STN-DBS on the levodopa response: Evidence for gain of long duration response

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Objective: To explore effects of STN-DBS on levodopa responses in patients with Parkinson's disease (PD).

Background: It has been proposed that motor fluctuation in PD patients is derived from loss of long duration response to levodopa, which is in turn caused by chronic drug treatment and/or progressive loss of dopamine neurons. STN-DBS improves off-parkinsonism, hence reducing motor fluctuations. Such beneficial outcomes from STN-DBS can be expected in PD patients showing good responses to levodopa before surgery, suggesting a close interaction between levodopa response and STN-DBS. It is however not clearly understood how STN-DBS influences two types of the levodopa response, i.e., short-duration response (SDR) and long-duration response (LDR).

Methods: We analyzed the clinical data from 48 patients with advanced PD who underwent bilateral STN-DBS. Levodopa tests were performed using UPDRS III before and 6 months after DBS surgery: twice before surgery (levodopa-off, -on), and three times after surgery (levodopa-off/DBS-off, levodopa-off/DBS-on, levodopa-on/DBS-on). △UPDRS scores after 6 months' STN-DBS were segmented into three mutually exclusive components: (1) △levodopa-off/DBS-off scores induced by 6 months' STN-DBS (△levodopa-LDR with DBS off), (2) △UPDRS scores caused by turning DBS on with levodopa off (i.e., △DBS-SDR with levodopa off), and (3) △UPDRS scores caused by levodopa with DBS on (i.e. △levodopa-SDR with DBS on).

Results: STN-DBS for 6 months improved levodopa-off/DBS-off UPDRS III scores compared with baseline off-UPDRS scores before surgery. The extent of improvement correlated significantly with baseline off-scores ($r=0.611$, $p<0.0001$). Multiple regression analysis revealed that the magnitude of levodopa-SDR before surgery correlated highly significantly with all three components of △UPDRS scores after 6 months' STN-DBS: levodopa-SDR before surgery$=0.602*a +0.981*b +0.803*c +4.924$ ($r=0.795$, $p<0.0001$; a=△levodopa-off/DBS-off scores, b=△DBS-SDR, c=△levodopa-SDR).

Conclusions: We found that the magnitude of levodopa-SDR before surgery predicts improvement of parkinsonism after STN-DBS, which is accounted for by improvement of SDR and LDR of levodopa. These observations suggest that STN-DBS reverses the trend of losing levodopa-LDR over time, leading to improvement of motor fluctuations.

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Stereotactic surgery for Parkinson's disease (PD): Two years experience with 57 patients from a single center in Sao Paulo, Brazil

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Objective: To present our two years experience with stereotactic surgery for PD at the Movement Disorders Surgery Center at Brigadeiro Hospital (São Paulo, Brazil).

Background: Stereotactic neurosurgery constituted an important therapeutic option in patients with PD over the last decades. The complexity of this form of treatment requires a team work and collaboration of different professionals including neurosurgeons, neurologists, psychologists and social workers. Moreover, adequate hospital infrastructure, including physical and technological resources, is essential to develop this activity.

Methods: Fifty seven PD patients underwent stereotactic surgery (42 men) from September (2007) to December (2009). Patients were evaluated using the following scales: UPDRS (Part III: "*on*" and "*off*" status), Schwab and England, Hoehn and Yahr, Mini-Mental State Examination, detailed neuropsychological battery and PDQL. Mean age was 58.6±8.4 years and duration of disease was 10.3±4.4 years. Seventeen patients were submitted to DBS; thalamotomy was performed in 11 and pallidotomy in 31 patients (in three patients an ablative procedure was associated with DBS). Results from the pallidotomy group, which had the longer follow-up so far are presented.

Results: In the pallidotomy group, there was a significant (30%) reduction in the UPDRS motor scores (44.8±9 to 29.1±6.5) in "off" state at 12 months postoperatively. The cohort had a cognitive profile at 12 months similar to the initial evaluation. We also noted improvement in quality of life score at final evaluation. In the whole series, two patients had symptomatic intracranial hematoma. Others two patients had convulsions few days after the procedure. There was no mortality or intracranial infection.

Conclusions: Our postoperative results regarding PD motor symptoms, cognition, QOL and complication rates were similar to those found in the literature. Although there was a clear tendency for increasing the use of DBS (as opposed to lesions), some patients with unilateral pathology continued to be submitted to ablative procedures. As the series increases, details from specific clinical presentations and targets will be analyzed.

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Deep brain stimulation and Parkinson's disease: New movements call old rheumatic pain

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Objective: To analyse postoperative rheumatic complaints in patients with Parkinson's disease (PD) submitted to bilateral subthalamic nucleus (STN) stimulation.

Background: Continuous bilateral high-frequency stimulation of the STN usually improves pain, in particular painful *off*-period dystonia. However, recent studies suggest that osteo-articular complications may occur in almost 20% of PD patients following STN stimulation.

Methods: Fifty-three PD patients (mean age, 59.9 (8.3) years; mean disease duration, 11.5 (4.2) years) referred for STN stimulation were enrolled. Patients were prospectively asked to refer and describe any rheumatic pain they experienced at any time during the preoperative period and within the 6 postoperative months. Pre-existing rheumatic pain, therapeutic changes, parkinsonian motor disability and weight gain were assessed as explanatory factors for rheumatic pain occurrence after surgery.

Results: Thirty patients (57%) complained of rheumatic pain whereas all demonstrated great functional improvement after surgery. Twenty (67%) among the 30 experienced similar pain sensation before surgery. Symptoms occurred rapidly, between 4 and 26 postoperative weeks, while the preoperative treatment was reduced. Multiple stepwise regression analysis showed that pre-existing rheumatic pain, 6-month postoperative UPDRS III motor score and axial subscore improvements in the *off*-drug/*on*-stimulation condition were accurate independent predictors of rheumatic pain after surgery ($F(8,41)=2.20$, $p<0.047$).

Conclusions: Our results highlight the high prevalence of rheumatic pain arising shortly after STN implantation. An accurate pain and osteo-articular assessment should be performed preoperatively in PD candidates for STN stimulation in order to limit emergence of complications in the early postoperative period.

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Subthalamic nucleus deep brain stimulation for alleviating of dystonia symptoms among NBIA patients

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Objective: The authors present a group of patients with clinically and radiologically diagnosed NBIA with genetically confirmed PANK2 mutation, treated with deep brain stimulation.

Background: Treatment of Neurodegeneration with Brain Iron Accumulation (NBIA) is difficult and frequently ineffective.

Methods: Six patients with confirmed PANK2 mutation (NBIA-PKAN) were treated with deep brain stimulation in 2008 and 2009. Age of the patients varied from 8 to 24 years. The clinical condition of the patients was evaluated with various scales. At all cases the permanent electrodes were implanted to the subthalamic nuclei. The surgical procedure was undertaken under general anesthesia. The target was identified with direct and indirect method. Intrasurgical macrostimulation and microrecording were used for neurophysiological evaluation of the target. Postsurgical local field potentials were recorded in all cases.

Results: Neither neurological deterioration nor surgical complication were reported among the group. Caregivers of the patients noted subjective improvement of the clinical state of the subjects that was confirmed with tailored scales.

Conclusions: Subthalamic deep brain stimulation reduces dystonic movements among NBIA patients. The technique carries minimal surgical risk, and improves quality of life of the patients.

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Multimodal, staged surgical treatment of Parkinson's disease. Case report

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Objective: The authors present a PD patient treated with unilateral pallidotomy and contralateral GPi deep brain stimulation (DBS), followed by unilateral STN DBS.

Background: Surgical targets for stereotactic treatment of Parkinson's disease (PD) include globus pallidus (GPi), thalamus (Vim) and subthalamic nucleus (STN). STN is believed to be the optimal target for most of PD symptoms.

Methods: The authors present 63-years old male patient with 20-years history of PD and identified PARK-2 mutation. In 2000 the patient was surgically treated with unilateral right-sided pallidotomy and unilateral left-sided GPi DBS. Because of progression of the disease, patient was qualified for unilateral right-sided STN DBS. Clinical status was evaluated and video recorded prior and after surgery. The surgical procedure was undertaken under local anesthesia. The target was identified with direct and indirect method. Intrasurgical macrostimulation and microrecording were used for neurophysiological evaluation of the target.

Results: Clinical status of the patient improved subjectively following surgery. Motor UPDRS decreased from 36 to 28 points (22% reduction). No surgery related complications were reported. Three months after surgery stimulation parameters were tailored as follows: GPi: C+, 1(-), 90us, 170Hz, 1,0V; STN: C+, 2(-), 60us, 130Hz, 2.6 V. L-dopa consumption decreased to 375mg/day.

Conclusions: Progression of PD among patients with functioning unilateral GPi deep brain stimulation and previous pallidotomy might force clinicians to perform unilateral STN DBS. Improvement of motor functions after unilateral implantation of subthalamic deep brain stimulation does not exclude possibility of future implantation of contralateral STN DBS, when progression of the disease will impact quality of patient's life.

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Bilateral GPi DBS for off dystonias and on dyskinesias in juvenile PD

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Objective: To describe a case of juvenile PD with homozygous PARKIN mutation and review the challenges of DBS target selection in juvenile PD.

Background: Data supporting preference of DBS target choice in juvenile PD are lacking. In particular, correlation between disabling symptoms and choice of target (between STN and GPi) represents an underinvestigated area.

Methods: Description of our experience with a juvenile PD patient who underwent bilateral GPi implants, including multiple video segments.

Results: Our patient had dramatic response to levodopa at age 11, helping him to move from a wheelchair to near-normal functioning. Over the years his levodopa use increased to nearly 4 grams daily. When the patient was first seen in our Center at 25 years of age, he was greatly disabled from grade 4 ON dyskinesias and severe OFF dystonias. Genetic testing, previously avoided, revealed homozygous deletions in PARKIN exon 4. Presurgically, the patient had virtually no meaningful ON time (without dyskinesias), despite taking levodopa no less frequently than hourly during waking hours. Bilateral GPi DBS electrodes were implanted, with moderate microlesioning benefit. There was no levodopa dose reduction. Multiple programming sessions allowed stable and sustained 70-90% reduction of OFF dystonias and near complete resolution of dyskinesias. The patient now spends most of the day ON without bothersome dyskinesias.

Conclusions: Many experts consider GPi a better suited target when the most disabling symptoms include dyskinesias and dysto-

nias. While prospective studies are needed to address site selection as a function of most disabling symptoms, our case supports the notion that GPi stimulation can work exceptionally well in reducing ON dyskinesias and OFF dystonias in juvenile PD with a homozygous PARKIN mutation.

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Predicative factors for the improvement of gait disorders by low-frequency subthalamic nucleus deep brain stimulation (STN DBS) in advanced Parkinson's disease

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Objective: To assess specific profiles of Parkinson's disease (PD) patients with bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) whose gait is improved with low frequency stimulation (LFS) instead of high frequency stimulation (HFS).

Background: LFS (60 Hz) has proven to be effective on gait disorders and Freezing Of Gait in some advanced PD patients. However, predicative factors of this benefit are largely unknown.

Methods: Thirty PD patients with longstanding (5.4 years on average) bilateral STN-DBS were consecutively evaluated in a prospective study assessing gait (*stand-walk- sit test, SWST* and GABS scale), freezing episodes and motor Unified Parkinson's Disease Rating Scale (UPDRS) score. Three conditions were compared in a randomized, double-blind manner: off-stimulation, low-frequency equivalent-voltage STN DBS and high-frequency (130-180 Hz) STN DBS. Primary outcome was the measure of the time during the *SWST*. Predictive factors of benefit were also studied.

Results: Nineteen patients (63.3 %) walked faster with LFS, whereas 7 patients (23.3%) did better with HFS. Four patients failed to complete the tests. Patients responding better to LFS presented with a specific profile at time of surgery: they were older (in spite of the same disease duration compared to HFS responders), with more severe UPDRS motor score, and worse score at depression and cognitive evaluations. After surgery, LFS responders had more decline in axial subscore dopasensitivity at 1-year follow-up. Additionally, cognitive, apathy and depression evaluation were worse than the non responders' evaluation.

Conclusions: Our data suggest that LFS responders seem to rapidly develop "axial deterioration" quicker than HFS responders. This might suggest a more severe brain dopaminergic and non dopaminergic depletion.

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The effects of pedunculopontine nucleus (PPN) and subthalamic nucleus (STN) deep brain stimulation (DBS) on whole body turning in a patient with advanced Parkinson's disease (PD)

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Objective: To report on the preliminary kinematic findings of simultaneous bilateral STN & PPN DBS for advanced PD.

Background: As PD progresses, many patients develop axial motor symptoms of postural dysfunction and gait problems which are generally drug resistant. DBS of the STN is the current surgical method of treating these patients. Stimulation of this area has been shown to improve the cardinal symptoms of PD but has been less effective in treating the axial motor symptoms. It has recently been shown however, that a combination of bilateral stimulation of the STN and PPN may improve both the cardinal symptoms of PD and the axial motor symptoms.

Methods: A 56-year-old, right-handed man with advanced idiopathic PD of 8-years duration and history of Freezing Of Gait, postural instability, marked "Off" akinesia and "On" dyskinesia underwent simultaneous bilateral STN and PPN DBS implantation. With the patient in half "Off"-half "On" medication state, gaze displacement and inter-segmental co-ordination during large whole body voluntary rotations were analysed during bilateral STN and PPN DBS.

Results: Successful simultaneous implantation of bilateral STN & PPN electrodes was confirmed on post-operative stereotactic imaging. On DBS of STN at 2.5 V, 130 Hz, 60 microseconds and PPN at 2.0 V, 20 Hz, 60 microseconds, the following kinematic improvements were noted: 15% & 62% in trunk & feet latencies respectively, 54% & 302% in trunk & feet velocities respectively, 60% in the number of steps needed and 93% in the fraction of the desired angular displacement achieved with the first step ($p<0.01$).

Conclusions: Simultaneous bilateral STN and PPN DBS offer the possibility of ameliorating both the cardinal and the axial motor symptoms in advanced PD. The motor paradigm adopted provides objective evidence of performance changes in the relevant axial motor segments.

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A systematic review of the effects of bilateral subthalamic nucleus stimulation after one year in patients with Parkinson's disease

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Objective: To perform an updated systematic review on the effects of STN-DBS after one year.

Background: A previous systematic review of deep brain stimulation (DBS) of the subthalamic nucleus (STN) in patients with Parkinson's disease (PD) showed substantial improvements. However, guidelines for patient eligibility have changed.

Methods: A systematic literature search identified 33 studies evaluating the efficacy of bilateral STN DBS with a follow-up of 12 months, dated up to 2009. As most studies were patient-series designs (N=23), the pre-post change scores were extracted for data analysis. A meta-analysis was conducted using the Unified Parkinson's Disease Rating Scale (UPDRS) III medication off score as primary outcome and UPDRS II (on and off medication) and UPDRS III (on medication) as secondary outcomes. Heterogeneity and predictive factors for surgical outcome were explored through metaregression and a cumulative meta-analysis.

Results: Heterogeneity amongst studies (I^2 ranged 74.2% - 96.4%) precluded pooled analysis of all studies. Subgroup analysis showed that studies in the tertile with the highest pre-operative scores (worst motor function) reported a greater improvement on the UPDRS-III off medication score (33.0; 95% CI 30.6-35.5) compared to those with the lowest scores (17.3; 95% CI 16.1-18.6). Metaregression models indicated that larger post-operative effects were consistently predicted by higher baseline UPDRS-scores for all outcomes, whereas levodopa responsiveness only predicted the UPDRS III off medication scores. A cumulative meta-analysis showed that effect sizes of the UPDRS-III off medication score decreased from 2004 onwards. Studies before 2004 included patients with significantly higher UPDRS III off medication scores than those after.

Conclusions: The present study indicates that patients with worse baseline motor function gained almost twice as much (in absolute terms) from STN-DBS. Overall, baseline UPDRS-scores were the most important predictors of change after surgery. This study points to the fact that the estimated effect sizes found in more recent studies were smaller than reported before, possibly reflecting a shift towards inclusion of patients with better disease profiles.

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Neuroendocrinology of weight gain in patients with Parkinson's disease (PD) treated with deep brain stimulation of the subthalamic nucleus (STN DBS)

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Objective: To test the hypothesis that weight changes in PD patients treated with STN DBS are mediated by changes of adipose tissue or digestive tract-derived hormones.

Background: Body weight (BW) gain has been reported as a frequent non-motor side effect in PD patients treated with STN DBS but its mechanisms remain unclear. Food related hormones may act centrally on receptors mostly found within the hypothalamic nuclei and other brain regions associated with feeding and energy balance.

Methods: We studied prospectively a group of 27 PD patients (21 men, 6 women) treated with bilateral STN DBS. BW, body mass index (BMI), waist circumference and body fat percentage were evaluated during the course of 1.5 years (the day of the implantation, 1, 2, 4, 6, 12 and 18 months later). At the same intervals biochemical nutritional parameters, leptin, resistin, adiponectin and ghrelin levels were measured.

Results: PD patients significantly gained BW after STN DBS. The mean BW gain in 12 months after the implantation was +5.2kg ($p=<0.001$), these changes were accompanied by significant increases in BMI, waist circumference and body fat ($p<0.001$.) We found significant time dependent changes in leptin ($r=0.20$, $p<0.01$) and adiponectin ($r=-0.17$, $p<0.05$.). From other nutritional parametres cortizol decreased significantly -158 nmol/l ($p<0.001$) during the 12 months of the study.

Conclusions: Our study suggests that STN DBS influenced peripheral hormones such as cortisol and leptin. Possible explanation is that DBS induces changes in hypothalamic catabolic/anabolic peptides balance thereby leading to weight gain. We suggest that STN DBS acts on hypothalamic level, where it suppresses the secretion of the corticotrophin releasing factor, leading to decrease in plasma levels of cortisol. Since glucocorticoids appear to act as a key modulator of BW and food intake, promoting leptin secretion by adipocytes and limiting central leptin induced effects, it could by hypothesized that significant decrease in cortisol may impair central action of leptin and therefore mitigate negative feedback action regulating food intake leading to BW increase. Study support: MSM0021620849, IGA1A/8629-5.

801

New unrelated involuntary movements during the immediate postoperative period following deep brain stimulation electrodes placement for treatment of Parkinson's disease caused by interference with cardiac monitoring devices

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Objective: To report a type of postoperative complication involving DBS and ICU monitoring devices.

Background: Hemiballismus, dystonia, tremor, athetosis and seizures may represent complications of DBS procedures for treatment of Parkinson's disease. Other motor disturbances were reported infrequently.

Methods: Methods: Five patients (four men) were studied. Age ranged from 62 to 71 years. They were submitted to DBS procedures using Medtronic electrodes targeted unilaterally (1 patient: VIM) or bilaterally (STN). All patients were operated under local anesthesia and placed under general anesthesia at the final stage of the procedure for tunneling and placement of the pulse generator over the right chest. All patients left the operating room with their generators turned off. After admission to the ICU they were submitted to conventional cardiac monitoring with electrodes placed over both left and right chest.

Results: All new involuntary movements started after ICU admission; their nature had no similarity to the pre-operative status. They were brisk abnormal involuntary movements. The patient with a unilateral implant had movements restricted to the opposite side. All others had alleatory movements involving their four limbs, with frequency varying between 4 and 60Hz, and pauses in the paroxysms of 10 to 30 seconds. The patient implanted unilaterally also had unique short periods (about 15 seconds) during which the abnormal movement had higher frequency similar to her cardiac rhythm. Misdiagnosis led three of such patients to receive intravenous anti-epileptic treatment without any success. In all patients, the new involuntary movements were suppressed when the cardiac monitoring electrodes were removed.

Conclusions: In all of these patients new abnormal movements were apparently generated by interference from the cardiac monitoring device, possibly related to a kind of antenna effect. Since misdiagnosis might lead to wrong treatment and patient anxiety, ICU personnel should be advised about this rare occurrence. At this point, we have no clue of what type of patient or procedure would be more likely to develop this complication.

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Deep brain stimulation and Parkinson's disease: Low stimulation frequency and gait disturbances

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Objective: To investigate effects of stimulation frequency (SF) reduction on gait disturbances in Parkinson's disease (PD) patients treated with deep brain stimulation of subthalamic nucleus (STN-DBS).

Background: STN-DBS is an effective surgical procedure for advanced PD. In some patients, despite an optimal control of motor signs, some gait disturbances (e.g. freezing, festination) or disabling symptoms (e.g. subjective sensation of blocked and heavy legs, stiffness) may appear or persist after surgery. It's matter of discussion if these symptoms may be related to the high frequency chronic stimulation, rather than to the direct effect of the electricity diffusion across areas near to the subthalamus. Recent data suggest that SF reduction can improve these disturbances.

Methods: We selected a sample of 21 patients who underwent STN-DBS for PD and experienced such gait disturbances and symptoms after surgery. SF was lowered to 70 Hz (T0), without variation of other stimulation parameters and maintaining a stable pharmacological therapy. During the next week, subjects were evaluated daily (T1); afterwards, in outpatients clinics, at one (T2) and eight (T3) months. Unified Parkinson's Disease Rating Scale (UPRDS) part II, UPDRS part III and Freezing Of Gait Questionnaire (FOG-Q) were administered in conditions of OFF-therapy and ON-stimulation.

Results: All the subjects experienced an immediate improvement. At T1 six patients (28,5%) showed a worsening of OFF-phases (mostly within 48 hours from T0), requiring a switch back to high SF. At T2, all the patients who had maintained low SF reported a persistent gait improvement, which was confirmed even at T3. In the subgroup of patients with Freezing Of Gait , there was a significant improvement of both the corresponding UPDRS sub-item score (T0 2.33 ± 0.5; T3 0.67 ± 0.5; $p<0.001$) and FOG-Q score (T0 13.9 ± 2.5; T3 9.4 ± 3.2; $p=0.004$).

Conclusions: Reduction of SF to 70 Hz can be an effective strategy to improve those gait disturbances which persist or begin after STN-DBS.

803

Anatomical situation of subthalamic nucleus (STN) from midcommissural point (MCP) in Parkinson's disease patients underwent deep brain stimulation (DBS): An MRI targeting study

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Objective: Our study was aimed to identify the anatomic location of STN from midcommissural point (MCP) in Iranian Parkinson's disease patients who underwent DBS by means of brain magnetic resonance imaging (MRI).

Background: It is demonstrated that the degree of clinical improvement in Parkinson's disease (PD) achieved by deep brain stimulation (DBS) is largely dependent on the accuracy of DBS lead placement. In addition, individual variability in the situation of subthalamic nucleus (STN) is responsible for spatial inter-individual fluctuations of the real patient's target.

Methods: Forty-six patients with diagnosis of PD who candidated for bilateral implantation of STN-DBS (92 subthalamic nucleuses) were recruited. All these patients had bilateral implantation at the same operation. DBS and MRI parameters including the target coordinates (X, Y, Z) and the distances from MCP to the center of STN in all three axes on both sides were reported and calculated for PD patients.

Results: The location of STN was approximated by a site 11 *mm* lateral, 3 *mm* inferior and 3 *mm* posterior to the midcommissural point. This distance was significantly lower in PD patients who aged >50 years in both right and left sides in the antero-posterior (Y-axis) direction.

Conclusions: Our findings lead to a considerable set of information which could help neurosurgens during DBS procedure in Iranian PD patients. Despite the differences observed between various population of PD patients in the anatomical location of STN, our results further emphasize the clustration of active contact points in same region.

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Cerebral blood flow changes induced by concomitant pedunculopontine nucleus and subthalamic stimulation in patients with Parkinson's disease: A [(15)O] H2O PET study

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Objective: To assess the effect of deep brain stimulation (DBS) of the Pedunculopontine nucleus (PPN) and Subthalamic (ST) region on regional cerebral blood flow (rCBF) using PET scanning whilst stimulating these two regions separately and in combination.

Background: The ST region has progressively become the preferred target for DBS in PD patients as this procedure dramatically improves bradykinesia and rigidity. The PPN is a novel target for DBS and its modulation is believed to be beneficial in the treatment of gait dysfunction and akinesia in PD patients with such symptoms. Pioneering clinical trials are currently underway to assess safety and efficacy of concomitant PPN and ST stimulation in patients with PD.

Methods: 4 PD patients (mean age 63.25 years and mean disease duration 14.5 years) underwent implantation of bilateral caudal Zona Incerta (cZi) and Pedunculopontine nucleus (PPN) electrodes using an implanted guide-tube and high resolution MRI guided technique. Each subject had a block of 16 [(15)O] H2O PET measurements of rCBF at rest at least 3 months after surgery. We performed four sets of four rCBF measurements: 1) PPN off/ cZi off, 2) PPN on/ cZi off, 3) PPN off/ cZi on, 4) PPN on/ cZi on.

Results: At baseline, the mean UPDRS-motor score in the off medication state for the group was 46.7; with PPN stimulation this improved by 12.9% (40.7), with cZi stimulation this improved by 49.3% (23.7) and combined stimulation resulted in a 55% improvement (21.0). PPN stimulation induced significant rCBF increases ($P<0.001$), in thalamus, cerebellum, and midbrain region. cZi stimulation induced significant rCBF increases ($P<0.001$), in striatum, thalamus and midbrain region but caused rCBF decreases in sensorimotor cortical areas (Brodmann areas 4, 5, and 6). Concomitant PPN and ST stimulation resulted in a cumulative effect on rCBF by combining the changes induced by stimulation of either target in isolation.

Conclusions: These findings suggest that concomitant stimulation of both the ST region and PPN induces additive functional changes in the areas of the motor networks and provides improved control of PD symptoms.

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Subthalamic deep brain stimulation in Parkinson's disease: Ten years follow up

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Objective: To evaluate efficacy of subthalamic deep brain stimulation on motor symptoms in parkinsonian patients after 10 years from surgery.

Background: At the moment there are some papers and studies stating that the benefit of subthalamic deep brain stimulation (STN-DBS) are still present at 5 years follow-up improving motor disability and levodopa related complications, but there are no data regarding longer follow up.

Methods: We prospectively analyzed 22 patients underwent bilaterally STN DBS from June 1997 to August 1999 at the Department of Neurological and Psychiatric Sciences in Florence, Italy. Patients were evaluated with Unified Parkinson's Disease Rating Scale (UPDRS) and Schwab and England scale (SE) before and ten years after surgery with (med ON) and without (med OFF) dopaminergic medication. Post-operative evaluations were performed with the stimulation ON. 11 patients did not reach the last follow up: 5 patients died, 6 patients were lost at follow up. The analysis were performed with a non parametric Wilcoxon test.

Results: At surgery the mean age of the analyzed group was 58,5±7,6 years and the mean duration of the disease was 13,3±4,4 years. Compared to the pre-operative conditions the group showed an improvement that is still present after ten years in UPDRS III in MED OFF condition ($p=0,008$), in UPDRS IV ($p=0,005$) and in SE scale in MED OFF condition ($p=0,006$) Adverse events were: one symptomatic intra-cerebral haemorrhage, dementia in one patients, 3 post-traumatic electrode dislocation, one dermo-epidermic graft on the scalp, two persistent disartrophonya, peri-operative confusion in seven patients, two cases of transient depression and one case with persistent apathy.

Conclusions: STN DBS in well selected advanced parkinsonian patients, is a valid treatment option that, even at ten years from surgery, maintains the motor improvement and the independence in activity of daily living without medication and the reduction of drug related motor complications.

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Speech treatment for individuals with IPD post deep brain stimulation: LSVT-DBS

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Objective: To optimize speech treatment outcomes in individuals with bilateral DBS-STN through development of LSVT-DBS.

Background: The reported effects of DBS-STN on speech/voice have been mixed. Although a few studies have documented improvements in speech following DBS-STN the majority have reported worsening. LSVT LOUD is a speech treatment for individuals with PD that has level 1 evidence. Preliminary data have demonstrated that LSVT LOUD can be effective for certain individuals with PD post DBS-STN; however, speech treatment outcomes are not satisfactory for some patients.

Methods: Six subjects (Ss) with PD (1 female, 5 males) with bilateral DBS-STN participated in this study. Ss were 54 to 69 years of age and 6 months to 3 years post-surgery. All Ss participated in LSVT LOUD (4, 1-hour sessions per week for 4 weeks). Immediately post- LSVT LOUD, subjects were assigned to one of two treatment groups for an additional 8 1-hour sessions in two weeks. These groups addressed difficulties with articulation (Loud and Clear, LC) or with carryover into all communication settings (Calibration, CAL). Acoustic data were collected using standard protocols at pre-treatment (pre), post-treatment (4wk) and post the additional 2 weeks of

treatment (6wk). Ss and significant others (SO) completed perceptual forms at pre, 4wk and 6wk. Acoustic data were analyzed for sound pressure level (dB SPL) from a variety of voice and speech tasks. Perceptual forms (Voice Handicap Index (VHI) and Visual Analogue scale) were analyzed according to standard protocols.

Results: All Ss increased in dB SPL from pre to 4wk. Three Ss continued to improve from 4wk to 6wk. The VHI improved for all Ss from pre to 4wk. Four Ss continued to improve from 4wk to 6wk. Visual analogue ratings conducted by SO's demonstrate that four Ss were perceived as improved in loudness from pre to 4wk and four Ss were rated as louder from 4wk to 6wk. Four Ss were rated as less slurred from pre to 4wk and the 2 Ss continued to improve from 4wk to 6wk.

Conclusions: Individual trends demonstrate the potential benefit of LSVT-DBS for optimizing treatment outcomes for PD individuals post STN-DBS. This Phase I study provides the first step towards development of a treatment to optimize speech treatment outcomes in individuals with bilateral DBS-STN.

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Factors related to extended hospital stays following deep brain stimulation for Parkinson's disease

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Objective: This study examined potential factors that might have corresponded to increased post-operative stays following unilateral DBS surgery.

Background: Patients with Parkinson's disease (PD) are typically discharged from the hospital the day following deep brain stimulation (DBS) surgery; however, factors extending hospital stay are largely unknown.

Methods: A retrospective review was performed on 115 unilateral PD DBS patients. Age, gender, number of microelectrode passes, duration and severity of illness, and pre-operative neuropsychological scores were considered as possible contributors to length of stay.

Results: Most patients (79%) had a hospital stay of one day following surgery. The most frequent reasons for delayed discharge (>1 day) included mental status change (N=6) and hemorrhage (N=5). Those with delayed discharge had significantly lower pre-surgical cognitive screening scores (Mini-Mental State Evaluation; MMSE), higher pre-surgical "on" medication motor score, and more microelectrode passes than those with immediate discharge. In correlation analyses, increasing length of hospital stay was significantly associated with more microelectrode passes, higher pre-surgical "on" medication motor scores, and decreasing MMSE scores. When the significant variables from the preliminary analyses were entered into a Poisson regression model, a greater number of microelectrode passes as well as lower MMSE scores remained significant predictors of increased length of stay.

Conclusions: The number of microelectrode passes utilized for DBS surgery as well as a patient's general cognitive status may be important factors related to extended hospital stay. UPDRS "on" medication motor score may also provide some predictive power for immediate post-operative morbidity in unilateral DBS patients.

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Effect of subthalamic deep brain stimulation on acceleration of the swing phase of gait in Parkinson's disease

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Objective: To measure the effects of high frequency bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) on gait parameters in Parkinson's disease (PD).

Background: The effects of DBS of the STN on kinematic parameters of gait are not well understood. Gait impairment is a major cause of disability in PD. Few reports have addressed how STN DBS affects the swing phase of gait using accelerometry. We hypothesized that linear acceleration in the swing phase and other gait parameters improve with STN DBS.

Methods: Four PD patients underwent bilateral STN DBS (3 men). Linear acceleration, gait velocity, stride length and cadence were measured using a Micro Strain® Inertia-Link sensor attached to the left ankle in 2 conditions: both STN stimulators OFF and both STN stimulators ON. Two trials of walking over a five meter distance were performed in each condition, which were videotaped. Examiners and patients were blinded to conditions.

Results: Linear acceleration during the swing phase of gait increased from 2.36 to 2.95 m/seg^2 (one tail T test=0.04, α=0.05). Compared with stimulation OFF, stride length improved from 0.94 (SD=0.10) to 1.14 m (SD=0.16) (one tail T test=0.003, α=0.05) and cadence decreased from 0.89 (SD=0.13) to 0.75 steps/sec (SD=0.19) (one tail T test=0.019915, α=0.05). Gait velocity was not statistically different between stimulator conditions. UPDRS motor subscale III improved from 31.8 to 23.6 (34.4% improvement).

Conclusions: STN DBS increases linear acceleration of the swing phase of gait in PD. Stride length improvement occurs along with a change in cadence.

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Persistent hemidystonia after STN DBS implantation for Parkinson's disease

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Objective: To describe a Parkinson's disease patient with persistent hemidystonia following DBS lead placement in the STN.

Background: STN and GPi are established targets for DBS in Parkinson's disease. Stimulation of these sites are beneficial for tremor, bradykinesia, rigidity, motor fluctuations and dyskinesias. We describe an unusual case where hemidystonia began shortly after a staged second side STN DBS implant. This persisted after lead repositioning within the STN and then the GPi.

Methods: Case report accompanied by video.

Results: This 64 year old PD male patient was deemed an excellent candidate for STN DBS based on preoperative evaluations which documented intractable symptomatology with major motor fluctuations which included "on" time with marked dyskinesias alternating with random deep "off" episodes. All surgical procedures utilized microelectrode mapping for localization. He underwent staged implantation and did well after the right STN implantation (first side). Six months later he underwent second side STN implantation with the subsequent gradual and progressive development of right sided painful dystonic contractions. Despite MRI evidence of appropriate lead placement, multiple programming sessions failed to alleviate the dystonia. The dystonic contractions continued with the DBS turned off. Six months later it was opted to reposition the lead within the left STN, again using MER guidance. Post-op MRI again revealed the lead to be well placed. Despite multiple variations in programming parameters no relief was obtained. 1.5 years later the lead was repositioned to the left GPi. Interestingly, for one month prior to programming the dystonia disappeared, but with initial programming the hemi-dystonia returned and remained present despite turning the device off. Again, numerous attempts to program the stimulation with wide ranging parameters provided no relief.

Conclusions: Although unusual, a potentially unrecognized adverse event related to STN DBS implantation for PD is persistent dyskinesia (in this case dystonia). Although the etiology is unclear, it

is likely that a permanent change in signaling within the basal ganglia circuitry was induced by insertion of the lead within the STN.

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Pallidal stimulation in advanced Parkinson's patients with contraindications for subthalamic stimulation

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Objective: The aim of this study was to evaluate the efficacy and safety of bilateral pallidal (GPi) deep brain stimulation (DBS) at 6 months of surgery in advanced parkinsonian patients whose dopa-resistant axial motor signs or cognitive decline constituted contraindications for subthalamic nucleus (STN) DBS.

Background: The STN is the target of choice for treating advanced parkinsonian patients refractory to medical treatment. There is, however, increasing evidence that STN DBS may more frequently lead to axial motor signs, cognitive decline and adverse changes of mood than GPi DBS. As a consequence, patients with levodopa-resistant axial motor signs, cognitive impairment at baseline or severe psychiatric disturbance are now excluded from STN surgery.

Methods: 17 patients with a mean age of 59±7.1 years (range, 45-70), mean disease duration of 12.5±4.3 years (range, 7-20) and contraindications for STN DBS underwent bilateral GPi DBS. They were evaluated before and 6 months afterwards according to the Core Assessment Program for Intracerebral Transplantations recommendations.

Results: There were mean improvements of 41.1% in the UPDRS III motor score in the off-dopa condition and 20.3% in the activities of daily living score. Motor fluctuations were reduced by 22.9% and dyskinesias by 68.6%. Axial motor signs improved in the off-dopa condition by 34.2%. Neuropsychological performances remained unchanged at 6 month assessment.

Conclusions: Bilateral GPi DBS is both safe and effective in advanced parkinsonian patients with untreatable motor fluctuations, for whom STN DBS is contraindicated due to dopa-resistant axial motor signs or cognitive decline. As such, it should be regarded as a viable option for these patients.

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Does subthalamic DBS directly impact levodopa-induced dyskinesias?

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Objective: To study the effects of subthalamic (STN) DBS on levodopa-induced dyskinesias (LID) in a large cohort of patients with Parkinson's disease (PD).

Background: LID is one of the major indications for DBS therapy, but the mechanism of improvement is still a matter of controversy. While pallidal stimulation is thought to exert a direct beneficial effect on LID, improvement observed after STN DBS is attributed to lower medication need and intake.

Methods: We retrospectively evaluated 113 consecutive patients treated with STN DBS for advanced PD. Four variables were systematically analyzed, including pre-operative presence of LID, response to stimulation, concurrent dose reduction of dopaminergic medications and the active electrodes used to control symptoms.

Results: 95 patients (84%) had pre-operative LID, which were successfully treated in 82 of them (86%). Out of those that improved, 60 (73%) reported almost immediate LID resolution after programming. Ten patients reported LID resolution even before activating the electrodes. 42 (51%) responders did not require lowering of medication dosage, and 5 more patients only had slight reductions in dosage. Of the 38 patients (who remained at higher doses of medications), 21 (55%) had their settings set to include activation of one or more of the dorsal contacts. Only 17 patients (20% of responders) had recurrence of their dyskinesias.

Conclusions: We observed a direct effect of STN DBS on LID in a large cohort of advanced PD patients. Improvement was very rapid in the majority of cases, well before (and in some cases without) the possible effects of medication reduction. Frequently, activation of contacts likely positioned outside of the STN was associated with dyskinesia control, suggesting that there may be concurrent and alternative effects of different contacts along the implanted electrode.

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Efficacy of re-programming of subthalamic deep brain stimulation parameters

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Objective: To evaluate clinical effect of re-programming of subthalamic deep brain stimulation (STN-DBS) parameters on motor impairment and medication sparing effect in advanced Parkinson's disease patients.

Background: STN-DBS improves motor fluctuation markedly; about 50% reduction of off-time, 30 to 50% reduction of anti-PD medication dosage, 80% reduction of troublesome dyskinesia. Motor symptoms progress gradually after STN-DBS, however, because clinical effect of STN-DBS is symptomatic. Therapeutic optimization with both of re-programming of STN-DBS parameters and accompanied medication adjustment has potentials to ameliorate symptom control during time course after STN-DBS.

Methods: Four patients (one male and three females) had participated hospitalized re-programming of STN-DBS. Mean disease duration was 14.1 years, and mean post-operative duration was 30.5 months. Appropriate contacts for cathode were evaluated with overnight medication discontinuance. Medication was reduced in accordance with enhanced STN-DBS effect with parameter re-programming. Pre- and post-reprogramming motor symptoms were evaluated with Unified Parkinson's Disease Rating Scale (UPDRS).

Results: The mean score of UPDRS motor function score was reduced from pre-reprogramming 30.5 to post- reprogramming 16.5. The mean medication dosage was also reduced from pre-reprogramming 62.5.1mg/day to post-reprogramming 432.1mg/day (levodopa equivalent dosage). The mean period required for stimulation re-programming and medication adjustment was 12 days.

Conclusions: We found marked effect on motor symptom with combined therapeutic optimization of re-programming of STN-DBS and medication adjustment, after more than two years of STN-DBS lead implantation. Re-programming of STN-DBS is suggested to be efficacious. Further study is needed to consider appropriate interval of re-programming in a long time course during follow-up after STN-DBS.

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Subthalamic nucleus deep brain stimulation for camptocormia associated with Parkinson's disease

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Objective: To evaluate the effect of subthalamic nucleus deep brain stimulation (STN-DBS) for camptocormia associated with Parkinson's disease (PD).

Background: Camptocormia becomes increasingly recognaized as a disabling symptom associated with PD, however, the optimal therapy for PD-associated camptocormia remains to be established. We here report six patients with PD whose disabling camptocormia was substantially alleviated by bilateral STN-DBS.

Methods: Six patients who showed camptocormia associated with PD underwent bilateral STN-DBS. We estimated characteristic of these patients, Unified Parkinson's Disease Rating Scale (UPDRS) and the thoracolumbar angles of the bent spine before and after surgery.

Results: Bilateral STN-DBS produced substantial (mean 78%±9.1% of the thoracolumbar angle) improvement of camptocormia along with other motor symptoms. The mean UPDRS lll score in the ''off'' phase decreased from 48±16.6 (baseline) to 15±9.9 (postoperative); in the ''on'' phase it decreased from 41±14.7 to 15±9.9.

Conclusions: Our present findings suggest axial poturing may be controlled by the STN as a function of the basal ganglia, and that bilateral STN-DBS can be as a potential surgical means to address camptocormia in PD patients.

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Effect of globus pallidus internus and/or pedunculopontine nucleus DBS on posture and gait ignition in advanced Parkinson's disease

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Objective: To assess the effect of deep brain stimulation (DBS) of globus pallidus internus (GPI) and/or the pedunculopontine nucleus (PPN) on posture and gait ignition in very advanced Parkinson's disease (PD).

Background: GPI DBS in IPD is an established procedure to treat hyperkinetic dyskinesia and to some extent also dystonia, yet it has not been shown to be effective in gait ignition failure and postural instability. For the latter aspects, however, there recently was promising data on the beneficial effect of PPN DBS.

Methods: A 66-years old male PD patient with motor fluctuations including severe peak-dose dyskinesia, on-freezing, and postural instability underwent bilateral GPI and PPN DBS. In best medical on, posture while level walking and gait ignition while turning on the spot were examined using clinical gait analysis (Vicon Motion System Ltd, Oxford, UK) with GPI DBS only (bipolar, 3,0V, 210μs, 130 Hz), with PPN DBS only (bipolar, 2,5 V, 60μs 25 Hz), and with combined GPI/PPN DBS. Posture was assessed by the upper body tilt angle (UBTA) in left-right body side for stance phase; to depict gait ignition, maximal rotational angle while turning on the spot (MaxRAWTOTS), mean time for turning 45° (MTT45) and the range of motion for the centre of mass while turning (ROMCOM) were measured.

Results:

TABLE 1 (814).

	UBTA [°]	MaxRAWTOTS [°]	MTT45 [s]	ROMCOM [mm]
PPN DBS only	22,3	59	7,2	62
GPI DBS onliy	22,3	29	8,1	200
PPN and GPI DBS	16,1	217	1,7	37

Conclusions: Isolated GPI and PPN DBS had a similar impact on posture, but the combination of both significantly improved the upright posture. Gait ignition was worst with isolated GPI DBS and better with isolated PPN DBS. Again the combined stimulation yielded the biggest benefit. This combined approach may be useful in treating drug-resistant features of advanced PD and encourages future studies.

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Clinical predictors for early staged placement of subthalamic DBS in Parkinson's disease

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Objective: To determine whether the preoperative Parkinson's disease (PD) phenotype predicts the need for early placement of the second electrode in staged subthalamic deep brain stimulation (STN DBS).

Background: Bilateral STN DBS has been shown to be superior to best medical therapy for the motor symptoms of Parkinson's disease (PD), albeit at greater risk of serious adverse events. PD is an asymmetric disease, and unilateral STN DBS followed by a staged contralateral procedure (when needed) has emerged as a treatment option, but little is known about phenotypic characteristics that may predict when staged placement of a brain stimulator in the opposite subthalamic nucleus may be required.

Methods: Eighty-two consecutive patients with moderate to advanced PD underwent unilateral STN DBS with the initial electrode placed contralateral to the most affected hemibody and had at least 24 months of follow-up. Multivariate logistic regression was used retrospectively to determine preoperative characteristics that predict placement of the contralateral STN electrode. Preoperative phenotypes that were analyzed included duration of disease, Unified Parkinson's Disease Rating Scale (UPDRS) total score, UPDRS motor score, UPDRS dyskinesia subscore, motor asymmetry index, tremor subscore, and body weight.

Results: At the time of analysis 28 patients had undergone staged placement of a contralateral electrode, and 54 patients remained unilateral. Multivariate regression analysis showed that the most important predictors for early staged placement of a second STN stimulator were low asymmetry index (odds ratio (OR) 11.28; 95% confidence interval (CI) 2.81, 45.36), high tremor subscore (OR 7.69; CI 1.89, 32.25), and low body weight (OR 3.88; CI 1.227, 12.28). UPDRS total score, UPDRS Part 3 motor score, UPDRS dyskinesia subscore, and the presence of akinetic rigid disease were less predictive of early staged placement of a second STN DBS electrode.

Conclusions: This single center study provides evidence that elements of the PD phenotype may serve as predictors for whether early staged bilateral STN DBS in PD will be required. These data may help guide the management of patients with PD who undergo STN DBS.

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Role of mesocorticolimbic dopaminergic denervation in postoperative apathy and depression in Parkinson's disease

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Objective: To determine the role of mesocorticolimbic dopaminergic degeneration in the physiopathology of apathy in PD patients operated with STN stimulation using [^{11}C]-Raclopride, a D2/D3 dopamine receptor ligand.

Background: Apathy is the most frequent behavioural complication in Parkinson's disease (PD) patients after subthalamic nucleus (STN) stimulation. However its precise physiopathology remains unknown.

Methods: 12 patients who developed apathy in the year following surgery and a control group of 13 patients who did not were enrolled. Dopamine agonist drugs were stopped after surgery and L-dopa dosage was reduced as required by motor state. All patients underwent two [^{11}C]-Raclopride PET scans. The first was performed before, and the second after, an oral intake of 0.5 mg/Kg of methylphenidate (MP). The motor effect of MP was assessed using a timed tapping test, and the psychotropic effects of MP using the Norris visual analogic scale (VAS).

Results: Apathetic patients presented greater apathy, depression and anxiety scores than their non apathetic counterparts. Without MP, [^{11}C]-Raclopride BP values, (a measure of dopamine D2/D3 receptor availability) were greater in apathetic patients bilaterally in the orbitofrontal, dorsolateral prefrontal (DLPFC), posterior cingulate and temporal cortices and in the left dorsal and ventral striatum and

the right amygdala. After MP, only the apathetic patients experienced a beneficial effect on asthenia and affective subscores of the VAS. The variations of [^{11}C]-Raclopride BP values before and after MP (an indirect measure of endogenous dopamine release into the synapse) were greater in the non apathetic group of patients in the left orbitofrontal cortex, DLPFC, thalamus and internal globus pallidus and bilaterally in the anterior and posterior cingulate cortex.

Conclusions: The present study demonstrates that PD patients, who develop apathy, anxiety and depression after STN stimulation have greater mesocorticolimbic dopaminergic denervation than patients without apathy.

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The use of a novel side-outlet curved test electrode in deep brain stimulation (DBS) for the per-operative assessment of patients with Parkinson's disease (PD)

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Objective: A novel per-operative tip side-outlet curved test-electrode has been designed to reduce the number of trajectories and therefore the risk of adverse events in patients with PD undergoing DBS surgery.

Background: Peroperative macrostimulation and/or microrecording in DBS for PD is the standard method to assess the clinical response and determine the location for the placement of the definite quadripolar electrode. If the response is unsatisfactory, new trajectories are necessary for repeat clinical testing. Increasing the number of trajectories, increases the risk of serious adverse events, such as intracerebral hemorrhages. To reduce the number of trajectories, we have designed a novel tip side-outlet curved test-electrode for macrostimulation.

Methods: The new electrode (Inomed, Germany) has at 5 mm of the electrode tip a side opening, through which a curved electrode can pass. Therefore, this electrode allows us to test an indefinite number of locations within a virtual cylinder with a radius of 4 mm. All possible stimulation sites are well within the range of the targets used in Parkinson's disease.

Results: 57 patients (32 men, 25 females, mean age 62.5 years) with idiopathic PD underwent DBS surgery using the novel electrode. In 17 patients it was necessary to use the side electrode, because of a limited or absent clinical response using the straight electrode. In 8 patients one new target testing was required, whereas in 9 patients several new targets were explored in a pre-determined method, i.e. anteromedial, posteromedial, anterolateral and posterolateral. None of the 17 patients experienced any side effects and in particular none of the 57 had any per-operative nor post-operative intracerbral hemorrhages.

Conclusions: The use of this novel side-outlet curved test electrode is a safe and efficient method to explore the entire range of the target with only one trajectory and, if necessary, only one extra trajectory for the placement of the definite electrode. Moreover, we have not encountered any serious per- and/or post-operative adverse events, such as intracerebral hemorrhages in all patients. A side-outlet curved test electrode for microrecording is under development to further safely optimalize target selection.

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Stimulation of zona incerta in Parkinson's disease: A first look at speech outcomes

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Objective: To evaluate speech outcomes 6 months after deep brain stimulation (DBS) of the caudal zona incerta (cZi) for patients with Parkinson's disease (PD).

Background: An increasing number of patients with advanced PD are now treated using surgically implanted electrodes to stimulate deep brain structures. The subthalamic nucleus is the most usual target. Recent surgical trials have indicated that cZi may be a better target[1]. To date there are no reports of the effects of cZi stimulation on speech, other than a recommendation that the caudal rather than rostral region be targeted to avoid speech disturbances[1].

Methods: Six PD patients (5 males, 1 female; mean age 61;9 yrs) participated in the study. They were the first 6 patients in a study at Umeå University Hospital to evaluate cZi stimulation as a PD treatment. All 6 patients received bilateral cZi stimulation. Speech function was evaluated in detail before (with a test dose of 1.5 times usual medication) and 6 months after surgery (with Stimulator Off and On). A speech reading passage was analyzed perceptually and acoustically and compared across the 3 conditions.

Results: Perceptual analysis showed that speech responses to surgery were variable. Before surgery 3 patients had no detectable speech problems while 3 others had mild problems. Two of the 3 patients with no presurgical speech problems showed no speech changes after surgery. However, the third patient's voice and articulatory precision had deteriorated after surgery and was worse for stimulator on. None of the 3 patients with incipient speech problems before surgery showed any speech improvement after surgery. For 2 of them, voice and clarity of articulation were worse after surgery, while changes in the third patient's speech were small and inconsistent. Acoustically, voice pitch frequency (fo) and intensity (I) were affected occasionally by surgery. Mean fo increased for just one patient and mean I increased for two others after surgery.

Conclusions: These preliminary results indicate that PD patients with pre-existing speech problems cannot expect improved speech outcomes after surgery. There is also the chance that patients without any speech problems prior to surgery may experience worsened speech after surgery. [1]Plaha P et al 2006. Brain 129, 1732-47.

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The national DBS brain tissue network pilot study: A need for more tissue and for more standardization

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Objective: To establish a deep brain stimulation-Brain Tissue Network (DBS-BTN) for use by clinical and research communities to help understand DBS.

Background: Over 50,000 DBS devices have been implanted worldwide; however, there is a paucity of well-characterized post-mortem DBS brains available. We propose that the overall understanding of DBS can be improved through the establishment of the DBS-BTN which will preserve high-quality specimens from well-documented tissue samples for the clinical and basic research communities.

Methods: Standard operating procedures for processing DBS brains were developed. Complete data files were created for individual patients and included demographic information, clinical information, imaging data, pathology, and DBS lead locations/settings. In select cases, post-mortem MRI was performed.

Results: 19 DBS brains were collected from 11 DBS centers from across the U.S. The average age at the time of death was 69.2 years. The male:female ratio was approximately 3:1. The average post-mortem interval from death to brain collection was 10.6 hours. The brain areas targeted for DBS included: subthalamic nucleus (STN; n=19 leads, 12 patients), globus pallidus interna (GPi; n=8 leads, 5 patients), and ventralis intermedius nucleus of the thalamus (Vim; n=2 leads, 2 patients). One patient had targets in both STN and Vim. In 16.7% of cases, clinical diagnosis failed to match pathological diagnosis. We provide neuropathological findings, and peri-lead responses to the DBS procedure. One of the most important observations made in this pilot study was missing data, which approximated 25% of all available data fields.

Conclusions: Preliminary results demonstrated the feasibility and utility of creating a National DBS-BTN resource for the scientific

community. We plan to improve techniques to remedy omitted clinical/research data, and expand the Network to include a larger donor pool. We will enhance sample preparation methods to facilitate more advanced molecular studies as well as progenitor cell retrieval. This abstract has been presented at the WFN PD Congress in Dec, 2009.

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Influence of deep brain stimulation in the subthalamic nucleus in Parkinson's disease on comprehension of emotional prosody

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Objective: To evaluate the influence of subthalamic deep brain stimulation (DBS-STN) on comprehension of emotional prosody in patients with Parkinson's disease (PD).

Background: Recent research reveals the involvement of the basal ganglia in processing of emotions and the impact on this cognitive function by modulation of the cortico-subcortical loops. Patients with PD seem to be impaired in processing of emotions and at an intervall after DBS-STN implantation this deficit seems to be aggravated.

Methods: We tested non-demented, non-depressed PD patients (n=10) with STN-DBS on and off and compared them to age- and education matched healthy controls (HC) (n=10) with different tasks: a) identification of vowels b) identification of emotional prosody c) identification of emotional semantics.

Results: Comparison between groups PD vs. HC showed a main effect of groups in accuracy rate but not in reaction time, indicating that deficits in task performance were not due to motor impairments. Comparison of PD with STN-DBS on and off showed a significant difference in motor abilities as assessed by UPDRS III. However withingroup comparison with STN-DBS on vs. STN-DBS off showed no significant influence on accuracy or reaction time during any of the three different task conditions.

Conclusions: PD causes impairment in comprehension of emotional prosody, which is not altered by DBS-STN. These results are in line with research pointing to an involvement of the basal ganglia in processing of emotions. However STN-DBS affecting the motor cortico-striatal loop does not modulate perception of emotional prosody, which is most likely mediated by more ventral striatal structures.

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Effects of zona incerta lesions upon striatal neurochemistry and behavioural asymmetry in 6OHDA-lesioned rats

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Objective: To determine the effects of lesions of the zona incerta (ZI) upon striatal neurochemistry and behavioural asymmetry in the 6-hydroxydopamine (6OHDA)-lesioned rat.

Background: The ZI lies immediately dorsal to the subthalamic nucleus. This region is often involved in patients with PD who have lesions or placement of DBS electrodes. When efficacy of different target sites is analysed, lesions of the ZI are reported to have clinically beneficial effects upon PD symptoms.

Methods: We performed electrolytic lesions of the ZI in control and 6OHDA-lesioned rats. Parallel groups of rats underwent behavioural testing before and after ZI lesions. Tests included; amphetamine-induced rotations, forepaw stepping, forepaw reaching with whisker stimulation, and cylinder exploration. Separate groups of rats with and without ZI lesions had striatal microdialysis probes placed for measurement of striatal extracellular glutamate, dopamine, DOPAC, and HVA. One week later 20 minute samples were collected by microdialysis for 6 hours.

Results: In intact rats ZI lesions had no effect upon striatal extracellular glutamate or absolute levels of dopamine or metabolites, but dopamine metabolism decreased. Following ZI lesions, contralateral forepaw use decreased in the forepaw adjusting steps test, but there was no change in response to whisker stimulation or cylinder exploration. There was no development of rotational asymmetry with amphetamine. In 6OHDA-lesioned rats striatal extracellular glutamate levels were elevated compared to controls. ZI lesions reduced the increased levels of glutamate back to normal values. ZI lesions reduced dopamine and HVA levels, and showed a trend towards a decrease in dopamine metabolism. 6OHDA-lesioned rats demonstrated the expected asymmetry of motor behaviours. Following ZI lesions ipsilateral turns following amphetamine injection were reduced, and there was a trend towards improved symmetry of forepaw use as determined with the forepaw adjusting steps test. There was no change in forepaw use with whisker stimulation or cylinder exploration.

Conclusions: These data indicate that lesions of the ZI can affect striatal neurochemistry and motor behavioural asymmetry, and suggest potential mechanisms by which ZI lesions may improve symptoms in Parkinson's disease.

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Postoperative verbal fluency decline after subthalamic deep brain stimulation surgery correlates with laterality of the microlesion. Results of a prospective longitudinal study

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Objective: To determine the impact of postoperative microlesion versus stimulation-induced effects on cognitive functions in subthalamic (STN) deep brain stimulation (DBS) surgery in Parkinson's disease (PD).

Background: DBS of the STN in PD is a safe and powerful treatment to improve quality of life. On the other hand DBS can cause cognitive or psychiatric side effects especially in the first months after surgery. It is not known whether the operation procedure and postoperative microlesion or electrical stimulation itself has the main impact on neuropsychological outcome.

Methods: 14 patients with PD (7 male) were included into a prospective longitudinal study. The neuropsychological test battery comprised tests on emotion, attention, executive functioning and memory. Measurement time points prior to surgery were 12 weeks (T -12) and one week (T-1) and following surgery one week (T+1), three weeks (T+3) and 12 weeks (T+12). At "T+1" tests were performed without stimulation to determine microlesion effects. At "T+3" and "T+12" tests were done with and without stimulation. Analysis of variance was used to find timepoints with significant changes in cognitive scores. Relative changes in test performance were correlated with stereotactic coordinates of the stimulation electrode.

Results: Significant change in cognitive tests was mainly found in verbal fluency with decline one week (T+1) after implantation without stimulation. Relative decline in categorial VF at "T+1" compared to "T -1" was positively correlated especially with the x-coordinate (laterality) of the left ventral electrode tip (r=0.69).

Conclusions: This study provides evidence that direct postoperative microlesion effect has more impact on changes in verbal fluency than stimulation itself. Furthermore a more lateral electrode position seems to be critical. That should be taken into account in preoperative planning.

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Protruding exposure of the internal pulse generator (IPG) through the skin: A rare complication of the deep brain stimulation (DBS)

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Objective: Our aim is to report the case of a rare complication of IPG presenting protruding exposure after DBS surgery.

FIG. 1 (823).

Background: Deep brain stimulation (DBS) is used increasingly worldwide for the treatment of advanced Parkinson's disease, intractable essential tremor, and dystonia. As with any implanted system, however, DBS introduces a new series of problems related to its hardware. The most commonly reported hardware-related adverse effects are infections, migration or misplacement of the leads, lead fractures, and skin erosion. Complications caused by implantable pulse generator (IPG) of DBS are uncommon and protruding exposure of IPG is very rare.

Methods: Single case report.

Results: A 53-year-old man admitted to emergency room because of the protruding exposure of IPG following skin erosion after DBS surgery. He had developed bradykinesia and resting tremor of left hand 13 years ago. He was diagnosed as Parkinson's disease two years later, and then he had been treated with levodopa and dopamine agonist. Ten years later, he had motor complications presenting as severe motor fluctuation and on-time dyskinesia. Eventually he was operated on bilateral subthalamic nucleus (STN) DBS surgery two years ago, and the surgery was successful. Although he had taken more reduced dosage of levodopa drugs and off symptoms had been better, he had intermittently his stiff shoulder and neck massaged with vibrating machine. Several months ago, he felt the mild mobility of IPG which was not fixed in the inner chest wall, and then skin erosion developed in the margin area of movable IPG. After all, IPG protruded with exposure through the skin, and then he should have emergent reoperation and intensive hospitalized treatments additionally.

Conclusions: For now, we report for the first time a rare complication of IPG presenting protruding exposure after DBS surgery. As if in this case, we should consider the risk of more serious complications in the early stage of skin erosion and movable device associated with IPG as well as lead of DBS.

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Coherent activity in the parkinsonian STN and PPN: Preliminary findings

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Objective: To improve understanding of the pathological activity in the parkinsonian subthalamic nucleus (STN) and pedunculopontine nucleus (PPN) based on preliminary findings from local field potential (LFP) recordings from a single bilaterally implanted patient, and to observe how this activity changes due to deep brain stimulation (DBS).

Background: The PPN is emerging as a novel target for DBS in Parkinson's disease (PD) to specifically treat intractable axial symptoms such as gait freezing and loss of postural control. However, the underlying mechanisms of DBS remain unclear, as does the nature of the pathological activity associated with PD. In order to understand the effect of stimulation on the underlying physiology of the brain, LFP recordings from implanted DBS electrodes allow direct neurophysiological observation of targeted nuclei and their correlated activity.

Methods: A 55-year-old, right-handed man with advanced idiopathic PD, previously treated with unilateral left pallidotomy, history of Freezing Of Gait, postural instability, marked "off" akinesia and "on" dyskinesia, underwent simultaneous bilateral STN and PPN DBS implantation. Electrodes were externalized for one week post-implantation, during which STN and PPN LFP recordings were made before and after test stimulation. STNs were stimulated individually at 2.5 V, 130 Hz, and 60 μs, and PPNs at 2.0 V, 20 Hz, 60 μs in turn. LFPs were recorded at a sampling frequency of 2 kHz and filtered between 0.5-500 Hz. Data analysis included Fourier transforms, short-time Fourier transforms and magnitude squared coherence between channels.

Results: Prior to test stimulation, Fourier spectra of all LFP channels showed a peak within the alpha band (7-11 Hz), and a strong component at this frequency was observed in STN-PPN coherence. Following each period of test stimulation, this alpha coherence was absent between STN and PPN, and accompanied by clinical improvement in motor control. This coherence re-emerged in the post-stimulation rest phase.

Conclusions: These initial findings suggest that the PPN-STN network is synchronised at the alpha band in Parkinson's disease and that DBS acts to de-synchronise this network. These findings should be corroborated in future patients.

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Safety of intraoperative microelectrodes multiple recording tracks in deep brain stimulation of subthalamic nucleus in advanced Parkinson's disease

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Objective: to evaluate safety of five intraoperative microelectrodes multirecording tracks during deep brain stimulation (DBS) of subthalamic nucleus (STN) in Parkinson's disease (PD).

Background: Currently most groups who perform DBS of STN in PD patients usually utilize microelectrodes recordings and then microstimulation of the better trajectory. However there is no general agreement regard the number of tracks to explore.

Methods: We have studied 10 patients treated with DBS of bilateral STN. For neuroradiological targeting of the nucleus we used a TC-MRI fusion algorithm. We used five parallel trajectories (central, lateral, medial, anterior, posterior) to recognize STN. Then we performed microelectrode stimulation evaluating side effects and motor improvement of rigidity, bradykinesia and tremor.

Results: In 7 patients we utilized five recording tracks while in 3 cases we needed to exclude lateral trajectory in respect to cerebral sulcus in two cases and sulcal artery in one patient. Considering both sides central trajectory was selected in 12 records and it was chosen as definitive track where implant the final electrode in 9 situations. Posterior track was selected in 3 registrations and it was chosen as final implant in 2 patients. Anterior tracks was selected in 4 records and it was chosen for final implant in 3 patients. Lateral track was selected in 4 studies but it was not considered useful for final implant in our series because the selective stimulation was responsible of transitory side effects (dyplopia anf facial hemispasm). We observed only one major side effects consisting in mild frontal haemorrhage along the trajectory of the definitive electrode in one patient with spontaneous recovery. The duration of the surgery was about 4-5 hours including the final placement of the stimulator in the chest. All 10 patients showed a marked clinical improvement after one year of chronic stimulation with great reduction of dopaminergic therapy.

Conclusions: our experience with five intraoperative microelectrodes recording tracks allows to establish that this procedure is safe,

fast and useful to define the best site where implant the definitive electrode.

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Eight-year follow-up of bilateral deep brain stimulation of the subthalamic nucleus (STN-DBS) in Parkinson's disease (PD)

M. Zibetti, A. Cinquepalmi, L. Rizzi, S. Angrisano, M. Lanotte, L. Lopiano (Torino, Italy)

Objective: To provide an 8 year follow-up of advanced PD patients treated with bilateral STN-DBS.

Background: STN-DBS has become the surgical treatment of choice for severe levodopa responsive forms of PD with motor complications. Whereas the short term benefits of bilateral STN-DBS are well documented, only few studies reported 5-year follow-up, and no data are available for longer term outcome.

Methods: 61 consecutive PD patients treated with bilateral STN-DBS were evaluated preoperatively and 1, 3, 5 and 8 years after neurosurgery. Parkinsonian motor disability, activity of daily living and complications of therapy were evaluated using the Unified PD Rating Scale (UPDRS). Parkinsonian status was assessed with and without levodopa treatment, with and without bilateral STN stimulation. Medication intake, stimulation parameters, neuropsychological and mood assessments were also evaluated at each time point.

Results: 15 patients could be followed-up 8 years after surgery and 16 others 5 years after surgery; of the remaining cases, 13 died, 4 could not be evaluated further because of dementia, and 13 were lost at follow-up. Eight years after surgery, STN-DBS reduced the UPDRS part III score by 43% compared to the off-medication condition. Tremor, rigidity, bradykinesia, postural stability, and gait improved by 56%, 39%, 52%, 40% and 31% respectively. Activity of daily living (UPDRS part II) was improved by stimulation of STN by 25%. The severity of levodopa related motor complications was decreased by 58% and the levodopa daily doses were reduced by 48%. Parkinsonian motor disability without medication and without stimulation deteriorated 19% with respect to the baseline condition without medication over eight years.

Conclusions: Our data show a sustained beneficial effects of STN-DBS in advanced PD patients eight years after neurosurgery despite a moderate motor decline due to disease progression.

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Comparison of bilateral subthalamic deep brain stimulation (STN-DBS) and duodenal levodopa infusion (DLI) in advanced Parkinson's disease (PD) patients

M. Zibetti, A. Cinquepalmi, S. Angrisano, C. Azzaro, L. Rizzi, M. Lanotte, L. Lopiano (Torino, Italy)

Objective: to compare the clinical and neuropsychological outcome in advanced PD patients after 12 month of bilateral subthalamic deep brain stimulation (STN-DBS) or duodenal levodopa infusion (DLI).

Background: Bilateral STN-DBS and DLI are effective strategies in the management of motor fluctuations and dyskinesias in patients with advanced Parkinson's disease (PD). Both techniques have been shown to provide a substantial improvement in quality of life for patients. However, the two procedures are also associated with adverse effect, mainly neuro-cognitive effects for STN-DBS and dislocation of the intestinal tube problems for DLI.

Methods: 20 Patients with advanced PD and medically untreatable motor complications undergoing either DLI (10 patients) or STN-DBS (10 patients), were evaluated clinically at baseline and after 12 months of treatment by means of the Unified PD rating Scale (UPDRS II, III and IV, off and on medication, off and on stimulation). Patients were also tested with an extensive neuro-psychological test battery assessing reasoning, attention, memory and frontal executive functions, depression and anxiety.

Results: We found a comparable improvement in the activities of daily living and parkinsonian motor features, with a comparable reduction in daily off time. There was a greater reduction of dyskinasias in STN-DBS treated patients compared to DLI patients (p=0,007). Minor neuropsychological changes have emerged in the STN-DBS treated patients. Frequent dislocation of the intestinal tube were noted for DLI.

Conclusions: Our findings show a clinical improvement and a satisfactory therapeutic response with both STN-DBS and DLI in advanced PD patients.

POSTER SESSION 3
WEDNESDAY, JUNE 16, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-18:00
Authors Present: 13:30-15:00

SURGICAL THERAPY: OTHER MOVEMENT DISORDERS

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Deep brain stimulation for segmental dystonia: Long-term (6-year) follow-up

C. Blahak, H.-H. Capelle, H. Baezner, T. Kinfe, M.G. Hennerici, J.K. Krauss (Mannheim, Germany)

Objective: Evaluation of long-term outcome of chronic deep brain stimulation (DBS) in patients with segmental dystonia with respect to motor symptoms, disability and quality of life.

Background: DBS has been proven as an effective and safe treatment for medically intractable dystonia. Studies on long term efficacy, however, focused mainly on patients with primary generalized dystonia, and there are almost no data regarding the long term impact of DBS on quality of life.

Methods: In a prospective study design outcome was assessed one and a half years (FU1; range 13-21 months) and six years (FU2; range 70-75 months) after DBS surgery in twelve consecutive and regularly followed-up patients with segmental dystonia, using a comprehensive protocol including the Burke-Fahn-Marsden (BFM) motor and disability scores and the SF-36 questionnaire for quality of life. Ten patients had chronic DBS of the globus pallidus internus (GPi) and two patients of the ventral intermediate (VIM) nucleus of the thalamus. Statistical analysis used non parametric testing for paired (Wilcoxon rank test) variables.

Results: All patients experienced a sustained improvement in motor symptoms, the mean BFM motor score decreased from 34.3+/-17.8 (mean+/-SD) preoperatively (pre-OP) to 14.3+/-9.9 ($P<0.01$) at FU1 and 14.7+/-10.6 ($P<0.01$) at FU2, reflecting an improvement of 58.2% (range 26-77%) at FU1 and 57.0% (range 24-85%) at FU2. The BFM disability score decreased from 5.6+/-3.5 pre-OP to 3.5+/-4.5 at FU1 ($p<0.05$) and 3.5+/-3.5 at FU2 ($p<0.05$). Quality of life as assessed by the SF-36 also improved significantly with DBS. The SF-36 total score increased from 56.6+/-19.5 pre-OP to 75.0+/-12.9 at FU1 ($P<0.05$) and 66.5+/-13.4 at FU2 ($P<0.05$), though only the physical but not the mental subscore retained a significant improvement at FU2 as compared to pre-OP.

Conclusions: Overall, chronic DBS is an effective treatment option for medically refractory segmental dystonia with a sustained long-term improvement of motor symptoms, disability and quality of

life in the vast majority of patients. However, in long-term outcome the postoperative amelioration of mental health aspects of quality of life is reduced, potentially caused by long-ranging changes in patients' self-perception and illness-related coping.

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Deep brain stimulation for camptocormia in dystonia and Parkinson's disease

H.-H. Capelle, C. Schrader, C. Blahak, T.M. Kinfe, W. Fogel, H. Baezner, J.K. Krauss (Hannover, Germany)

Objective: To evaluate the effect of deep brain stimulation for camptocormia in dystonia and Parkinson's disease.

Background: Camptocormia or the "bent spine syndrome" may occur in various movement disorders such as primary dystonia or idiopathic Parkinson's disease (PD). Although deep brain stimulation (DBS) is an established treatment in refractory primary dystonia and advanced PD there are only few data available on the effect of DBS on camptocormia comparing these two conditions.

Methods: Seven patients (4 with dystonia, 3 with PD; mean age 60.3 years at surgery, range 39-73 years) with camptocormia were included in the study. Five patients underwent bilateral GPi DBS and two patients underwent bilateral STN DBS guided by CT-stereotactic surgery and microelectrode recording. Pre- and postoperative motor assessment included the BFM in the dystonia patients and the UPDRS in the PD patients. Severity of camptocormia was assessed by the BFM subscore for the trunk at a mean last available follow up at 17.3 months (range 9-36 months).

Results: There were no surgical complications. In the four patients with dystonia there was a mean improvement of 63 % in the BFM motor score (range 50-72%) and of 69% (range 50-75%) in the BFM subscore for the trunk at the last available follow-up (mean 14 months, range 9-18 months). In the three patients with camptocormia in PD who underwent bilateral STN DBS (2 patients) or pallidal DBS (1 patient) the PD symptoms improved markedly (mean improvement in the UPDRS motor subscore stimulation on/medication off 53%, range 46-61%) but there was no or only mild improvement of camptocormia, however, in the two patients who underwent STN DBS and only moderate improvement in the patient with GPi DBS at the last available follow-up (mean 22 months, range 12-36 moths).

Conclusions: GPi DBS is an effective treatment for camptocormia in dystonia. The response of camptocormia to chronic STN or GPi DBS in PD is more heterogenous. The latter may be due to a variety of causes and needs further clarification.

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A pilot study of laughter induction in the NIH OCD DBS cohort: A predictor of efficacy

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Objective: To examine the relationships between intraoperative stimulation-induced behaviors and long-term clinical improvement.

Background: DBS of the anterior limb of the internal capsule and nucleus accumbens (ALIC-NA) is an investigational treatment for medication resistant OCD. We have previously published qualitative data regarding stimulation-induced mood elevation, smiles, and laughter in the ALIC-NA. We have here analyzed these behaviors in the full cohort of six patients, including two years of follow-up.

Methods: Six subjects with medication-refractory OCD enrolled in a NIMH/NIH sponsored study underwent test stimulation during implantation of bilateral DBS devices. Each DBS contact was intraoperatively stimulated from 0 to 8 volts. Those locations that elicited smiles/laughter were recorded. Patients were videotaped rating their mood and describing their state. Coordinates of the center of each contact eliciting smile/laughter phenomena were calculated after CT-

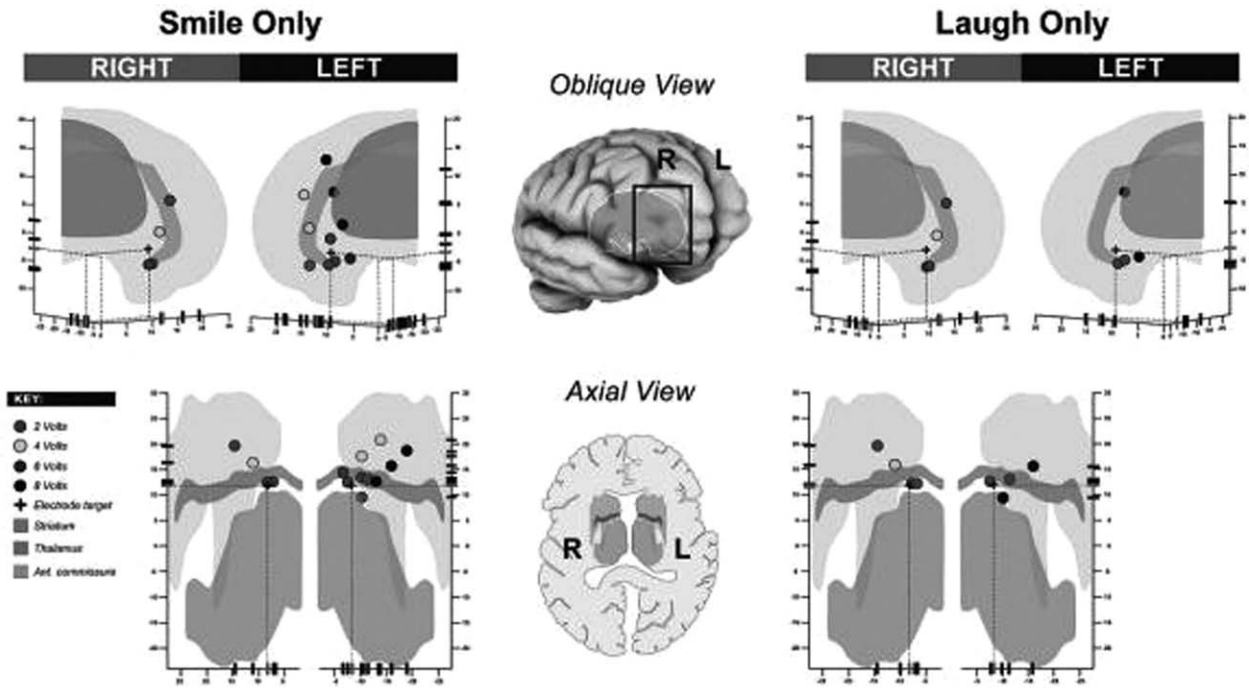

FIG. 1 (830).

MRI fusion. Patients returned for follow-up visits at 1, 6, 12, and 24 months following DBS activation. OCD symptoms were assessed via the Y-BOCS, depressive symptoms by the HAM-D.

Results: 5/6 patients experienced smile responses during testing (4/6 experienced laughter). Stimulation-induced laughter correlated with OCD improvement at 2 year follow-up: a higher percentage of laugh conditions in an individual correlated with greater reduction in YBOCS (p=0.034, Spearman's rho=0.841). We did not observe a relationship between smiles/laughter and reduction in HAM-D scores. Stimulation-induced behaviors seldom occurred postoperatively. Mood during stimulation-induced smiles/laughter was elevated (average 6.1/10 versus -0.9 at other conditions). At contacts at which smiles/laughter were observed, voltage elevation correlated with mood elevation (p=0.0004). At all other contacts mood negatively correlated with voltage (p=0.0591 right, p=0.0086 left). Smile/laughter-inducing sites were located medial, posterior, and deep in the ALIC-NA.

Conclusions: Intraoperative stimulation-induced laughter may predict long-term improvement in OCD-DBS. We identified bilateral regions of brain at which stimulation consistently produces transient mood elevation. A larger sample size will be required to further delineate these relationships.

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What Is the best surgical target for dystonic tremor–GPi or VIM

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Objective: To analyze the clinical outcome of patients with idiopathic dystonic tremor (DT) who underwent deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) or the nucleus ventralis intermedius (VIM).

Background: DT is defined as a coexistence of tremor and abnormal dystonic posturing in the same segment, most commonly affecting upper extremities or neck. DT is often medically refractory and DBS is an important therapeutic option. However, the optimal surgical target for DT remains uncertain with VIM, GPi and zona incerta previously reported as effective.

Methods: We retrospectively reviewed the outcome data from all patients with DT involving at least one upper extremity who underwent DBS at Vanderbilt University from July 2006 to July 2009. We evaluated the improvement of tremor and dystonia after their response to DBS was judged to be maximal.

Results: Nine patients (5 men and 4 women, average age 36.7±12.7 years) met the inclusion criteria. DT was observed on both upper extremities in six individuals, while three had only unilateral DT. VIM was targeted in three patients and they all had unilateral severe DT and contralateral VIM DBS was performed. GPi was targeted in four patients with bilateral DBS procedure in every patient from this subgroup. A combined bilateral GPi and unilateral VIM surgery was performed in two patients. The best results for tremor control were observed in three patients with unilateral VIM surgery who had essentially a complete tremor control; however, they had persisting mild dystonia which was not improved after VIM DBS and required additional pharmacological and chemodenervation therapies. Patients with isolated GPi DBS had average DT improvement by approximately 50% but their dystonia symptoms were markedly improved. Patients with a combined GPi and VIM surgeries had average tremor improvement for 80% and we did not observe a complete tremor control as in the group of unilateral VIM DBS patients.

Conclusions: Patients with DT with a mild dystonia should be considered for VIM DBS procedure but no improvement of dystonia is expected. GPi targeting resulted in average 50% reduction of DT symptoms, and patients with a severe DT and moderate to severe dystonia may benefit from a combined GPi and VIM DBS surgeries.

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Steady or not following thalamic deep brain stimulation for essential tremor

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Objective: This study evaluates postoperative gait worsening in a cohort of patients treated with deep brain stimulation (DBS) for essential tremors (ET).

Background: DBS can be very effective for medication-refractory ET, but may contribute to worsened gait.

Methods: A retrospective review was performed utilizing the University of Florida Movement Disorders Database and individual chart review. Factors examined: tremor duration, baseline gait difficulties/falls, Fahn-Tolosa-Marin tremor rating scale (TRS) scores at baseline, 6 months after unilateral DBS implantation, and 6 or 12 months after bilateral implantation. All implantations targeted nucleus ventralis intermediate (Vim) and utilized Medtronic (3387, Medtronic, Minneapolis, MN, USA) implantable device.

Results: Thirty-eight patients (25 males, 13 females) were analyzed. Twenty-seven patients (71.1%) had unilateral DBS implantation and 11 (28.9%) bilateral. Mean age at surgery was 67.1 years +/- 11.4 (range 34-81 years). Mean disease duration was 31 years +/- 18.3 (range 6-67 years). Fifty-eight percent of patients exhibited post-DBS worsened gait (14 had balance difficulty, 8 had falls). Seventy percent of patients with unilateral DBS and 55% bilateral DBS had worsened gait. Patients with post-DBS worsened gait had higher baseline pre-DBS TRS scores than those without worsened post-DBS gait problems (43.1 +/- 8.4 versus 33.1 +/- 10.1) (p=0.002). Baseline rest tremor subscore was 0.7 +/- 1.3 in patients without gait difficulties and was higher at 1.1 +/- 1.3 in patients with balance difficulties and highest in fallers at 2.2 +/- 0.4 (p=0.02). The odds ratio for resting tremor and balance difficulties was 2.5 (coefficient estimate 0.9, p=0.02).

Conclusions: Gait may worsen post-DBS for medication refractory ET. Higher baseline TRS score is a risk factor although larger confirmatory studies are required. The larger percentage of difficulties in unilateral versus bilateral cases may reflect the bias to not proceed to second-sided surgery if gait/balance problems were encountered after unilateral surgery.

This abstract was previously presented at the American Academy of Neurology in Toronto, BC, Canada on 4/2010.

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Globus pallidus internus deep brain stimulation for hemidystonia following penetrating head injury

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Objective: To describe a patient with post-traumatic hemidystonia treated successfully with globus pallidus internus (GPi) deep brain stimulation (DBS).

Background: The treatment of dystonia with GPi DBS is well described. There are, however, very few cases reported in the context of post-traumatic dystonia[1]. To our knowledge, this is the first description of the use of DBS following penetrating head injury.

Methods: We present the case of a 47 year-old man with phasic hemidystonia (see video). At the age of 3 ½ he had suffered a penetrating head injury from a welding needle, which had entered the right medial canthus and traversed the right frontal lobe across to the left parietal lobe. Initially, he had severe right hemiparesis and was not able to speak or walk. These deficits improved, but he had developed dystonic and phasic right-sided movements in lieu of the hemiparesis. These abnormal movements, which could be painful, embarrassing and disturb his balance, greatly limited his ability to perform his day-to-day activities including his job as a supermarket worker.

MRI scan of his brain showed a linear encephalomalacic track traversing the right inferior frontal lobe and left cerebral peduncle, thalamus and parietal lobe. There was no left GPi lesion. Because of poor response to medical therapy, decision was made in favour of surgery. Following satisfactory completion of a full multidisciplinary review, including neurological, neuropsychological and neuropsychiatric assessments, a left GPi DBS electrode was inserted. Stimulation settings were case +, contact 2-, pulse width 60 microseconds, frequency 130 Hz, with threshold for clinical improvement at 0.7 volts, and a final setting of 1.3 volts.

Results: At six months following DBS, the patient's arm was more relaxed and his spasms lessened in their severity and frequency (see video). There were no complications or side effects.

Conclusions: GPi DBS is a safe and effective treatment for a selected group of patients with post-traumatic hemidystonia, including following penetrating head injury. 1. Chang JW, Choi JY, Lee BW, Kang UJ, Chung SS. Unilateral globus pallidus internus stimulation improves delayed onset post-traumatic cervical dystonia with an ipsilateral focal basal ganglia lesion. J Neurol Neurosurg Psychiatry 2002; 73: 588–90.

834

Generalized dystonia treated with bilateral pallidotomy and bilateral subthalamic deep brain stimulation

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Objective: The authors present a patient treated with bilateral pallidotomy and followed by bilateral subthalamic deep brain stimulation (STN DBS) because of disease progression.

Background: Medical treatment of generalized dystonia (GD) is frequently ineffective. Surgical treatment of GD, where globus pallidus is a target is well accepted. Clinical improvement observed after bilateral pallidotomy may vanish in a group of patients.

Methods: The authors present 32 years old female patient that has been diagnosed with GD. The patient was surgically treated with bilateral pallidotomy in 2006. Clinical improvement observed after surgery vanished three months after. The patient was qualified to bilateral implantation of STN DBS. Clinical status was evaluated with Global Dystonia Scale, Fahn-Marsden Movement Scale and Unified Dystonia Rating Scale and video recorded. The surgical procedure was undertaken under general anesthesia. The target was identified with direct and indirect method. Intrasurgical macrostimulation and microrecording were used for neurophysiological evaluation of the target.

Results: Clinical status of the patient improved subjectively following surgery that was confirmed with previously mentioned scales. No surgery related complications were reported. Intrasurgical microrecordings of STN were similar to those recorded among Parkinson's disease patients.

Conclusions: Globus pallidus pars interna (GPi) is believed to be the optimal target to treat stereotactically dystonic movements among GD patients, but when GPi is destroyed by previous lesion subthalamic nucleus might be chosen as a target with good clinical outcome.

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Comparison of merged CT analysis and direct MRI visualization of GPi lead placement for deep brain stimulation

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Objective: Compare direct MR visualization of GPi lead placement with merged pre-operative MRI and post-operative CT images in a pediatric population.

Background: The US FDA has set strict guidlines regarding the use of MRI in patients with implanted DBS electrodes, which has limited the ability of most centers to obtain these images. Between September 2007 and December 2009, 24 patients have undergone 28 surgical placements of DBS leads (Medtronic 3387) in the GPi for treatment of primary (10) or secondary (14) dystonias. Prior to August 2009, all patients had postoperative imaging with CT. Following extensive safety testing with our MRI systems, we now perform postoperative MR imaging.

TABLE 1 (835). *Patient diagnoses*

Diagnosis	≤17 Yrs	≥18 Yrs
DYT-1	5	1
NBIA	2	1
Cervical Dystonia	1	
Cerebral Palsy	8	3
Traumatic Brain Injury	1	
Cerebrovascular Accident	1	
HIE	1	

TABLE 2 (835). *Imaging studies*

Diagnosis	Pre-Op MRI	Post-Op CT	Post-Op MRI
Primary dystonia (10)	10	10	3
Secondary dystonia (14)	15	16	1

Methods: SAR values were calculated on Siemens 1.5T MRI by an independent consultant using a phantom gel model with embedded electrodes (Medtronic 3387) and a series of temperature probes. Hermes Medical Imaging software is used to co-register pre- and post-operative images from the differing modalities. The fused images are archived using Hermes or Amide Medical Imaging software for post-merger analysis. Postopertive MRI is done on using MPRAGE sequencing. Images are reviewed by a team consisting ot two pediatric neurologists (WM,FA) and a pediatric neurosurgeon (JH).

Results: Post-operative CT is available on all 24 patients; direct postoperative MRI imaging is available on 4 patients.

Even with co-registration, image distortion makes precise anatomic localization difficult by CT. With direct MR imaging, the individual contacts from each lead can be discerned with minimal distortion of brain anatomy. Based on direct MR imaging, 2 patients with suboptimal response after at least 6 months of stimulation underwent lead relocation.

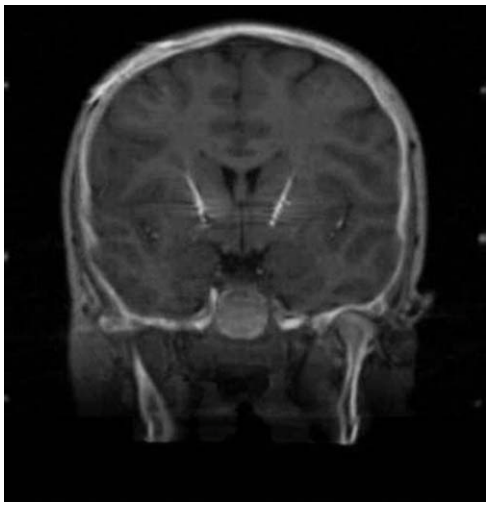

FIG. 1 (835).

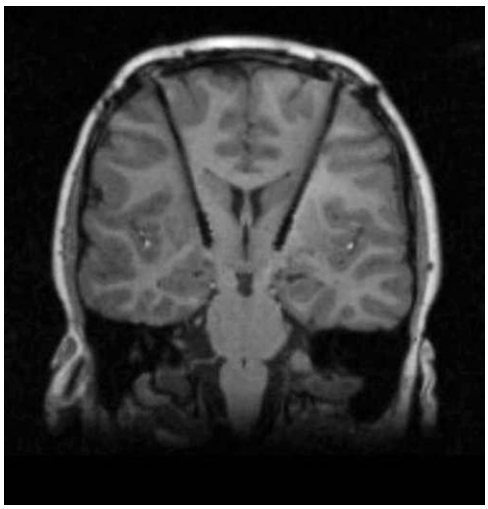

FIG. 2 (835).

Conclusions: The ability to archive so-registered images allows on-demand viewing for analysis. Although merged CT/MRI analysis and direct MRI visualization allow assessment of lead placement, direct MRI visualization is superior due to decreased distortion artifact on surrounding brain anatomy. This is important for lead placement analysis. Direct MRI visualization may particularly useful in secondary dystonias where basal ganglia anatomy is often less distinct.

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Two year experience with DBS for pediatric onset dystonias: Generator selection

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Objective: Review our experience with the various generators in patients receiving DBS therapy.

Background: In July 2009, dual channel Activa PC and RC generators became available in the United States. Prior to that, patients were implanted with the single channel Soletra or dual channel Kinetra IPGs. All dual channel generators require that both channels run at the same frequency.

Methods: Ongoing review of patients receiving DBS generator implants at Cook Children's Medical Center.

Results: Between September 2007 and December 2009 25 patients received initial DBS leads and generators at our institution; 19 were less than 18 years of age. Seven patients have had generator replacement surgery, including 2 with initial implants elsewhere. Bilateral implant sites include: GPi (23); STN (1); VIM (1). One patient with a CVA had implant of unilateral GPI followed by the addition of a second lead in the corresponding VIM. Through June 2009, one patient with tremor received a Kinetra generator. All other patients received Soletra generators (1 unilateral). Soletra was chosen due to the small chest wall of our pediatric patients. Some patients benefit from different rate settings in each hemisphere (range 30-185 Hz). Since July 2009, we have used Soletra (7 patients), Activa PC (1) and RC (2) generators for initial implants. Generators used for replacement of Soletra for end of battery life include:n: Soletra (2), PC (3), and RC (2). Soletra was used when there was interhemispheric frequency asymmetry. PC was selected over RC for family compliance, concerns about chest wall integrity, or financial concerns.

TABLE (836). *Initial and replacement generators*

Diagnosis	Number	Initial IPG	Replacement IPG	Implant Site
DYT-1	6	S (5);RC (1)	S (1);RC (2)	GPi
NBIA	3	S (3)		GPi
Cervical Dystonia	1	RC (1)		GPi
Cerebral palsy	11	S (11)	S (1); PC (2)	GPi
CVA	1	S (1)	PC (1)	GPi;GPi+VIM
Juvenile Parkinson's	1	S (1)		STN
Tremor	1	K (1)		VIM

Conclusions: For pediatric patients, we have found that initial implant with bilateral soletra generators offers the most opportunity for initial programming, particularly the ability to use differing frequencies in each hemisphere. For replacement of failed soletra generators, we have used PC and RC generators when a single effective frequency can be established for both hemispheres. Individual soletras are continued in patients with incompatible frequency settings. Despite obvious size and longevity advantages the increased initial cost of the RC which has not been appealing to all payors. Not all families were able to demonstrate the willingness and ability to follow through with recharging requirements of the RC generator.

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Length of surgery in paediatric patients receiving Activa RC® neurostimulator devices may not be longer then with previous neurostimulator devices

E. McKintosh, D.E. Lumsden, M. Choo, M. Kaminska, K. Ashkan, R. Selway, J.-P. Lin (London, United Kingdom)

Objective: To review the length of surgery required for insertion of the Activa RC® neurostimulator in comparison to previous neurostimulator devices in children.

Background: Bilateral pallidal deep brain stimulation (DBS) has now been established as an important treatment modality in the management of paediatric dystonia. Historically the physical size of neurostimulator devices has restricted DBS to children above a body weight of 20 kg. The recent introduction of the Medtronic Activa RC® neurostimulator creates the potential for reduction of this weight limit to 10kg, in addition to reducing the frequency of neurostimulator replacement due to battery failure. We sought to determine if there was an extra burden of operative time required for insertion of the Activa RC® system.

Methods: The operation notes of the first 20 paediatric patients undergoing insertion of the Activa RC® neurostimulator were reviewed. 11 underwent initial DBS system insertion and 9 patients had replacement of the existing neurostimulator alone. The recorded operative times were collected and compared to operative times for previous neurostimulator units.

Results: The median operative time for complete DBS system insertion was 4 hour 41 minute (range 3 hours 28 minutes to 8 hours and 41 minutes). For a control group of 10 patients receiving complete DBS systems with a Kinetra® Neurostimulator device the median operative time was 5 hours and 56 minutes (range 3 hours and 1 minute to 7 hours and 14 minutes) The median operative time for neurostimulator replacement alone was 57 minutes (range 25 minutes to 1 hour and 33 minutes). For a control group of 8 patients undergoing neurostimulator exchange alone with the Kinetra® device the median operative time was 38 minutes (range 20 minutes to 56 minutes).

Conclusions: The operative time for DBS Activa RC® neurostimulator insertion does not appear to be longer than implanting the Kinetra® stimulator. Operative times for neurostimulator replacement alone may be slightly longer, but this difference is likely to be more than offset by the potential benefits of this device.

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Rescue DBS leads: Tailoring deep brain stimulation (DBS) when clinical symptoms do not respond as anticipated

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Objective: To report six cases where an added "rescue DBS lead" was placed in an attempt to enhance clinical benefits.

Background: DBS has been widely accepted as a treatment for both medically refractory dystonia and tremor. A subset of patients receiving DBS may fail to obtain the anticipated clinical benefits despite well-placed leads and no evidence of lead migration, hardware malfunction, or disease progression.

Methods: All patients signed informed consents and outcomes were tracked by an Institutional Review Board (IRB) approved database. A database query yielded 295 total patients who underwent DBS at the University of Florida between 2002 and 2009. Six patients were identified as rescue lead recipients. Of these six cases, three had medically refractory tremor (essential tremor (ET) and tremor secondary to radiation damage) incompletely addressed by VIM (nucleus ventralis intermediate) -DBS and added VOA/VOP (oralis anterior/oralis posterior) leads (n=2), or alternatively a STN (subthalamic nucleus) lead (n=1). The remaining three cases were patients with dystonia initially treated with bilateral GPi (globus pallidus interna) -DBS, and due to suboptimal benefit a second GPi lead (n=2; DYT-1 positive generalized dystonia, cervical dystonia) and bilateral STN leads (n=1; tardive dystonia) were added.

Results: The Fahn-Tolosa-Marin Tremor Rating Scale improved by 76.1% (mean -22, range -11 to -33) in the tremor cases, and the Unified Dystonia Rating Scale improved by 35.1% (mean -10.7, range -2 to -22) in the dystonia cases after rescue surgery. The ET patient who underwent STN implantation developed stimulation-induced dyskinesia. None of the cases had postoperative cognitive decline or neuropsychiatric issues. The symptom specific patient/clinician global impression scales (7 point scale) following rescue surgery were minimally to very much improved in all cases (tremor cases; mean 2.0, range 1 to 3, dystonia cases; mean 1.7, range 1 to 2).

Conclusions: Rescue leads may provide meaningful clinical benefits in well selected patients, but larger, prospective randomized control studies would be needed to confirm the benefits and help guide which target site of implantation would lead to optimal results.

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Successful bilateral pallidal stimulation for idiopathic camptocormia: Case report

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Objective: The authors report the neurological and functional effect of bilateral pallidal deep brain stimulation (DBS) in a case of disabling idiopathic camptocormia.

Background: The term camptocormia defines a posture disorder caracterized by forward flexion of the trunk, that abates in the recumbent position. It is frequently described in association with pathological conditions such as Parkinson's disease, while the primary form, called idiopathic camptocormia, is rare and it is regarded as an abdominal segmental dystonia. Pallidal and subthalamic DBS has been reported to improve camptocormia associated with Parkinson's disease, but only few cases of dystonic camptocormia treated with pallidal stimulation have been described so far.

Methods: Before surgery, clinical evaluation, acute and chronic farmacological test with l-dopa, encefalic MRI and presynaptic dopamine transporter (DAT) SPECT were performed, in order to exclude a diagnosis of parkinsonism. Deep brain stimulation electrodes were implanted stereotactically in globus pallidus internus,bilaterally. Stimulation was started 15 days after implantation and progressively optimized. Videotaped evaluation of camptocormia was recorded before surgical procedure and three and six months after stimulation activation.Functional outcome was assessed by means of Euro Qual (EQ) and pain analogic scale.

Results: Patient was a 70 years old female, with progressive camptocormia initiated at age 66; clinical evaluation showed no evidence of parkinsonian features, and no benefit was obteined from levodopa and dopamine agonist therapy; encefalic MRI and DAT-SPECT resulted normal. Deep brain stimulation was safe and well tollerated: there were no procedure or stimulation related adverse event. At the three months follow up there was a clear improvement of camptocormia: the trunk flexion angle passed from 75 to 30 degrees while standing and walking, and patient was able to achieve a quite erect position adopting some "sensitive" treaks. Patient report a release of back pain and functional improvement in activity of daily leaving. These effects remained stable at the six months follow up.

Conclusions: Pallidal stimulation is a safe and efficacious therapeutic strategy for dystonic camptocormia.

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Routine AICD interrogation in a patient with unilateral DBS: A case report

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Objective: To report a case where an AICD routine test interrogation lead to tremor resolution in a patient with unilateral VIM DBS.

Background: Essential tremor is the most common movement disorder, with an increasing incidence in the aging population. Because the patient population is older there are multiple comorbidities that need to be considered when evaluating surgical candidates. One of these considerations should be the interaction of the DBS device with implantable cardiac defibrillators and pacemakers.

Methods: Case report.

Results: 74 year old female with a twenty year history of refractory ET. She underwent evaluation for placement of DBS with a WHIGET tremor rating scale score of 18 on the right and 18 on the left. She has a past medical history of nonischemic cardiomyopathy requiring an AICD. The initial AICD was placed in 2006 with replacement in 2009. On 2/27/09 she had replacement of her AICD without any complications. On 3/5/09 she underwent uneventful left unilateral VIM DBS with a Soletra IPG. On 8/4/09 she underwent a routine interrogation of her AICD with a 1.7 Joules shock. At the time of the testing she developed a sensation of tightening of the right side of her face and a headache. At a follow up visit, on 10/29/09, she stated that when she turned on her stimulator she would have the sensation of tightening involving her right face, arm and leg. Her exam showed complete resolution of her right tremor with her stimulator off. She continued to have a moderate left tremor. A repeat CT scan did not show any change in the lead position, nor was there evidence of a lesion. A MRI was unable to be performed secondary to hospital protocol.

Conclusions: This case report indicates that even routine testing of an implantable cardiac defibrillator could result in a suspected anatomical lesion. Rosenow et al. indicated that there was no interaction between DBS and the AICD when a patient was cardioverted multiple times after the ventricular lead dislodged. Our patient had a very different outcome and thus it is evident there should be careful consideration in patients requiring AICD placement with DBS, and other possible options considered for routine testing of the AICD. Rosenow JM, et al. Simultaneous use of bilateral subthalamic nucleus stimulators and an implantable cardiac defibrillator. J Neurosurg. 2003 Jul;99(1):167-9.

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Successful pallidal DBS therapy in an elderly patient with DYT-1 dystonia

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Objective: To describe the case of a 73 year-old right-handed woman with a diagnosis of DYT-1 positive generalized dystonia, surgically treated with pallidal deep brain stimulation (DBS).

Background: Although a diagnosis was made only at age of 24, initial symptoms of handwriting difficulty occurred as early as fourth grade (age 9). Symptoms progressed into involuntary shaking and posturing of the right arm. She eventually developed generalized dystonia, affecting gait and posture in her 20's. Family history was positive for generalized dystonia, as paternal grandmother, father and daughter were all affected. Approximately at age 30 she underwent left thalamotomy with no significant improvement of motor symptoms, while developing a moderately dysarthric speech. Over the years, pharmacological treatments including levodopa, clonazepam, botox and baclofen pump were not effective. She was wheelchair bound. Bilateral pallidal DBS was performed at age 71, in October 2007 (right implant) and March 2008 (left implant). Clinical symptoms were evaluated using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). Baseline scores were 82 (motor) and 14 (disability). Initial improvement (27%) was observed with unilateral stimulation as early as 10 days after initial programming at 2.5 volts, 180 μs, 60Hz with active contacts 0 and 1. Head tremor improved first, followed by left limbs involuntary movements and truncal dystonia. After bilateral implants, BFMDRS scores continued to progressively improve in all body segments. At last follow-up in December 2009, BFMDRS motor score was 11 and disability score was 8 (87% and 43% improvement, respectively). Contacts 0 and 1 were bilaterally active at a frequency of 70Hz, amplitude of 3 volts and pulse width of 120 μs. There was no cognitive impairment.

Conclusions: To our knowledge, this is the first case of DYT-1 generalized dystonia successfully treated with DBS at an age older than 70 years. This report confirms the important role of pallidal DBS in the treatment of generalized dystonia. The age range of patients with dystonia eligible for DBS surgery may be wider than previously expected.

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Long-term clinical outcome in Meige syndrome treated with posteroventral lateral internal pallidum deep brain stimulation (GPi-DBS)

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Objective: To evaluate the long-term clinical outcome in patients suffering from Meige syndrome treated with GPi-DBS.

Background: GPi-DBS is effective in the treatment of primary segmental and generalized dystonia. While limb, neck or truncal dystonia are markedly improved, orofacial dystonia is ameliorated to a lesser extent. Nevertheless, several case reports and small cohort studies have described favorable short-term results of GPi-DBS in patients with severe Meige syndrome. Here, we extend this preliminary experience by reporting long-term outcome in a multicenter case series, following 12 patients with Meige syndrome for up to 78 months after bilateral GPi-DBS.

Methods: We retrospectively evaluated dystonia severity based on the video documentation of the pre- and postoperative neurological assessments. Symptoms were scored on the Burke Fahn Marsden Dystonia Rating Scale (BFMDRS), the Blepharospasm Movement Scale (BMS) and the Abnormal Involuntary Movement Scale (AIMS).

Results: There were 6 men and 6 women with a mean age of 64.5±1.3 years at surgery and a mean disease duration of 8.3±1.4 years. The BFMDRS showed a mean improvement of 45% at short term follow-up (4.4±0.5 months; $p<0.001$), and of 53% at long term follow-up (38.8±6.5 months; $p<0.001$). BFMDRS subscores for eyes were improved by 38% ($p=0.004$) and 47% ($p<0.001$), for mouth by 50% ($p<0.001$) and 56% ($p<0.001$) and for speach/swallowing by 44% ($p=0.058$) and 64% ($p=0.004$). The mean improvement in the BMS was 25% ($p=0.006$) and 38% ($p<0.001$), and in the AIMS 44% ($p<0.001$) and 49% ($p<0.001$).

Conclusions: This series, which is the first to demonstrate a long term follow-up in a large number of patients, shows that GPi-DBS is a safe and highly effective therapy for Meige syndrome. The benefit is preserved, and even more pronounced in the long-term, for up to 6 years.

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Need for bilateral thalamic deep brain stimulation (DBS) to address unsuccessful single-sided procedure for Tourette syndrome: A case report

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Objective: This case report aims to discuss unilateral versus bilateral deep brain stimulation (DBS) in one patient with Tourette syndrome (TS).

Background: DBS is often used as a treatment mainly of motor symptoms in medication refractory TS. A positive result of DBS is also reported over non-motor issues, while the effects of bilateral versus unilateral stimulation are still unknown.

Methods: This study presents the case of a 47-year-old male who initially underwent right unilateral ventralis oralis/centromedianus-parafascicularis (Vo-CM/Pf) region DBS implantation for suppression of self-injurious tics as well as obsessive-compulsive behaviors. Single-sided procedure on the right side was indicated after an MRI documented the possibility of a vascular abnormality at the left thalamus.

Results: A follow-up evaluation demonstrated some improvement with a single lead, but it was less than anticipated. Motor tics and behavioral comorbidities were improved, but remained disabling. The patient's tics were active, even when the stimulator was in the "on" position at optimal stimulation parameters. A second lead was therefore placed in the contralateral thalamus, and MRI confirmed intended targeting. We will present the results of the case study, which revealed incremental improvement with a second contralateral DBS.

Conclusions: Even if there was no somatotopic distribution of residual tics after the first procedure, a significant improvement was demonstrated with bilateral DBS when compared to the single-sided procedure. Moreover, we have concluded the importance of preoperative MRI evaluation.

844

Efficacy of subthalamic nucleus stimulation for tremor dystonia: A case report

D.V. Roccatagliata, L. Castana, M.G. Rizzone, C. Ferrarese, G. Lo Russo, R. Sterzi (Milano, Italy)

Objective: To evaluate the efficacy of deep brain stimulation (DBS) of the subthalamic nucleus (STN) for the treatment of a patient with dystonic tremor (DT).

Background: DBS is a valid therapeutical option for the treatment of movement disorders unresponsive to pharmachologic measures. The globus pallidus internus and the nucleus ventralis intermedius of the thalamus are considered the target of choice for dystonia and non-parkinsonian tremors, respectively. STN-DBS is effective for the treatment of Parkinson's disease, but in the last years some papers described its efficacy for dystonic disorders too. We evaluated the

efficacy of STN-DBS for the treatment of a patient with severe DT refractory to medical treatment.

Methods: In 2007 we implanted bilaterally a DBS system in the STN of a 63 years old patient with severe DT. The disease onset was at the age of seventeen, with a bilateral postural tremor of the upper limbs. The tremor worsened with time, involving the lower limbs. Moreover dystonia, involving limbs, trunk and cranial district appeared. All the pharmachologic treatments failed, and at the time of the implant he suffered from a severe dysability. The stereotactic position of the STN was calculated by ventriculography and MRI, and confirmed by intraoperative multi-track microrecording and microstimulation. For the clinical evaluation we used preoperatively and at the 2 years follow-up the Burke-Fanh-Marsden-Dystonia scale (BFM) and the Fahn-Tolosa-Marin-Tremor scale (FTM).

Results: Both tremor and dystonia significantly improved with STN-DBS. Preoperatively, the BFM movement-score was 53, the disability score was 19 and the FMT score was 102. Two years later at follow-up, in the stim-on condition (parameters: 3.2V (right STN), 2.9V (left STN); 60us; 130Hz), the BFM movement-score was 18, the BFM disability-score was 12 and the FMT score was 58.

Conclusions: Despite the necessity of larger studies, STN-DBS could be considered as an effective therapeutical option for uncommon movement disorders, as DT.

845

Long term continuous deep brain stimulation to the internal globus pallidus in DYT1-gene positive dystonia induces lasting neural reorganization in the motor system

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Objective: To test long term physiology effects of DBS in dystonia.

Background: Deep brain stimulation (DBS) to the Globus Pallidus (GPi) is an effective treatment option for dystonia. Unlike rapid effects observed in Parkinson's disease, the response often takes weeks to reach peak effect. We showed previously that clinical improvement is accompanied by slow normalization of motor cortical (short interval intracortical inhibition, SICI) inhibition. However, it is preceded by a rapid reduction of enhanced motor cortex plasticity (paired associative stimulation, PAS) normally seen in primary dystonias. We speculated that an early reduction in plasticity allows the system to remove strong motor memories of abnormal movement and slowly improve function (Ruge et al 2009).

Methods: If DBS was transiently turned OFF after 6 months of continuous stimulation, plasticity recovered towards normal values and measures of inhibition declined towards those seen in untreated dystonia. Here we test whether 5+ years of continuous DBS is accompanied by further changes in motor physiology. Using Transcranial Magnetic Stimulation we studied inhibition and plasticity ON and OFF DBS (2 days) in dystonia patients on continuous DBS for five years or more.

Results: Prior to discontinuing DBS, plasticity was absent and inhibition was slightly reduced compared with normal. Switching OFF DBS had variable clinical effects from restoration of dystonia to no change compared with ON DBS. Plasticity [ON: post PAS effect 109.8%(6.5SE) of pre PAS; OFF: 93.2%(20.1SE) and inhibition [ON: 74.1% (8.3SE) of unconditioned MEP; OFF: 62.3%(7.5SE) remained at similar levels to those seen ON DBS. No obvious relationship between individual effects on physiology and clinic was seen.

Conclusions: We conclude that continuous DBS for several years induces lasting changes in excitability of motor cortical circuits which persists when DBS is turned OFF. It is therefore consistent with the idea that DBS may have long term plastic effects on brain function. These changes do not restore a completely normal pattern typical of healthy individuals but seem to adjust to a new pattern. The findings are important for future DBS strategies.

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Deep brain stimulation in Lesch-Nyhan disease (LND): Report of two cases

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Objective: To investigate the effect of bilateral GPi stimulation for Lesch-Nyhan disease.

Background: The Lesch-Nyhan disease is a rare X-linked genetic and biochemical disorder caused by a complete deficiency in hypoxanthine-guanine phosphoribosyltransferase (HPRT). It is characterized by metabolic disorders caused by an overproduction of uric acid and by an abnormal behavioural phenotype with repetitive severe self-mutilations, mental retardation and general dystonia. The management of LND by pharmacological treatments has not been effective and few patients have been subjected to DBS therapy with initial good results for both dystonic and self-aggressiveness disorders. We report our initial experience of two patients with LND.

Methods: Two patients (5- and 19-year old at the time of surgery) with LNS diagnosis, presenting dyskinesia, generalised dystonia and self-mutilating behaviour, were subject to stereotactic bilateral implantation of DBS electrodes (model 3389, Medtronic, USA) in the posterior area (motor) of GPi. In addition, in the second case the anterior/medial (limbic) area of Gpi was also target. The targets were determined by direct visualization using 1.5 T axial and coronal MRI. Chronic DBS therapy was applied using 130Hz; 450μs and 1.8-2.0 V.

Results: MRI performed after surgery confirmed the localization of the implanted electrodes in the GPi. In both patients a markedly decreased aggressiveness was the first detectable change one week after surgery. A follow-up performed 38 and 20 month respectively after DBS therapy showed a significant reduction in the self-mutilating behaviour and movement disorders evaluated with Burke-Fahn-Mardsen scale. However, in the first patient the worsening of the effect late disruption of one electrode was associated with the recurrence of the preoperative symptoms.

Conclusions: The data provide more evidence that GPi stimulation is effective to treat dystonia and self-aggressiveness in LND. However, the effectiveness of single or dual pallidal DBS for LND is not well established yet due to very few cases reported in the literature.

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Pallidal deep brain stimulation may induce freezing of gait in patients with focal and segmental dystonia

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Objective: The objective of this study was to explore the frequency and presentation of spontaneously reported (and therefore clinically relevant) gait disorders in patients with deep brain stimulation of the globus pallidus internus (GPi-DBS) for treatment of focal or segmental dystonia.

Background: GPi-DBS offers effective, well-tolerated, and safe treatment for patients with medically refractory segmental and generalized dystonia. However, concerns about bradykinesia and parkinsonism as possible adverse effects have occurred.

Methods: All patients who received GPi-DBS for focal or segmental dystonia during the last 3 years were included in this study, were interviewed, and received full neurological examination by a movement disorders specialist 0, 5 to 3 years after DBS implantation.

Results: Altogether 52 patients we included in this study. 5 patients (2 males, 3 females, mean age 58 years (48 - 69 years), 1 cranio-cervical dystonia, 1 DYT-1 positive segmental dystonia of the arms, 2 tardive dystonia, 1 dystonic camptocormia) spontanously reported a newly emerged gait disorder that closely resembled Freezing Of Gait (FOG) with difficulties with gait initiation, tripping steps, turning and the feeling of having their feet glued to the ground. Under a standard bipolar stimulation at a frequency of 130 Hz increase of the amplitude in higher ranges pro-

duced significant reduction of dystonia, but mostly immediate induction of FOG, sometimes worsening over a period of a few hours and vanishing within minutes after DBS cessation. In one patient FOG was abolished by reduction of the stimulation frequency from 130 to 60 Hz although dystonia was well controlled. In the remaining 4 patients extensive testing of different stimulation settings (monopolar/bipolar stimulation, pulse width 60-210μs, stimulation frequency 60-180Hz) did not abolish FOG without compromising the antidystonic effect.

Conclusions: A FOG-like gait disorder may follow GPi-DBS in almost 10% of patients with focal or segmental dystonia. This should be considered when the indication for GPi-DBS is discussed. Larger cohorts should be studied to identify potential predictive factors.

848

Treatment-refractory status dystonicus after bilateral pallidal DBS in a child with pantothenate kinase-associated neurodegeneration

L.E. Schrock, J.L. Gooch, P.A. House (Salt Lake City, Utah, USA)

Objective: To report a case of a 10-year-old child with the classic form of pantothenate kinase associated neurodegeneration (PKAN) who developed treatment-refractory status dystonicus (SD) 2 mo. after bilateral GPi DBS surgery.

Background: PKAN is an autosomal recessive neurodegenerative disorder of brain iron accumulation. It is classified into a classic form with early onset and rapid progression, and an atypical form with later onset and slower progression. 11 cases of GPi DBS for PKAN have been reported in the literature, but the majority of these have been of the atypical PKAN type, with only 3 cases reported with onset of symptoms <4yrs. These early onset cases have generally responded less favorably to DBS.

Methods: A 10-year-old male presented in our clinic with the typical clinical features of classic PKAN. At 15 months he was noted to have motor delay and regression of language. He never could walk normally and was wheelchair-bound at the age of 7 due to progressive generalized dystonia. A G-tube was placed for nutrition at age 9. Genetic testing revealed a PANK2 mutation. After responding poorly to intrathecal baclofen trial he underwent bilateral GPi DBS.

Results: Lead placement in the posteroventral GPi was confirmed on postoperative HCT fused to preoperative axial IR-FSE MRI. Preoperative Burke-Fahn-Marsden Dystonia Rating Scale motor subscale (BFMDRS-m) was 95. 1 week after bilateral GPi DBS the patient was able to open his hands and feed himself for the first time in several years, had improved jaw-closing dystonia and could eat food by mouth. BFMDRS-m at 1 month was 79. Two months post-operatively he had progressive worsening dystonia and was admitted to the ICU for SD requiring IV sedation to suppress severe dystonic spasms. Any attempt at lightening sedation led to reemergence of severe painful dystonic spasms despite titration of DBS, bilateral thalamotomy after 1.5 month ICU stay, and intraventricular baclofen pump (IVP) after 3 months ICU stay. 1 week after IVP he was discharged home with hospice care. He required complete sedation to control dystonic spasms and supplemental oxygen.

Conclusions: We report a case of classic PKAN that developed treatment refractory SD after bilateral GPi DBS. Very early onset classic PKAN may respond less favorably to GPi DBS.

849

Suboccipital craniotomy for decompression of the seventh cranial nerve curative in a 7 year old with hemifacial spasm

A.R. Torres, R.M. Laine (Boston, Massachusetts, USA)

Objective: To review a case of effective surgical intervention for a 7 year old with hemifacial spasm, and educate the field on surgical intervention as a possible option for individuals with hemifacial spasm and abnormalities found on MRI. Hemifacial spasms are rare in children, and this is the youngest child upon record who had surgical intervention for hemifacial spasm.

Background: A 7 year old presented to the Neurology clinic with what was originally diagnosed as tics. Upon further investigation, the movements included the right side of the mouth only, and were not suppressible, even in sleep. Due to the unilateral presentation and persistence of the movements, an MRI was performed for further investigation.

Methods: Multiple MR sequence of the brain and temporal bone were obtained before and after gadolinium was administered, including saggital T1, axial T2 FSE and FLAIR, axial T1 high-resolution and 3-D fiesta through the temporal bone, and axial diffusion weighted images. The right anterior inferior cerebellar artery was found to have an intracanalicular course, appearing to abut the canalicular portion of the right 7th cranial nerve. Neurosurgery was therefore consulted, who reviewed the MRI findings and clinical presentation. The hemifacial spasm had been persistent for five months, and therefore surgical decompression of the nerve was planned. A suboccipital craniotomy with microdissection and intraoperative nerve monitoring was performed for decompression of the seventh cranial nerve.

Results: Following decompression of the facial nerve, the hemifacial spasm nearly fully resolved. The movements noted post-surgically were less frequent and less severe, and at two months post-surgery, the movements are continuing to decline in frequency and severity. The patient maintained full voluntary facial movement.

Conclusions: Hemifacial spasms are rare in children. In these situations, MRI is a useful tool to diagnose anatomical abnormalities that may contribute to hemifacial spasm in children. In these situations, neurosurgical intervention can be explored as a possible intervention.

POSTER SESSION 4
THURSDAY, JUNE 17, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-16:00
Authors Present: 13:30-15:00

GENETICS

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GABA A receptor RHO1 (GABRR1) polymorphisms and risk for essential tremor

H. Alonso-Navarro, E. García-Martín, C. Martínez, J. Benito-León, I. Puertas, L. Rubio, T. López-Alburquerque, J.A.G. Agúndez, F.J. Jiménez-Jiménez (Alcazar de San Juan, Spain)

Objective: To investigate the possible association between the PON1 genotype and allelic variants of the single nucleotide polymorphisms rs1186902 (His27Arg) and rs832032 (Tyr205X) of the GABA A receptor rho1 (GABRR1, Chromosome 6Q14-Q21, OMIM 137161) and the risk for essential tremor (ET).

Background: Some clinical and experimental data suggest a possible role of gamma-aminobutyrate (GABA)-ergic mechanisms in the pathophysiology of essential tremor (ET), such as the improvement of ET with some GABAergic drugs and the development of an experimental model of ET in GABA A receptor alpha-1 knockout mice (postural and kinetic trermor and motor incoordination similar to human ET.

Methods: We studied the frequency of the previously mentionedc GABRR1 genotypes and allelic variants in 202 patients with ET and 232 healthy controls using a PCR-RLFP method.

Results: The frequencies of the GABBR1 genotypes and allelic variants of the polymorphisms (His27Arg) and rs832032 (Tyr205X) did not differ significantly between patients with ET and controls.

Conclusions: The single nucleotide polymorphisms studied in the GABBR1 gene are not related with the risk for ET.

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Analysis of LRRK2 variants in Parkinson's disease

W.L. Au, P. Ho, Y. Zhao, L.C.S. Tan, E.K. Tan (Singapore, Singapore)

Objective: To analyze a group of coding LRRK2 SNPs in a case control cohort of PD and controls.

Background: Two polymorphic LRRK2 variants have been shown to associate with a two-fold risk of PD in Chinese. Additional risk variants may yet to be identified.

Methods: In addition to the two established polymorphisms (rs33949390, rs34778348), another 62 polymorphic markers in the *LRRK2* gene were genotyped in 250 cases and 250 controls from the Singapore Chinese population. This was carried out with the MALDI-TOF mass spectrometry using the Sequenom MassARRAYTM system (San Diego, CA, USA). Multiplex genotyping assays were designed using the Sequenom DESIGNER software (San Diego, CA, USA). Initial PCR (5ng of genomic DNA) and primer extension reactions were carried out according to the Sequenom genotyping assay iPLEX^{TM} protocol. Confirmation of the variants with sequence analysis was carried out for selected samples in ABI 3730 automated DNA sequencer (Applied Biosystems).The frequency of each SNP and haplotypes were determined in both cases and controls. Haplotype analysis was carried out using Haploview. The two haplotype blocks were defined on the basis of r2 values, and haplotype-based test of associations were conducted for the haplotypes in these two blocks with frequency >1%.

Results: Of these 62 markers, 45 were monomorphic across all 500 samples. Analysis of the remaining 17 non-monomorphic SNPs in 250 PD and 250 controls revealed significant or marginal significance association in 5 SNPs. Two markers displayed moderate evidence of disease association (p-values=0.043 and 0.047 respectively). Two haplotype blocks were identified. Haplotype block 2 comprises two SNPs that were identified in the SNP analysis. In Haplotype block 1, 5 of the SNPs do not lead to an amino acid change.

Conclusions: We identified additional LRRK2 SNPs that may modulate the risk of PD.

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A study on L/I272 and S/N167 single nucleotide polymorphisms in the *parkin* gene in South Indian population with parkinsonism

Keerthana, S.V. Avathvadi (Chennai, Tamilnadu, India)

Objective: To determine the mutational frequencies of L/I272 and S/N167 single nucleotide polymorphisms (SNPs) in exons 7 and 4 respectively, in 50 cases diagnosed with various forms of parkinsonism, and 50 age-matched controls of South Indian origin; to compare the genotype frequencies in different age groups, and to analyze the influence of variables like sex and family history on the genotype frequencies in cases.

Background: The mutation is implicated in both genetic and sparadic forms of Parkinson's disease particularly among those Ashkenazic Jewish or north african origin. A study is needed in the South Indian population for the Genotype frequencies.

Methods: The genotype of the cases and controls was determined using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) analysis. The population was tested to see if it followed Hardy Weinberg's equilibrium. Odds ratio (OR) at 95% confidence intervals (CI) was calculated to compare the genotype frequencies between cases and controls. Chi-square (χ^2) analysis was performed to check the significant difference of genotype frequencies occurring in patient groups stratified according to sex, family history and age at onset of disease.

Results: The L/I272 SNP was not found in both cases and controls. The S/N167 SNP heterozyote frequency was found to be significantly higher in controls than in cases (OR=0.2, P=0.02), with higher number of male controls carrying the heterozygous genotype than male cases (OR=0.11, P=0.009). The wild type allele was found at a higher frequency in male cases than females (68% vs. 26%).

Conclusions: Both L/I272 and S/N167 SNPs could be rare polymorphisms in the population studied. Absence of L/I272 SNP suggests that this polymorphism may not be crucial in PD pathogenesis in this population. Since the wild type genotype (G/G) of the S/N167 polymorphism was found to have a significantly higher occurrence in male cases over female cases, the wild type genotype could play a role in protecting males in this population from developing PD.

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Investigation of the *LRRK2* G2019S mutation in South African Parkinson's disease patients

S. Bardien, R. Keyser, A. Marsberg, S. Lesage, J. Carr (Cape Town, South Africa)

Objective: To determine the prevalence of the *LRRK2* G2019S mutation in South African Parkinson's disease (PD) patients.

Background: Mutations in the leucine-rich repeat kinase 2 gene (*LRRK2*) are a significant cause of PD. One mutation G2019S, situated in the MAPKKK domain, has been implicated as an important genetic determinant of PD, particularly in the North African Arabic and Ashkenazi Jewish populations. A common disease-associated haplotype has been identified indicating that many G2019S-carrying patients share a common ancestor. To date, the majority of studies have focussed on the European and North American populations, and the present study is the first investigation of G2019S in the South African population and only the second from a sub-Saharan African country.

Methods: A total of 205 South African PD probands (65% were male) were recruited for genetic analysis. The average age at onset of PD was 54.4 years (range 17 to 80 years) and 36% had a positive family history of PD. Some of the patients (n=105) had already been screened for mutations in *parkin*. High resolution melt analysis on a Rotor-Gene 6000 analyzer (Corbett Life Science) and DNA sequencing was used to identify the G2019S mutation. Haplotype analysis was performed using microsatellite markers and single nucleotide polymorphisms.

Results: G2019S was found in 2% (4/205) of the patients studied. Reduced penetrance was observed in the families, which is in agreement with other studies. In all four of the G2019S-positive probands the mutation was shown to be present on the common disease-associated haplotype referred to as 'haplotype 1'.

Conclusions: Compared with many other countries the frequency of G2019S was found to be relatively low in the South African patients studied indicating that genetic screening for G2019S is possibly less important in the South African setting. The fact that all four G2019S-positive probands have haplotype 1 reveals that they are, in fact, related to each other and share a common ancestor with the other haplotype 1-associated families reported worldwide.

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The co-occurence of early onset Parkinson's disease (PD) and 22q11.2 deletion syndrome (22qDS): More than a coincidence

H. Baudoin, A. Jacquette, D. Grabli, S. Whalen, T. Lenglet (Paris, France, Metropolitan)

Objective: To report a new case of a co-occurrence of early onset PD and 22qDS.

Background: 22qDS is a multi-system disorder caused by a chromosomal microdeletion on the long arm of chromosome 22. Most common features are characteristic facial appearance, velopharyngeal insufficiency, conotruncal heart disease, parathyroid dysfunction, developmental delays. Recently its association with early onset PD has been described in 2 patients (Zaleski et al., Am J Med Gen A, 2009, 149A(3):525-8).

Methods: Case report of a patient who started PD at the age of 38 years and whose characteristic facial appearance led to the diagnosis of 22qDS.

Results: A 45-years-old man was referred to our center for a 7 years history of progressive movement disorder combining rigidity, rest tremor and akinesia predominant on the right side, with significant response to Levodopa. Brain magnetic imaging and biological assessement were normal. DAT scan showed a bilateral putaminal denervation. At the time of the examination he complained of motor fluctuations. They where not adequately controlled despite optimised medical therapy, with potential indication to a deep brain stimulation (DBS). However neuropsychological assessment suggested a cognitive impairment with marked dysexecutive syndrome. He also presented anxious disorders with pathological shyness and past history of transient major depression. Voice examination was indicative of hyper nasal speech. Because of unusual facial appearance cytogenetic analysis were required. Fluorescence in situ hybridization analysis confirmed chromosome 22q11.2 deletion. Cognitive disorders and hyper nasal speech were assumed to be explainable by 22qDS. Thus feasability of a DBS remains evaluated.

Conclusions: As for the two cases reported by Zaleski et al, our patient with 22qDS presented a typical PD marked by its relatively young onset. Although a chance association remains possible it suggests that the occurrence of PD in the context of 22qDS may not be coincidental. Thus neurologists should be aware of this possible association. The etiologic association remains to be explained. Within the commonly deleted region which spans over 40 genes, the catechol-*O*-methyltransferase (COMT) gene is of interest as a possible modifier of PD based on its pharmacogenetic role in Levodopa inhibition.

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Mechanism of the epigenetic defect in Friedreich ataxia

Y. Chutake, S.I. Bidichandani (Oklahoma City, Oklahoma, USA)

Objective: To determine the mechanism of the epigenetic defect in Friedreich ataxia.

Background: Over 15 inherited neuromuscular diseases are caused by expansion of triplet-repeats. Friedreich ataxia patients are homozygous for an expanded GAA triplet-repeat sequence in intron 1 of the FXN gene. The expanded GAA triplet-repeat results in deficiency of FXN gene transcription, which is reversed via administration of histone deacetylase inhibitors indicating that transcriptional silencing is at least partially due to an epigenetic abnormality. However, the precise nature and mechanism of the epigenetic abnormality in Friedreich ataxia remains poorly characterized.

Results: We show that the critical +1 nucleosome of the FXN gene displays the hallmarks of heterochromatin formation in Friedreich ataxia, offering a plausible mechanism for the deficiency of FXN gene transcription. We also show that patients have higher levels of a long antisense transcript and a small regulatory RNA overlapping the +1 nucleosome, consistent with a mechanism involving RNA-mediated heterochromatin formation.

Conclusions: These findings provide a mechanistic basis for the transcriptional silencing of the FXN gene in Friedreich ataxia, and provide novel therapeutic targets for reversal of this deficiency. Moreover, these results broaden our understanding of disease pathogenesis caused by expanded triplet-repeats.

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Parkinsonian features and motor network plasticity in LRRK2 patients and asymptomatic mutations carriers in comparison to sporadic PD and healthy controls

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Objective: To evaluate motor and non-motor symptoms as well as imaging characteristics in LRRK2 patients in comparison to sporadic PD (sPD) and healthy controls and to assess potential premotor markers in asymptomatic mutation carriers.

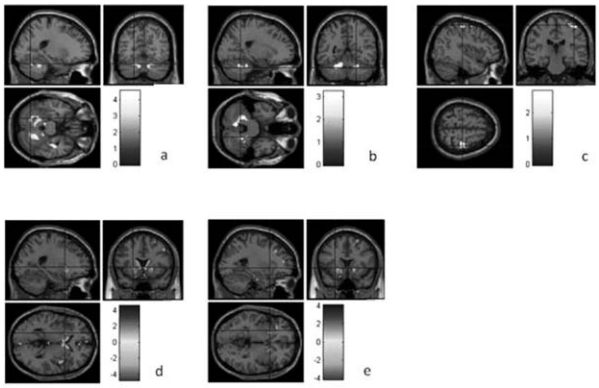

FIG. 1 (856). VBM analysis of grey matter volume. a) Increased cerebellar grey matter volume in LRRK2 patients vs. controls. b) Increased cerebellar grey matter volume in LRRK2 vs. sporadic PD patients. c) Increased precentral gray matter volume in LRRK2 patients vs. sporadic PD patients. d) Decreased basal ganglia grey matter volume in LRRK2 patients vs. controls. d) Decreased basal ganglia grey matter volume in LRRK2 patients vs. sporadic PD patients.

Background: Clinical features in patients with LRRK2 mutations resemble those of sPD. Voxel-based morphometry (VBM) comparing these groups has not been reported so far.

Methods: 15 LRRK2 patients, 18 asymptomatic LRRK2 mutation carriers, 24 sPD patients and 24 matched healthy controls underwent clinical assessment including UPDRS-III, UPSIT, BDI and MMSE, transcranial sonography (TCS) and MRI. VBM analysis was used for categorical comparison of grey matter volume.

Results: *a) LRRK2 patients, sPD patients and age-matched controls.* LRRK2 patients had a significantly earlier onset and longer disease duration but only sligthly higher scores in UPDRS than sPD patients. Also, they scored higher in BDI. There were no differences between these groups in other non-motor tests, but both differed regarding olfactory dysfunction from controls. TCS in sPD and LRRK2 showed hyperechogenicity of the substantia nigra (SN) compared to controls ($p<0.0001$). VBM data revealed bilaterally increased cerebellar grey matter volume in LRRK2 compared to sPD ($p<0.01$) and controls ($p<0.01$), and higher grey matter volume of the precentral gyrus than in sPD ($p<0.03$). In contrast, there was significantly decreased basal ganglia grey matter volume in LRRK2 compared to sPD and controls. *b) Asymptomatic LRRK2 mutation carriers and age-matched controls.* No clinical differences were found regarding motor and non-motor symptoms. TCS revealed hyperechogenicity of the SN in asymptomatic mutation carriers but not in controls ($p<0.0001$). VBM results showed bilaterally increased grey matter volume of the cuneus in asymptomatic mutation carriers ($p<0.03$).

Conclusions: The combination of longer disease duration but only sligthly higher scores in UPDRS and more pronounced atrophy of the basal ganglia but increased cerebellar grey matter volume in LRRK2 compared to sPD patients might indicate compensatory mechanisms. In asymptomatic mutation carriers hyperechogenicity of the SN indicates a presymptomatic stage of disease.

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The GIGYF2 variants are not associated with Parkinson's disease in the Chinese population

S. Chen, L. Cao, T. Zhang, L. Zheng, Y. Wang, Q. Xiao (Shanghai, China)

Objective: To determine the prevalence of GIGYF2 (Grb10-Interacting GYF Protein 2) variants in the Chinese population and to better understand the association between GIGYF2 and Parkinson's disease (PD).

Background: The mutations in PD associated genes contribute to the etiopathogenesis of both familial and sporadic PD. Lautier et al. reported GIGYF2 plays a causal role in family PD, but other studies indicate that common genetic variants of GIGYF2 are not pathogenic for PD patients of various origins.

Methods: The genetic screening of GIGYF2 in the Chinese population was conducted.

Results: Twelve exonic variants were identified in 52 familial PD probands and 56 healthy controls. Non synonymous point variants (Thr25Ala, Asn457Thr and Pro460Thr) were analyzed in 510 PD patients and 481 healthy controls of Chinese Han ethnicity. The insertion and deletion variants in Exon 25 (Ins Q 1212, Ins QQ 1217, Del Q 1210, Del Q 1216 and Del PPQ 1217_1219) are not related to the onset of familial PD.

Conclusions: Our data indicate the GIGYF2 variants are not associated with Parkinson's disease in the Chinese Population.

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A novel ATP13A2 frameshift mutation leading to juvenile parkinsonism and dementia

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Objective: To identify the genetic cause of juvenile parkinsonism and dementia in a patient of Afghan origin, who was born to consanguineous parents.

Background: Mutations in the ATP13A2 gene on chromosome 1p36 are known to cause a juvenile parkinsonian disorder, which has been named Kufor-Rakeb syndrome. The prominent features of this syndrome are parkinsonism, pyramidal signs, supranuclear gaze palsy and dementia.

Methods: We performed direct sequencing of known genes that are associated with parkinsonism: PARK2, PINK1, DJ1, ATP13A2, FBXO7, LRRK2. Biochemical, imaging and further genetic tests were also carried out.

Results: Clinical: The proband noticed difficulties with writing at 10 years of age. Bradykinesia and dystonic posturing in the right hemicorpus was accompanied by a rapid cognitive decline, leading to dementia at age 13. A transient response to levo-dopa was present, but it was complicated by the emergence of dyskinesias and visual hallucinations. The severe disease progression in this patient was documented with video recordings. FP-CIT scan showed almost absent ligand binding in both putamina. Genetics: Mutation screening in the proband was negative for all above-mentioned genes, except for ATP13A2. A homozygous 2 bp deletion was detected in exon 23, leading to a frameshift mutation with introduction of a premature stop codon and a probable truncation of the last 295 amino acids of the ATP13A2 protein. Protein and transcript analyses are in progress to confirm truncation of the protein.

Conclusions: We describe the clinical features of the youngest patient, that has been reported in the literature, suffering from Kufor-Rakeb syndrome. This novel genetic variation in ATP13A2 further extends the genetic and clinical spectrum of this rare disorder. We observe variable penetrance of this mutation in the family, which might be due to a dosage effect. Further functional research is needed to elucidate the effect of the frameshift mutation.

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Unexpected combination of ataxia with oculomotor apraxia type 2 and anti- GAD antibodies

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Objective: To report the first case of genetically confirmed ataxia with oculomotor apraxia type 2 (AOA2) associated with anti-Glutamic Acid Decarboxylase (GAD) antibodies.

Background: AOA2 is an autosomal recessive cerebellar ataxia due to mutations in the *SETX* gene and clinically characterized by the association of a progressive cerebellar ataxia, axonal sensorimotor neuropathy and optional oculomotor apraxia (OMA). Symptoms usually begin between 7 and 25 years. Serum level of alpha-foetoprotein (AFP) is elevated and brain Magnetic Resonance Imaging reveals a marked cerebellar atrophy. Cerebellar ataxia related to anti-GAD antibodies has been reported. This auto-immune affection can be treated with intraveinous immunoglobulins.

Methods: We describe the case of a 57-year-old woman presenting with a severe progressive cerebellar syndrome, that occurred when she was 16-year-old, associated with a severe chronic sensorimotor axonal neuropathy without OMA.

Results: When she was 46-year-old, a diagnosis of cerebellar ataxia with anti-GAD antibodies was established because of high levels of anti-GAD antibodies (282 U/mL, N<1) and she was treated during 10 years by immunosuppressive therapy (azathioprine) or corticosteroids with partial efficacy regarding acute oculomotor deterioration distinct from OMA. However, the association of a severe sensorimotor neuropathy and elevated AFP serum level (55 ng/mL, N>7) was consistent with the diagnosis of AOA2 which was confirmed by genetic analysis that revealed compound heterozygosity of *SETX* (3213insT and 5275G>A) when she was 57-year-old. A new assessment confirmed the presence of high titers of anti-GAD antibodies (115 U/mL).

Conclusions: The presence of anti-GAD antibodies has never been previously described in AOA2. The case suggests that cerebellar degeneration induced by the genetic disease could trigger the secretion of anti-GAD which could increase the cerebellar impairment. Thus, it could be interesting to search systematically for anti-GAD antibodies in AOA2 patients given the potential response to intraveinous immunoglobulins, plasma exchanges or immunomodulative treatment.

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Woodhouse-Sakati syndrome: Four new mutations of a movement disorder syndrome

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Objective: To study new cases of Woodhouse-Sakati syndrome (WSS).

Background: WSS is a rare autosomal recessive neuroendocrine disorder caused by mutation of the *C2orf37* gene which encodes a nucleolar protein. To date 25 families have been reported, mostly from Middle Eastern countries (Saudi Arabia, Jordan, Lebanon, Turkey). Clinically, the syndrome is characterized by the association of hypogonadism, alopecia, sensory neural deafness, mental retardation, diabetes mellitus and progressive extrapyramidal symptoms as dystonia and chorea. Brain Magnetic Resonance Imaging revealed white matter lesions or decreased signal intensity in the basal ganglia. Depressed insulin-like growth factor 1 (IGF-1) level represents a biological marker of the disease.

Methods: We examined clinically and genetically seven new cases of WSS from Italian, French Gypsy and Turkish origins, in an effort to extend both the phenotype and mutational spectrum associated with this disorder.

Results: Genetic analysis revealed a new mutation in each of the four families investigated, of which three were nonsense mutations and the fourth was an ablation of an acceptor splice site. Supplementing this cohort with others that have already been published did not reveal any genotype-phenotype correlation.

Conclusions: With the four new mutations described in this study, we confirm that the eight known mutations for this disorder are trun-

cating mutations in *C2orf37* which lead to a loss-of-function of the protein. Until now, pathophysiology of WSS remains unknown but the lack of any apparent genotype/phenotype correlation strongly argues for an important role of modifiers in the pathogenesis of this multisystemic disease.

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A clinicopathological study of a case of parkin disease

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Objective: To study the clinical and pathological features of a case with confirmed parkin mutation.

Background: Compound heterozygous mutations of the parkin gene on chromosome 6 are a common cause of autosomal recessive young onset parkinsonism. The phenotype differs from idiopathic Parkinson's disease by the early disease onset, limb dystonia and leg tremor as common clinical features, marked levodopa responsiveness and slow disease progression. Postmortem studies are few, but suggest pathological involvement largely restricted to the substantia nigra and locus coeruleus without the presence of Lewy bodies. Parkin disease has recently been suggested to be a primary mitochondrial disorder.

Methods: A 36-year old female developed abnormal posturing and tremor of her left foot in 1958. Focal dystonia was diagnosed and she was treated with anticholinergics to good effect. Ten years later a diagnosis of Parkinson's disease was considered when she was noted to have facial hypomimia, reduced arm swing and postural instability. Twenty years from disease onset she first received Levodopa treatment with excellent response. In her 70's she began to experience falls and required a wheelchair due to frequent motor fluctuations, but she still walked unaided when 'on'. She died aged 86 years, after 50 years of parkinsonism.

Results: Postmortem study revealed pallor of the substantia nigra and locus coeruleus and histological examination confirmed loss of pigmented neurons in the substantia nigra and the locus coeruleus with no tau or α-synuclein pathology. A number of nigral pigmented neurons contained ubiquitin immunoreactive inclusions, some of which were also immunoreactive for p62 but not other disease associated markers. Genetic analysis of the gene encoding parkin utilising frozen brain tissue revealed a compound heterozygote state: c823C>T; p.Arg275Trp mutation in parkin was detected combined with a heterozygous deletion of parkin 6 exon.

Conclusions: Very few parkin brains have come to autopsy and this case shows limited nigral involvement without tau or α-synuclein pathology similar to previous reports. The clinical feature of note in this case is absence of observed or documented dyskinesias by the patient's Neurologist or family, despite 30 years of Levodopa treatment. This case also highlights the potential longevity of patients with this form of parkinsonism.

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Novel *PRKN* exon is identified

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Objective: To screen *PRKN* gene in Iranian Parkinson's disease (PD) patients with average age at onset of 42 years.

Background: *PRKN* encodes a component of the ubiquitin proteasome system. *PRKN* mutations have been observed in PD patients, most often in early onset PD patients. A feature of disease causing mutations in *PRKN* is that many are large deletions or duplications that they may not be detected by common mutation screening protocols.

Methods: All 12 exons of *PRKN* were amplified by PCR from DNA of PD patients and sequenced to detect single nucleotide variations. Additionally, changes in dosage of exons were screened by a semiquantitative PCR protocol. The validity of dosage changes observed was checked using a reverse-trasncription-PCR (RT-PCR) protocol.

Results: Nine different *PRKN* disease associated mutations were found. Four were single nucleotide changes, and one of these that affects splicing was novel. Additionally, the semiquantitative PCR results suggested five different gene rearrangements. Three of these were confirmed by RT-PCR. The electrophoretic pattern of RT-PCR products of one of the rearrangements suggested the existence of an unexpected transcript. Sequence analysis and comparison with *PRKN* genomic sequences revealed that it represents a novel alternative spliced transcript. The novel transcript was found to be expressed in control individuals and PD patients.

Conclusions: Our most important finding is the identification of a novel *PRKN* transcript. Till now, a few alternatively spliced human *PRKN* transcripts have been reported. However, the previously described transcripts lack one or more exons of the standard transcript. The novel transcript reported here contains an exon absent in the standard transcript that is entirely coded within one of its introns. The novel exon is bounded by canonical splice site sequences. Relative levels of expression of the transcipts in controls and patients remains to be established. Finally, disease associated *PRKN* mutations were mostly observed in very early onset patients.

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Genome-wide analysis and accuracy of self-reported data: The 23andMe Parkinson's disease project

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Objective: To assess the accuracy of self-reported data concerning Parkinson's disease (PD) diagnosis, symptoms, response to medication, and risk factors using a novel web-based method for patient recruitment and data collection. Also, to use this data with whole-genome SNP data to reproduce known common genetic factors that influence PD and to find new genes.

Background: Sseveral relatively common mutations have been associated with PD (in SNCA, LRRK2, GBA, and MAPT). However, there are probably other genes yet to be discovered that influence PD risk or that interact with known risk factors for PD.

Methods: Participants were recruited online beginning in March 2009, mainly via emails sent by PD foundations and clinics. Saliva was collected by mail and all participants were genotyped on a whole-genome platform (Illumina 550 plus a custom chip). They were encouraged to fill out web-based surveys covering their diagnosis, symptoms, medications, and environmental risk factors for PD. To assess the accuracy of this data collection, we compared survey responses to clinical guidelines for PD diagnosis (requiring diagnosis by a neurologist, gradual disease onset, no change in diagnosis, a worsening of symptoms, and response to L-DOPA if tried). For the genetic aspect, we performed a genome-wide association study (GWAS) among the unrelated Europeans with PD, using other 23andMe customers who did not have PD or a first degree relative with PD as controls.

Results: Almost 3000 participants sent in their DNA and consented for research. 78% filled out the main survey, and over 80% of those responding met our criteria for certainty of diagnosis. The most common cause for exclusion was reported sudden onset of symptoms. The GWAS showed that the genes SNCA, GBA, LRRK2, and MAPT are associated with PD. Odds ratios for the relevant mutations were quite concordant with those published.

Conclusions: Our study suggests that patient recruitment and data collection online can be a quick way of generating accurate phenotypic data. Almost all participants reported symptoms consistent with a diagnosis of PD. The replication of known genetic associations provides additional evidence that the participants overwhelmingly had PD.

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G2019S and R1441G mutations and R1628P SNPs throughout LRRK2 gene in patients with Parkinson's disease from Argentina

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Objective: To determine the frequency of G2019S, R1441G mutations in exon 41 and additional R1628P single nucleotide polymorphisms across LRRK2 gene in a cohort of patients with PD from Argentina.

Background: Variation in the LRRK2 gene is found in autosomal dominant familial and sporadic parkinsonism with a variable prevalence affected by ethnicity. Few data are available from Latin America and no data were reported from Argentina. The association between polymorphisms located within LRRK2 gene and the risk for PD remains under discussion.

Methods: Informed consent was obtained and all studies were approved by the Institutional review boards. 55 consecutive patients with PD were recruited. Demographic, clinical and molecular data were recorded. Blood samples were obtained and DNAs extracted from patient venous blood. All patients were screened for G2019S and R1441G, which are the most common LRRK2 mutations in populations with European ancestry.

Results: A mutation screening of *LRRK2* was performed in 30 women and 25 men with PD, mean age 68.8±10.6 years (range 44-88 yrs). Jewish and Basque ancestries were respectively positive in 9/55 and 7/55 patients, and 16/55 reported a positive family for PD. The G2019S mutation in exon 41 was determined in 3 Ashkenazi Jewish individuals with familial PD (5.45%). Although Argentina possesses one of the largest Basque communities outside Spain, non R1414G mutation was identified in this cohort. Eleven R1628P SNPs were identified, and 5/11 were previously identified in populations with Ashkenazi and European ancestry. The phenotype of G2019S carriers was indistinguishable from patients with idiopathic PD. A nonsignificant increase in dyskinesias was identified in these patients, and 2/3 developed Dopamine Dysregulation Syndrome and visual hallucinations.

Conclusions: The prevalence of G2019S mutations in this Argentinean cohort was similar to other international series. The role of R1628P SNPs as a risk factor for developing PD in this cohort remains to be elucidated. Although the present study reports concerns regarding sample size and the lack of a control group, it represents the first approach to a genetic study in an Argentinean cohort with PD.

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Penetrance and frequency of the LRRK2-G2019S mutation in the Italian population: An update

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Objective: to evaluate frequency and penetrance of LRRK2-G2019S mutation in Italian PD population.

Background: The mutation G2019S in the LRRK2 gene is associated to autosomal dominant Parkinson's disease (PD). Its frequency in PD patients is variable in different populations ranging from approximately 0 in Asia to 40% in North Africa. We previously reported the analysis of LRRK2-G2019S in 1245 consecutive, unrelated Italian patients with primary degenerative parkinsonism (Goldwurm et al. Park Relat Disord, 2006;12:410).

Methods: 2,346 unrelated consecutive patients with degenerative parkinsonism who contributed to the DNA Bank of the Parkinson Institute, Milan-Italy were tested for the G2019S mutation. The penetrance, the conditional probability to develop PD in a mutation carrier, was estimated using the Kin-Cohort method (Wacholder S et al. American Journal of Epidemiology 1998;148:623). The kin-cohort method can directly estimate the cumulative risk of disease in carrier kin on the base of Mendelian inheritance patterns and regardless of genetic testing result.

Results: The G2019S mutation was identified in 27 of the 2000 PD probands (1.35%; 8 males and 19 females) and in none of the 346 probands with other parkinsonisms. The mutation was more common in patients with a family history of PD (3.6%) than in sporadic cases (0.8%). Maximum frequency was recorded in patients with at least one parent suffering from PD (4.7%). Mean age of onset was 53.55 years (SD±11.59) and disease duration 13.63 (SD±5.81). Penetrance evaluation in the 172 first degree relatives of G2019S probands was 10.7% (CI 1.3-21.0) at 60 years, 20.6% (CI 8.1-33.4) at 70 years and 30.1% (CI 9.9-54.6) at 80 years.

Conclusions: LRRK2-G2019S is confirmed to be a very frequent mutation causing PD in the Italian population. Only a minority (approximately one third) of G2019S carriers develop PD in their lifetime.

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Role of the H1 haplotype of microtubule-associated protein tau (MAPT) gene in Chinese patients with sporadic Parkinson's disease

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Objective: To determine the broader significance of this association with sporadic PD, replicative studies in distinct ethnic populations are required. In this study, we set out to determine whether the H1 haplotype and additional single nucleotide polymorphisms (SNPs) included in H1 are associated with sporadic PD in a sample of Chinese patients.

Background: The extended tau haplotype (H1) that covers the entire human microtubuleassociated protein tau (MAPT) gene has been implicated in Parkinson's disease (PD).

Methods: We investigated MAPT for its potential association with PD using two haplotype-tagging SNPs (rs242562 and rs2435207) and the del-In9 polymorphism of MAPT in 519 PD patients and 504 healthy controls from southern China.

Results: The samples we analyzed were all identified as H1/H1 genotype. The two SNPs (rs242562 and rs2435207) demostrated no signifcant association with PD.However, a risk haplotype [G-G] for PD was identified (Chi Square=4.102; p=0.0428).

Conclusions: Our results demonstrate that the genetic factors involved in sporadic PD with Chinese Han may different from Caucasian. This is the first association study from southern China conducted on *MAPT* among PD patients and provides valuable information for comparison with other ethnic groups.

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The research on two hotspot variants in mainland China, Pro755Leu and Gly2385Arg in *LRRK2* gene, reported to be associated with sporadic Parkinson's disease

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Objective: To report the two previously reported most likely pathogenic variants, Pro755Leu and Gly2385Arg in LRRK2 in a large sample involving 799 individuals from central part of mainland China.

Background: Some variants in LRRK2 reported from Asian populations appears to be susceptive for elevating risk for PD.

Methods: We conducted a case-control study to determine the prevalence of Pro755Leu and Gly2385Arg variants in *LRRK2* gene in 401 patients with sporadic Parkinson's disease (PD) and 398 unrelated healthy controls in Han population in central part of mainland China, which were previously reported to be likely pathogenic var-

iants among ethnic Chinese patients with PD. We also performed meta-analyses on each variant in population of Chinese ancestry throughout Asia.

Results: Then firstly we identified heterozygous *LRRK2* Pro755-Leu variant in four patients and two healthy controls, and there was no statistical differences in genotypic or allelic frequencies between PD and control groups (genotype: $\chi 2$ =0.657, P=0.686; allele: $\chi 2$ =0.654, P=0.687). Secondly, the allele of G for the Gly2385Arg variant was significantly more frequent among PD patients compared to controls ($\chi 2$ =3.92, P=0.048, OR=1.66, 95%CI:1.00-2.76), when thirty-three heterozygous and four homozygous patients while twenty-three heterozygous and one homozygous controls for Gly2385Arg variant were identified through our study.

Conclusions: It is quite reasonable to suppose that Pro755Leu is not a genetic risk factor for PD in Han population in central part of mainland China, it is rare in this region. On the other hand, our study offers repetitive and solid evidence for the conclusion that Gly2385Arg in LRRK2 gene increases risk for PD in Han population in mainland China. Furthermore, the meta-analyses of Pro755Leu and Gly2385Arg variants for PD in ethnic Chinese population in Asia are consistent with our inference.

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Clinical manifestation of patients with Parkinson's disease carriers of "severe" mutations in the GBA gene

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Objective: To describe the phenotype of Ashkenazi PD patients who are carriers of sever mutations in the glucocerebrosidase gene (GBA) gene.

Background: Mutations in the GBA gene have recently been associated with the development of Parkinson's disease (PD). Depending on GBA mutation severity, risk of developing PD can increase up to 30%. The severe GBA mutations include 84GG, L444P, IVS2DS_1G-A, and V394L but little is known about the phenotype of those patients.

Methods: 13 Ashkenazi PD patients (9 men) who are carriers of sever mutations in the GBA gene, participated in this study. Evaluation included a battery of tests about clinical status, cognitive state, autonomic function, emotional state and olfaction. All tests were given by neurologist who was blinded to the genetic background.

Results: Seven patients carried the 84GG mutation, 2 patients had the L444P mutation, 2 were carriers of V394L mutation and 1 patient carried the IVS2+1 mutation. Mean age of motor symptoms onset was 56.1±7.9 yrs with mean motor symptoms duration at time of evaluation of 8.1±6.4 yrs and mean UPDRS score of 27±12.1. Motor symptoms were consistent with postural instability type of manifestation, with 54% of patients reporting problems in balance and stability (mean scores on the Berg Balance Scale of 43.7±12.7; ranging from 12-56) and none of the patients demonstrating tremor. Seven patients reported excess salivation with difficulty in swallowing. Mean score on the Montreal Cognitive Assessment was 24±2.5 and all patients had considerable decrease in attention and memory as measured using a computerized cognitive test. Patients also demonstrated a severe decrease in the sense of smell (>12 on the UPSIT test) with a particular impairment in identification of citron smell. Mental features as anxiety or depression were observed in 4 patients.

Conclusions: This group of PD patients with severe mutations in the GBA gene exhibited slightly earlier PD motor symptoms onset then reported for sporadic PD. These patients demonstrated severely impaired sense of smell as well as changes in autnomic functions and balance control. Given the small sample size, additional investigation is necessary to validate these results and to further determine the contribution of severe GBA mutations to PD phenotype.

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Fragile X gray zone alleles: Association with clinically diagnosed PD in women

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Objective: To test the hypothesis that the prevalence of *FMR1* repeat expansions in a movement disorder population would be higher than a general population sample, we screened patients with all types of tremor, ataxia, and parkinsonism subjects in a university movement disorder center.

Background: Carriers of fragile X mental retardation 1 (*FMR1*) repeat expansions in the premutation range (55-200 CGG repeats), especially males, often develop tremor, ataxia, and parkinsonism, known as the fragile X-associated tremor/ataxia syndrome (FXTAS). In addition, some premutation carriers have a predominantly PD phenotype. These neurological signs are believed to be due to elevated levels of expanded CGG repeat *FMR1* mRNA. It is not known if formes frustes or milder variants of FXTAS manifest as other movement disorders among subjects with CGG repeats in the "gray zone" (41-54 CGG repeats).

Methods: Consecutive movement disorders patients (n=335) were recruited, interviewed, and then examined using standardized rating scales. Prevalence rates were compared to historical population rates.

Results: The overall prevalence of *FMR1* expansions in this movement disorders population was 5% compared to a population rate of 2% (p<0.01). In the movement disorder population, 88% of the expansions fell into the *FMR1* gray zone. Among PD subjects (n=218), a strong female gender association with *FMR1* gray zone expansion occurred in comparison with controls: 11.2% vs. 2%

TABLE (869). *Prevalence of FMR1 expansions compared to population controls for any expansion (2.3%) or gray zone expansion (2%)*

	Overall prevalence of expansions	Overall prevalence gray zone expansions	Prevalence of gray zone expansions in males	Prevalence of gray zone expansions in females
Movement Disorders	17/335 5% (p<0.01)	15/335 4.5% (p<0.1)	3/189 1.6% (p=0.9)	12/146 8.2% (p<0.01)
Parkinsonism	15/273 5.5% (p<0.01)	14/273 5% (p<0.01)	3/155 1.9% (p=0.95)	11/118 9.3% (p<0.01)
Parkinson disease	13/218 6% (p<0.01)	12/218 5.5% (p<0.01)	1/120 0.8% (p=0.36)	11/98 11% (p<0.01)

TABLE (869). *Clinical Features of the FMR1 Repeat Expansion Carriers*

Age	Gender	CGG repeat	Diagnosis	Age of onset	Age of diagnosis	UPDRS	Dopaminergic response
68	F	41, 23	PD, tremor	56	66	11	yes
76	F	41, 30	PD	74	76	20	yes
64	F	42, 30	PD	57	59	27	yes
71	F	42, 30	PD	56	56	46	yes
66	M	43	PD	55	55	8	yes
36	F	43, 37	ataxia	32	36	18	not tried
78	F	43, 20	PD	66	66	11	yes
57	M	44	parkinsonism	52	56	23	yes
56	F	44, 29	PD	32	32	25	yes
53	F	45, 28	PD	45	46	9	yes
59	F	46, 20	PD	47	50	24	unknown
59	F	47, 24	PD	44	58	8	yes
63	F	48	parkinsonism	55	57	31	yes
79	F	48, 30	PD	69	71	16	yes
70	F	51, 21	PD	66	67	14	yes
48	M	60	PD	45	46	11	yes
69	M	109	ataxia, tremor	58	58	35	mild improvement

($p<0.01$). In men with PD (n=120), no significant association with *FMR1* expansion occurred (0.8%, vs 2% in controls, p=0.36). In addition, we collected 100 normal control subjects (64% female) from our local Colorado population and found the female gender association remained despite the small sample size ($p<0.01$).

Conclusions: This study reports an unexpectedly high prevalence of *FMR1* gray zone alleles in women with clinically diagnosed PD. Review of these cases confirmed that all were levodopa responsive and none had clinical features to suggest other diagnoses. Gray zone alleles have been associated with parkinsonism in Australian men, with 8% having expansions compared to a control population of 3.4%. Our study findings suggest that fragile X gray zone alleles may also play a genetic role in the risk for PD in women.

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H63D polymorphism in the hemochromatosis gene is associated with sporadic amyotrophic lateral sclerosis in China

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Objective: To investigate the frequency of H63D polymorphism in the hemochromatosis gene in a Chinese population.

Background: Iron misregulation induces oxidative stress. Elevated levels of iron have been found in the spinal cords of patients with amyotrophic lateral sclerosis (ALS). H63D (His-63→Asp), a polymorphism in the hemochromatosis (HFE) gene, has been reported as a risk factor for ALS in the United States, Italy, the United Kingdom, Ireland, and the Netherlands.

Methods: The study included 195 patients with sporadic amyotrophic lateral sclerosis (sALS) from three treatment centers in China and 205 unrelated healthy controls. The HFE H63D polymorphism was determined by restriction fragment length polymorphism (RFLP) analysis.

Results: sALS was significantly related to H63D polymorphism in heterozygous carriers (odds ratio 3.41, CI: 1.33 to 8.79, $P=0.007$).

Conclusions: The HFE H63D polymorphism may therefore contribute to the development of sporadic ALS in Chinese.

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Genetic control of DNA methylation and expression in the context of neurological disease

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Objective: (1) Investigate the effects of genetic variation on levels of transcript expression and DNA methylation on genome-wide genotype, DNA methylation and gene expression data in the cerebellum and frontal cortex regions of 400 neurologically normal brains (2) establish biological effects of Parkinson's disease (PD) risk loci in normal brains where a proportion of the sample cohort are PD risk hapotype carriers.

Background: Common genetic variability has recently been shown to play a substantial role in typical PD. The biological basis of the associated risk variants has not been established. We examined the effects of common genetic variability on DNA methylation and mRNA expression in normal human brain. We found genetic cis regulation of mRNA expression and novel QTLs for DNA CpG methylation. Integrating genetic, epigenetic and expression data allows an understanding of the normal regulation of DNA methylation and gene expression in human brain and is a first step to understanding the pathobiological consequences of genetic variants linked to disease.

Methods: To establish the biological effects of recently identified PD risk loci alpha synuclein (SNCA), LRRK2 and MAPT, we examined the mRNA expression levels and methylation status of CpG sites spanning these genes in normal human brain. We performed a regression of CpG methylation staus and gene expression levels with genotype at risk loci to determine whether these loci act as quantitative trait loci for these traits. To further refine the SNCA risk locus, bisulfite converted DNA samples were used to map the status of an additional 384 DNA methylation sites spanning this gene.

Results: We show quantitative trait loci for expression at the MAPT locus; indicating that the MAPT risk alleles are associated with increased microtubule associated protein tau expression levels. We also provide dense mapping of CpG methylation levels in human brain across the SNCA locus and the effect of SNCA risk alleles on DNA methylation sites and SNCA expression.

Conclusions: This is the first work to provide a dense survey of DNA methylation across the PD linked gene SNCA. We show the utility of genome wide expression, genotyping and DNA methylation assays in understanding the biological basis of risk associated genetic variability.

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Deep brain stimulation outcome in parkin, LRRK2, and glucocerebrosidase mutation carriers and non-carriers in early onset Parkinson's disease

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Objective: To determine whether parkin, LRRK2 or glucocerebrosidase (GBA) mutation status in subjects with early onset Parkinson's disease (EOPD), defined as age at onset (AAO) <51, is associated with outcome after deep brain stimulation (DBS).

Background: Few studies have investigated the association between DBS outcome and parkin or LRRK2 mutation status, and no studies have investigated association with GBA mutation status.

Methods: Clinical and demographic data were collected from 46 EOPD subjects at our center who underwent DBS placement and genotype testing. DNA samples were analyzed for parkin, LRRK2 G2019S, and GBA N370S and L444P mutations. Analysis of variance and chi-square tests were used to compare baseline demographics and disease characteristics among the genetic groups and linear regression models were constructed to examine the association between mutation status (predictor) and change in "off" UPDRS-III motor score (outcome) from preoperative to post-operative follow up assessment.

Results: Of the 46 subjects, 4 (8.7%) carried parkin mutation(s) (3 heterozygous, 1 homozygous), 2 (4.3%) carried the LRRK2 G2019S

TABLE 1 (872). *Baseline demographics and disease characteristics*

	Non-carriers (n=36)	Parkin carriers (n=4)	LRRK2 carriers (n=2)	GBA carriers (n=3)	Total (n=45)	p-value
Gender (% female)	36.1%	0%	100%	33.3%	35.6%	NS
Ethnicity (% Hispanic)	16.7%	25%	0%	0%	15.6%	NS
AAO (years)	40	33	47	44	40	NS
Age at pre-op visit (years)	54	46	63	57	54	NS
Disease duration (years)	14	13	16	13	14	NS
Baseline "off" UPDRS-III score	34	42	15	27	33	NS
Total tremor score (UPDRS-III subscore)	4	11	2	3	4	0.001[1]
Daily levodopa equivalent (mg)	1271	1003	653	2452	1302	0.054[2]

[1] Significance is driven by parkin carriers, who had higher tremor scores. [2]p-value is driven by GBA carriers.

mutation, and 3 (6.5%) carried the GBA N370S mutation. One subject carried both G2019S and L444P mutations (excluded from statistical analyses and Table 1 data), and 36 (78.3%) were non-carriers. Subjects' baseline demographics and disease characteristics are described in Table 1. In linear regression models there were no significant differences in DBS outcome as measured by UPDRS-III off-medication scores between carriers and non-carriers for any mutation group.

Conclusions: We find no association between parkin, LRRK2, or GBA mutation status and DBS outcome. Larger studies are needed to confirm this lack of association.

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Tau gene polymorphism influences risk of sporadic tauopathy by allele-specific changes in transcription and alternative splicing

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Objective: To study the activity of three common *MAPT* promoter variants (H1b, H1c and H2) *in vitro* in order to ascertain whether the genetic differences in disease risk are conferred by differences in *MAPT* expression and alternative splicing.

Background: Tauopathies, including Alzheimer's disease (AD) and progressive supranuclear palsy (PSP), are a group of neurodegenerative diseases characterised neuropathologically by brain lesions comprising aggregates of the microtubule associated protein, tau. Common variation in the gene encoding tau (*MAPT*) affects the production of tau protein and its six isoforms and has been shown to modulate disease risk.

Methods: Combinations of the allelic variants of three regions of the *MAPT* promoter - the minimal core promoter and an upstream and a downstream putative enhancer domain - were cloned into luciferase reporter plasmids. Reporter gene expression was analysed *in vitro* in SH-SY5Y and BE(2)-M17 neuroblastoma cell cultures. We have now extended this to studies of co-transcriptional regulation of splicing using *MAPT* minigenes.

Results: The H1c promoter variant had a 4.2-fold increase in transcriptional activity over the H2 variant ($p<0.0001$). When only the core promoter and the downstream putative enhancer domain were included, the H1c variant had 2.7-fold greater transcriptional activity than the H1b variant ($p<0.01$) and 4.2-fold greater than the H2 variant ($p<0.01$). We also observed coincident H1c allele-specific changes in alternative splicing of *MAPT* exon 10 *in vivo* with increased 4R-tau transcripts.

Conclusions: The H1c *MAPT* variant, previously associated with increased risk of neurodegenerative disease, has higher transcriptional activity *in vitro* than the neutral (H1b) and protective (H2) variants and this appears to be driven by the putative downstream enhancer. This is coupled with H1c-specific elevation of mRNAs coding for the more fibrillogenic 4R-tau variants. We are currently conducting an independent replication of this study, and also an investigation of other conserved putative regulatory promoter regions in order to obtain a better picture of the allele-specific differences in *MAPT* expression and the effect of promoter strength on alternative splicing. The results of this further work will also be presented.

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Regional distribution of subtypes of spinocerebellar ataxia in Korea: A nation-wide survey

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Objective: In this study, using a nationwide survey, authors investigated the prevalence and relative frequency of different subtypes of spinocerebellar ataxia (SCA) in Korea and then evaluated their regional differences.

Background: The prevalence and relative frequency of specific subtype of SCA varies between different ethnic groups. Furthermore, some reports showed that there are regional differences in the relative frequency of specific subtype of SCA even within an ethnic group.

Methods: This study included Korean patients with genetically confirmed SCA, including SCA 1-29, DRPLA, and 16q-ADCA, regardless of the presence or absence of family history. Patients who had clinical symptoms and family history suggestive of SCA but had not undergone gene test were excluded. A structured survey forms regarding the information of SCA patients including birthdate, sex, subtype of SCA, and birthplace or current address, were sent to the neurology departments in all the training hospitals in Korea. Neurologist in each hospital was asked to complete this survey form using the hospital data of SCA patients who were followed-up at each hospital. The returned forms were analyzed to evaluate the prevalence and relative frequency of different subtypes of SCA in Korea and in each subregion. In familial cases, only one patient per family was counted in the analysis.

Results: Of 82 training hospitals in Korea, 53 hospitals (65%) returned the survey forms, including 21 hospitals with 'no genetically-proven SCA patient.' A total of 348 SCA patients were identified. The most frequent diagnose was SCA2 (97 patients, 27.9%), followed by SCA3 (80, 23%), SCA6 (79, 22.7%), SCA1 (29, 8.3%), SCA7 (25, 7.2%), SCA17 (18, 5.2%), DRPLA (14, 4.0%), SCA8 (4, 1.1%), and 16q-ADCA (2, 0.6%). Relative frequency of different subtypes of SCA differed among subregions. In mid to northern region of Korea, SCA3 was the most prevalent subtype while SCA2 was the most prevalent subtype in southern region. Interestingly, in Jeju Island, 15 of 16 SCA patients were SCA6.

Conclusions: The most common SCA subtype in Korea is SCA2, followed by SCA3 and SCA6. However, there are considerable regional differences in the relative frequency of subtypes of SCA. This study also shows that the relative frequency of subtypes of SCA in Korea is distinct form that of neighboring countries.

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Novel Nurr1 point mutations identified in ethnic Chinese patients with Parkinson's disease

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Objective: To identify whether there is any mutations in *NR4A2* gene associated with Parkinson's disease in ethnic Chinese population.

Background: *NR4A2,* a member of the nuclear receptor superfamily of transcription factors, is highly expressed in the midbrain dopmine neurons and it is essential for the development and survival of the nigro-striatal dopaminergic system. Recently it has been reported several mutations in this gene associated with Parkinson's disease (PD) in Caucasian population, suggesting that *NR4A2* may play an important role in the cause and pathogenesis of PD. The genetic study in ethnic Chinese is still lacking.

Methods: We conducted a mutational analysis of *NR4A2* from genomic DNA collected from a cohort of total of 523 ethnic Chinese. All research subjects signed an informed consent, which was approved by our three collaborator's Institutional Review Board for Human Research. Among the research subjects, 245 are patients with PD (208 sporadic PD and 37 familial PD), and 278 are healthy controls. We designed primers amplifying the whole exon regions (Bio-Rad iCycler Optical Module), and sequenced the PCR product using 454 GS-FLX and ABI SOLiD systems.

Results: We identified two novel heterozygous mutations in *NR4A2* gene in 245 PD patients. The first point mutation was found in exon 2 (A-G transition at position of 388) in a 69-year-old male sporadic PD. The second point mutation (C-A substitution in 709 at exon 3 causing an amino acid change from a serine to tyrosine) in a 61-year-old female sporadic PD. This mutation is different from the 709 C-G transition reported in a Canadian cohort (Mov Dis, 2006. 21:906-9). We did not find these two mutations in 278 healthy controls nor did we find other mutations in the gene in 245 PD patients.

Conclusions: It is the first time we report novel *NR4A2* mutations in ethnic Chinese population. The results from this study further support the notion that transcription factors that regulate central dopamine neuron development and functional maintenance might be associated with PD.

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The c.-237_236GA>TT *THAP1* sequence variant is not associated with a significantly increased risk for primary dystonia

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Objective: To examine the *THAP1* c.-237_236GA>TT *THAP1* sequence variant in subjects with primary dystonia and normal controls.

Background: Many different sequence variants in *THAP1* have been linked to primary dystonia. In previous work, Djarmati and colleagues (*Lancet Neurology* 2009;8:447-452) suggested that a sequence variant in the 5'untranslated region (UTR) of *THAP1* might increase the risk for dystonia.

Methods: High resolution melting was performed in 1508 subjects with mainly adult-onset primary dystonia and 1520 normal controls. Samples with shifted melting curves were sequenced in the forward and reverse directions.

Results: The TT allelic frequencies were 65/3016 (2.16%) and 55/3040 (1.81%) in subjects with dystonia and normal controls, respectively ($P=0.191$). Subgroup analyses for laryngeal dystonia, cervical dystonia, blepharospasm, segmental and multifocal dystonia also failed to attain statistical significance ($P > 0.1$, for all).

Conclusions: There is no significant association between the c.-237_236GA>TT *THAP1* sequence variant and risk for dystonia.

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Differential genetic susceptibility in diphasic and peak-dose dyskinesias in Parkinson's disease

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Objective: To examine whether there is a differential genetic susceptibility in the diphasic and peak-dose forms of levodopa-induced dyskinesias (LID) in patients with Parkinson's disease (PD).

Background: Not all patients with peak dose dyskinesia have diphasic dyskinesia, and the symptomatologies and responses to therapy is quite different between the two types of LID, thus there might be distinct genetic predisposition.[1,2]

Methods: The study cohort comprised 503 unrelated Korean PD patients who were treated with levodopa and had a disease duration of at least 5 years. The presence of LID was identified during a routine follow-up, and special care was taken to separate the two distinct forms of LID into diphasic and peak-dose dyskinesias. Genotyping was performed in the 503 patients and in 559 healthy controls to search for polymorphisms of *DRD3* p.S9G, *DRD2 Taq1A*, *GRIN2B* c.2664C>T, c.366C>G, and c.-200T>G, and the promoter region of *SLC6A4* (5-HTTLPR).

Results: A total of 229 patients expressed LID (peak-dose in 205, diphasic in 57, and both in 33). The presence of diphasic dyskinesia was independently associated with the *DRD3* p.S9G variant after adjusting for clinical risk variables. Carrying the AA genotype was likely to shorten the onset of diphasic dyskinesia according to the duration of levodopa therapy ($p=0.02$). Other genetic variants were not significantly associated with diphasic dyskinesia. The presence of peak-dose dyskinesia was not associated with any of the six genetic variants studied.

Conclusions: A distinct association between *DRD3* p.S9G and diphasic dyskinesia suggests that genetic susceptibility plays a role in the expression of diphasic dyskinesia in PD patients on chronic levodopa therapy, and that its underlying pathophysiological mechanism is distinct from that of peak-dose dyskinesia. References> 1. Fahn S. The spectrum of levodopa-induced dyskinesias. Ann Neurol 2000;47(suppl.1):S2-11. 2. Fabbrini G, Brotchie JM, Grandas F, et al. Levodopa-induced dyskinesias. Mov Disord 2007;22:1379-1389.

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Study of the *SGCE* gene in Tourette syndrome patients of Taiwanese

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Objective: To investigation the possible association of the ε-sarcoglycan (*SGCE*) gene in a cohort of patients with Tourette's syndrome (TS) in Taiwan.

Background: Tourette's syndrome (TS) is characterized by the presence of motor and phonic tics with onset in childhood and is often accompanied by other behavioral disorders, such as obsessive-compulsive disorder (OCD). In the previous two papers reported by de Carvalho Aguiar et al. and Orth et al., they did not find any mutation of *SGCE* gene in patients with TS with OCD and in one big family with myoclonus dystonia and TS respectively. In our recent genetic investigation, we found that mutations and large deletion of *SGCE* gene might be contributed to Taiwanese patients with myoclonus dystonia which was frequently associated with OCD. We further extended to study the TS which is characterized by the multiple motor and voice tics and OCD.

Methods: We carried out a serial genetic analysis including single strand conformation polymorphism (SSCP), denaturing high-performance liquid chromatography (DHPLC), direct sequence and multiple ligation-dependent probe amplification analysis (MLPA) on a group of 33 patients (woman : man=2 :31) with TS and 147 age matched controls (woman : man=95 : 52). The mean age at examination was 35.52±11.9 years (range, 16-66) in the patient group and 31.44±4.2 years (range, 23-40) in the control group.

Results: We identified a heterozygous variant R342Q (1025G>A) in exon 7 in one patient, which was not found in the control group. Therefore, it might be a mutation. Another heterozygous variant (c.391-43 A>C,) in exon 4 was detected in four patients (12.1%) which was also identified in the normal control (36%). Thus, the variant is a single nucleotide polymorphism (rs2272091). No copy number abnormality was found. The patient with R342Q mutation was presenting with multiple motor tics, sniffing, vocal noise and OCD since the age of 14. His mother also showed the same genomic mutation, but her clinical features were not available.

Conclusions: We have identified a possible novel heterozygous mutation of *SGCE* gene in one patient with TS and OCD. However, this finding should be verified further in a large scale patient population to determine its significance as a genetic cause of TS with OCD in Han Chinese ethnicity.

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The M129V polymorphism in the prion protein (PrP) gene in Wilson's disease (WD)–a reappraisal

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Objective: To reevaluate the significance of the M129V polymorphism in the PrP gene in WD.

Background: The normal PrP is best known for its involvement in prion diseases where the disease-associated form induces the normal PrP to change its conformation. Apart from that PrP has been suggested to play a role in copper metabolism or to act as genetic modifier in neurodegenerative diseases. Accordingly, in WD, a neurodegenerative disorder characterized by disturbed copper metabolism, the M129V polymorphism in the PrP gene has recently been

investigated by two independent groups. Grubenbrecher et al. found a more severe neurological phenotype in patients homozygous for the M allele (n=15) than in heterozygous patients (n=10). Merle et al. (n=134) found a significantly later age of onset in patients homozygous for the M allele when compared with patients carrying at least one V allele.

Methods: Here we investigated a large sample of 288 European patients with genetically confirmed WD with respect to the effect of the M129V polymorphism on the age of onset and the clinical symptoms at first manifestation (excluding 34 patients with a mixed phenotype).

Results: The age of onset (21.6±10.2 vs. 21.1±9.1 years, p=0.7) and the type of first manifestation (MM: 59 hepatic and 47 neurological/psychiatric vs. MV/VV: 70 hepatic and 78 neurological/psychiatric; p=0.19) were not significantly different between both groups.

Conclusions: Accordingly, our results argue against a strong effect of the M129V polymorphism on the phenotype and/or course of disease in WD.

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Latin American research consortium on the genetics of Parkinson's disease: LARGE-PD

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Objective: To create the first genetics consortium for Parkinson's disease (PD) in Latin America.

Background: Human genetics has proved to be a valuable tool for better understanding the molecular pathophysiology of PD. However, to date such studies have largely been limited to Asians (primarily from Japan) and individuals of European ancestry from Western Europe and North America. Current data indicate that the spectrum and frequency of both pathogenic mutations and common risk variants for PD vary greatly between Asian and European-derived populations, and even among some European subpopulations. If this pattern holds true across the world, a great deal of knowledge stands to be gained by conducting PD genetic analyses in understudied populations.

Methods: With funding from the Parkinson's Disease Foundation, we have established the "Latin American Research Consortium on the Genetics of Parkinson's Disease" (LARGE-PD). LARGE-PD is comprised of five sites at major academic institutions in Lima (Peru), Montevideo (Uruguay), Buenos Aires (Argentina), and Sao Paulo and Ribeirao Preto (Brazil). Over the first two years, a total of 1,750 PD patients and 1,650 controls will be recruited using uniform clinical diagnostic criteria. Detailed clinical, demographic, and environmental exposure data, and blood samples will be collected from each subject using standardized protocols. The coordinating center, located in Seattle, Washington, will maintain the Consortium database and DNA bank, and be responsible for quality control across all sites.

Conclusions: LARGE-PD will generate a unique resource that in future years will be used to seek novel susceptibility loci, characterize genotype-phenotype relationships and mutation distribution for known PD genes, and investigate gene x environment interactions in PD.

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Gait in healthy carriers and non-carriers of the LRRK2 G2019S mutation: Preliminary evidence of subtle pre clinical motor changes

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Objective: To compare gait features of healthy asymptomatic first degree relatives of Ashkenazi Parkinson's disease (PD) patients who are carriers (C) of the LRRK2 G2019s mutation to those of first degree relatives who are non-carriers (NC).

Background: The asymptomatic first degree relatives of Ashkenazi PD patients who carry the LRRK2 G2019s mutation represent a population at increased risk for developing PD. While previous work has identified pre-clinical changes in smell and autonomic function, gait has never been examined in those individuals.

Methods: 50 asymptomatic, first degree relatives of Ashkenazi, PD patients who are carriers of the LRRK2 G2019s mutation participated in this study. Gait speed and stride-to-stride variability (CV) were evaluated, prior to genetic testing, using an accelerometer placed on the lower back. Data was collected during 3 gait conditions: usual-walk, fast walk and during dual tasking (serial 7 subtractions).

Results: 25 subjects were carriers of the LRRK2 G2019s mutations. No significant differences between groups were observed in age (C: 53.6±11.8 yrs; NC: 50.1±8.1yrs; p=0.23), gender (C: 44%F; NC:56%F; p=0.39), height (C: 170.1±6.7; NC: 167.8±4.3; p=0.17) and cognitive function. There were no differences in any of the gait measures during usual-walk between the groups (p>0.15). Stride time variability (CV) was slightly higher (worse) during dual tasking condition in the mutation carriers group (1.82±1.04% vs.1.26±0.48%; p=0.021). Similar findings were observed during fast walking (C: 1.41±0.78; NC: 1.06±0.31; p=0.044). Spectral analysis confirmed these findings, demonstrating that the width of the dominant frequency mode in the locomotion band (0.5-3hz) was bigger (representing more variance) for the C (0.16±0.04 Hz) vs. the NC (0.14±0.2 Hz) groups (p=0.03) in both fast and dual task conditions.

Conclusions: This is the first study to report differences in gait between asymptomatic Carriers and Non-carriers of the G2019s mutation. The asymptomatic carriers group demonstrated higher variability of gait when challenged by dual tasking and fast walking supporting the idea that early pre-clinical symptoms are well compensated during routine activity but may appear under challenging situations.

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A pilot genome-wide association study of Ashkenazi Parkinson's disease patients

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Objective: We aimed to detect novel genomic regions, genes and genetic pathways associated with Parkinson's disease (PD) in the Ashkenazi patient's population.

Background: Although PD is a complex disorder, associated with multiple genetic, environmental and age-related risk factors, disease-associated mutations were surprisingly detected in more than a third of the Ashkenazi patients in the two major PD-associated genes, *LRRK2* and *GBA*. This population is therefore valuable for further genetic studies aimed to understand PD pathogenesis in the world population-at-large.

Methods: A pilot GWAS was performed using Affymetrix SNP6.0 Array (~900K SNPs). Four study groups were analyzed: Ashkenazi PD patients with either *LRRK2* G2019S (75 samples) or founder *GBA* mutations (93 samples), PD-patients without these mutations (130 samples) and age- and sex-matched controls (128 samples). Note, that the patient-population was enriched for *GBA* or *LRRK2* mutation carriers (56%), and did not represent the actual proportions of carriers in our entire cohort (34%).

Results: High quality data was obtained, with call rates >97.8% and Identity-by-Descent of up to 4% sharing in the study population. Analysis of all GWAS samples confirmed *LRRK2* and *GBA* as two

major loci associated with PD in Ashkenazi Jews. However, when a proportional population was randomly selected (191 PD-patients and 128 controls), SNPs in the *LRRK2* and *GBA* loci did not reach nominal significant level ($P<10^{-8}$). We performed a simulation, based on the distribution of these SNPs in the proportional population. We showed that significant ($P<10^{-8}$) *LRRK2* and *GBA*-linked SNPs can be detected in about 400 and 500 PD-patients, respectively, a much smaller populations than what recently used for GWAS analyses in Japan and in North-America and Europe. It is of interest that SNPs linked to *SNCA* gene were not near significance level. Additionally, GWAS comparing all PD-patients to controls detected novel candidate SNPs, including SNPs on chromosomes 14 and 20, which were not confirmed in a larger patient and control populations by real-time PCR.

Conclusions: Our results demonstrate the importance of the Ashkenazi PD-patients population for studying the complex genetic basis of PD, and that at least 3-4 fold larger Ashkenazi population is needed for informative GWAS.

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Analysis of LRRK2 S1647T as a risk factor for Parkinson's disease among Han-Chinese from mainland China

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Objective: To determine whether there were any associations between LRRK2 S1647T variant and Parkinson's disease (PD).

Background: Mutations in the LRRK2 gene are responsible for up to 13% of familial PD and for 1–2% of sporadic PD cases. Different mutation substitutions appear to be prevalent in different populations. G2019S appears to be more common among Ash-kenazi Jews and North African Arabs, but rare in Chinese. However the variant G2385R has been found more prevalent in Asian race, especially in Chinese. And the variant R1628P has been found as the second common genetic risk factor for PD in the ethnic Chinese population from Taiwan, Singapore and China.

Methods: A total of 628 patients from department of Neurology in West China Hospital enrolled our study, and 510 controls matched by age and gender were recruited from the same ethnic group. Genomic DNA was extracted from venous blood using standard protocols. And the association analysis of LRRK2 S1647T variant between PD and normal controls were performed with polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results: The frequency of the LRRK2 S1647T substitution in 628 patients with PD and 510 controls were analyzed. In the PD cohort, 314 patients (50.0%) were heterozygous and 72 (11.5%) were homozygous for the variant. This was significant higher than in the controls (42.9%, 11.6%) (Odds ratio=1.33, 95% Confidence interval, CI: 1.05-1.69, $P=0.018$). When compared the frequency of allele A and T, there was no significant association between patients with PD (36.5%) and controls (33.0%) (OR=1.16, 95% CI:0.98-1.38, $P=0.088$). Considering the age at onset, the frequency of this variant was a little higher in patients with early onset PD (EOPD, onset <50 years) than in controls (Odds ratio=1.46, 95% Confidence interval, CI: 1.02-2.10, $P=0.040$). But there was not any significant difference being found between patients with late onset PD (LOPD, onset ≥50 years) and controls (Odds ratio=1.29, 95% Confidence interval, CI: 1.00-1.66, $P=0.051$). In clinical presentation, we didn't find any difference between the S1647T variant carriers and non-carriers for onset age, onset symptoms, Hoehn and Yahr stage and UPDRS, either.

Conclusions: Our study indicates that the LRRK2 S1647T variant is a potential genetic risk factor for PD in the Han Chinese population from mainland China. However, we didn't find any associations between the clinical presentations in different genotypes.

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MAO-B G polymorphism influences time to onset of parkinsonian symptoms in male Parkinson's disease patients

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Objective: To assess the effect of MAO-B intron 13 polymorphism on age of onset of sporadic Parkinson's disease.

Background: The pathophysiology of sporadic Parkinson's disease remains unknown, but it seems to results from an interaction between environmental factors and genetics. Therefore, the study of genetic polymorphisms with biological plausibility is essential in understanding its determinants. MAO-B is an enzyme responsible for degrades dopamine and its gene is located in X chromossome and shows a G-A transition in intron 13. The G allele was associated with higher enzymatic activity.

Methods: Patients from Movement Disorders clinic of Hospital de Clnicas de Porto Alegrewith sporadic Parkinson's disease and age of onset beyond 45 years old were recruited. Blood samples were collected for DNA extraction. MAO-B gene was amplified by polymerase chain reaction and the product digested by Tsp45I endonuclease. Fragments were separated through electrophoresis in agarose.

Results: In 53 male patients the mean age of onset of symptoms was earlier in the group with G genotype (mean 58.23+/-3.5), compared with A genotype (mean 63.34+/-3.3; p=0.035). This effect was not demonstrable in 54 female patients.

Conclusions: Male patients with MAO-B G polymorphism have an earlier age of onset of parkinsonian symptoms. This could be explained by the fact that patients with MAO-B G genotypes degrade more dopamine than MAO-B A genotype.

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Val158Met COMT polymorphism is not associated with the presence of motor fluctuation or hallucination in Parkinson's disease

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Objective: To assess the effect of COMT Val158Met polymorphism in the presence of motor fluctuation and hallucination induced by levodopa.

Background: The use of levodopa in patients with sporadic Parkinson's disease is one of the most eficacious ways to relief disease symptons. However, its chronic intake can lead to some complications, as motor fluctuation and hallucination. The factors influencing the appearance of these complications are not well understood and it is reasonable to think that could be some genetic effect. COMT is an enzyme responsible for degrades dopamine and shows a functional polymorphism (Val158Met), that determines high and low activities.

Methods: Patients from Movement Disorders clinics of Porto Alegre and Rio de Janeiro (Brazil) with sporadic Parkinson's disease, age of onset beyond 45 years old and levodopa use for at least 2 years were recruited. Motor fluctuation was defined by patient or caretaker report of wearing-off or on-off phenomenon or by the use of levodopa four times a day or more. Hallucination was defined by patient or caretaker report. Blood samples were collected for DNA extraction. COMT gene was amplified by polymerase chain reaction and the product digested by NlaIII endonuclease. Fragments were separated through electrophoresis in acrilamide. Statystical analysis was made with logistic regression controlling for duration of disease and levodopa dosage.

Results: In 158 patients, there was no effect of COMT genotypes in development of motor fluctuations induced by levodopa (OR 2,16 CI 95% 0,8-5,8) nor in the presence of hallucinations (OR 3,35 CI95% 1-11,4).

Conclusions: Our study suggests that Val158Met COMT polymorphism is not associated with the presence of motor fluctuation or hallucination induced by levodopa. Larger samples are needed to define this lack of association.

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Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease

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Objective: To identify susceptibility variants for Parkinson's disease (PD).

Background: PD is a complex disorder caused by multiple genetic and environmental factors. Association studies have evaluated variants in many candidate genes for PD, but only a few genes, such as common variants of *alpha-synuclein* and rare mutations of *GBA*, have been identified as PD-susceptibility genes with genome-wide significance.

Methods: We performed a genome-wide association study (GWAS) and two replication studies in a total of 2,011 cases and 18,381 controls from Japan.

Results: We identified a new susceptibility locus on 1q32 ($P=1.52 \times 10^{-12}$) and designated this as *PARK16*, and we also identified *BST1* on 4p15 as a second new risk locus ($P=3.94 \times 10^{-9}$). We also detected strong associations at *alpha-synuclein* on 4q22 ($P=7.35 \times 10^{-17}$) and *LRRK2* on 12q12 ($P=2.72 \times 10^{-8}$), both of which are implicated in autosomal dominant forms of parkinsonism. By comparing results of a GWAS performed on individuals of European ancestry, we identified *PARK16*, *alpha-synuclein* and *LRRK2* as shared risk loci for PD and *BST1* and *MAPT* as loci showing population differences.

Conclusions: Our results identify two new PD susceptibility loci, show involvement of autosomal dominant parkinsonism loci in typical PD and suggest that population differences contribute to genetic heterogeneity in PD.

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Accumulation of 27-hydroxycholesterol in SPG5 patients may offer new therapeutical possibilities

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Objective: To describe the biochemical consequences of SPG5 mutations in oxysterol 7α-hydroxylase (CYP7B1) and identify possible starting points for therapeutic interventions.

Background: Patients with autosomal recessive Spastic Paraplegia SPG5 have mutations in the gene coding for oxysterol 7α-hydroxylase (CYP7B1), an enzyme involved in bile acid biosynthesis. One of the expected metabolic consequences of such mutations is accumulation of oxysterol substrates due to decreased enzyme activity.

Methods: Methods based on isotope dilution mass spectrometry were used to measure the levels of oxysterols in the circulation and in cerebrospinal fluid of four patients with SPG5. Levels of bile acids in the circulation were also measured.

Results: The four patients with SPG5 were found to have 6-9 fold increased plasma levels of 27-hydroxycholesterol. A much higher increase, 30-50 fold, was found in cerebrospinal fluid. The pattern of bile acids in serum was normal, suggesting a normal bile acid synthesis.

Conclusions: The findings are of interest in relation to two transgenic mouse models with increased levels of 27-hydroxycholesterol in the circulation but without neurological symptoms: the cyp27A1 transgenic mouse and the cyp7b1 knockout mouse. The absolute plasma levels of 27-hydroxycholesterol in the latter models are however only about 20% of those in SPG5 patients. If the accumulation of 27-hydroxycholesterol is an important pathogenetic factor, a reduction of its levels may reduce or prevent the neurological symptoms. Healthy subjects have been reported with levels of 27-hydroxycholesterol about 40% of those in the SPG5 patients. A possible strategy to achieve a reduction of the levels of 27-hydroxycholesterol in the SPG5 patients is suggested.

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Mutational screening of the coding regions of MEIS1 and BTBD9 in patients with restless legs syndrome

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Objective: To scrutinize RLS-associated genes for coding variants, which by exerting a stronger phenotypic effect than the previously identified single nucleotide polymorphisms (SNPs), could provide an important basis for assessing the genes' functional role in RLS.

Background: In genome-wide association studies, SNPs in or close to four genes—MEIS1, BTBD9, LBXCOR1, and PTPRD—could be linked to RLS. Yet, to date, only one potentially causal mutation leading to the occurrence of RLS has been reported and the pathophysiology behind the disease remains unclear.

Methods: We used Idaho Light Scanner technology® to screen 188 RLS patients known to harbor RLS risk alleles of either MEIS1 or BTBD9 (MEIS1: 72.8% female, mean age 60.0±11.2 yrs.; BTBD9: 74.2% female, mean age 59.7±11.0 yrs.) for aberrant melting patterns in the thirteen exons of MEIS1 or the ten exons of BTBD9, respectively. The exons of patients showing changes suggestive of variants were sequenced. Identified variants were subsequently genotyped in an independent sample of 735 RLS patients (70.8% female, mean age 61.5±14.2 yrs.) and 735 controls (74.5% female, mean age 59.8±11.3 yrs.).

Results: We identified four novel nucleotide substitutions in exons 3, 6, and 13 of MEIS1. In addition, one of the patients also showed the R272H mutation in exon 8, recently related to the RLS-phenotype in familial RLS. In the second sample, variants in exon 6 and 8 were only found in one RLS case each but not in controls while the variant in exon 3 was present only in 2 of the controls. No variants were found in any of the exons of BTBD9. One novel common intronic variant in BTBD9 was present in approximately 10% of RLS patients.

Conclusions: Exonic variants in MEIS1 or BTBD9 do not seem to be common in RLS. However, it cannot be excluded that rare exonic variants exerting a strong effect could play a causative role in bringing about the RLS phenotype in rare cases. While they may only represent a small fraction of cases, their study is important as they could provide significant clues towards understanding the underlying mechanism of disease. Further experiments to evaluate the impact of the novel variants upon the physiologic function of MEIS1 or BTBD9 will be performed.

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Pathway based genome wide association study on Parkinson and Alzheimer's disease reveals common pathway

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Objective: Application of pathway based approaches to find novel risk factors for Parkinson's disease.

Background: Genome wide association studies (GWAS) focus on single marker analysis. This approach has led to nominate SNPs/genes with strongest evidence of association, while paying little attention to the rest of the data. Pathway based methodologies jointly consider multiple SNPs or genes in the same pathway and may therefore complement the single marker test statistic approach to uncover

TABLE (889). *List of top hit pathways in combined and in stratified GWAS cohort*

Pathways	ES (Combined GWAS)	P-value	ES (US-GWAS)	P-Value	ES(German-GWAS)	P-value
Wnt-signaling	0.60	0.02	0.51	0.04	0.47	0.02
mTOR	0.47	0.02	0.38	0.05	0.47	0.03
Macromolecular complex disammebly	0.42	0.00001	0.37	0.03	0.34	0.69

ES: Enrichment Score.

the genetics of complex diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD).

Methods: A modified gene set enrichment algorithm (GSEA) was used to perform a pathway based analysis on GWAS data. This approach implicitly overcomes the problem of handling linkage disequilibrium (LD) between SNPs, multiple testing and an adjustment of different sizes of genes. We applied this approach on GWAS data (1713 cases and 3978 controls) ascertained from Germany and United States for PD.

Results: Our study highlighted the role of the WNT-signaling (p=0.02), mTOR-signaling (p=0.02) and macromolecular complex disammebly (p=0.000001) pathways in PD. These pathways remains significant after excluding top hits SNPs from our study, suggesting the role of these pathways are not influenced by top hit SNPs. Furthermore, we applied this approach on Alzheimer's disease (AD). Interestingly, WNT-signaling pathway again showed up as top most pathway. The WNT signaling pathway contains multiple genes, some of which are differentially expressed in whole genome expression profiling of isolated human substantia nigra neurons from patients with PD. Interestingly, cyclin-dependent kinases and proto-oncogenes such as c-MYC (MYC), one of the gene involved in the WNT-signaling pathway reported to be involved in neuronal cell death and cognitive decline: hallmark for neurodegenerative disorders such as AD and PD.

Conclusions: Our observation of a common pathway in two phenotypically distinct neurodegenerative diseases highlights the role of common mechanisms in these disorders. Our study, thus, suggests the importance of pathway–based approaches to decipher the etiology of complex neurodegenerative diseases.

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Studies of alpha-synuclein in brain samples from patients with Lewy body disorders carrying glucocerebrosidase mutations

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Objective: To evaluate the relationship between glucocerebrosidase (GBA) and alpha synuclein using brain samples from patients with synucleinopathies.

Background: Mutations in the gene encoding the lysosomal enzyme glucocerebrosidase (*GBA*) are an important risk factor for the development of Parkinson's disease and related disorders. This association is based upon the concurrence of parkinsonism and Gaucher disease, the identification of *GBA* mutations in cohorts with Parkinson's disease from centers around the world, and neuropathologic findings.

Methods: Brain samples from subjects carrying *GBA* mutations with a pathologic diagnosis of Parkinson's disease or Lewy body dementia were studied. All samples were screened for GBA mutations by sequencing. The cases were all sporadic, with a mean age of disease onset of 59 years (42-77).Immunofluorescence studies using confocal microscopy were performed on samples stained with antibodies to alpha synuclein, glucocerebrosidase and ubiquitin. Proteins were extracted fractionated into TBS-soluble, SDS-soluble and urea-soluble fractions, electrophoresed, and probed with antibody to alpha-synuclein.

Results: In brains from these subjects, immunofluorescence studies showed that glucocerebrosidase was present in both ubiquitinated and non-ubiquitinated Lewy bodies, and in Lewy neurites. Proteins were extracted from cerebral cortex from several subjects and compared to cases with the same pathologic diagnoses, but without *GBA* mutations. Some of the patients with *GBA* mutations and synucleinopathies exhibited aggregation of oligomeric forms of alpha-synuclein in the insoluble fraction, while others showed monomeric form of alpha-synuclein in the same fraction. Those with more extensive Lewy body pathology tended to have more of the oligomeric forms of alpha-synuclein.

Conclusions: In parkinsonism associated with *GBA* mutations, glucocerebrosidase is a component of synuclein positive intraneuronal inclusions. Furthermore, these patients show biochemical characteristics typical of Lewy body disorders. Unraveling the role of mutant glucocerebrosidase in the development of this pathology will further our understanding of pathways contributing to the aggregation and/or clearance of alpha-synuclein.

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Pathogenic mutations in ATP13A2 (PARK9) causing Kufor-Rakeb syndrome, a form of hereditary parkinsonism

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Objective: To determine the pathogenicity of mutations in the ATP13A2 (PARK9) gene in two family members with Kufor-Rakeb syndrome (KRS).

Background: Kufor-Rakeb syndrome (KRS) is a form of autosomal recessive juvenile or early-onset, levodopa responsive parkinsonism and has been associated with mutations in ATP13A2 (PARK9). ATP13A2 is a lysosomal type 5 P-type ATPase that has 10 transmembrane domains. The function of ATP13A2 is still largely unknown. To date, only 4 families with KRS have been reported to have mutations in the ATP13A2 gene.

Methods: We investigated the cellular effects of two novel mutations in the ATP13A2 at c.3176T>G (p.L1059R) and c.3253delC (p.L1085WfsX1088), that caused KRS in another family with two affected siblings. We over-expressed V5 or GFP-tagged wild-type and mutant PARK9 in vitro. We performed confocal microscopy to determine the localization of wild-type and mutant species.

Results: When expressed in mammalian cells, wild-type PARK9 localised to the lysosomal membrane whereas both mutant PARK9 constructs were found to be retained in the endoplasmic reticulum. Mutant PARK9 was degraded by the proteasomal but not the lysosomal pathways.

Conclusions: These findings indicate that these PARK9 mutations are indeed pathogenic and further support the notion that alterations in the proteasomal pathways contribute to the aetiology of Parkinson's disease.

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Multiple sclerosis (MS) and Parkinson's disease (PD) in a patient with the LRRK2 variant E334K

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Objective: To report a rare case of MS and PD co-occurrence.

Background: Co-occurrence of MS and PD in a same patient is rare and has never been described in a familial setting of PD.

Methods: Clinical file review and molecular biology of LRRK2 gene.

Results: A 54-year-old woman suffered from relapsing remitting multiple sclerosis (MS) since age 24 which eventually became secondary progressive. MS was clinically and MRI defined. Finally, a right-sided bradykinetic-rigid syndrome with rest tremor appeared at age 46. Motor symptoms were fully responsive to levodopa. Dopamine transporter SPECT imaging (DAT scan) demonstrated a bilateral putaminal loss of tracer binding which was more marked on the left. Brain MRI did not disclose any basal ganglia lesions. Her family history was remarkable for the diagnosis of PD in her father and paternal aunt. Molecular analysis showed a variant of the LRRK2 gene (E334K).

Conclusions: In this case report, there was a co-occurrence of PD and MS, a situation rarely reported in the literature. According to the clinical presentation with fully levodopa responsive parkinsonism and the results of imaging, there were no arguments to believe that MS was the cause of parkinsonism. Indeed, the association may be fortuitous. However, the family history and the finding of a LRRK2 variant are more than intriguing. Although this LRRK2 variant has not yet been described as causative of PD with certainty, it is of interest to note that LRRK2 and its protein dardarin are expressed in both, neurones and oligodendocytes. This raises the question whether a disrupted expression of LRRK2 in neurons and oligodendrocytes could have favoured the appearance of both diseases in our patient.

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A new family with apparently dominant inheritance of PARK2

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Objective: To describe a family with apparently dominant inheritance of PARK2.

Background: Pseudo-autosomal dominant inheritance of parkin gene mutations is uncommon.

Methods: Direct sequencing of the 12 exons of the parkin gene and semi-quantitative exon dosage by multiplex ligation-dependent probe amplification.

Results: A 34 y old male of indo-vietnamese-french ancestry without known consanguinity presented at age 16 intermittent resting tremor and dystonia of the left leg, followed by a slowly progressive asymmetric left-sided, dopa-responsive akineto-rigid syndrome. Beside motor signs, disease progression was also remarkable for the occurrence of psychiatric disorders, mainly manic and depressive episodes and a dopamine dysregulation syndrome. He had 2 siblings, a brother aged 37 who presented a strikingly similar history, also beginning at age 16, including depression and a dopamine dysregulation syndrome. DaTSCAN SPECT revealed bilateral severe putaminal denervation in both. The younger sister aged 25 presented since age of 19 a mild postural tremor of both arms with little progression. DaTSCAN SPECT revealed mild bilateral putaminal denervation. The mother presented since the age of 38 an intermittent resting tremor and dystonia of the left leg. There was little progression with onset of mild akinesia of the left lower limb at age 50. DaTSCAN SPECT revealed marked putaminal denervation. The father was asymptomatic. Sequencing of the parkin gene revealed the presence of compound heterozygous mutations (C-673delG/exon 5 deletion) in the 2 brothers. The mother had the heterozygote deletion of exon 5 and the father the exon 6 C-673delG mutation. The molecular analysis in the sister is underway.

Conclusions: This family is remarkable for the apparently dominant inheritance, which is uncommon in PARK2 without consanguinity. This strengthen the fact that apparent dominant inheritance should not exclude PARK2. Interestingly, the mother with a mild phenotype had an heterozygote exon 5 deletion and a denervation on a DaTSCAN SPECT, while the father with the exon 6 mutation was asymptomatic. However the screening for another mutation in the normal allele in the mother is mandatory to conclude upon the pathogenic effect of the exon 5 deletion and the mode of tinheritance of the disease.

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^{123}I-MIBG cardiac uptake and smell identification in patients with LRRK2 mutations

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Objective: To study the ^{123}I- metaiodobenzylguanidine (MIBG) cardiac uptake and smell in patients with Parkinson's disease carrying LRRK2 mutations (LRRK2).

Background: ^{123}I-MIBG cardiac reduced uptake and impaired odor identification are markers of neurodegenerative diseases in which Lewy bodies (LB) are the pathological hallmark such as IPD. LRRK2 patients present with a clinical syndrome indistinguishable from IPD, but the pathological substrate is diverse and LB have not been found in some cases.

Methods: We studied 14 LRRK2 patients, 14 IPD patients matched by age, gender, disease duration and severity and 13 age and gender matched control subjects. All subjects signed an informed consent. Patients with heart diseases, diabetes mellitus or receiving medications interfering with MIBG uptake were excluded. All patients were assessed through the Unified Parkinson's Disease Rating Scale (UPDRS). Olfaction was analyzed through the University of Pennsylvania Smell Identification Test (UPSIT). ^{123}I-MIBG cardiac uptake was evaluated through the late heart-to-mediastinal ratio (H/M4h). For statistical analyses we used the ANOVA test with the Bonferroni correction and Pearson correlation coefficient.

Results: The H/M4h was (mean$\pm$standard error) 1.42$\pm$0.06 for LRRK2 patients, 1.19$\pm$0.06 for IPD patients, and 1.65$\pm$0.06 for control subjects. LRRK2 patients presented lower ^{123}I-MIBG cardiac uptake than controls ($p=0.02$) and higher uptake than IPD patients ($p=0.01$). UPSIT mean scores were 21.5$\pm$7.3 for LRRK2, 18.7$\pm$6.2 for IPD, and 29.7$\pm$5.7 for control subjects. UPSIT score was lower in both LRRK2 and IPD than in controls ($p<0.01$). In IPD patients both smell and ^{123}I-MIBG uptake were correspondingly impaired. In LRRK2, a positive correlation was found between ^{123}I-MIBG and the UPSIT scores, ($R=0.801$, $p<0.001$).

Conclusions: In LRRK2 patients, ^{123}I-MIBG cardiac uptake was found to be abnormal but significantly less impaired than in IPD and a positive correlation between ^{123}I-MIBG cardiac uptake and UPSIT scores was observed. As ^{123}I-MIBG cardiac reduced uptake and impaired odor identification are markers of LB pathology, the findings of the present study could be attributed to neuropathological heterogeneity among LRRK2 patients.

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More evidence of population specificity of LRRK2 G2019S mutation

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Objective: To analyze the frequency of LRRK2 G2019S mutation in sporadic and familial cases of Parkinson's disease (PD) and normal controls of common ethnicity from South India.

Background: The frequency of leucine-rich repeat kinase 2 (LRRK2) G2019S mutation, the most common genetic cause of Parkinson's disease (PD), shows significant variation based on ethnicity. Earlier reports suggest a very low frequency of this mutation in Asians.

Methods: We used direct sequencing technique of all DNA samples in a movement disorder clinic-based study of sporadic ($n=100$) and familial PD patients ($n=86$ index cases) and normal controls ($n=100$) of common ethnicity from South India.

Results: None among the patients or controls had the G2019S mutation.

Conclusions: The founding events which influenced a number of other populations/ethnicities have no impact on the genetic make up of PD patients from South India. Our findings support the current view that G2019S- associated PD may be population-specific. This

has implications in genetic testing for PD and selection of subjects for potential future gene-based therapeutic trials for G2019S carriers in such populations.

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Shared genetic susceptibility in primary and secondary restless legs syndrome: A case-control association study in end-stage renal disease patients

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Objective: To analyse the contribution of the primary RLS (pRLS) risk factors to uremic RLS (uRLS) in a case-control association study in ESRD patients.

Background: There are two forms of the restless legs syndrome (RLS), pRLS and secondary RLS. The most common form of secondary RLS is uRLS in end-stage renal disease (ESRD). In recent genome-wide association studies (GWAs) we have identified variants (MEIS1, BTBD9, PTPRD, and MAP2K5/LBXCOR1) as risk factors for familial and sporadic pRLS. It is not known if the same genetic variants are implicated in uRLS.

Methods: A total of 642 ESRD patients were scrutinized for symptoms of RLS in face-to-face interviews. 199 were classified as RLS-positive cases (38 familial, 161 sporadic), 443 as RLS-negative controls. We genotyped 10 pRLS-associated SNPs in these groups using the Sequenom iPLEX technology. Statistical analysis was performed using logistic regression with age and sex as covariates.

Results: Basic dialysis parameters of both groups did not differ significantly (duration of dependence on dialysis, $P>0.09$; average time on dialysis per week, $P>0.7$). After correction for multiple testing, MEIS1 (rs12469063, Pcorr=0.006) and BTBD9 (rs3923809, Pcorr=0.002), were associated with uRLS. SNPs in PTPRD and MAP2K5/LBXCOR1 did not show any association ($P>0.15$) with uRLS.

Conclusions: These results support the concept of a partially overlapping genetic predisposition mechanism in pRLS and uRLS.

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Spectrum of clinical features in two sisters with early-onset Parkinson's disease (EOPD) and identical mutations in parkin gene

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Objective: To report phenotypic heterogeneity in two sisters with identical parkin mutations.

Background: Parkin mutations account for the majority of familial and sporadic EOPD and juvenile-onset PD cases. More than 100 mutations have been described in the parkin gene. parkinsonism associated with parkin mutations generally has symmetric involvement and dystonia at onset, a good response to levodopa therapy and levodopa-induced dyskinesias during treatment. Phenotypic heterogeneity from identical mutations in the parkin gene has rarely been reported.

Methods: We reviewed the medical records, sequenced all exons of the parkin gene, and screened for exon deletions and duplications by semiquantitative multiplex polymerase chain reaction in both cases.

Results: Here we report a pair of sisters with EOPD, who have an identical homozygous Exon 3 deletion of 40 bp (c.438-477) and a heterozygous Exon 4 deletion. They lived in the same living environment throughout their lives, but had a strikingly different clinical course. One sister began with left leg dragging and right hand tremor at age 39. Her symptoms are well controlled after 22 years of PD on less than 400mg of levodopa daily, without motor fluctuations, dysautonomia or psychosis except for restless legs syndrome. The other sister began with left hand tremor at age 38 but developed severe motor fluctuations after 14 years of PD, with very short duration of "on", severe "off"s and psychosis taking 1400mg of levodopa daily. She eventually required bilateral STN DBS after 16 years of PD.

Conclusions: These cases suggest that marked phenotypic heterogeneity can be seen with identical parkin mutations. We cannot tell whether genetic variation, environmental factors or both account for this heterogeneity.

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Case-control study of the *UCH-L1* S18Y variant in sporadic Parkinson's disease in Chinese population

X.-X. Yan, L. Wang, J.-F. Guo, L.-L. Nie, B.-S. Tang (Changsha, Hunan, China)

Objective: The aim of this paper was to report the association of this polymorphism in Chinese patients with sporadic PD and controls.

Background: The ubiquitin carboxy-terminal hydrolase L1 gene (*UCH-L1*) has been implicated in the aetiology of Parkinson's disease (PD). A S18Y (C54A) polymorphism in exon 3 of *UCH-L1* gene was found to be protective in PD patients compared to controls in several studies.

Methods: PCR-restriction fragment length polymorphism analysis was performed in 408 PD patients and 398 healthy controls.

Results: For the S18Y variant, there was no significant difference either in the individual allele or genotype frequencies between cases and control subjects. Possession of the S18Y variant did not alter risk of developing PD (OR=0.827, 95%CI=0.596-1.147). In addition, there was no significant difference between S18Y genotypes or allele frequencies in stratification of the patient group for early-onset or late-onset PD.

Conclusions: The S18Y polymorphism may not have protective effect in Chinese population.

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Coincidence of two novel *SPG11* genemutations in Korean patient causing atypical hereditary spastic paraplegia with thin corpus callosum

B.-K. Kim, J.Y. Ahn, W.T. Yoon, W.Y. Lee, H.-T. Kim (Seoul, Republic of Korea)

Objective: Our aim is to report an atypical phenotype of hereditary spastic paraplegia with thin corpus callosum (HSP-TCC) with two novel spastic paraplegia-11 (*SPG11*) gene mutations.

Background: HSP-TCC is one of the most common complicated forms of autosomal recessive hereditary spastic paraplegia (HSP). Clinical feature of HSP-TCC is characterized by slowly progressive spastic paraparesis, mental retardation or deterioration and thin corpus callosum. Some patients show also dysarthria, dysphagia and upper limb spasticity, urinary incontinence, sensory deficits in the lower limbs and distal amyotrophy, seizure and cerebellar ataxia. Mutation of *SPG11* gene in chromosome 15q21 was recently found to be a major cause of this variant form of HSP, which encodes the spatacin protein of unknown function.

Methods: Single case report and description of genetic analysis about novel *SPG11* mutations.

Results: A 22-year-old man referred to us with aggravated gait disturbance and both leg weakness one years ago. His spastic gait problem occurred 9 year ago and slowly progressed, but his cognitive function and social activity was normal. His neurological examination revealed not only both lower limb weakness and spasticity, but also both foot drop and leg muscle atrophy. Brain magnetic resonance images (MRI) showed neuroradiologically distinctive thinning of the corpus callosum. Genetic studies revealed two compound heterozygous mutations (c.168delC/p.Leu57X and c.733_734delAT/p.Met245ValfsX2) in *SPG11* gene. Further genetic studies from all family confirmed that these novel mutations respectively were inherited from his parents who could be identified as asymptomatic carriers.

Conclusions: For now, we report the atypical HSP-TCC with two novel gene mutations presenting progressive spastic paraparesis, both foot drop and lower limb atrophy without cognitive impairment.

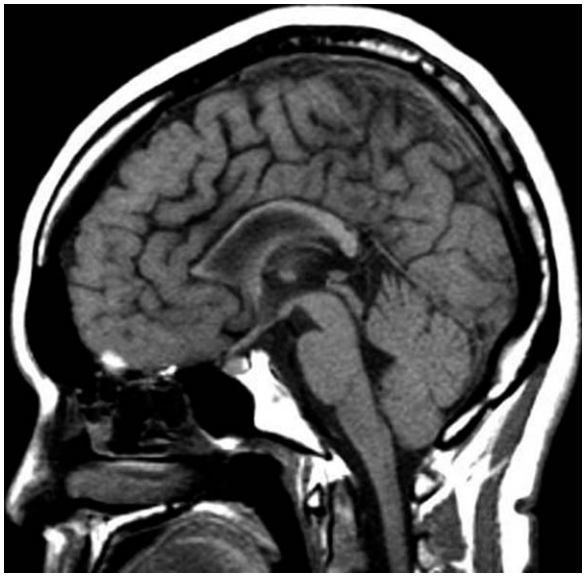

FIG. 1 (899).

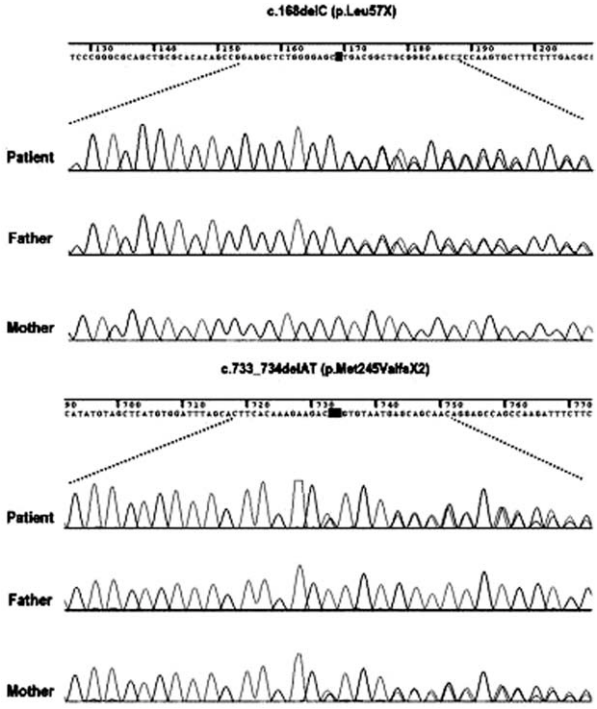

FIG. 2 (899).

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SNP rs7684318 of the α-synuclein gene is associated with Parkinson's disease in Chinese Han population

L. Yu, X. He, F. Hu, P. Xu, Z. Lin, M. Zhu, Z. Liu, L. He, Y. Xu (Chengdu, Sichuan Province, China)

Objective: To investigate the association between the SNP rs7684318 and Parkinson's disease in Chinese Han population.

Background: Mutations in the α-synuclein (SNCA) gene have been shown to be responsible for a rare familial form of Parkinson's disease (PD). Furthermore, polymorphic variants in multiple regions of the gene have been associated with susceptibility to idiopathic PD in different populations. Previous studies in Japanese have found strong association between the single nucleotide polymorphism (SNP) rs7684318 (which is located within an intron of the SNCA gene) and idiopathic PD. Our aim was to verify these findings and to determine the nature of the association in a subset of our PD patients.

Methods: A case-control study of the SNP rs7684318, comprising 332 PD patients and 300 healthy controls, was carried out in Chinese Han populations from two separate centers of mainland Chins. SNP rs7684318 polymorphism was determined by PCR-Restriction Fragment Length Polymorphism (PCR-RELP) analysis.

Results: The SNP rs7684318 of the SNCA gene showed great evidence for an association with PD (P=0.00). There were no differences in the mean age at onset or gender between the rs7684318 carriers and the non-carriers in PD patients.

Conclusions: Our findings suggest that SNP rs7684318 (T>C) transition of the SNCA gene contributes to PD susceptibility in Chinese Han population.

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The phenotypic spectrum of neurodegeneration associated to PLA2G6 mutations

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Objective: To report the phenotypic spectrum of neurodegeneration associated to mutations in the *PLA2G6* gene.

Background: Mutations in the *PLA2G6* gene have been identified in patients with typical and atypical Infantile neuroaxonal dystrophy (INAD), neurodegeneration with iron brain accumulation (NBIA), Karak syndrome, and dystonia-parkinsonism, demonstrating that the phenotypic spectrum is far to be precisely characterized.

Methods: Clinical, radiological and genetic features of 15 patients carrying mutations in the PLA2G6 gene were reviewed.

Results: Twelve patients displayed the clinical features of classical INAD. All presented with psychomotor regression within the second year of life, with rapid neurological deterioration. MRI disclosed in all cerebellar atrophy with high signal intensity of the cerebellar in most; increased iron deposition in the pallida was present in 3. Three patients had a different and less homogeneous phenotype. Disease onset during infancy or adolescence with predominant ataxia (pts. 13 and 14) or parkinsonism (pt. 15) associated to cognitive impairment. Dystonia, myoclonus and epilepsy appeared later in two patients. MRI disclosed in all increased iron deposition in the pallida, giving reason for the inclusion of these patients among the NBIA.

Conclusions: PLA2G6 associated neurodegeneration displays a wide range of phenotypes.

POSTER SESSION 4
THURSDAY, JUNE 17, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-16:00
Authors Present: 13:30-15:00

HISTORY

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Lauri Laitinen and the contributions of the Swedish school of Umeå to functional neurosurgery

P. Blomstedt, J. Linder, L. Forsgren, G.-M. Hariz, T. Bergenheim, M.I. Hariz (Umea, Sweden)

Objective: To present the contributions of Lauri Laitinen to surgical treatment of Parkinson's disease (PD).

Background: Lauri Laitinen who died on November 9, 2005, was one of the pioneers of functional and stereotactic neurosurgery.

Methods: We review here some of his contributions to surgical treatment of PD and their impact on today's surgical practice.

Results: After fellowships in Freiburg with Mundinger, in Paris with Talairach, and in London with Gerald Stern and Sid Watkins, Laitinen designed in 1971 his own stereotactic frame which combined the arc-centered principle of the Leksell frame with the base-ring design of the Riechert-Mundinger frame. After performing hundreds of thalamotomies and subthalamotomies, he devised in the mid-80ies the first device to adapt the emerging imaging modalities (CT and MRI) to stereotactic imaging in functional stereotaxis, avoiding thus the use of ventriculography. At the same time, Laitinen re-vitailized Leksell's posteroventral (PV) pallidotomy of the firfties, and demonstrated its effect on symptoms of post-levodopa PD, well before the Alexander-Delong basal ganglia model was known. Laitinen's seminal paper on pallidotomy from January 1992 (J Neurosurg, 1992) marked the renaissance of surgery for PD and was the most quoted single paper in the functional neurosurgical literature. Laitinen was also clinically and academically active in non-surgical management of PD, something that is today very uncommon for a neurosurgeon. He published studies such as "Desipramine in treatment of Parkinson's disease. A placebo-controlled study" (Acta Neurochir,1969) and "Effect of amantadine on some psychomotor performances in parkinsonism. A double blind study" (Ann Clin Res, 1971).

Conclusions: Even though DBS of the STN is now the main surgical procedure for PD, the work of Laitinen has greatly contributed to establishing the posteroventral pallidum as a safe and efficient surgical target for Levodopa-induced dyskinesias and for dystonias.

903

A historical case of Hallervorden-Spatz disease

P. Cras, A. Van Craenenbroeck, M. Gebruers, J.-J. Martin (Edegem, Antwerpen, Belgium)

Objective: To explore the nosology of Hallervorden-Spatz disease by reviewing a historical case filmed by Ludo Van Bogaert in 1936.

Background: In 1936, a case of Hallervorden-Spatz disease (HSD) was reported by Ludo van Bogaert, a famous Belgian neurologist and Clovis Vincent, a distinguished French neurologist. Ludo van Bogaert (1897-1989) spent a great part of his life studying neurologic disorders. He often filmed patients with movement disorders, resulting in an extensive collection of 35mm and 16mm films. Presently, all the original articles, neuropathological samples and films are preserved in the Born Bunge Institute in Antwerp (Belgium).

Methods: Review of a 35mm film, detailed study of the case history and review of early publications on HSD. Exploration of the historical data on the role of Hallervorden and Spatz in wartime neurology and their relationship with Ludo Van Bogaert.

Results: The film illustrates the clinical condition of the patient in 1923, 12 years after the onset of symptoms. The patient is 21 years old at the time of filming. Textual description and images of the patient alternate in the film fragment. Moreover, the main clinical features, in case disturbances of balance and gait in presence of preserved proprioception, club feet, spasm of the limb muscles, spasm of mouth and the orbicular eye muscles and dystonia, have been strikingly put on the screen.

Conclusions: Genetic testing revealed that in the majority of cases of HSD a missense mutation in the pantothenate kinase gene PANK2 could be found. A classification of the new designation 'pantothenate kinase associated neurodegeneration' (PKAN) was then made according to the clinical presentation. In general, a reason to use an eponym is to honour the pioneers of the disease recognition. Although Hallervorden and Spatz described the disease already in 1922, given the war record of Hallervorden it seems inappropriate to convey him honour aby using the eponym. Ludo van Bogaert had a good relationship with Hallervorden and Spatz. Thanks to the efforts of Spatz, who was stationed in Antwerp during World War II, the Born Bunge Institute could continue to function in wartime. Van Bogaert had faced criticism already during his life concerning his relations with German colleagues. Indeed, in the years after the war Ludo Van Bogaert remained loyal to Spatz as well as to Hallervorden.

904

Dystonia and art

P.J. Garcia Ruiz, J.C. Martinez Castrillo (Madrid, Spain)

Objective: To review descriptions of dystonia in Art across the History.

Background: Dystonia has a recent History in Medicine. Focal dystonia was described by Gowers in 1888 and Thompson in 1896; generalized dystonia was described at the turn of the century by Oppenheimer. However, it is possible to find precise descriptions of dystonia in Art, even centuries before the "official" definition.

Methods: We have classified those pieces of art that could represent descriptions of dystonia.

Results: In classic times, the first reference to abnormal posture can be tracked back to the New Empire of Egypt (equinus foot), not to mention some recently described examples of dystonia from the Moche sculptures in Peru. In Medieval times it is possible to find many examples of sculptures in European Cathedrals representing peasants with dramatic dystonic postures that coexist with amputation of limbs. This unique combination of dystonia and limb amputation probably represents ergotism, very frequent in middle ages (see figure). Literature is also a source of precise pre-neurological descriptions; in David Copperfield, Dickens depicts characters with generalized dystonia (Uriah Heep); cervical dystonia (Mr Sharp) and even spasmodic dysphonia (Mr Creakle). Finally, even in modern Art, dramatic descriptions can be found, such as painful cervical dystonia ("Suffering" from Brancusi).

Conclusions: Art is a source of Neurological information, including primary and secondary dystonia.

FIG. 1 (904).

905

FMR1 gene expansion may be associated with DAT/SPECT SWEDD in parkinsonism patients

D.A. Hall, D. Jennings, J. Seibyl, F. Tassone, K. Marek (Chicago, Illinois, USA)

Objective: To determine if patients with parkinsonism and *fragile X mental retardation 1 (FMR1)* gene expansions have a striatal dopamine deficit similar to Parkinson's disease (PD) patients.

TABLE (905). *Clinical findings of the cases*

Age, y	66	68	46
Age at onset, y	56	64	45
Gender	F	F	M
Clinical features	Head tremor, right hand rest tremor, kinetic tremor, orthostatic tremor, rigidity, bradykinesia	Head tremor, left hand rest tremor, kinetic tremor, bradykinesia, retropulsion, tandem difficulties	Head tremor, rest tremor, kinetic tremor, blepharospasm, bradykinesia, rigidity, facial masking, slowed gait initiation
Family history	Cousin with hand tremor	2 siblings with PD	5 relatives with tremor and/or balance problems, niece and nephew with learning difficulties
Response to dopaminergic meds	Positive	Positive with motor fluctuations	Positive
UPDRS (motor) score	11	13	11
UPSIT	22	30	36
FMR1 repeat	41, 23	51, 21	60
MRI	Nonspecific white matter hyperintensities	Nonspecific white matter hyperintensities	Normal

Background: Individuals with *FMR1* premutation range expansions (55-200 CGG repeats) are at risk to develop the fragile X-associated tremor/ataxia syndrome (FXTAS), which is characterized by kinetic tremor, ataxia, parkinsonism, autonomic dysfunction, peripheral neuropathy, and cognitive decline. In addition, some premutation carriers have a PD phenotype. Gray zone expansions (41-54 CGG repeats) in the *FMR1* gene have recently been associated with parkinsonism in females. PD patients with scans without evidence of dopaminergic deficits (SWEDD) were identified in several clinical trials enrolling early PD subjects. In some of these parkinsonism cases, there is no explanation to account for the lack of dopamine transporter (DAT) deficit on imaging.

Methods: The authors studied three patients with parkinsonism carrying small expansions in the *FMR1* gene (41-60 CGG) with [^{123}I]b-CIT SPECT imaging and compared the imaging to a preexisting healthy subject database.

Results: In our patients with small *FMR1* repeat expansions (41-60 CGG repeats), parkinsonism was mild to moderate. The patients had been diagnosed with PD and had a positive response to dopaminergic medications, despite having features atypical for PD, to include kinetic tremor or tandem difficulties. None of the patients met criteria for FXTAS. The striatal uptake of [^{123}I] ß-CIT was normal in all three patients.

Conclusions: These results suggest that parkinsonism in some carriers of *FMR1* gray or premutation repeat expansions is not associated with a presynaptic dopamine receptor deficit like that commonly seen in PD. In a prior study, [^{123}I]FP-CIT SPECT imaging was done in four *FMR1* premutation carriers (73-105 CGG repeats) with clinical parkinsonism and showed normal uptake. In contrast, our patients had lower CGG repeat sizes and better response to dopaminergic medications. Our results suggest that parkinsonism associated with smaller *FMR1* expansions may be related to mechanisms other than presynaptic dopaminergic changes and may represent a potential explanation for at least some parkinsonian cases with scans without evidence of dopaminergic deficits (SWEDD).

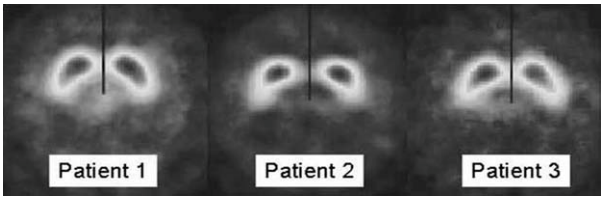

FIG. 1 (905).

906

Movement disorders in the works of Charles Dickens

A. Lavrov, O.S. Levin (Maidenhead, United Kingdom)

Objective: To review descriptions of movement disorders in Dickens' characters and to assess these against current manifestations and diagnostic criteria.

Background: It is well recognized that Charles Dickens depicted characters in his works with characteristic presentations of medical conditions, including neurological. Whereas his portrayal of Pickwickian syndrome is well-known, less attention has been paid to characterizations of movement disorders.

Methods: We reviewed Dickens's original texts and the literature on the subject.

Results: Dickens' books contain vivid images of movement disorders that are highly likely to be consistent with Parkinson's disease (Frederick Dorrit, "Little Dorrit"), Lewy Body Dementia (Ebenezer Scrooge, "A Christmas Carol") as well as Progressive Supranuclear Palsy (an old man from "Lazy tour of two idle apprentices"). Description of the latter was remarkably detailed, and closely resembled Richardson's syndrome. Some characters also appear to suffer from various dystonias and dyskinesias, namely cervical dystonia (Jeremy Flintwinch, "Little Dorrit"), spasmodic dysphonia (Mr Creakle, "The personal history of David Copperfield") and, possibly, generalized dystonia (Uriah Heep, "The personal history of David Copperfield"). Moreover, motor phenomena matching Tourette syndrome (Mr Panks, "Little Dorrit"), essential tremor (Mrs Skewton, "Dealings with the firm of Dombey and Son: wholesale, retail and for exportation") and posttraumatic tremor (Mrs Gargery, "Great expectations," as well as restless legs syndrome (sleepy waiter, "The personal history of David Copperfield") are also present. Additionally his works also described palatal myoclonus in the convict in "Great expectations" and also a condition resembling X-linked dystonia-parkinsonism syndrome (Lubag syndrome) in Miss Tox from "Dealings with the firm of Dombey and Son: wholesale, retail and for exportation". It is also noteworthy that descriptions of Tourette syndrome (1855) and Progressive Supranuclear Palsy (1857) predate considerably the first "formal" medical publications which appeared in 1885 and 1964, respectively.

Conclusions: Dickensian works provide a wealth of excellent representations of movement disorders which are highly illustrative even in our era of advanced diagnostic technology.

907

To review the interesting history of restless legs syndrome

A.Q. Rana (Toronto, Ontario, Canada)

Objective: To discuss the interesting aspects of history of restless legs syndrome.

Background: Restless leg syndrome (RLS) is characterized by an unpleasant sensations in the limbs described as crawling, creeping, tingling, cramping, pulling, pain or electric tension, or discomfort or itching with an uncontrollable urge to move legs. The symptoms mostly occur at rest and are relieved by walking. These symptoms are worse at night and interfere falling sleep. Although there has been a increasing awareness about this disorder in last decade or so but RLS has been known in human history for centuries.

Methods: We reviewed all available resources including web, textbook chapters and pubmed, medline to study how long RLS has been known in human history.

Results: RLS has been described in the medical literature for over 300 years. The first description of RLS was by Thomas Willis in 1672. In 1685 in his text book he wrote, "Wherefore to some, when being in bed they betake themselves to sleep, presently in the arms and legs. Leaping and contractions of the tendons and so great a restlessness and tossing of the members ensure, that the diseased are no more able to sleep, than if they were in the place of the greatest torture." Wittmaack in 1861 described a similar condition which he called "anxiety tibiarum". He attributed this as a very frequent symptom of hysteric neurosis. Oppenheim described it as neurological condition and he was the first to recognize the genetic component of this disease. Karl Ekbom in 1945 also described this condition. He divided it in to two forms, the one with prominent paresthesia, "asthenia crurum paresthetica," and the other form presenting mainly with prominent pain, "asthenia crurum dolorosa." The most recent criteria for RLS diagnosis has been described by Arthur Walters and colleagues.

Conclusions: Like most movement disorders, RLS has been known in human history for centuries. With time various aspects of this condition are coming to our attention.

908

Lumpers and splitters: Lessons from pellagra

A.C. Williams (Birmingham, United Kingdom)

Objective: Clinical and etiological classification of diseases such as parkinsonism and dementia conflict lumpers (neurodegenerative & multifactorial) and hair-splitters (an infinity of parkinsonisms & genetic/toxic/infectious causes). It is instructive to remember the discussions at the time of the now cured disease, Pellagra.

Background: Pellagra is now known as a dietary deficiency disease due to a lack of nicotinamide causing bioenergetic and metabolic disarray. 100 years ago the phenotypic manifestations spanned organs with many neurological manifestations including parkinsonism. Strong views were held that the condition was genetic and there were infectious lobbies. Most ideas including mitochondrial/redox theories in retrospect have an element of truth including a "lumpers" view that the condition was due to premature ageing.

Methods: Review Pellagra.

Results: Familial cases were common and genetic predispositions and epigenetic effects likely. Infections in gut and skin including TB were the rule and may be symbiotic producing nicotinamide/NADH for the host. Lack of NAD(P)(H) made it a mitochondrial and redox and free radical mediated disorder. Lack of NAD to supply SIRT/PARP axes now explains why it was noted to be a (DNA) repair and premature ageing phenomenon and loss of ATP would affect protein homeostasis explaining the amyloidosis. Clinically there was remarkable diversity with no two patients the same: many were undiagnosed as symptoms could be non-specific. Parkinsonism was common and included autonomic features reminiscent of non-motor manifestations. Dementias were well described with features of AD, Frontotemporal, Vascular and Lewy body type with many with combined features.

Conclusions: Splitters were not wrong however Lumpers prevailed as a single dietary intervention solved the problem. Overarching ageing and bioenergetic theory that follows energy and informatic fluxes and NAD/NADH ratios from the outside through mitochondria and metabolism to gene expresssion and neuronal function down to dendritic spine synapses and back to the environment as behaviour (noting some homeostatic responses such as autophagy and reversions to fermentations in inflammatory and proliferative tissue that improve local energy landscapes) may be a way forward. Low or high NADH energy flows varying over a lifetime or between generations if extreme and involving early "trade-offs" may explain many apparently separate diseases and ageing in general.

909

Homeostatic breakdowns cause diseases including movement and intellectual disorders: Historical sketch to a systems approach

A. Williams, B. Simpson, J. Mitchell (Birmingham, United Kingdom)

Objective: Loss of homeostasis causes disease (triggered by environmental extremes or genetic perturbations) including the Movement disorders so we elaborate on the history of thought on this subject.

Background: Systems involved in homeostasis are co-ordinated by brains attempting to ensure energy and informatic balances whatever the present and future ecological circumstances.

Methods: Historical Review.

Results: Claude Bernard and Walter Cannon equated homeostasis with the "Wisdom of the Body". Brown-Sequard, Cushing, and Starling elaborated on hormonal responses to "fight or flight" stress paths. Sampson-Wright, Selve and Harris integrated the neurohormonal axis that through cortisol and other messengers influences the immune, limbic and hippocampal system. Appetite and foraging are integrated by related circuitry ensuring the energy supply, aided by immune tolerance and gut and genomic symbiotic activity. Symbionts and diet are co-evolved communicating through food "hormones"/vitamins such as Nicotinamide, whose metabolite NAD carries the hydrogen based energy. Organisms live in co-evolved biotic (symbiont, predator/prey and social networks) and abiotic constructed microenvironments and create inner microenvironments that epigenetically define differentiation and division of labour between different organs and cell types. Survival of the whole "superorganism" crosses delicate interfaces that need a system to keep control in ever changing and only partly predictable (through circadian rhythms and testing by "hormetic" stresses) environments. These pathways traditionally thought of as independant fields such as the immune and endocrine and sensory systems converge on the brain/hypothalamus and on energy pathways linked with ageing, disease and stress responses including autocarnivory and reversions to fermentation reactions (as emergency energy sources).

Conclusions: The bottom line is that the brain/hypothalamus receives information from the environment that is translated through neurohormones acting as release factors affecting endocrinology and immunity and through dopamine and other neurotransmitters and neuropeptides behaviour that influences energy supplies, rewards, learning and stress avoidance strategies. The brain integrates systems and is a target when they fail in circuits that earlier on in life took the strain.

POSTER SESSION 4

THURSDAY, JUNE 17, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-16:00
Authors Present: 13:30-15:00

LEWY BODY DEMENTIA AND OTHER DEMENTIAS IN MOVEMENT DISORDERS

910

Baseline data from a long-term safety study of rivastigmine capsules and patch in mild to moderate Parkinson's disease dementia

P. Barone, P. De Deyn, M. Emre, J. Kulisevsky, W. Poewe, E. Pourcher, T. van Laar, N. Tenenbaum, S. Tekin (Naples, Italy)

Objective: To describe the study design and baseline patient characteristics in a long-term study evaluating primarily the safety of rivastigmine 12 mg/day capsules and 9.5 mg/24 h patch in patients with mild to moderate Parkinson's disease dementia (PDD).

Background: Rivastigmine is a pseudo irreversible cholinesterase inhibitor, previously shown to improve the symptoms of dementia associated with PD in a 24-week placebo-controlled trial. This study was set up to further investigate the long-term safety of rivastigmine capsule and patch.

Methods: This is a 76-week, prospective, randomized, multicenter, open-label study of rivastigmine 12 mg/day capsules and 9.5 mg/24 h patch. Patients are 50–85 years old with mild to moderate PDD, a MMSE score of 10–26, and a Modified Hoehn and Yahr Stage <5 in "on"-state. Capsule treatment is titrated from 3–12 mg/day over 16 weeks, and patch treatment increases from 4.6 mg/24 h to 9.5 mg/24 h patch after 4 weeks. Primary outcome measures are the incidence rate of pre-defined adverse events (AEs; tremor, muscle rigidity, bradykinesia and fall) and the discontinuation rate due to these AEs. Other safety assessments include: Unified Parkinson's Disease Rating Scale (UPDRS) Part III; AEs; serious AEs; Pulmonary Function tests (PEF and FEV1); Schellong test; and Epworth Sleepiness Scale. Efficacy assessments include: Mattis Dementia Rating Scale (MDRS); Neuropsychiatric Inventory (NPI-10); Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL); and Modified Hoehn and Yahr Stage.

Results: Patient enrollment was closed in April 2009, with 583 patients randomized to treatment. At screening, mean age was 72.4 (SD 6.31) years, 32% were women and mean MMSE score was 20.9 (SD 3.36). Mean (SD) baseline safety and efficacy scores were: UPDRS Part III 29.7 (11.89); MDRS 109.6 (19.09); NPI-10 11.3 (11.62); ADCS-ADL 49.5 (17.29). The modal stage of the Modified Hoehn and Yahr Stage was 3 with 235 (40.3%) patients.

Conclusions: This 76-week prospective study is expected to add to the longer-term safety data on treatment of PDD with rivastigmine, in particular the effect of rivastigmine on the underlying motor symptoms of PD.

911

Extrapyramidal symptoms in frontotemporal dementia

A.R. Chade, M. Roca, E. Gleichgerrcht, T. Torralva, F. Manes (Capital Federal, Buenos Aires, Argentina)

Objective: To evaluate the prevalence of parkinsonism in patients with behavioral variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA).

Background: FTD is pathologically heterogeneous, both macroscopically and on a molecular level, with tau positive, TDP-43 positive, and FUS positive intraneuronal inclusions recognized on immunohistochemical analysis. The prevalence of extrapyramidal signs in patients with behavioral variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA) has not yet been systematically studied.

Methods: We enrolled patients fulfilling diagnosis of FTD. Patients with parkinsonian symptoms were diagnosed according to the diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank. The study participants were assessed with the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS) to quantify their motor status and with the Hoehn and Yahr rating scale for severity of motor signs. The results were compared with those of patients with temporal variant of FTD using U Mann Whitney's test for between-group comparison on each item of the UPDRS.

Results: A total of 23 patients with bvFTD and 9 primary progressive aphasia were compared. Mean age was 69.84, SD 8.65, range 49 to 84, 62.5 % were men. A total of 78.26 % with bvFTD presented parkinsonism and 55.5 % of temporal FTD. The mean total UPDRS score for bvFTD was 17.35 SD 12.74 (range 0 to 37) vs temporal FTD 10.72 SD 15.67 (range 0 to 51).The Hoehn & Yahr scale for bvFTD was 2.13 SD 0.92 (range 0 to 4) and for temporal variant FTD was 1.72 SD 0.75 (range 0 to 3). Tremor when present was postural or action type. Left side predominance was 44 % and left side was 22 % of all FTD cases. The two groups differed significantly for speech ($p=0.018$), facial expression ($p=0.045$), left arm postural tremor ($p=0.035$), left arm rigidity ($p=0.031$).

Conclusions: Rigidity, bradykinesia, postural tremor were the most typical findings more severe in bvFTD than in primary progressive aphasia. Detecting parkisonism in patients with FTD is crucial for good clinical practice given potential therapeutic possibilities targeting Tau.

912

Depression in dementia with Lewy bodies and Parkinson's disease dementia

F. Fritze, U. Ehrt, D. Aarsland (Stavanger, Rogaland, Norway)

Objective: To examine the frequency of depression and its characteristics and correlates, in people with mild dementia.

Background: Depression is common in dementia, with important clinical implications. Little is known regarding frequency and correlates of depression in patients with dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD).

Methods: All referrals for patients with a first time diagnosis of mild dementia to outpatient clinics in geriatric medicine and old age psychiatry in the counties of Rogaland and Hordaland in Western Norway from March 2005 to March 2007 were screened for the study. Participants and their caregivers underwent a comprehensive and standardised diagnostic and assessment procedure, and diagnosed according to NINDS-ADRDA, ICC DLB, and MDS-TF PDD criteria. The depression sub item of the Neuropsychiatric Inventory (NPId) and Montgomery and Åsberg Depression Rating Scale (MADRS) were used to estimate depression. Cut-off scores for any depression were 0/1 (dNPI) and 6/7 (MADRS), and for clinically significant depression 3/4 and 14/15, respectively.

Results: 223 subjects with dementia participated, of whom 59 % and 50% showed symptoms of depression assessed by NPI or MADRS, respectively, and 25% and 16% had clinically significant depression as measured by NPI and MADRS, respectively. Compared to AD; depression was more frequent in PDD ($p<.05$) and DLB ($p<.05$). In a generalized linear model, the presence of APOEε4 allele was the only variable significantly associated with depression ($F=5.48$; $p=0.022$).

Conclusions: Depression is common even in mild dementia, and more common and severe in PDD and DLB compared to AD. Future studies should explore the longitudinal course and neural underpinnings of depression in Lewy body diseases.

913

Lack of beta-synuclein expression defines a specific group of dementia with Lewy bodies

K. Beyer, M. Domingo-Sabat, L. Ispierto, C. Carrato, R. Alvarez, P. Latorre (Badalona, Spain)

Objective: To study relative beta-synuclein (BS) mRNA expression levels in post-mortem brains from patients with dementia with Lewy bodies (DLB) and to evaluate the existence of a possible correlation between BS expression levels and the distribution of alpha-synuclein (AS) pathology.

Background: AS oligomerization and aggregation are primary events in the development of Lewy body diseases. BS and AS are characterized by their elevated homology and co-localize within presynaptic terminals. Due to its structure, BS is able to interact directly with AS, regulating its function and toxicity. Moreover, BS inhibits AS oligomerization and aggregation.

Methods: Frozen samples from frontal cortex, temporal cortex and caudate nucleus of 11 patients with pDLB, 12 patients with cLBD and 18 controls were analyzed. RNA integrity was ensured after extraction. Relative BS expression levels were investigated by real-time PCR using SybrGreen for cDNA detection and beta-actin and GUS as housekeeping genes. BS expression changes were calculated using the deltadeltaCt method, permitting the establishment of the corresponding expression profiles. AS-pathology was evaluated by immunohistochemistry.

Results: Results revealed the drastic diminution of BS mRNA expression in temporal and frontal cortex for both pDLB and cLBD, all presenting broad standard deviations. Therefore data were analyzed taking into account the previous clinical diagnosis of the patients and three groups could be defined: (1) pDLB with disease duration of 6.3 ± 3.4 years and lack of BS expression in the temporal cortex and 50-fold diminution in frontal cortex; (2) cLBD with dis-

ease duration of 6.4±2.1, 50-fold decrease in temporal and 3-fold decrease in frontal cortex; (3) PDD with disease duration of 21.0±6.4, 20-fold decrease in temporal and unchanged BS expression in frontal cortex. In contrast, BS expression was not affected in the caudate nucleus. No correlation between BS expression and AS-pathology charge could be detected.

Conclusions: Our data suggest that pDLB without previous clinical diagnosis of PDD, develops by specific mechanisms that involve lack of BS in the affected brain regions. If BS lack causes this subtype of DLB or defines disease progression remains to be determined.

914

Mixed resting and postural tremor with overflow in orthostatism is observed in PDD/DLB patients

L. Bonanni, A. Thomas, F. Ciccocioppo, D. Monaco, F. Anzellotti, E. Mancino, M. Onofrj (Chieti, Italy)

Objective: To evaluate tremor prevalence and quality in DLB patients.

Background: Parkinsonism is among the core features of the diagnostic criteria for Dementia with Lewy Bodies (DLB), but the prevalence and quality of parkinsonian signs in DLB is not clear. Rest tremor is considered uncommon in DLB.

Methods: Tremor was evaluated according to the Consensus Statement of The *Movement* Disorder Society on Tremor criteria and rated according to the Tremor Research Group Rating Scale. Tremor was also recorded by EMG.

Results: Among 106 new referrals to our Movement Disorder Clinic during the years 2007-2008, we found in 12 DLB and 2 Parkinson's disease with Dementia patients a peculiar tremor characterised by rest and postural components. Tremor showed to have a frequency of 5.6-6.0 Hz, it was overflowing in 5-20 seconds to the four limbs (in 4 patients also to the head) when assuming the standing position. The tremor was responsive to L-dopa treatment. The presence of this tremor was coexistent with all the core features for the diagnosis of DLB, including parkinsonism, visual hallucinations, fluctuating cognition. All the patients presented also with REM Sleep Behaviour Disorder.

Conclusions: We suggest that the presence of diffuse Lewy Body Pathology could account for the mixed overflowing tremor pattern.

915

Probable dementia Lewy body type is rare among Parkinson's disease patients

J.M. Rabey, E. Dobronevsky, A. Miniovitz, T. Prokhorov (Zerifin, Israel)

Objective: Our aim was to evaluate PD demented pts in our Center to distinguish between PDD (Emre criteria, 2007) and probable DLBT (McKeith, criteria, 2005).

Background: Dementia is a common occurrence in Parkinson's disease (PD) with a prevalence of 20-40% in cross sectional studies. Although the presence of amyloid plaques and vascular lesions has been reported, cortical Lewy bodies (LB) (which contain synuclein) are considered the most significant finding in the brain of PD patients (PDpts). However, they may also occur in other neurological disorders and even in PDpts without dementia. Consensus criteria artificially divide patients with PD and dementia according to a "one year rule". Cases with parkinsonism of <1 year duration are classified as dementia LB type (DLBT), whereas those PDpts who develop dementia later are designated PD dementia (PDD). Today, it is claimed that DLBT is very common and that its occurrence constitutes a "continuum" with PDD.

Methods: Among 150consecutive PDpts, we identified 51 patients (34 males) with dementia according to the Dementia Rating Scale (DRS) (DRS 1=31; 2=20); mean age 73.4 (±SD) (±8.7y); disease duration 12.8 years (±7.2 y); Hoehn and Yahr scoring II-7 pts; III-13 pts; IV-23 pts; V: 9 pts. Patients were treated with Levodopa (mean 587.5 mg (+ 297) and Dopamine agonists (Cabergoline 3 pts, Pergolide 3 pts, Ropinirol 6 pts and Pramipexole 4 pts). Some also received cholinesterase inhibitors: Rivastigmine 3 pts; Donepezil 3 pt2 and Memantine 1 pt.

Results: Duration of dementia 5.9y (±3.9; MMSE 20.3 (±4.7); Mattis 121.1 (±11.5) (N-136-138 age adjusted) (performed in 24 pts). In addition, 15 pts (40%) suffered from visual hallucinations; 5 pts from delusions; and 7 pts from mixed hallucinations and delusions. Clozapine was given to 19 pts (mean dose 21.36±12.9). Two patients from the demented pool presented with probable DLBT features.

Conclusions: In the clinical setting, we found patients with long term PD who develop psychosis usually after long term exposure to drugs while dementia is a risk factor for psychosis. In summary, applying published criteria DLBT very rarely identifies DLBT in an outpatient clinic for movement disorders.

916

The SNCA locus in dementia with Lewy bodies

A. Sailer, M. Kurzawa, P.F. Chinnery, I.G. McKeith, C.M. Morris, H. Houlden (London, United Kingdom)

Objective: Investigation of an association of the alpha-synuclein gene locus with the synucleinopathy Dementia with Lewy Bodies (DLB).

Background: Alpha-synuclein inclusion body pathology is a common feature of several disorders termed the synucleinopathies, the most common ones being Dementia with Lewy Bodies (DLB), Parkinson's disease (PD) and multiple system atrophy (MSA). They were considered as sporadic diseases but growing evidence now suggests that in PD there are a number of genetic risk factors that contribute to the development of the disorder. Due to the pathological findings, SNCA, the gene coding for alpha-synuclein, is a strong candidate as a genetic risk factor for all three diseases. A genome wide association study (GWAS) identified single nucleotide polymorphisms (SNPs) within SNCA as being strongly associated with the risk for developing PD. The same locus was confirmed to be associated with MSA accordingly providing additional evidence that genetic variation at the SNCA locus is associated with an increased risk of synucleinopathy.

Methods: 157 pathologically confirmed British Dementia with Lewy Body cases were tested for 6 SNPs in the SNCA locus that had previously shown highly significant association with PD and MSA using Taqman technology. Results were compared to the frequencies in 5116 British controls.

Results: All six SNPs tested in DLB cases showed no difference in frequency when compared to controls. These results clearly differ from those found in other synucleinopathies.

Conclusions: PD, MSA and DLB have several disease features in common. Pathologically it can even be difficult to distinguish between PD and DLB. Genetically, however, DLB seems to be distinct and does not share the same risk associations with the SNCA locus as seen in PD and MSA.

917

Parkinsonian features and apraxia in frontotemporal lobar atrophy behavioural variant (FTLA bv)

S. Schmidegg, W. Struhal, S. Hoedl, C. Dorninger, M. Steffelbauer, M. Ortmayr, G. Ransmayr (Linz, Austria)

Objective: FTLA bv is clinically characterized by behavioral abnormalities, progressive cognitive deterioration including a frontal–dysexecutive syndrome and loss of insight.

Background: Recently, mild parkinsonian features and a decrease in dopaminergic neurotransmission have been discovered. Moreover, apraxia has been described in the spectrum of the diseases of focal cortical atrophies.

Methods: FTLA bv patients (disease duration ≤2 years) were analyzed regarding parkinsonian symptoms, apraxia and frontal-dysexecutive syndrome by means of UPDRS-III, De Renzi ideomotor apraxia scale, the frontal assessment battery (FAB) including the Luria test and demographic and other neuropsychological parameters comprising also constructional practise.

Results: Mild parkinsonian symptoms were found in all of the FTLA bv patients (N=14). The mean UPDRS–III Score was 12 (±9) and did not correlate with age (average: 71,9 years). The preponderant parkinsonian symptom was symmetrical akinesia of finger tapping, hand movements and rapid alternating movements. Rigidity was not present, action tremor only in 2 patients. Mild apraxia was observed in all except 3 patients (De Renzi ideomotor apraxia scores ranged from 54-70). There was a trend towards negative correlation between akinesia and the Luria test (of the FAB). Constructional practise was not affected.

Conclusions: Mild akinesia was found in FTLA bv patients. In this group of patients also ideomotor apraxia could be assessed. These preliminary findings suggest further studies in larger samples.

POSTER SESSION 4
THURSDAY, JUNE 17, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-16:00
Authors Present: 13:30-15:00

MYOCLONUS

918

Cervical injury-related polyminimyoclonus: Case report

C.M. Akbostanci, N.F. Durmaz, B.S. Arica, R. Yilmaz (Ankara, Samanpazari, Turkey)

Objective: Polyminimyoclonus is a phenomenon, characterized by low amplitude intermittent and irregular movements of the fingers or toes. Movements are observed in both hands and occur independently or simultaneously on either one.

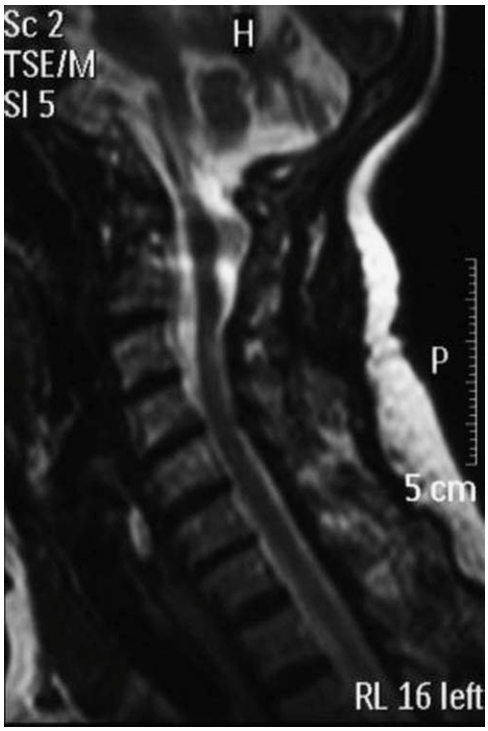

FIG. 1 (918).

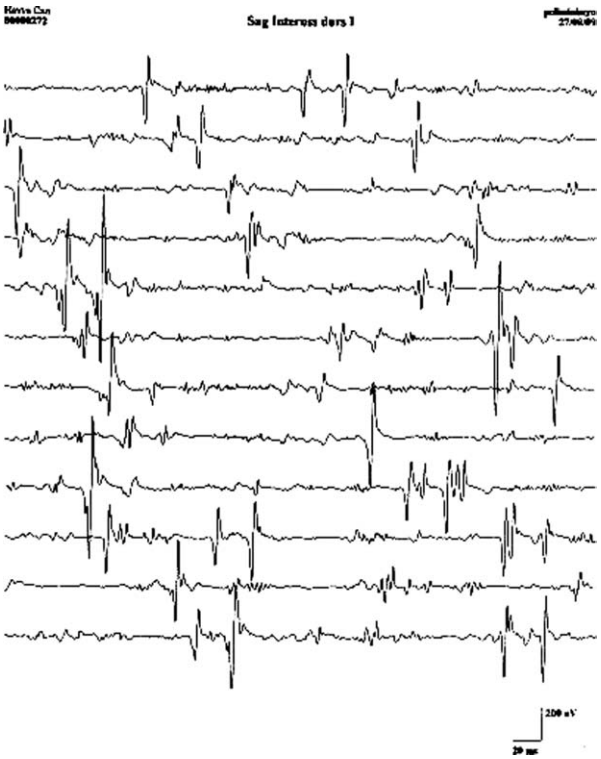

FIG. 2 (918).

Background: Poliminimyoclonus can be seen in spinal disorders like Hirayama Disease, cervical syringomyelia and also in Alzheimer's disease.

Methods: In this case we present a cervical injury - related polyminimyoclonus due to trauma of a motor vehicle accident or implanted screws for fixation of the injured neck.

Results: 62-year-old female was admitted with complaints of slowly progressive unsteady gait, ataxia, urinary incontinence and drop attacks. She was diagnosed to have multiple system atrophy. Following the diagnosis, she suffered a motor vehicle accident and she had an atlantoaxial fixation operation with posterior C1-C2 screws. One year later, the patient began to experience some involuntary twitching like movements in her fingers. A neurologic examination revealed hypomimia hypofonia, bilateral rigidity, bradikynesia prominent on the left side and unsteady gait. Also, intermittent, myoclonic jerks with 8-10/sc frequency in the hands, which were not synchronous during an electrophsyciologic investigation were interpreted as polyminimyoclonus. Cervical magnetic resonance imaging showed midline hyperintesity of the cervical spinal cord and fixation screws at C1-C2 levels.

Conclusions: Poliminimyoclonus is a rather rarely reported clinical phenomenon in the medical literature. The mechanism of this phenomenon has not been yet understood completely. Polyminimyoclonus may be due to microvascular changes caused by chronic trauma to the spinal cord during flexion and extension of the neck, related to anterior horn cell ischemia following microcirculatory disturbances. Review of the literature fails to show any association between poliminimyoclonus and multiple system atrophy. In our report we present a case of polimyoclonus, in our opinion related with cervical trauma. Cervical fracture or an atlantoaxial fixation operation with screws may have caused microvascular ischemia of the spinal cord. When involuntary low amplitude irregular jerks of fingers were recognised, a probable diagnosis of poliminimyoclonus due to cervical spinal cord injury should be kept in mind.

919

Abdominal myoclonus associataxed with vitamin B12 deficiency: Report of three cases

B.S. Arica, R. Yilmaz, C.M. Akbostanci (Ankara, Turkey)

Objective: Involuntary movements due to the deficiency of vitamin B-12 are poorly understood.

Background: Spinal segmental myclonus associated with low levels of vitamin B-12 is previously reported in infants and adults.

Methods: In this report, we present three cases with spinal myoclonus related to low levels of vitamin B -12.

Results: Case 1: A 76-year-old male admitted with abnormal movements in his belly. Neurologic examination revealed hemiparesis of the left side indicating a stroke and rhythmic, spontaneous, jerks in his abdominal wall.Tests showed low vitamin B-12 levels (134 pg/dl.) A CT scan revealed chronic ischemia of right frontal lobe.His EEG was normal and his endoscopic biopsy showed gastric atrophy. A thoracoabdominopelvic CT scan was normal. Myoclonic jerks recovered in two days with 1000 Mg/day valproic acid and IM vitamin B-12 replacement. After valproic asid was discontinued two weeks later, there were no recurrence of abdominal jerks.Case 2:A 43-year-old female admitted with involuntary abdominal movements. Bilateral, rhythmic, synchronous jerks were observed in her abdominal wall. Her spinal MRI and EEG were normal. Serum vitamin B-12 level was 192 pg/ml. Electrophysiological examination revealed arrhythmic bursts with 200-400 ms. duration with a frequency of 4-5 per second detected in rectus abdominis muscle. Movements recovered completely after the administration of 2000 mcg. IM B-12 replacement. Case3: A 20-year-old female admitted for preterm labor, suffered from involuntary movements in her umbilical region. Neurologic examination showed rhythmic, bilateral, synchrone myoclonic movements on her abdominal wall. Her blood sample tests showed low vitamin B-12 levels (122 pg/dl). She refused imaging or electropysiological test and her myoclonic jerks stopped after 2000 mcg.of vitamin B-12 given IM.

Conclusions: Review of the literature shows that, involuntary movements associated with low levels of vitamin B-12 were rarely reported.Yet the underlining pathophysiological mechanism is not well documented. There should be a relation between low B-12 levels and abdominal dyskinesia since dyskinesia resolved in a short time after vitamin B-12 administration. All our cases recovered completely with vitamin B–12 treatment. Spinal segmental myoclonus is a rarely seen phenomenon and vitamin B–12 deficiency should be considered in etiology.

920

Creutzfeldt-Jakob disease presenting with various positive myoclnous

J.C. Chen, C.H. Tsai, M.K. Lu (Taichung, Taiwan)

Objective: To evaluate casual link between the myoclonus found in CJD patients and the PSDs.

Background: Myoclonus, the most common involuntary movement observed in CJD patients, was supposed to be associated with the appearance of the periodic synchronous discharges (PSDs) on traditional electroencephalogram (EEG) recordings. The casual link between the myoclonus found in CJD patients and the PSDs, however, remains highly assumptive and not conclusive because of a limited number of the reported cases.

Methods: We evaluated a 75-years-old patient with typical clinical manifestations of CJD. By identifying and separating the distinct types of myoclnic jerks recorded from the patient, we adopted the jerk-locked EEG back average technique to investigate link between the myoclonus and PSDs.

Results: Three different types of positive myoclonus were recorded from the left triceps muscle. The waveform, particularly the amplitude, of each type of myoclonus was distinct (Fig. 1).Some PSDs were not accompanied with any muscle jerks. Type A jerks have a mean duration of 60.35±10.11 ms and a mean amplitude of 179.13±64.12 μV. The mean latency of the jerk onset to the maximal EEG negativity is 24.22±11.07 ms. Type B jerks have a smaller amplitude (60.86±40.43 μV) and similar duration (56.85±9.01 ms) compared to type A jerks. No significant EEG potentials were detected by locking the onset of type C jerks which have a mean duration of 32.45±3.69 ms and a mean amplitude of 24.3±3.40 μV. Some PSDs were not jerk-locked (Type D). The number of the EEG epochs used for average is 193, 43, 114 and 129 for type A to D jerks, respectively.

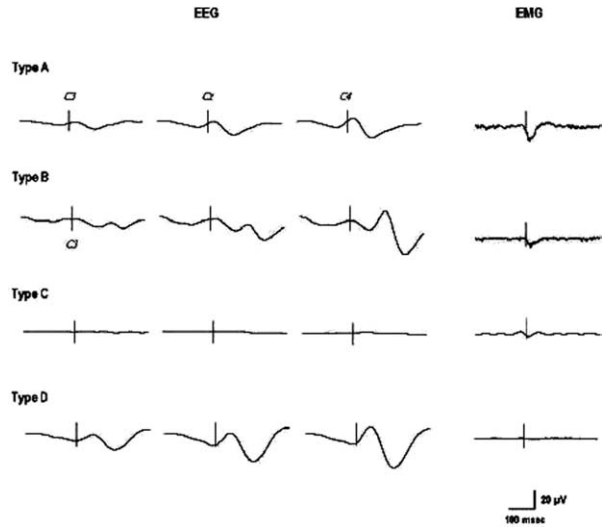

FIG. 1 (920).

Conclusions: The cortical potentials locked to the different types of jerks in this CJD patient were not uniform. One of the possible explanations is the generators of the myoclonic jerks were located at different cortical or subcortical levels. The fact that some jerks were not associated with any detectable cortical potentials may indicate their generator could be too far away from the cortex to be recorded by the current scalp EEG recording, or these jerks were randomly evoked. In contrary, robust cortical potentials or PSDs were not necessary to appear with a constraint to any myoclonic jerks. Our findings supported the notion that the generalized PSDs may have different influences on the motor neuron excitabilities at cortical and subcortical levels.

921

Hemifacial spasm as the first manifestation of multiple sclerosis

M. Gallardo, A. Soto, A. Abreu (Caracas, Miranda, Venezuela)

Objective: To describe the case of a woman who presented hemifacial spasm as the initial symptom of relapsing-remiting Multiple Sclerosis (MS).

Background: Movement disorders occurring in association with Multiple Sclerosis (MS) are uncommon. Among them paroxismal dystonia is the most common, although chorea, ballism, myoclonia have been reported.

Methods: We studied a patient who was referred our centre with diagnosis of relapsing-remitting Multiple Sclerosis.Detailed clinical history was taken. Physical examination and routine laboratory test were performed. Magnetic resonance imaging of the brain, CSF Analysis and immunological test also were performed.

Results: In June 2007, a 54 year-old woman developed hemifacial spasm followed of weakness in upper left limb and lower limbs and was later parestesias. Symptoms lasted 4 months after which they remitted spontaneously except hemifacial spasm which improved

with botulinum toxin. In December 2007, she presented gait difficulty, lower limb weakness, dizziness and urinary incontinence. The patient consulted our service in November 2008. On examination she had paraparesia with alterations to the deep sensory and decreased sensation below the level T8-T9. Deep tendón reflexes were brisk in lower limbs and left Babisnky sing was present. Mild gait ataxia was observed. Brain magnetic resonance imaging (MRI) of May 2007 showed hyperintense FLAIR and T2-weighted images in periventricular areas, corpus callosum. In July 2008 another Brain MRI was made demostrated new images in cerebral hemispheres. At that time Spinal cord MRI was normal. Visual evoked potential was normal. Cerebrospinal fluid analysis no show oligoclonal bands. Inmunological test was normal

Conclusions: Except for tremor, movement disorders (MD) associated with multiple sclerosis (MS) occur infrequently. When they are present it could be caused by demyelinating lesions and release of inflammatory soluble factors, and dysfunction of ion channels and accumulation of extra-cellular potassium. The report of involuntary movement in previous studies and the case described in our study suggest that movement disorder could be a sign or even could be the first clinical manifestation of Multiple Sclerosis.

922

Hemibody myoclonus associated with contralateral medullary compression by a dolichoectatic vertebral artery

N.K. Iwata, P.T. Lin, C. Toro, Z. Mari, M. Hallett, S.G. Reich (Bethesda, Maryland, USA)

Objective: To report a patient with right hemibody myoclonus associated with compression of the left medulla by a dolichoectatic vertebral artery.

Background: Myoclonus is typically generalized or segmental and it is rare to affect exclusively one half of the body. A patient identical to ours was reported by Coelho et al (Mov Dis 2005). He had hemibody myoclonus with contralateral compression of the medulla by an ectatic vertebral artery. These cases illustrate that hemibody myoclonus may arise in the medulla in addition to generalized (reticular reflex) and segmental (palatal) myoclonus.

Methods: Case report with video, neurophysiology and imaging.

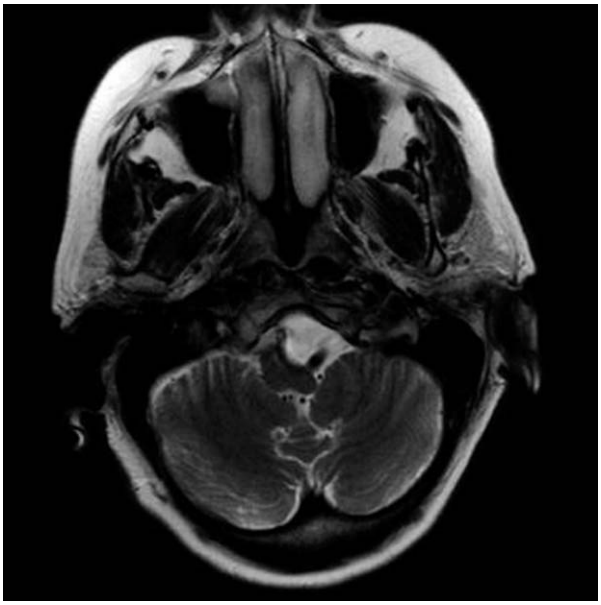

FIG. 1 (922).

Results: In 2004, a 60 year old dentist experienced intermittent jerks of the right thumb. With time the jerks spread proximally and also involved the right leg. Examination in 2007 demonstrated single or brief trains of myoclonic jerks of the right limbs. There was a mild right hemiparesis. MRI/MRA demonstrated dolichoectasia of the left vertebral artery with displacement of the left ventrolateral medulla. EEG/EMG polygraph showed either single or trains of 5-10 jerks of 50ms duration followed by a 50s tonic contraction. The jerks began in the right forearm and spread distally and proximally. After 10ms the jerks spread to the right leg. EEG and MEG back-averaging did not demonstrate a pre-movement potential prior to the jerks. EEG monitoring did not reveal epileptiform activity. BAEPs and SSEPs were normal. The following medications were either not beneficial or tolerated: clonazepam, levetiracetam, acetazolamide and carbamazepine. By 2009, the right-sided jerks were still present but had decreased in frequency and the right hemiparesis was mildly worse. There was also mild vibratory loss on the right as well as torsional-downward beating nystagmus.

Conclusions: We report a second case of hemibody myoclonus associated with vascular compression of the contralateral medulla. The lack of an alternative etiology for the myoclonus, its unique topographic distribution, and the presence of other signs referable to the ventrolateral medulla suggest that this clinical-anatomical correlation is not coincidental. We hypothesize that mass effect on the medulla induced abnormal activation of descending motor tracts causing contralateral myoclonus.

923

Unilateral cortical myoclonus

P. Katschnig, P. Schwingenschuh, M.J. Edwards, K.P. Bhatia (London /Graz, United Kingdom)

Objective: To report three patients who presented with unilateral cortical myoclonus without evidence of a contralateral structural or symptomatic etiology.

Background: Cortical myoclonus is the most common form of myoclonus and is predominated by action and stimulus sensitive jerks of distal muscles. In the majority of cases the jerks are multifocal, while reports of strictly unilateral cortical myoclonus are scarce. In such circumstances epileptic or symptomatic myoclonus due to a structural lesion or neurodegeneration has to be excluded.

Methods: We describe clinical features and the detailed diagnostic work-up of three illustrative cases presenting with a unilateral cortical myoclonus.

Results: All patients had a unilateral myoclonus affecting one arm, patients 2 and 3 had additional involvement of the ipsilateral lower limb and face. In all patients the myoclonus was elicited or clearly aggravated by action and touch. Patient 2 was also diagnosed with a metastatic carcinoma of the prostate with para-aortic and iliac lymphadenopathy. Brain imaging was reported as unremarkable in all patients. An EEG was reported as unremarkable in patient 1. EMG revealed brief jerks with a typical pattern of muscle activation suggestive of cortical origin in patients 2 and 3, associated EEG changes on back-averaging could only be demonstrated in patient 3. Cortical SEPs were enhanced in patient 3. DaT-SPECT scans in patients 2 and 3 were unremarkable, as were CSF examinations including Whipple's PCR in all patients. A whole body PET scan was conducted in patient 2 to rule out a paraneoplastic syndrome. Extensive blood analyses were unremarkable except for positive anti-gliadin antibodies in patient 3. A subsequent gut biopsy was negative. The etiology of the unilateral myoclonus in all three patients could not be established yet.

Conclusions: The clinical presentation and diagnostic workup in all three patients was suggestive of a unilateral cortical myoclonus. There was no evidence for a symptomatic cause, hence the underlying etiology in these three cases remains unknown and may even be regarded as idiopathic.

924

Lance-Adams syndrome in El Salvador: Effects of piracetam therapy follow-up. A case report

R. Lopez-Contreras, R. Lopez-Castellanos (San Salvador, El Salvador)

Objective: To Evaluate efficacy, safety and tolerability of high doses of piracetam in a case of Lance-Adams Syndrome, during 18 years follow-up.

Background: Piracetam has been show to improve myoclonus in Lance-Adams Syndrome.

Methods: We conducted open administration of high doses of Piracetam during 15 years follow-up. Changes of movement disorder, cognitive function, living activities daily, were evaluated up to 18 years.

Results: A 30-year-old woman had an epileptic status 10 minutes after a surgical procedure in 1991. She was managed in the ICU with an IV infusion of antiepileptic drugs and respiratory support. Twelve hours later she developed moderate focal touch-sensitive-myoclonus in limbs and 3 days later evolved to multifocal and tactile and sound stimulus-sensitive-myoclonus. She was extubated 12 days after and presented a severe functional disability (Barthel index: 20) due to severe spontaneous and reflex myoclonus, synchronic and asynchronic myoclonus and action myoclonus. She had normal cognitive function. MRI, CT scan and laboratory studies were normal. From September 1991 to July 1994 the oral drug combination of Valproic Acid (1.5 g/day), Clonazepan (6 mg/day) and Phenobarbital (0.2 g/day) was maintained with no myoclonus improvement and a Barthel index of 20. On July 1994 Piracetam IV (12 g/day) for 3 days was added as an adjunctive therapy presenting a 50% overall improving in Barthel Index: 65. Next day Piracetam IV dose was increased (24 g/day) for 2 days with no additional improvement so the Piracetam was switched from IV to oral (12 g/day) maintained until 1996 preserving the previous achieved improvement, Clonazepan was discontinued. In 1997 Barthel index improves notoriously to 85 points with the same Piracetam (12 g/da) dose until 1998 when a gradually dose reduction was performed (4.8 g/day) preserving the previous gained improvement. In 2001 after a new evidenced improvement in Barthel index: 100 a new Piracetam dose reduction was performed (3.2 g/day) until date with kinetic and postural tremor in upper limbs as the only remaining symptom. Actual MMSE score: 30. In a lower Piracetan dose the action myoclonus reappeared.

Conclusions: High-dose piracetam treatment resulted in a complete resolution of severe post-anoxic myoclonus and good tolerability without side effects.

FIG. 1 (924).

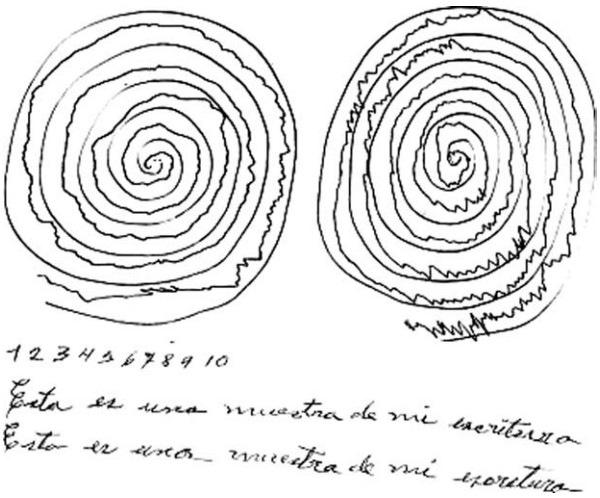

FIG. 2 (924).

925

Very rare mitochondrial DNA mutation (G13042A) in a young man with MELAS/MERFF overlap syndrome and with good response to levetiracetam

M. Schinwelski, A. Szpiech, W. Soltan, J. Szady, B. Kierdaszuk, K. Tonska, A. Kodron, J. Slawek (Gdansk, Pomorskie, Poland)

Objective: To present a very rare mitochondrial DNA mutation (G13042A) in a young man with an overlap syndrome of MERRF and MELAS and with good response to levetiracetam.

Background: Pathogenic mutations of the human mitochondrial genome are associated with well-characterized, progressive neurological syndromes. Although mutations in the transfer RNA genes are particularly prominent, the mitochondrial DNA gene encoding subunit 5 of complex I (ND5) seems to be an the important site for mutations associated with mitochondrial encephalomyopathy with lactic acidosis and stroke like episodes (MELAS) and myoclonic epilepsy with ragged-red fibres (MERRF). Treatment of primary myoclonic epilepsy of mitochondrial origin must consider the lack of interaction with mitochondrial respiration and metabolism. Levetiracetam could be considered the drug of first choice for the treatment of myoclonus in MERRF.

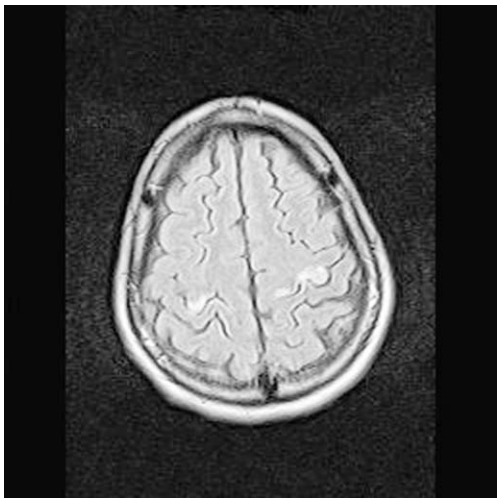

FIG. 1 (925).

Methods: Case report of 22-year old man with no family history of neurological diseases and clinical presentation of myoclonus, seizures, ataxia, focal dystonia (writers cramp), physical exercise intolerance, optic nerve atrophy and ragged-red fibres in muscle biopsy commonly found in MERRF syndrome. However, disseminated, mostly cortical hyperintensities T2 and FLAIR MRI scans (Fig. 1), headache and vomitus, exacerbation of the disease after valproate treatment characteristic for MELAS were also noted.

Results: Molecular analysis revealed a very rare heteroplasmic mutation (G13042A) in the ND5 gene. Finally MERRF/MELAS overlap syndrome was diagnosed. Myoclonus improved dramatically, as well as the quality of life and no side effects were observed after levetiracetam in 2 g daily dose.

Conclusions: This very rare (second published so far) heteroplasmic mutation in a patient with MERRF-MELAS overlap syndrome supports the view that the ND5 gene should be added to the transfer RNA gene as another hot spot for MELAS mutations. This gene should be sequenced in every MERRF/MELAS case, where no common mutations for MELAS or for MERRF were found. Levetiracetam can be considered the drug of choice for the treatment of myoclonus and epilepsy in this syndrome.

926

Isolated progressive subcortical myoclonus associated with *POLG 1* mutations

S.M.A. van der Salm, J.P.P. van Vugt, M.C.F. Gerrits, M.A.J. Tijssen (Amsterdam, Netherlands)

Objective: Over the recent years, *POLG* gene mutations receive increasing attention as a frequent cause of mitochondrial disorders. Our aim is to illustrate the involvement of POLG mutations in movement disorders.

Background: The nuclear encoded DNA polymerase gamma (*POLG*) replicates the mitochondrial DNA (mtDNA) and mutations in this gene give rise to heterogeneous clinical manifestations. These vary in severity and onset, and include Alpers syndrome, progressive external ophthalmoplegia (PEO), parkinsonian features, ataxia and myoclonus.

Methods: We report two young females with progressive distal myoclonus and extreme fatigue due to *POLG 1* mutations.

Results: The myoclonus is likely to be localized subcortically, as the SSEP was normal and no EEG abnormalities were found. Muscle biopsy was normal.

Conclusions: Our two cases are strikingly similar and broaden the spectrum of neurological disorders associated with *POLG 1* mutations, which now includes slowly progressive subcortical myoclonus.

927

A case of subacute encephalopathy, ataxia and myoclonus due to amantadine toxicity in chronic renal insufficiency

A. Hardwick, M. Devereaux, B.L. Walter (Cleveland, Ohio, USA)

Objective: This is an unusual cause of encephalopathy, myoclonus and ataxia due to amantadine toxicity.

Background: Amantadine is a renally metabolized drug with a $T_{1/2}$ of 9 hours, although it lengthens in elderly populations. Common side effects include dizziness, insomnia and impaired concentration. Rare side effects are hallucinations, falls, tremulousness and disorientation.

Methods: This is a case report with video documentation of the patent's exam on presentation and after discontinuation of the medication.

Results: A 63 year-old gentleman presented with 3 years of progressive involuntary movements, ataxia, cognitive impairment and visual hallucinations His PMHx included a 30 year history of pruritus of unknown etiology controlled with amantadine, DM, HTN, CHF and CRI diagnosed 1 year prior. Examination was significant for multifocal myoclonus in the arms with posture, not aggravated with action and myoclonus in the lower face and neck. His upper extremities were ataxic and his gait was wide based and severely ataxic with myoclonic truncal movements which resulted in him being wheelchair bound. (Video 1) An exhaustive outside neuroimaging, neurophysiological and laboratory workup was negative including normal EEG, anti-Thyroglobulin and Anti-Hu antibodies. We sent a serum amantadine level and tapered the drug over 3 weeks. The level returned at 4900 (>1000 range for toxicity). Gradually, his symptoms improved, but the pruritis returned. After 8 weeks he walked into the office without assistance. He reported improved cognition, and absence of hallucinations. Exam revealed complete resolution of myoclonus, and ataxia (Video 2).

Conclusions: This case documents a rare side effect of amantadine. It highlights the importance of cautious use of this medication in the elderly with impaired renal metabolism. Further, it reinforces the important point that careful examination of a patient's medication list may reveal a reversible cause of neurological symptoms. In this case, one may have assumed that this progressive encephalopathy, myoclonus and ataxia could have been a result of a devastating neurological condition such as CJD. The progressive symptoms with no recent changes in medications was likely a result of worsening renal function. Fortunately, these symptoms were completely reversible with the discontinuation of amantadine.

928

Lingual myoclonus associated with brain tumour

R. Yilmaz, B.S. Arica, A. Yigit (Ankara, Turkey)

Objective: Introduction: Isolated lingual myoclonus is an uncommon and poorly understood clinical phenomenon.

Background: It usually is observed with palatopharyngeal myoclonus and associated with brainstem pathologies.

Methods: We report a patient who presented with lingual myoclonic jerks and cerebral glial tumour.

Results: Case report: A 59-year-old man, suffering from a left-sided weakness, had been diagnosed as having a brain tumour on the right frontoparietal lobe. He was operated and the pathologic diagnosis was oligodendroglioma. After the operation his initial neurologic examination disclosed a left facial paresis of central type, hyperreflexia, and left-sided hemisensory deficit. One month after the hospitalization, he complained of perioral numbness and slurred speech, which recovered in about an hour, and neurologic examination discovered dysarthric speech and repetitive, rhythmic jerks on the tongue and the lower lip from right to the left side, without any accompanying cervical, palatal or pharyngeal abnormal movements [see video]. Lingual myoclonic jerks being contralateral to the cerebral lesion, we diagnosed epilepsia partialis continua and started sodium valproate, 1000 mg/day per os. In EEG no abnormal epileptiform activity was observed. An MRI showed residual glial tumour. Sodium valproate was discontinued two weeks later and lingual jerks did not recur.

Conclusions: Discussion: The pathophysiology of lingual myoclonus is not well understood and the origin is not well documented. Li et. al. described a case of lingual myoclonus associated with a cerebral cavernoma, interictal epileptiform EEG abnormality and complete resolution of tongue movements by antiepileptic drug treatment and suggested an epileptic origin. In our case, we demonstrated a cerebral tumour on the right

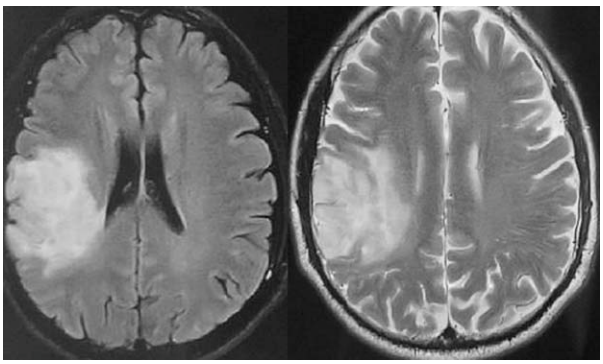

FIG. 1 (928).

side, and observed contralateral rhythmic jerks of the tongue, from the right to the left side. Therefore, we also suggest an epileptic origin, although the interictal EEG did not show any epileptiform abnormality. In conclusion, isolated lingual myoclonus can be considered as a rare manifestation of focal seizure. References: Li JY, Chen CC, Lee CH. Epileptic lingual myoclonus associated with cavernoma. Mov Disord 2009;24:000-000. Postert Th, Amoiridis G, Pöhlau D, Hoffmann V, Przuntek H. Episodic undulating hyperkinesias of the tongue associated with brainstem ischemia. Mov Disord 1997;12:619-621.

POSTER SESSION 4

THURSDAY, JUNE 17, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-16:00
Authors Present: 13:30-15:00

PARKINSONISM (SECONDARY AND PARKINSONISM-PLUS)

929

Atypical parkinsonism with apraxia and supranuclear gaze abnormalities in type 1 Gaucher disease: Expanding the spectrum

A. Alonso-Canovas, P. Katschnig, A. Tucci, M. Carecchio, N. Wood, M. Edwards, J.C. Martinez-Castrillo, D. Burke, S. Heales, K. Bhatia (London, United Kingdom)

Objective: To describe a type 1 Gaucher disease (GD) patient with an atypical parkinsonism and review the association of atypical parkinsonism and GD.

Background: GD is caused by mutations in glucocerebrosidase gene (GBA). GD heterozygosity is found in 5% of sporadic Parkinson's disease and parkinsonism has been reported as a late feature of type 1 GD, so far believed to spare the central nervous system.

Results: A 66 year old man of Ashkenazi Jewish ancestry was diagnosed with GD at the age of 17 (mild thrombopenia and hepatosplenomegaly). At the age of 60, he developed difficulty in complex intellectual tasks, forgetfulness and apathy, along with a mildly asymmetric akinetic-rigid syndrome with early falls, depression and REM sleep disorder. Cobeneldopa provided modest benefit. The condition progressed to render him dependent for most daily tasks. Examination showed generalized bradikinesia, rigidity, prominent supranuclear gaze abnormalities (difficulty initiating and hypometry of saccades, especially in the vertical plane), stimulus sensitive myoclonus and gestural apraxia, with abnormal posturing of his right arm. There was global cognitive decline, with executive dysfunction and involvement of language, memory and visual perceptual functions. Analysis of CSF indicated marked impairment of serotonin and dopamine turnover (undetectable 5-hydroxyindoleacetic acid and homovanillic acid with elevation of 3-methyldopa). Brain MRI showed asymmetric cortico-subcortical atrophy. LRRK2 and tau gene mutations were negative. He was a compound heterozygote for GBA mutations (N370S/L444P) and had plasma chitotriodase elevation. Sixty patients with GD1 and parkinsonism have been reported. Eighteen had cognitive impairment. Two of them had myoclonus and five horizontal gaze abnormalities. Apraxia and vertical gaze abnormalities have not been reported so far.

Conclusions: We report a case of GD1 with a rapidly progressive dementia resembling corticobasal degeneration (CBD). Our literature analysis supports the association between atypical parkinsonism and GD. A wide spectrum of parkinsonian phenotypes is associated with GD, which should be included in the list of CBD look-alike syndromes.

930

Parkinsonism and progressive external ophthalmoplegia with multiple mitochondrial DNA deletions: Report of two new cases

B.R. Barton, S. Jackson, N.J. Diederich (Chicago, Illinois, USA)

Objective: To present two new cases illustrating a rare genetic cause of neurodegenerative parkinsonism.

Background: Parkinson's disease (PD) is a heterogeneous disorder with several possible causes, including genetic, environmental, metabolic, or toxic factors. Mitochondrial dysfunction is implicated in the pathophysiology of PD, including primary mutations in mitochondrial proteins and secondary dysfunction of mitochondrial metabolism. Parkinsonism may rarely develop in the context of more widespread signs of mitochondrial disease, including syndromes of progressive external ophthalmoplegia (PEO), most commonly associated with POLG1 mutations. We report two unusual cases of PEO and parkinsonism in association with *non*-POLG1 mutations.

Methods: Case reports of two subjects, including videos, and literature review.

Results: Case #1: A 71 year old man with a nine year history of bilateral ptosis, PEO, left-sided weakness, and fatigue on exertion presented with mild, asymmetric rest tremor and bradykinesia (UPDRS I-III total score 20). Muscle biopsy showed a mitochondrial myopathy, and mitochondrial DNA analysis revealed multiple deletions. A heterozygous c.907C>T, p.Arg303Trp mutation was identified in exon 1 of the nuclear gene C10orf2/PEO1/Twinkle. Symptomatic antiparkinsonian treatment was not yet required. **Case #2**: A 71 year old man was diagnosed with PEO and mitochondrial myopathy seven years previous, with symptoms including ptosis, fatigue with exertion, hearing loss, neuropathy, and cardiomyopathy. After five years, he developed asymmetric rest tremor, bradykinesia, and rigidity (UPDRS-III total score 26). Muscle biopsy showed a mitochondrial myopathy and mitochondrial DNA analysis showed multiple deletions, with POLG1 unaffected. Parkinsonism improved with carbidopa/levodopa (to UPDRS III score 14).

Conclusions: The co-occurrence of parkinsonism and PEO is unusual. We add to this scarce literature with the third reported patient with a C10orf2 mutation, and with a probable autosomal dominantly inherited case with multiple deletions. The very slow evolution of both patients supports the hypothesis of a key role of mitochondrial dysfunction in the insidious progression of neurodegenerative parkinsonism.

931

Articulatory dysfunction in Parkinson's disease: An fMRI study

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Objective: We studied the neural activity related to utterance of articulatory stop consonants.

Background: Parkinson's disease (PD) patients demonstrate hypophonia with monotonous voice. Problems in voice are seen in all the five stages of the PD. The motor speech disorder ranges from 75% to 89%. Impaired speech has been variably reported to improve with levodopa therapy.

Methods: Eighteen PD patients and 8 age and gender matched healthy controls were recruited for the study.

TABLE (931).

Subject	Number	Age Mean± SD	Duration of illness	LED mg/d	H&Y stage	MMSE	UPDRS III
PD	18	59.8 ±14.3	6.53 ±3.5	712.5 ±303.5	1.7 ±0.7	27.2 ±2.67	20.5 ±10.8
Cotrol	8	48.6 ±5.2	-	-	-	29.0 ±1.0	-

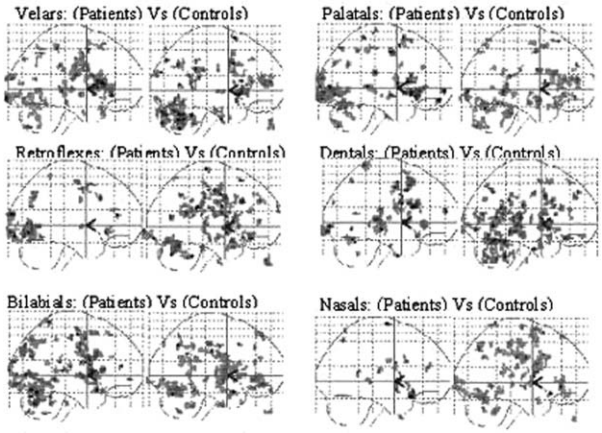

FIG. 1 (931). Brain activation pattern for the various categories of articulatory stop consonants as depicted by functional MRI data analysis.

Single-shot echo planar imaging (EPI) sequence in the whole brain on 1.5T (Siemen's Avanto Scanner); during "off" state for patients and controls were obtained. Using Subjects read audibly, the image of two syllable Hindi words belonging to the six articulatory stop consonant categories (namely velars, palatals, retroflexes, dentals, bilabials and nasals) according a standardized block paradigm. Processing was carried out on an offline server using SPM2. Bold activation pattern was overlaid onto the MNI template using the Talairach and Tornoux co-ordinates. One way ANOVA ($p<0.001$, cluster threshold 5) was used for group analysis.

Results: For velars, Insula (BA13), Wernicke's (BA 22)) and Brocca's area showed no activation. However, the primary motor cortex (M1), and supplementary motor area (SMA) were activated more in patients. For Palatals, M1 and SMA activity was high. For retroflexors, insular activity, Wernicke's and Brocca's were missing, while the lingual gyrus showed enhanced activation. For dentals, activation was observed for insula, M1 and SMA, while underactivation in Wernicke's and almost no activation in Broca's area was observed. The Heschel's Gyrus (BA 41) was active only in PD. The bilabials exhibited no insular and M1 activity, while Wernicke's and Brocca's showed under-activation. The nasals exhibited no activation for M1 and SMA The nasalization of such words probably required a great effort of the motor cortex.

Conclusions: We observed that insula responsible for articulatory planning, Brocca's and Wernicke's (for language area) showed fewer clusters in PD patients as compared to controls.

932

Immunmodulatory treatment-responsive corticobasal degeneration-like symptomatology secondary to antiphospholipid syndrome

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Objective: To report a rare case of intravenous immunoglobulin (IVIG) responsive corticobasal degeneration (CBD)- like symptomatology secondary to antiphospholipid syndrome (APS).

Background: APS- induced thrombo-occlusive vasculopathy can lead diverse neurological presentations. Movement disorders including chorea, parkinsonism, dystonia, CBD like syndrome have been previously reported. Here we report a case of APS-related CBD like syndrome who improved considerably in both cognitive and motor functions after IVIG treatment.

Methods: Case presentation.

Results: A 38 year-old man presented with rigidity, slowness and clumsiness in his right hand and forgetfulness. He reported to have hypertension and renal failure for twelve years. On examination, parkinsonism and dystonia on the right and a moderate impairment of executive functions and visuospatial skills were disclosed. A poor response was obtained with proper dopaminergic treatment. Magnetic resonance imaging (MRI) of the brain was remarkable with the presence of one acute and multiple chronic cortical and subcortical ischemic lesions including basal ganglia. Transcranial sonography demonstrated presence of SN hyperechogenicity. Laboratory examination revealed trombocytopenia and renal dysfunction. Anticardiolipin and antiphospolipid IgM and IgG antibodies were positive (up to 10 times of normal level). Lupus anticoagulant was positive. The other vasculitis markers including ANA were negative. He was diagnosed as fulminant antiphospolipid syndrome because of multiple system involvement. Acetylsalicylic acid and warfarin was administered. Pramipexole was added for treatment of parkinsonian symptoms. IVIG was also given at the dose of 0.4 mg/kg/day for five days and then every 3 weeks for 6 months. On follow-up, motor symptoms and cognitive function improved moderately.

Conclusions: APS can be an underlying cause of dopa-unresponsive parkinsonism. Immunomodulatory treatment would be beneficial in these patients.

933

Unilateral spatial neglect and visual exploration strategies in corticobasal syndrome

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Objective: To evaluate (1) unilateral spatial neglect (USN), (2) visual exploration strategies, (3) visually-guided eye saccades characteristics in patients with corticobasal syndrome (CBS).

Background: Visual disorders and USN have been exceptionally described in corticobasal degeneration (CBD). However, the fronto-parietal damages supporting this disease could determine such phenomena. Dystonia, parkinsonism and apraxia are commonly observed during the course of CBD and make difficult the diagnosis of USN by classical paper-and-pencil tests. Photo-oculography (POG) appeared to be a convenient tool overcoming this difficulty.

Methods: Ten patients presenting with CBS and 11 control subjects without neurological or visual disorder were assessed for USN and visual strategies using both a reference method (paper-and-pencil tests) and POG. Characteristics of visually-guided eye saccades (latency, amplitude, velocity) were recorded by electro-oculography (EOG). We used a Wilcoxon test (quantitative data) or a Fisher exact test (binary data) for group comparisons.

Results: Paper-and-pencil line bisection (Schenkenberg test) showed a rightward deviation of the midpoint in the CBS group ($p=0.025$), mainly for lines located in the right part of the sheet. During POG cancellation tests, CBS patients displayed shorter fixations in the left part of the screen ($p=0.02$) and tended to start the exploration in the right part of the screen ($p=0.012$). These anomalies were clearer in patients with left predominance of the corticobasal symptoms. CBS patients also presented non lateralized omissions, perseverations and an increased completion time during paper-and-pencil cancellation tests. The POG showed an instability of gaze during bisection tests and a disorganization of scene exploration strategies. The latency of visually-guided saccades was identical in the CBS group and controls. More direction errors were observed in the CBS group than in controls during the antisaccade task.

Conclusions: Our data indicate that a minor USN is possible in CBS patients. It also highlights a disorganization of visual strategies, which is probably linked to a dysexecutive syndrome and to a poor performance of working and visuo-spatial memory.

934

Parkinsonism, multiple lipomas and hearing impairment in a patient with reduced activity of mitochondrial respiratory chain complexes II+III

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Objective: To report a patient with parkinsonian syndrome, familial lipomatosis, hearing impairment and mitochondrial respiratory chain alterations.

Background: Multiple symmetrical lipomatosis is characterized by symmetrical lipomas of neck, trunk and upper limbs. A central role in its pathogenesis is attributed to mitochondrial dysfunction. Ragged-red fibres in muscle biopsy, reduced activity of respiratory chain enzymes and deletions of mitochondrial DNA (mtDNA) have been reported in affected subjects. Moreover, cervical lipomas can be part or the only manifestation of Myoclonus Epilepsy with Ragged Red Fibres (MERRF) caused by a point mutation of the mtDNA. Mitochondria may also be involved in the pathogenesis of Parkinson's disease, having a central role in the production of reactive oxygen species, cellular metabolism and apoptosis, and two familial-PD associated genes (PARK2 and PINK1) are involved in mitochondrial homeostasis and distribution.

Methods: We report a 74 year old man with a 9 year history of parkinsonism presenting with asymmetrical rest tremor and bradykinesia. He had multiple symmetrical lipomas in the forearms and trunk, hearing impairment since age 5, and a family history of lipomas, hearing loss and neurological abnormalities. The family tree was consistent with an autosomal dominant inherited lipomatosis.

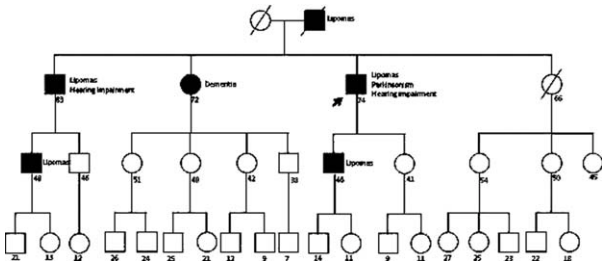

FIG. 1 (934).

Results: Screening for common mtDNA point mutations and rearrangements was negative, as well as LRRK2 analysis. Muscle histology revealed 3 ragged red fibres and 2 COX negative fibres and was considered within normal limits for the patient's age. Mitochondrial respiratory chain analysis showed reduced activity of complexes II+III (succinate:cyt c reductase 0.031; normal range 0.04-0.204, ratio to citrate synthase), with normal Coenzyme Q10 levels in muscle biopsy and peripheral blood mononuclear cells. Full POLG sequencing identified a novel variant (c.3511A>C) of uncertain significance in exon 22. Further studies are in progress.

Conclusions: The association of parkinsonism, familial lipomatosis and hearing impairment in this patient may suggest a role for mitochondrial dysfunction in the development of this condition. Reduced activity of complexes II+III has not previously been associated with multiple lipomatosis.

935

Serum and cerebrospinal fluid urate levels in Parkinson's disease and atypical parkinsonian disorders

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Objective: To evaluate urate levels in the serum and cerebrospinal fluid (CSF) from subjects with Parkinson's disease (PD) and atypical parkinsonian disorders (APD).

Background: Urate is a major natural antioxidant found in serum and brain. Low levels of serum urate were found to be associated with a higher risk for developing PD. In addition, higher serum and cerebrospinal fluid urate concentrations at baseline were associated with slower rates of clinical decline in PD.

Methods: *Patients:* Patients with PD and with APD, not treated with any dopaminergic medications. *Design:* Cross-sectional comparison of urate levels in the serum and CSF. *Biochemical analyses:* Serum and CSF were stored at -70 degree Celsius until the time of analysis. Urate concentrations were measured using the Roche Modular system (Basel, Switzerland). *Statistics:* Statistical significance of differences between groups was assessed using the Kruskal-Wallis test. Spearman's Rank Correlation Coefficient was used to evaluate correlations.

Results: The study included 6 patients with PD, and 37 patients with APD [13 multiple system atrophy (MSA), 18 progressive supranuclear palsy (PSP), and 6 corticobasal degeneration (CBD)]. Demographics and clinical characteristics are presented in table 1.

TABLE 1 (935). *Demographics and clinical characteristics*

Diagnosis	N	% males	Age	Disease duration	H&Y	S-urate (μmol/L)	CSV-urate (μmol/L)
PD	6	67	51.4 (40-69)	4 (2.9-7)	1.5 (1-3)	252.5 (159-298)	17.5 (12-27)
MSA	13	62	59.5 (54-74)	3.2 (1.9-9)	4 (3-5)	236 (177-398)	20 (12-36)
PSP	18	56	70 (53-77)	4 (0.3-6.3)	4 (3-5)	287.5 (192-550)	23.5 (12-56)
CBD	6	67	73 (60-81)	5 (2,4-10.5)	4.5 (3-5)	270 (192-670)	19.5 (12-85)
Synucleionopathies (PD and MSA)	24	63	58 (40-74)	3.7 (1.9-9)	3 (1-5)	237 (159-398)	19.5 (12-36)
Tauopathies (PSP and CBD)	19	58	71 (53-81)	4.1 (0.3-10.5)	4 (3-5)	286.5 (192-670)	21.5 (12-85)

Numbers represent median (lower and upper limits).

Patients with tauopathies (PSP and CBD) were significantly older and with higher Hoehn and Yahr (H&Y) scores compared with synucleinopathy (PD and MSA) patients. CSF levels of urate were about a 10-fold lower as compared to serum levels. Serum and CSF urate levels were highly correlated ($r_s=0.84$, $p<0.001$). No significant differences were seen when comparing serum and CSF urate levels in PD, MSA, PSP and CBD patients. However, serum urate levels were significantly higher in the tauopathy group compared with the synucleinopathy group ($p=0.048$), although with a broad overlap.

Conclusions: 1) Serum and CSF urate levels correlate, implying that urate levels in the CNS are regulated by the levels in the peripheral blood. 2) No major differences could be seen in serum or CSF urate levels across the diagnostic groups, although slightly elevated serum urate levels were seen in the tauopathy group (PSP and CBD) compared with the synucleinopathy group (PD and MSA).

936

Abnormal cortical plasticity in primary motor cortex in progressive supranuclear palsy

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Objective: To investigate mechanisms of cortical plasticity in primary motor cortex (M1) in patients with PSP we used the technique

of intermittent-theta-burst stimulation (iTBS) (Huang et al.2007) known to induce LTP-like processes at M1 level in humans.

Background: Previous neuropathological studies in patients affected by Progressive Supranuclear Palsy (PSP) showed a decreased pallido-thalamic inhibitory activity coupled with a decrease in inhibitory intracortical interneurons activity at the level of primary motor cortex.

Methods: i-TBS was delivered with a biphasic Magstim connected to a focal coil positioned over the hand primary motor area in 10 PSP patients and in 10 age-matched healthy subjects. Changes in M1 excitability were probed with single TMS pulses elicited by a monophasic Magstim 200 connected to a focal coil before and 5, 15, 30 minutes after iTBS. The intensity of monophasic pulses was chosen to obtain an MEP of about 1mV at baseline. Six out of the ten patients were also studied one year later.

Results: RMT, AMT and the intensity for 1mV MEP at baseline were significantly lower in PSP patients. iTBS in PSP patients elicited an increase in MEP size at 5, 15 and 30 minutes after iTBS, that was significantly higher in PSP patients in comparison to healthy subjects. The abnormal MEP facilitation was still present one year after the baseline evaluation and correlated with the clinical worsening of the disease.

Conclusions: The findings showed that in PSP patients there is an abnormal M1 plasticity, possibly due to a reduced inhibitory intracortical interneuron activity.

937

Progressive supranuclear palsy (PSP) with prominent corticospinal tract degeneration mimicking motor neuron disease (MND)

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Objective: To describe the clinical and pathological features of a case of "atypical PSP" presenting as MND.

Background: In recent years a number of variants of PSP have been identified, each with a characteristic clinical presentation. These include Richardson's syndrome (RS) with the classical clinical features of PSP, PSP-parkinsonism (PSP-P), pure akinesia and gait freezing (PAGF), corticobasal syndrome (PSP-CBS) and progressive non-fluent aphasia (PSP-PNFA) (Williams et al, Brain 2005;128:1247-1258). The latter four are collectively known as "atypical PSP" and have been shown to have a different distribution of pathology when compared to that seen in classical PSP (Richardson's syndrome). A recent study (Josephs et al, J Neuropathol Exp Neurol 2006;65:396-405) has also suggested that corticospinal tract (CST) degeneration in the setting of PSP pathology could represent another subgroup of atypical PSP.

Methods: A case with pathlogically confirmed PSP, diagnosed clinically as MND was extensively studied using various immunohistochemical stains and histopathology was compared with that seen in cases with classical PSP.

Results: Neuropathological examination of the brain and spinal cord of the index case demonstrated PSP-type 4R tau pathlogy in both neurons and glia in an atypical distribution for the classical form of the disease. In addition, severe CST degeneration and tau pathology in the anterior horn cells of the spinal cord were prominent features.

Conclusions: The neuropathological findings in this case are similar to the cases of PSP characterised by CST degeneration previously reported (PSP-CST). The extensive CST degeneration modified the clinical picture in this case, resulting in upper motor neuron signs, leading to the clinical diagnosis of MND. This case report supports the suggestion that PSP with CST degeneration represents an additional atypical variant of PSP, thereby broadening the clinicopathlogical spectrum of PSP.

TABLE (937).

Features	Current case	PSP-CST	PSP-P	PSP-RS
Common clinical diagnoses	MND	PSP, MND	PSP, IPD	PSP
Asymmetry	Yes	75%	45%	18%
Pyramidal signs	Yes	92%	4%	17%
Early supranuclear gaze palsy	No	No	Yes	Yes
Tufted Astrocytes	Yes	Yes	Yes	Yes
Severe CST degeneration	Yes	Yes	No	No
Globular glial tau inclusions	Yes	Yes	No	No

938

A case of parkinsonism perhaps caused by pellagra in Tanzania

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Objective: To explore whether, in a region where the population is prone to nutritional deficiencies, parkinsonism is ever a feature.

Background: Parkinsonism was reported as a feature of pellagra in older literature and could respond to nicotinamide therapy, as did the dementia and other features that are not dissimilar to the non-motor complications of PD.

Methods: Case Report.

Results: Whilst conducting a community-based prevalence study of Parkinson's disease (PD) in Tanzania, we met a patient who, despite satisfying UK PD Society Brain Bank criteria for PD, had a history suggestive of nutritional deficiency. AM is a 78 year old man with a 7 year history of worsening tremor, starting in his right upper limb and progressing to involve all 4 limbs, and mobility problems. He had lost a significant amount of weight and had a skin complaint. He also complained of urinary frequency, mood and sleep disturbance and short term memory impairment. AM had consulted a traditional healer who had diagnosed "a type of eczema" and given him herbal medication. This had not improved his symptoms. As part of the study all patients were commenced on levodopa. Whilst sourcing a sustainable supply of levodopa, all patients were given multivitamin tablets with a high concentration of B vitamins for 3 months. Once levodopa was available, patients discontinued the vitamin tablets. AM, however, made a remarkable improvement even before the levodopa had been started.

Unfortunately due to the distance and expense, it was not possible to review patients after multivitamins, but prior to levodopa, as well as post commencement of levodopa. This case is a potential case of parkinsonism secondary to pellagra. The striking improvement in symptoms, and dramatic reduction in UPDRS scores may not be compatible with levodopa alone. None of the other patients made such an improvement after multivitamins, although all have had benefit from levodopa.

Conclusions: Nicotinamide deficiency has been reported to cause a variety of neurological symptoms and parkinsonism was clearly described. We suggest that this case of parkinsonism, which has responded remarkably well to multivitamins, may well have had pellagra. As there is a simple, inexpensive and widely available treatment for nicotinamide deficiency, we feel it is a diagnosis and treatment worth considering in such patients with similar backgrounds.

TABLE (938). *Pre and post treatment characteristics*

	Baseline	1 year follow up
Weight	40kg	50kg
Hoehn and Yahr	5	3
UPDRS III	40	24
UPDRS Total	71	36
Mobility	Transfers with assistance	Independently with stick
Timed Get Up and Go	Unable	33 seconds

939

Syndrome of primary progressive freezing gait: A study of striatal dopamine transporter and of response to treatment

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Objective: To study dopaminergic (DA) transporter density and the response to DA and alternative treatments in patients with primary progressive freezing gait disorder (PPFG).

Background: PPFG is a syndrome with diverse causes characterized by early gait freezing. It is unresponsive to dopaminergic medications but the extent to which the DA nigrostriatal pathways are affected is unknown.

Methods: Seven patients with a clinical diagnosis of PPFG (Factor et al, 2002) were evaluated using morphological imagery and SPECT imaging of the dopamine transporter with FP-CIT. DA innervation loss was quantified using occipital cortex as a radioactivity uptake reference. All patients underwent acute L-dopa test and received a chronic DA treatment. The effect on gait of rasagiline (1mg/day during one month) and of repetitive transcranial magnetic stimulation (rTMS) at 1hz of the primary motor or premotor cortices (4 consecutive days) was studied in respectively 3 and 2 patients.

Results: At the time of imaging, the 7 patients (5 men) had a mean age of 79 years (range 72-87) and a mean duration of illness of 6 years (range 2-9). All patients had a low FP-CIT binding. Mean binding potentials ($\pm$SD) on the most and the least affected side were 1.04 ± 0.31 and 1.31 ± 0.38 ($N>2.00$) for the caudate nucleus, 0.67 ± 0.34 and 0.75 ± 0.43 ($N>1.80$) for the anterior putamen, and 0.27 ± 0.09 and 0.41 ± 0.14 ($N>1.10$) for the posterior putamen. The mean asymmetry index was 43% (range 12-74). Neither acute L-dopa test, nor chronic L-dopa treatment (mean daily dose 800mg, range 600-1250), rasagiline or rTMS had significant effect on gait.

Conclusions: We found a severe presynaptic dopaminergic loss in the striatum while no improvement of gait occurred under L-dopa in both acute and chronic conditions. This contrast suggests that, if the nigro-striatal lesion is involved in the pathophysiology of PPFG, additional lesions in the basal ganglia system counteract gait improvement. Alternatively, gait disorder in PPFG may result from extra-nigral lesions. Both hypotheses are in line with studies showing that PPFG may be caused by neurodegenerative diseases characterized by widespread subcortical lesions (Factor et al, 2006). Neither rTMS nor rasagiline seem to be promising alternative treatments.

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Parkinsonism secondary to primary progressive multiple sclerosis

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Objective: To describe a patient with a diagnosis of Primary Progressive Multiple Sclerosis (PPMS) who presented signs of parkinsonism.

Background: Multipe Sclerosis (MS) is a demyelinating disease with a wide phenotypic spectrum. Although tremor is the most frequent extrapyramidal manifestation of Multiple Sclerosis, parkinsonism has been described in few reports in the literature.

Methods: We studied a patient with Multiple Sclerosis. clinical history was taken. Physical examination and routine laboratory test were performed. Magnetic resonance imaging of the brain, CSF Analysis and immunological test also were performed.

Results: The patient is a 51 years old Venezuelan man who in July 2005 developed rigidity in upper and lower left limbs followed by gait difficulty, slowness and tremor left side of the body. A progressive worsening of symptoms was reported. On physical examination a moderate resting and action tremor was observed in the left arm. He scored 45 at the Unified Parkinson's Disease Rating Scale (UPDRS) part III. Ocular movement and ocular fundi was normal. Deep tendon reflexes were brisk in all 4 limbs.Brain magnetic resonance imaging (MRI) demonstrated multiple hyperintense Flair and T2- weighted images located in the periventricular areas, corpus callosum and subcortical white matter in both cerebral hemispheres. No lesions in the basal ganglia were observed. Visual evoked potential was normal. Cerebrospinal fluid analysis showed oligoclonal bands. Inmunological tests were normal. Treatment with levodopa was started without improvement of the symptoms. One daily gram of IV methylprednisolone for five days was administered followed by methylprednisolone 1 gr (IV) monthly. Three months later the patient was evaluated with improvement of the symptoms. He scored 36 at the UPDRSS.

Conclusions: Parkinsonism secondary to Multiple Sclerosis has been described in a few reports in the literature. We describe a patient with a diagnosis of Primary Progressive Multiple Sclerosis who presented signs of parkinsonism. The patient received treatment with lcorticosteroid with a remarked improvement of the symptom. This observation support MS as the cause of symptoms of parkinsonism. The relative involvement of basal ganglia and subthalamic nucleus by Multiple Sclerosis plaques may explain the presence of movement disorders as a clinical manifestation of Multiple Sclerosis.

941

Lithium in progressive supranuclear palsy and corticobasal degeneration

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Objective: To evaluate (1) safety and tolerability of lithium in subjects with progressive supranuclear palsy [PSP] or corticobasal degeneration [CBD] (2) study drug compliance and (3) effects of lithium on clinical measures using the PSP Rating Scale, Unified Parkinson's Disease Rating Scale Motor Subscale, PSP Quality of Life Scale, Frontal Assessment Battery, and Geriatric Depression Scale-15.

Background: PSP and CBD are characterized by accumulation of hyperphosphorylated tau. Glycogen synthase kinase-3β phosphorylates tau, and this activity is inhibited by lithium. Lithium is thus a rational therapeutic approach for disease modification in PSP/CBD.

Methods: Seventeen subjects with PSP or CBD were enrolled and received open-label lithium in a concentration-controlled design. The concentration was titrated over a 5-9 week period, and subjects received study drug for 28 weeks. Laboratory studies were conducted for safety monitoring, and all adverse events (AEs) and dosage adjustments were reported.

Results: Seventeen subjects enrolled in the study, and 14 were evaluable for the primary outcome. Of the evaluable subjects, 1 completed the 28-week treatment period, and 13 prematurely discontinued study drug. Reasons for premature discontinuation were: drug related AE > grade 3 (n=5); drug associated event resulting in subject requesting discontinuation (n=7); AE resulting in the PI feeling that study drug should be discontinued (n=1). There were 3 SAEs, 2 of which were assessed as possibly related to study drug (hospitalization associated with grade 2 fall or grade 3 balance disorder), and one which was assessed as probably not related (grade 4 hypernatremia). Adverse events occurring in greater than 20% of subjects included: tremor (59%), gait disturbance (35%), fatigue (29%), urinary tract infection (29%), asthenia (24%), and hypokinesia (24%). Three subjects withdrew from the study prematurely due to reasons unrelated to the study drug.

Conclusions: These data suggest that lithium is not well tolerated in this patient population. Trials of other GSK-3β inhibitors remain of interest.

942

Prospective 5-year natural history study of probable multiple system atrophy (MSA) in 175 North American subjects

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Objective: To examine disease progression and survival in 175 patients with probable MSA studied prospectively to determine (a) life expectancy as a prelude to designing pharmacologic interventions and (b) whether there is a difference in course between subjects who, at entry, show cerebellar ataxia and autonomic failure without parkinsonian features (MSA-C) as compared to those with parkinsonian features and autonomic failure without cerebellar ataxia (MSA-P) and subjects with mixtures of parkinsonian and cerebellar features plus autonomic failure (MSA-PC).

Background: Previous studies of the natural history of MSA have been retrospective. This prospective study of the disorder was designed to examine natural history in subjects who entered the study with the diagnosis of probable MSA.

Methods: We examined at six-month intervals 175 patients with the diagnosis of probable MSA based upon the Second Consensus Criteria. On entry, the subjects were divided into three groups, MSA-C, MSA-P and MSA-PC. Longitudinal follow-up included evaluations with UMSARS I, II, III, IV, COMPASS, and SF-36. Patients were followed for an average of 2.6 years. We analyzed data using Kaplan-Meier Survival Analysis.

Results: The study group consisted of 105 (60%) males and 70 (40%) females, mean age at entry 63.4±8.6 yrs. We enrolled 20 patients with MSA-C, 72 with MSA-P, and 83 with MSA-PC. After six years, 101 subjects had expired, of whom 39 received autopsy examination, with verification of diagnosis in 32 cases (6 pending, 1 MSA not confirmed). Half of the patients who died had lived less than 2 years after enrollment, and by 3 years after enrollment only 53 patients (30%) remained able to participate in the study. Kaplan-Meier Survival Analysis revealed no differences between groups and we found no differences between groups in progression on any of the UMSARS scales.

Conclusions: This study revealed a high mortality rate and a relatively short average survival time after enrollment. There was no difference in course or longevity based upon MSA type at enrollment. These data support enrollment of subjects at earlier stages to allow longer survival in pharmacologic intervention studies.

943

Clinical features of dystonia in atypical parkinsonism

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Objective: To evaluate the frequency and pattern of dystonia in a group of patients with atypical parkinsonism (multiple system atrophy-MSA, progressive supranuclear palsy - PSP, and corticobasal degeneration - CBD) and to investigate whether dystonia could be the first presenting symptom at disease onset in those patients.

Background: The association between Dystonia and Parkinson's disease (PD) has been well described especially for foot and hand dystonia. There is however few data on dystonic postures in patients with atypical parkinsonism.

Methods: A total of 38 medical charts were reviewed (n=23/MSA group; n=7/CBD group; n=8/PSP group) and data values were described as means/standard deviations. The variables evaluated were sex, age at onset, disease duration, first symptom, clinical features of dystonia and other neurological signs, response to levodopatherapy, Hoehn&Yahr scale >3 after three years of disease, and magnetic resonance imaging findings.

Results: The overall frequency of dystonia in our sample was 50% with 30.4% (n=7) in the MSA group, 62.5% (n=5) in the PSP group, and 100% (n=8) in the CBD group. In none of these patients, dystonia was the first complaint. Several types of dystonia were found: camptocormia, retrocollis, anterocollis, blepharoespasm, oromandibular, and foot/hand dystonia.

Conclusions: In our series, dystonia was a common feature in atypical parkinsonism (overall frequency of 50%) and it was part of the natural history although not the first symptom at disease onset. Neuroimaging abnormalities are not necessarily related to focal dystonia, and levodopa therapy did not influence the pattern of dystonia in our group of patients.

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Lower limb dystonia: A unusual symptom in a patient with a tauopathy

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Objective: To report the case of a patient with left lower limb dystonia that was a key clue for the diagnosis of tauopathy.

Background: Progressive supranuclear palsy (PSP) and cortico-basal degeneration (CBD) belong to a clinically heterogeneous but overlapping group of diseases referred as tauopathy. In affected patients, phosphorylated tau protein aggregation in various brain regions is a common feature. Upper limb dystonia and gait deficits were described as presenting manifestation in both PSP and CBD whereas unilateral apraxia is highly suggestive of CBD. Lower limb dystonia was not frequently reported in these pathologies.

Methods: We describe the clinical case of a 67 years old male patient that was admitted in a Movement Disorders unit because of recent gait disturbance together with subtle progressive cognitive and behavioral changes that had been noticed for 3 years. Diffuse cortical and sub-cortical atrophy (including mesencephalon) was previously evidenced by brain MRI. Clinical work-up included detailed videotaped neurological evaluation, cognitive testing, ocular movements recording, brain tomoscintigraphy with iode 123 Ioflupane (DatScan ®) and Bisicate-Tc-99m.

Results: Gait was impaired both by balance deficit and severe left lower limb (LLL) dystonia with equinism and plantar flexion of toes. Neurological examination also disclosed slight alteration of motor programming in LLL. In upper limbs, mild akinesia and hypertonia were noticed on the left side but there was no dystonia nor apraxia. Ocular movements study showed vertical gaze palsy. Cognitive testing mainly showed behavioral and cognitive frontal release syndrome. Finally, DatScan ® disclosed severe bilateral and asymmetric dopaminergic denervation with the right side being slightly more affected than the left side. Finally, Bisicate-Tc-99m scan showed a hypoperfusion of prefrontal cortex particularly for the right hemisphere. The patient was diagnosed as having a tauopathy but it was not possible to make a decision between PSP and DCB.

Conclusions: Although unusual, severe lower limb dystonia may be observed in tauopathy.

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Case report and literature review of levodopa-reponsive young onset Parkinson's disease in a patient with Down's syndrome

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Objective: To report a patient with Down's syndrome and levodopa-responsive young onset Parkinson's disease.

Background: Down's syndrome is associated with early onset Alzheimer's disease (AD). Parkinsonism in Down's patients with AD is generally poorly responsive to levodopa. One case has previously been reported of a 45-year-old Down's syndrome patient who developed levodopa-responsive Parkinson's disease.

Methods: Retrospective chart review.

Results: A 21-year-old female patient with Down's syndrome presented with a three-year history of generalized slowness. Her parents noted that she was not swinging her arms and was dragging her right side while walking. On examination, she had an MMSE of 30/30. She had a right-sided rest tremor as well as asymmetric, moderate bradykinesia and rigidity. No postural instability or dystonia were noted. The patient was given a test dose of carbidopa/levodopa 25/100 in the office. Her UPDRS III score improved from 36 to 22. She improved from lying listlessly in bed to running down the hallway.

She is currently on pramipexole with improvement in tremor, bradykinesia, and rigidity.

Conclusions: Most reports of parkinsonism with Down's syndrome have been in patients with AD with poor levodopa responsiveness. The parkinsonism in Down's syndrome has been thought to be associated with Lewy body formation. Our patient illustrates that Down's syndrome can be associated with typical levodopa-responsive young onset PD in the absence of AD. Further studies are needed to determine whether Down's patients are at increased risk of young onset PD, in addition to early AD.

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Respiratory disturbances in the early phase of progressive supranuclear palsy

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Objective: To investigate, whether respiratory disturbances are part of Progressive supranuclear palsy (PSP) in comparision to Parkinson's disease (PD) and Cortico-basal degeneration (CBD).

Background: Patients with PSP often have pneumonia associated with a poor prognosis and respiratory related causes of death are more common in patients with PSP than in patients with PD (Papadoupolos, 2005). Neurodegeneration in PSP also occurs in the medulla oblongata close to the site where respiratory neurons are located. Therefore disturbances of respiratory rhythms might be an early clinical sign of PSP.

Methods: We performed spirometric evaluations on patients with PSP (n=22), PD (n=17) and CBD (n=7). The following parameters were investigated: oxygen saturation, pH, vital capacity (VC), total lung capacity (TLC), residual volume (RV), forced expiratory volume (FEV), Tiffeneau test, functional residual capacity (FRC) and median ventilatory volume (MVV).

Results: All PD patients and patients with CBD have been able to perform the tasks. In PSP patients 3 out of 25 have not been able to perform the entire tasks and therefore, they have not been included. Patients with PSP had significantly reduced MVV (39±12 %), reduced VC (75±16 %) and lower rates in the Tiffeneau test (76±12 %) as compared to patients with PD. Furthermore, MEF75, MEF50, MEF25 and MMEF were significantly reduced as compared to patients with PD and CBD. In contrast RV % was elevated in PSP patients as compared to PD and CBD patients. P01 % was markedly increased in CBD patients as compared to PD and PSP patients. Results of blood gas investigation and TLC were within normal ranges in all patients investigated.

Conclusions: 1. Our data provide evidence, that control of breathing and volitional breathing might be impaired already in the early phase of PSP. 2. This respiratory phenomenon might be called respiratory apraxia. 3. The present series of patients suggests that the corticobulbar pathways causing pseudobulbar palsy lead to a partial functional interruption of the behavioural pathways. The resultant supranuclear disturbances of respiration may cause severe impairment of the capacity to perform respiratory tasks to command.

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Effectiveness of an inpatient movement disorders program for patients with atypical parkinsonism

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Objective: To investigate the effectiveness of an inpatient movement disorders program for patients with a primary diagnosis of Atypical parkinsonism and to determine whether gains made were clinically meaningful.

Background: Given the poor response to pharmacological intervention and the complexity of the motor and nonmotor signs in persons with Atypical parkinsonism, it is challenging to manage the complex medical and rehabilitation needs of this population on an outpatient basis. A movement disorders program in an inpatient rehabilitation setting may be a viable alternative.

Methods: Ninety-one patients with a diagnosis of atypical parkinsonism were admitted from January 2004 to August 2008 to an inpatient rehabilitation hospital with an interdisciplinary movement disorders program. Patients participated in a rehabilitation program consisting of a combination of physical, occupational, and/or speech therapy for a total of 3 hours per day, 5 to 7 days per week and pharmacologic adjustments based on objective data collected daily. The differences between admission and discharge scores were analyzed for the Functional Independence Measure (FIM), Timed Up and Go Test (TUG), Two-Minute Walk Test (TMW), Berg Balance Scale (BBS) and Finger Tapping Test (FT).

Results: Significant improvements were observed from admission to discharge for the Total FIM, Motor FIM, Cognitive FIM, TUG, TMW, BBS and Left and Right FT ($p>.001$). Clinically significant improvements in Total FIM score were evident in 74% of the patients. The results were similar for eleven patients whose medications were not adjusted during their stay (rehabilitation only).

Conclusions: Patients with a primary diagnosis of Atypical parkinsonism benefit from an inpatient interdisciplinary movement disorders program to improve functional status.

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Exclusion of linkage to chromosome 14q in Serbian family with idiopathic basal ganglia calcification

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Objective: to present a clinical, neuroradiological and genetic findings in Serbian family with idiopathic basal ganglia calcification (IBGC).

Background: Fahr disease or IBGC is a very rare neurodegenerative syndrome that is associated with a variety of movement disorders and neurobehavioral and cognitive manifestations. Despite numerous clinical, pathological, and biochemical investigations, its etiology remains unknown. Familial IBGC usually follows an autosomal dominant pattern of inheritance. Despite the mapping to chromosome 14q of a susceptibility locus for IBGC (IBGC1) in one family, this locus has been excluded in several others, demonstrating genetic heterogeneity in this disorder.

Methods: We have identified five members of one family in three generation with probable autosomal dominantly inherited IBGC. The diagnosis of IBGC was based on CT scans with exclusion of all secondary causes of calcification in proband. We performed neurological, neuropsychological and psychiatric assessment in all patients in order to show heterogeneity in clinical presentation in the same family. Our genetic analysis was focused on testing the evidence for linkage to the IBGC1 locus on chromosome 14q, previously reported to be associated with familial IBGC, using the set of microsatellite markers (D14S596, D14S1014, D14S75, D14S306, D14S288, D14S259).

Results: We observed marked differences in clinical and radiological findings in three generations. Three patients were presented with almost similar distributions of calcifications on CT scan, but two with mild hyperkinetic movements, and the other with severe gait disturbances. Two of them were asymptomatic, with less prominent and different distribution of calcification on CT scans. In our genetic analysis, the IBGC1 locus was excluded.

Conclusions: Linkage analysis excluded the IBCG1 locus in our family supporting the presence of a second locus for IBGC, which might help to elucidate this intriguing neuropsychiatric condition. The search for genetic markers related to IBGC is quite active and will be determinant for the definition of its physiopathology.

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Duodenal duodopa in MSA-p

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Objective: To assess the effectiveness of duodenal Duodopa infusion in advanced MSA-p.

Background: MSA is dopa responsive in 30% and in 5-10% this effect is longlasting. In MSA however, dysphagia often inhibits the use of oral medication over time.

Methods: A 76 year old woman with a probable MSA-p suffered from severe hypophonia and minimal control over her hands. She could mutter through a communicator-device, and could just control her electrical wheelchair. Dopa responsiveness was tested by dopamine effects on Time Up and Go (TUG), Nine Hole Peg Test (NHPT) and 10 Meter Walking Test (10MWT).

Results: Dopa responsiveness was proven by an apomorphine challenge. Performance improved on TUG (24.6 seconds versus 13.1 seconds), NHPT (54 seconds versus 38 seconds in right hand) and 10MWT (13.2 versus 12.6 seconds). Therapy with levodopa/carbidopa and a dopamine agonist was started orally and was later switched to duodenal Duodopa therapy due to dysphagia.To assess persisting dopa responsiveness in progressed disease, she was scored both with and without Duodopa infusion. On the 10MWT, stopping Duodopa infusion deteriorated performance (52 versus 90 seconds). TUG and NHPT were no longer possible both with and without Duodopa.During Duodopa infusion, there was a severe hypophony, but she was still intelligible. Motor control of her right hand improved to an extend where she was able to control her electronic wheelchair. Switching off Duodopa infusion renderred her aphonic and unable to control her wheelchair. The patient reported a vast improvement in Quality of Life on the Duodopa infusion. She still manages to live at home with additional care.

Conclusions: In dopa responsive patients suffering from MSA-p, duodenal Duodopa infusion should be considered when oral medication is no longer an option. Duodenal Duodopa is an expensive therapy and should be reserved for a select group of patients. Dopa-responsiveness should be monitored throughout treatment. The effect of dopamine treatment should not only be assessed in rating scales such as TUG and 10MWT, but also in terms of Quality of Life.

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Cerebral glucose metabolism, clinical features, neuropsychological profile and MR imaging in patients with corticobasal syndrome and multiple system atrophy

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Objective: To study cerebral glucose metabolism, MR imaging of consecutive patients with corticobasal degeneration and multiple system atrophy in correlation with their clinical and cognitive profile.

Background: Although considered pure movement disorders, recent studies have shown significant cognitive impairment in corticobasal degeneration and mild impairment in multiple system atrophy. Exact role of imaging with MRI Brain or FDG PET in picking up these cortical deficits is still not clearly known.

Methods: 17 and 9 consecutive patients with clinical diagnosis of corticobasal degeneration syndrome and multisystem atrophy, respectively were studied. They underwent detailed neurological examination including UPDRS III on and off scores, autonomic function tests. Detailed neuropsychological assessment was done to assess episodic memory, language, executive function, visuospatial functions and praxis. Imaging was done with 1.5 Tesla MRI brain and 18FDG PET CT brain.

Results: In 17 patients with CBD, executive dysfunction was seen in 82.3%, visuospatial impairment in 58.8%, language dysfunction in 23.5% and normal cognition in 17.6%. Asymmetric temporoparietal atrophy on MRI brain and asymmetric focal hypometabolism in basal ganglia, inferior parietal, temporal and frontal lobes on 18FDG PET were seen in 75% and 88% respectively. Among 9 patients with MSA, 3 had MSA-C and 6 MSA-P. 66.7% of patients with MSA had mild executive dysfunction.100% of MSA-C patients had MRI -brain and FDG PET abnormalities.MRI brain was abnormal in 40% and FDG PET revealed striatal, frontal and mild cerebellar hypometabolism in 60% of MSA-P patients. Significant concordance of imaging was seen with executive dysfunction and was significantly more with 18 FDG-PET (CBD-85.71%, MSA-80%), compared to MRI brain.

Conclusions: Cognitive impairment with involvement of frontal executive functions, visuospatial and language functions in patients with CBD and impairment of frontal executive function in patients with MSA are an integral part of the syndromes. Both MRI Brain and 18 FDG PET are equally sensitive in diagnosis of CBD and MSA but the true extent of involvement in patients with both MSA and CBD was better delineated by 18FDG PET.

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The *PINK1* gene: Investigating South African Parkinson's disease patients

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Objective: To assess the prevalence of PINK1 genetic variants in South African patients diagnosed with early- and late-onset Parkinson's disease (PD).

Background: Mutations in PINK1 are the second most common cause after parkin of autosomal recessive early-onset PD. PINK1 is a protein kinase that is localized to the mitochondrion and is ubiquitously expressed in the human brain. Recent studies aimed at elucidating the function of PINK1, have found that it has neuroprotective properties against mitochondrial dysfunction and proteasomally-induced apoptosis. PINK1 phosphorylates specific mitochondrial proteins, and in so doing modulates their functions.

Methods: For this study, 136 unrelated PD patients, from all South African ethnic groups, were recruited from the Movement Disorders clinic at Tygerberg Hospital, Cape Town, as well as from the Parkinson's Association of South Africa. The average age at onset (AAO) of the study group was 52 years. Their genomic DNA was screened for mutations in PINK1 using the High-Resolution Melt technique and direct sequencing.

Results: Eight different sequence variants were detected: five previously reported polymorphisms (L63L, IVS1-7A>G, A340T, N521T and 3'-UTR+37A>T) and three potentially disease-causing mutations (Y258X, P305A and E476K). The only novel variant is P305A, which is situated within an evolutionary conserved region of the gene as well as in the functional serine/threonine kinase domain of PINK1. The novel P305A variant was found in a female patient of Black Xhosa ethnicity who had a positive family history of the disease and an AAO of 30 years.

Conclusions: This is the first report on mutation screening of PINK1 in the South African population. The novel P305A variant identified in the study has the potential to influence the function of PINK1 due to its location. Studies are ongoing to determine the prevalence of the three potentially disease-causing mutations in ethnically matched control samples. Future work will be to assess the significance of these variants by means of functional studies. PINK1 is not the common cause of PD in the South African population.

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Comparison of frontal executive dysfunction and neuropsychiatric features in patients with PSP, PSP-P and PD in India

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Objective: To study and compare the range and severity of frontal executive dysfunction and neuropsychiatric manifestations in patients with PSP SR, PSP-P, PD and normal controls.

Background: PSP-P is now a recognized variant of PSP, and is believed to have features that resemble PD. It may be surmised that frontal executive dysfunction and neuropsychiatric manifestations in PSP-P would be less severe than those seen in classic PSP SR.

Methods: Six patients each of PSP, PSP-P and PD were compared on a variety of measures to assess frontal executive dysfunction, clinically obvious behavioural manifestations of frontal dysfunction and other neuropsychiatric derangements. Six age and sex matched normal controls were also included. The measures included the Frontal Assessment Battery, the Frontal Behavioral Inventory, Digit Forwards and Digit Backwards, Digit Symbol Test, Wisconsin Colour Card Sorting Test and the Stroop Test. The NPI was used to assess Neuropsychiatric features.

Results: Patients of PD performed best on all tasks compared to PSP-P patients. PSP-P patients performed better than classic PSP SR.

Conclusions: Findings confirmed our belief, based on previous experience, that frontal executive dysfunction and behavioural or neuropsychiatric manifestations in PSP-P are less severe that in PSP, and seem to lie midway between PD and PSP SR with respect to severity and range of involvement.

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Does the addition of new raters to a Parkinson's disease clinical trial result in increased noise? (Initial findings)

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Objective: To assess the potential impact of introducing new raters to a Parkinson's disease clinical program.

Background: Multiple factors, like study design; rater clinical, clinical trials and scale experience; and previous training and certification on scale administration and scoring contribute to data quality in clinical trials. In a large industry sponsored Parkinson's disease (PD) multiple-study program, UPDRS certification performance of raters who had previously qualified to rate in an earlier study, was retrospectively compared with those of new raters attempting to qualify on a different protocol within the program.

Methods: All raters intending to participate in this clinical trial of advanced PD needed to meet the identical pre-defined level of experience, and be trained and certified on the UPDRS part III prior to assessing study subjects. "Program raters" (those raters who previously qualified to rate in the earlier protocol) had the option to either attend the live training for the next study or review UPDRS training on a CDROM. They also had to successfully watch and score a single UPDRS video (#1) of a part III exam. "New raters", defined as not having been previously certified in this program, had to attend an Investigators' meeting (IM), where they received live, robust scale training and had to demonstrate competency on 2 UPDRS part III videos (#1 and 2). Program vs. New raters' performance on video #1, the only UPDRS video assessment they had in common, was compared.

Results: 228 raters (101="Program", 127="New") submitted scores for video #1. The mean total group score was 35.8 (+8.8), and a single factor ANOVA showed that not only did "Program" raters score statistically significantly lower compared to "New" raters at $\alpha=0.05$ (34.1 ± 6.0 vs. 37.2 ± 10.3), but they more closely approached the scores of the Expert Consensus panel.

Conclusions: The analysis demonstrates that the introduction of new raters into a clinical program can potentially be a source of signal noise. Future study of how these raters perform over the course of the study, as well as the potential benefit of additional pre-IM training for the "New" raters would be beneficial.

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Anticholinergic responsive freezing of gait as a presentation of pantothenate kinase-associated neurodegeneration

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Objective: To report a case of panthothenate kinase-associated neurodegeneration (PKAN) with an unusual presentation: Freezing Of Gait (FOG), which responds to anticholinergic treatment.

Background: PKAN is a neurodegenerative disorder associated with brain iron accumulation. The typical presentation is generalized dystonia. Prominent FOG is a rare presentation in PKAN. In parkinsonian syndromes, FOG is very difficult to treat, and the mechanism remains unknown.

Methods: We report an 18 year-old man with PKAN and developmental delay, spasmodic dysphonia starting at age 6, limb dystonia starting at age 10, and frequent falls from FOG starting at age 14. His MRI brain revealed the "eye of the tiger" and genetic analysis in his brother, who has generalized dystonia, revealed that he was a homozygote for a mutation of the PANK2 gene.

Results: Trihexyphenidyl 5mg TID improved his gait significantly with less FOG and falling. Baclofen 20mg TID helped the dystonic posturing of his feet.

Conclusions: PKAN should be included in the differential diagnosis in a young individual with FOG. Anticholinergics are not usually considered to be the treatment of FOG in parkinsonian syndromes but can be used in PKAN. Anticholinergic responsive FOG in PKAN might provide insights into the pharmacology of human gait generation.

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Clinical factors related to the size of carotid arterial plaque in patients with vascular parkinsonism

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Objective: Carotid arterial stenosis becomes more common and important risk factor for stroke patients in Asian area, also can be a risk factor for vascular parkinsonism.

Background: We reviewed stroke database to investigate clinical factors related to carotid arterial stenosis, including intracranial arterial stenosis and peripheral arterial disease which reflects advanced atherosclerosis in patients with vascular parkinsonism.

Methods: The patients with vascular parkinsonism whose stroke onset were within 1 week when admitted at the National Health Insurance Corporation Ilsan Hospital from January 2005 to December 2007 with available carotid ultrasound study, transcranial Doppler (TCD) examination and ankle-brachial indexes (ABI) formed the analysis cohorts. Retrospective review was performed.

Results: A total of 304 patients were included during that period. By duplex ultrasound, common/internal carotid arteries are examined and the greatest diameter of plaques are recorded. 3 groups of carotid arterial plaques are defined: diameter is less than 2mm (112 patients, 37%), 2-4mm (174 patients, 57%) and greater than 4mm (18 patients, 6%). As the size of carotid arterial plaques increased, ABI is decreased ($P=0.000$) and the number of intracranial arterial stenosis is increased ($P=0.008$). Among the risk factors, Age, diabetes, male patients are increased ($P=0.000$, $P=0.047$, $P=0.004$) and smoking history showed tendency of increase ($P=0.057$) as diameter of carotid arterial plaque increase. However hypertension, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride and past stroke history are not correlated with carotid arterial stenosis.

Conclusions: Among the patients with vascular parkinsonism, more than a half of them have carotid arterial plaque which diameters are greater than 2mm and these patients tend to have higher burden of advanced atherosclerosis as evidenced by a higher prevalence of diabetes, intracranial arterial stenosis and peripheral arterial occlusive disease.

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Vascular Parkinson's syndrome after cerebrovascular diseases: Comparision of one ischemic lesion and multiple silent lacunar infarction

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Objective: Study purposed to compare the prevalence, clinical features of Vascular parkinsonism (VaP) and MRI correlates of multiple silent lacunes (MSL) and One Ischemic Lesion(OIL).

Background: Vascular parkinsonism (VaP) symptom-complex, including tremor at rest, rigidity, slowness of movement, and difficulty in walking can be resulted of multiple silent lacunes (MSL) or One Ischemic Lesion(OIL). Establishing the risk factors, clinical features and radiological correlates of both conditions inducing the movement disorders as a consequence, might be helpful in improving patient rehabilitation.

Methods: 147 OIL and 91 MSL patients were prospectively studied. Initial stroke severity assessed by NIHSS. Type, side and size of stroke lesion were evaluated by conventional MRI. VaP was recorded in acute stage and 3 month later using the Unified Parkinson's Disease Rating Scale (UPDRS). Risk factors, clinical, demographic and radiological variables were set to multiple linear regression and binary logistic regression analysis to find the independent correlates of VaP.

Results: Post stroke parkinsonism (brady-hypokinesia, muscles tonus rigidity) in OIL found in 16(10,8%), which is not depending on stroke side. Tremor, mostly in affected side, occurs in 5(3,4%) patients. In MSL the incident of VaP more higher. Parkinsonism was found in 19 (20,8%) patients, tremor- in 7 (7,68%) patients. The follow-up UPDRS scale found to be worse in patients with movement disorders in MSL. Multiple linear logistic regression analysis revealed significant share of hypertension, atrial fibrillation, diabetus mellitus particularly untreated, on development of VaP.

Conclusions: According to the present study the risk VaP development seems to be higher in MSL than in OIL.

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Effect of rasagiline in patients with progressive supranuclear palsy (PSP)

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Objective: To assess the benefit of rasagiline in the treatment of PSP.

Background: Progressive PSP is characterized by early falls, vertical ophthalmoparesis, akinetic-rigid features, bulbar dysfunction and dementia. Patients rapidly lose the ability to stand and walk unassisted and the median disease duration is 6-7 years. There is currently no effective treatment. Rasagiline has been shown to improve postural instability in Parkinson's disease.

Methods: A total of 17 patients (8M:9F) were treated over 12 months with rasagiline 1 mg/day. Fall frequency was recorded using a diary. Postural instability was assessed using electronic posturographic measurements. PSP rating scale (PSPRS) scores, eye movements, dysarthria (BoDys), depression, dysphagia and impulse control disorders (ICD) were documented.

Results: Baseline: mean age 67±8 years; mean PSPRS score 54±14 points; disease duration 4–144 months. Twelve patients completed the study; 3 had minor side effects (headache and bladder disturbances) that were reversible after drug discontinuation and 2 died due to natural disease progression. After 3–5 months, there was a marked reduction in postural instability with improved gait. The mean number of falls decreased from 23±9 falls/week at baseline to 19±9 falls/week at month 7. At baseline, 16 patients had signs of a depressed mood; of these 3 patients already receiving antidepressants were able to stop. No patient receiving rasagiline required additional antidepressants. Ten patients showed a slight improvement in dysarthria from a mean of 2.5±0.5 to 2.7±0.5 on the BoDys scale. One patient had an ICD at baseline, which was not influenced by rasagiline. There were no effects on eye movements and no patient developed hallucinations. In addition, the frequency of pneumonia was low during rasagiline treatment. This may be an important finding as respiratory parameters are markedly reduced in PSP patients.

Conclusions: For this small group of patients with PSP, 12 months treatment with rasagiline improved postural instability and may have prevented the onset of depression. Rasagiline was well tolerated even in patients with advanced PSP. Following these positive results a randomized, double-blind, placebo-controlled study has been initiated.

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Autopsy confirmed multiple system atrophy (MSA) cases: Mayo experience and role of autonomic function tests

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Objective: To evaluate the Mayo experience with particular focus on clinical features and autonomic function tests in autopsy-confirmed MSA cases seen at Mayo Clinic, Rochester, Minnesota.

Background: The relentless progression of parkinsonism, cerebellar signs, and autonomic failure suggests the diagnosis of MSA. The Mayo experience has indicated that the severity and distribution of autonomic deficits may be helpful in the diagnosis of MSA.

Methods: We analyzed our experience with 29 autopsy confirmed cases of MSA evaluated at Mayo Clinic who had undergone formalized autonomic testing. Patients underwent evaluation of adrenergic, sudomotor, and cardiovagal function and thermoregulatory sweat test (TST) from which we derived the composite autonomic severity score (CASS). We also measured plasma catecholamines.

Results: Patient characteristics: M, 17; F, 12; age of onset, 57±8.1 yrs; disease duration to death, 6.3±3.1 yrs; first symptom: autonomic, 18; parkinsonism, 7; cerebellar 2. Clinical phenotype at onset was MSA-P, 19; MSA-C, 8; pure autonomic failure (PAF), 2. Clinical diagnosis at last visit was MSA for 28 cases. One case was diagnosed as PAF at his last (and only) Mayo visit. Autonomic manifestations included: orthostatic hypotension in 72%; neurogenic bladder in 89%; and severe constipation in 77%. Sleep disturbances included REM sleep behavior disorder (54%); sleep apnea (38%); and nocturnal stridor (30%). Autonomic failure was severe: CASS was 7.2±2.3 (maximum=10). TST% was 65.6±33.9% and exceeded 40% in 68%. The most common pattern was global anhidrosis. Other patterns suggesting of MSA were mixed, segmental or regional anhidrosis. 2/22 patients had normal patterns. Norepinephrine (NE) was normal supine (203.6±112.7) but orthostatic increment of 33.5±23.2% was reduced. Abnormalities evolved with duration of disease.

Conclusions: The pattern of severe and progressive generalized autonomic failure with prominent involvement of adrenergic and sudomotor failure combined with the clinical phenotype are highly predictive of MSA, with however only a small possibility of mismatches.

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Quantitative analysis of the pull test in patients with impaired postural reflexes

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Objective: Our objective was to characterize the postural response abnormalities that are associated with postural instability of parkinsonian type, as revealed by quantitative analysis of a clinical test for postural reflexes (the pull test).

Background: Parkinsonian postural instability (impaired ability to recover when pushed off balance) is a major risk of falls in patients with parkinsonism and related disorders. Reliable assessment of postural reflexes outside a specialized lab is difficult. The clinical "pull test" maneuver, in which the examiner pulls the patient from behind and observes how a patient recovers, suffers from variability of applied force and interpretation of patient's response. The nature of response abnormalities is also difficult to define.

Methods: We devised a method to quantitate the pull test maneuver using a single motion-capture camera. The method records both the amount of perturbation imposed on the patient by the examiner by calculating center-of-mass kinematics, and the patient's recovery by measuring the stepping response. We also devised single-camera methods to assess turning and bradykinesia, and we recorded gait on an digitizing mat. We tested patients with postural impairments as part of evaluation for NPH.

Results: We obtained detailed and reliable measurements of the perturbations imposed by the examiner during the pull test, and of patients' responses to these perturbations, using a semi-portable apparatus. Preliminary results suggest that patients with impaired postural reflexes responded to a postural perturbation with inappropriately small step size, for comparable pull "intensity" (shoulder acceleration). Latency of step initiation, in comparison, was relatively preserved. These results suggest that a form of hypokinesia, leading to inadequate scaling of foot step to the postural perturbation, may be a primary factor in parkinsonian postural instability, and not an impairment of reaction time.

Conclusions: The quantitative pull test allows detailed measurement of balance impairment in patients with postural instability, and may improve the evaluation of patients with parkinsonism and suspected NPH. (Presented in part at the American Academy of Neurology Annual Meeting, Toronto, April 2010).

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Quality of life in multiple system atrophy: Validation of the french version of the MSA-QoL

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Objective: To validate the French version of the patient-rated multiple system atrophy health-related Quality of life scale (MSA-QoL). To further evaluate changes of quality of life during follow-up in relation to other clinical markers of MSA.

Background: While specific scales assessing the impairment of activities of daily life, the severity of motor signs and disability have been used for many years in MSA patients, a specific scale evaluating quality of life has only recently been validated (Schrag et al., Mov Dis 2008).

Methods: Double back and forth translation in French language of the MSA-QoL. Prospective assessment of MSA-QoL and Unified MSA Rating Scale (UMSARS) scores in a cohort of 73 MSA patients who are followed by the French National Reference Centre for MSA. Follow-up data with a second examination after one year were available for 32 patients.

Results: Mean age and mean disease duration were 64.3 (7.4, SD) and 4.9 (2.7) years, respectively. Two thirds had MSA-P (63.0%) and one third MSA-C (37.0%). "Probable" MSA was the diagnosis in 80.2% of patients. Total MSA-QoL scores were 71.6 (30.1) and visual analogous scale mean scores were 43.4 (21.5). Mean scores for UMSARS I, II and IV were 21.0 (8.4), 25.7 (8.0) and 2.6 (1.1), respectively. Patients with "probable" MSA had higher total MSA-QoL scores. Multiple regression analysis revealed a relation between total MSA-QoL scores and UMSARS I as well as disease duration. By contrast, visual analogous scale scores were related to UMSARS II scores. All UMSARS subscores significantly increased during follow-up, while measures of quality of life were unchanged. Multiple regression analysis did not display any relation between changes in UMSARS subscores and changes in both quality of life measures during follow-up. Interestingly, visual analogous scale scores increased in MSA-P patients indicating a subjective deterioration in quality of life, while scores increased in MSA-C patients.

Conclusions: The impairment of activities of daily life and disease duration seem to be related to total MSA-QoL scores, while subjective markers of quality of life seem to be linked to the severity of motor signs. Although UMSARS subcores increased during follow-up, MSA-QoL did not indicate a significant deterioration in quality of life.

961

Late-onset neurological Wilson's disease without K-F rings or characteristic MRI findings

E.S. Molho (Albany, New York, USA)

Objective: Report an unusual case of genetically confirmed Wilson's disease (WD) presenting as late-onset parkinsonism without K-F rings or characteristic brain MRI abnormalities.

Background: The age of onset of WD is variable but, generally occurs in the 2nd or 3rd decade. A neurological presentation is rare beyond 40 years and has not been reported without K-F rings or characteristic brain MRI findings. As a result, screening for WD in patients presenting with a movement disorder is not routine after this age and it remains unclear what the upper limit is for age of neurological phenoconversion.

Methods: Case Report.

Results: A 50 year old man presented with a 15 month history of left hand tremor, left arm stiffness, insomnia and anxiety. Examination showed predominantly left sided parkinsonism with resting tremor, rigidity and bradykinesia. K-F rings were absent. Quetiapine and olanzapine were briefly used to treat anxiety after the onset of motor symptoms but, were discontinued at least 2 months prior to presentation. Parkinsonism was subsequently unresponsive to ropinirole, pramipexole and only minimally responsive to levodopa up to 200mg TID. Investigation included a normal brain MRI and normal EEG. Two years later, a low serum ceruloplasmin of 4.1 was unexpectedly found as part of a research project. Repeat studies at a commercial lab were ceruloplasmin 7.4 mg/dL (25-63), serum copper 28 μg/dL (70-150), urine copper 65 μg/24 hours (3-35). Iron studies and LFTs were normal. Formal ophthalmological exam did not reveal K-F rings. ATP7B gene sequencing (Mayo Clinic) revealed 2 different known pathogenic WD mutations (compound heterozygote). The patient was treated with zinc for 6 months without improvement. A liver biopsy revealed increased copper without cirrhosis and a repeat slit lamp examination at an academic medical center failed to reveal K-F rings. Current treatment is Trientine.

Conclusions: The diagnosis of WD was made fortuitously after a low serum ceruloplasmin was found as part of a research project. This case suggests that late-onset WD is more common than previously thought and expands the range of phenotypic expression to include parkinsonism presenting in later adulthood without the presence of K-F rings or MRI abnormalities. Screening for WD with a serum ceruloplasmin should be routine in patients presenting with parkinsonism, tremor or dystonia in later life.

962

Progression of cardinal symptoms and MRI findings in multiple system atrophy

M. Murata, M. Ogawa (Tokyo, Japan)

Objective: To study the variable progression of multiple system atrophy (MSA) by evaluating time course of appearance of cardinal symptoms and MRI findings.

Background: Considerable variation exists in progression of cardinal symptoms such as parkinsonism, cerebellar ataxia, and autonomic dysfunctions and time course of appearance of MRI findings in MSA. These variations may depend on different pathomechanisms of MSA.

Methods: Forty four patients with patients with MSA (MSA-C, 20; MSA-P, 24) followed by our hospital (2007.1.1-2009.12.25), were studied for the course of parkinsonism, cerebellar ataxia, and autonomic dysfunction and of MRI findings such as putaminal rim and hot cross bun sign. They were examined more than two years and MRI scans were performed once a year.

Results: Thirty-one of 44 patients (70.5 %) showed definite autonomic disturbances within 3 years after onset. Thirteen of 20 (65.5%) MSA-C patients showed hot bun sign and cerebellar and pontine atrophy in MRI within 3 years after onset of disease. Twelve of 24 (50%) MSA-P patients showed putaminal rim in MRI within 3 years. Of 24 MSA-P patients, 3 exhibited putaminal rim more than 6 years after onset of parkinsonism (1 patient, after 9 years; 2 patients, after 6 years). These 3 patients showed only slight autonomic dysfunction even at 6 years after onset of disease. They were somewhat responsive to L-dopa for 5 years. Therefore they had been diagnosed as Parkinson's disease for 6-9 years. Their ADL levels were better than those of other MSA patients.

Conclusions: A sub-group exits that shows only parkinsonism for up to 9 years without other typical symptoms or MRI findings. This group may be pathophysiologically different from typical MSA.

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Tractography in a case of corticobasal syndrome

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Objective: To report a patient with Corticobasal Syndrome (CBS) studied with Resonance Diffusion tensor imaging and tractography.

Background: The CBS initially described as a distinctive levodopa-resistant asymmetric, akinetic-rigid syndrome associated with prominent apraxia, focal cortical myoclonus and alien limb phenomena, has also cognitive features with considerable overlap in clinical grounds between Fronto Temporal Dementia, Progressive Supranuclear Palsy, Parkinson's disease and Alzheimer's disease.CBS was also considered a distinct pathologic disorder with cortical degeneration, swollen achromatic neurons, substantia nigra neuronal loss and extensive neuronal and glial cytoplasmatic Tau-positive inclusions.Current clinical classifications do not accurately predict the underlying specific pathological process (Bhaskara P. et al. Mov Disord 2009;24:1583).Modern MRI imaging techniques (voxel based morphometry) identified changes in white matter integrity that could help to reveal an involvement of corticospinal and transcallosal motor projections in CBS in vivo (Boelmans K. et al, Mov Disord 2009, 24:168).

Methods: A 72 year-old right handed man presented with a 5-year history of right upper action limb tremor and problems with manual dexterity. He was initially treated with dopamine receptor agonists with mild benefit, levodopa was added soon but no improvement was obtained. Two years after developed progressive rigidity of the right arm and the tremor changes to a focal cortical myoclonic jerks. Four years since the beginning of the process developed apraxia and dysarthria. Spontaneous and stimuli sensitive myoclonus of the right hand was confirmed by polygraphic recording. Transcraneal magnetic stimulation shows no response to stimulation of left frontal cortical areas. Conventional RMI demonstrate predominant left cortical frontal and parietal atrophy.

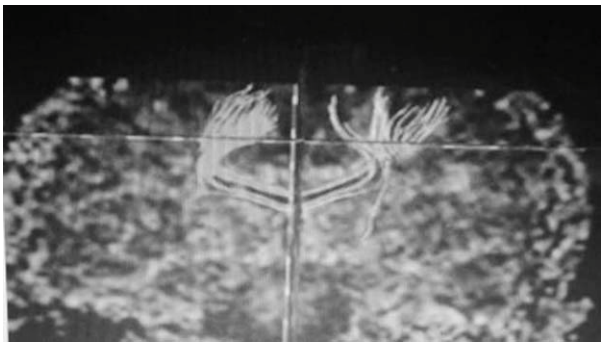

FIG. 1 (963).

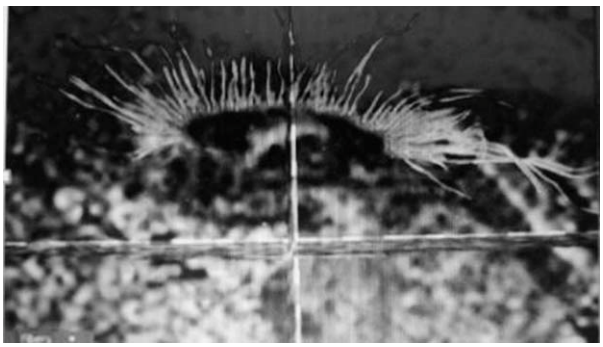

FIG. 2 (963).

Results: Fiber tractography shows reduction in the number of corticospinal tract fibers on the left hemisphere and transcallosal projections.

Conclusions: MRI fiber tractography can reveal involvement of corticospinal and callosal motor projections in CBS and may help to differentiate in vivo the different pathologies of CBS.

964

Retrospective study of the therapeutic effect of deep brain stimulation in multiple system atrophy

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Objective: To analyze outcomes after one year of bilateral STN DBS in patients with MSA.

Background: The efficacy of deep brain stimulation (DBS) has been demonstrated in idiopathic Parkinson's disease. However, the experience with DBS in multiple system atrophy-parkinsonism (MSA-P) is limited and controversial.

Methods: Information about the demographic and clinical data (Unified Parkinson's Disease Rating Scale) from six MSA patients treated with DBS currently followed in our clinic was entered into a database and analyzed.

Results: Six patients with MSA (mean age at onset 44.3±5.6 years, 2 women, 4 men) have been treated with bilateral STN stimulators, the mean duration between DBS surgery and disease onset is 6.5±3.4 years. All of the patients had dyskinesias and postural instability. Five of them had subjective benefit from levodopa. During the six months after surgery, the clinical status of four patients improved with a decrease of dyskinesia. However, by one year, the symptoms reappeared and progressed in all patients. Overall, The mean increase of "off medication" UPDRS score was 22.1+14.1 one-year after surgery. The levodopa dosage was not reduced after surgery. One patient developed paranoia and violent behavior, three patients developed hypotension after the surgery.

Conclusions: Our data shows that DBS can improve parkinsonian signs, especially dyskinesia, in MSA-P transiently and minimally. However, by one year, motor signs and other co-morbidities (autonomic, cognitive, etc.) continue to worsen. This data does not support the use of STN DBS for MSA-P.

965

Curcumin accelerates the clearance of mutant alpha-synuclein and injured mitochondria *via* autophagy induction

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Objective: To examine the role of curcumin in the clearance of mutant α-synuclein and/or injured mitochondria.

Background: Curcumin is a widely studied natural phenolic compound with a variety of biological activities. Neuroprotective properties of curcumin have been demonstrated in the toxin model of Parkinson's disease (PD). Previous reports that curcumin induces autophagy in malignant glioma cells and inhibits aggregation of α-synuclein led us to hypothesize that curcumin may have beneficial effects on PD *via* enhanced clearance of injured mitochondrial and/or of A30P and A53T mutant α-synuclein through autophagy induction.

Methods: Stable inducible PC12 cell lines expressing A30P, A53T mutant or wild-type α-synuclein, respectively, were maintained at Dulbecco's modified Eagle's medium (DMEM) containing 10% horse serum, 5% fetal bovine serum, 75 μg/ml hygromycin B, and 100 μg/ml G418 at 37°C, 10% CO_2. The cells were induced to express the transgenes, including A30P, A53T mutant or wild-type α-synuclein respectively with 1 mg/ml doxycycline applied for 48 hours. Mitochondrial complex I inhibitor 1-methyl-4-phenylpyridinium ion (MPP^+)-exposed PC12 cells were used as an *in vitro* model of PD-related neurodegeneration. Doxycycline-induced or uninduced PC12 cells, with or without exposure to MPP^+, were treated with curcumin for 48 hours.

Results: Curcumin treatment was associated with induction of autophagy in PC12 cells as demonstrated by immunoblotting assay showing the increased ratio of LC3II/I, a marker of autophagy. The induced expression of A30P and A53T mutant α-synuclein was decreased by curcumin treatment, but there was no change in the expression of wild-type α-synuclein. Curcumin attenuated MPP^+-induced apoptosis which was accompanied by a decrease of mitochondrial complex IV and cytochrome c, indicating a reduction in mitochondrial load. This protective effect was blocked by the autophagy inhibitor 3MA.

Conclusions: We report a novel role for curcumin as an autophagy enhancer, accelerating the clearance of mutant α-synuclein and/or injured mitochondria. Our findings suggest a potential therapeutic role for curcumin in PD by protecting cells from pro-apoptotic insults.

966

Gait characteristics in patients with progressive supranuclear palsy while dual task walking

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Objective: Gait alterations and gait performance characteristics are clinically observable phenomena in movement disorders patients. Aim of this study was to compare and correlate gait patterns in PSP patients during demanding dual-tasking (DT) while walking.

Background: Progressive Supranuclear Palsy (PSP), with rapidly progressive postural instability and slow, unsteady gait, vertical gaze palsy, parkinsonism unresponsive to levodopa, pseudobulbar palsy, without or with mild dementia may be difficult to differentiate from Parkinson's disease in its early stages when there are no oculomotor abnormalities. Further, gait analysis of two mayor clinical types of PSP, Steele-Richardson-Olszewski syndrome or disease (RD) and PSP parkinsonisms or PD-like form (PSP-P) may help to differentiate and improve accuracy of early diagnosis, and exclude and differentiate PSP types from related disorders.

Methods: Dual-task walking was performed and gait analyzed in 25 PSP patients, 15 with RD and 10 patients with PSP-P. Only neuropathologically typical cases who met the criteria were included in the study. Patients performed a simple walking task, a dual-motor task, a dual-mental task, and a combined motor-mental task. Measurement of spatiotemporal gait characteristics was performed on the GAITRite walkway system. Calculated parameters were gait velocity, cadence, step and stride length, single and double limb support, swing time, gait cycle and variability (CV) of those parameters.

Results: Results show that dual-task paradigm while walking has an effect on gait pattern in PSP patients. Gait performance during dual tasking while walking in PSP patients types was differently affected. Dual-task shows differences in stride time variability, double support time variability as well as swing time variability between RD type and PSP-P type patients. Variability (CV) of these parameters increased with more demanding parallel tasks.

Conclusions: Changes associated with unstable gait during demanding dual tasking might imply contribution of clinical symptoms and features to disturbances of gait, and could help to differentiate PSP subtypes, as well as to differentiate PSP from related disorders.

967

Long-term experience with 110 Wilson's disease patients

M. Relja, V. Miletic (Zagreb, Croatia)

Objective: Present our Center long-term experience with 110 patients with the neurological presentation of Wilson's disease (WD).

Background: WD (hepatolenticular degeneration), an autosomal recessive inherited disorders of copper metabolism, is one of the very few chronic neurological disease for which specific and effective therapy is available.

Methods: We performed a complete analysis of WD patients with neurological presentation who have been treated in our Movement Disorder Centre during 25 years. Clinical features at presentation and diagnosis, as well as laboratory findings, liver biopsy and magnetic resonance imaging (MRI) were investigated. In addition gene analysis (ATP7B) was performed in 25 patients.

Results: Total 110 patients (61 man and 49 woman) were investigated. Their mean age (SD) at diagnosis was 28.2 (10.7) years, and mean age at onset of symptoms was 23.7 (10.6) years. All patients at diagnosis had neurological form of ilness, with superimposed hepatic dysfunction in 45 % of them. The most common symptom in our patients was tremor (75% of patients), dysarthria (40%), rigidity (30%), followed by dyskinesia (20%) and dystonia (15%). Psychiatric problems as first symptoms were present in 38% of all patients. Kayser-Fleicher ring (KF) on slit-lamp ophtalmologic examination was less common than expected (75% of patients at initial evaluation). In addition, ceruloplasmin level was normal in 25% of all patients. However, copper concentration in liver biopsy was increased (>300 ugr/gr) in all patients with negative KF and/or ceruloplasmin level.

Conclusions: WD is one of the very few treatable chronic neurological disease. Therefore, it is important taht it be considered in the differential diagnosis of neurological disorders presenting with involuntary movements and/or in young patients who develop behavioral changes with or without liver dysfunction.

968

Extrapyramidal symptoms as first manifestations in adult neuronal ceroid lipofucsinosis

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Objective: To describe the case of a female 20 year old patient that began her disease with extrapyramidal symptoms such as parkinsonism and myoclonus.

Background: The neuronal ceroid lipofuscinoses (NCLs) are a group of neurodegenerative disorders. They are considered the most common of the neurogenetic storage diseases; they are associated with variable yet progressive symptoms including seizures, dementia, visual loss, and/or cerebral atrophy. Few reports have reported some clinical improvement with antiparkinsonian treatment.

Methods: A 17 year old female with a history of parent's consanguinity. She had a normal life until 11 year old when she began with slightly asymmetric motor signs of left arm, in the following month's rigidity and writing problems were added. At 13 year old she developed partial complex seizures associated with stereotyped movement of the left side with a frequency of 2-3 episodes per week. She began treatment with sodium valproate and seizures were controlled but neurological worsening was observed, progressive mental alterations including dysphasia, gait apraxia, irritability and inappropriate social behavior were observed in the following months. She was referred to our hospital and upon admission neurological examination added maculopathy with diminishes central vision. Bilateral opthalmoparesia and collier sign. General rigidity and atavic sign. A videoEEG record showed generalized dysfunction without epileptic graphoelements. A muscular biopsy was provided considering the diagnosis of mitochondriopathy but not ragged red fiber was observed. MR imaging showed generalized atrophy with frontal predominance. A brain biopsy was performed and neuronal loss in the neocortex, meganeurites and extensive gliosis was observed. Antiparkinsonian treatment was added and a moderate clinical improvement in motor symptoms was observed.

Conclusions: NCL's are characterized by accumulation of lipopigments in neurons and clinically there are associated with seizures. In this patient extrapyramidal symptom predominate as first manifestations and after some years a progressive demential syndrome appeared, some clinical improvement was observed with antiepileptic and antiparkinsonian treatment.

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Can BOLD brain activation pattern differentiate the different classes of parkinsonism for a simple motor task

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Objective: To differentiate the brain activation pattern for a simple motor task in the three classes of parkinsonism and to study the effect of dopa administration on each of these.

Background: Movement disorders in parkinsonism have always been most debilitating for the patients. The motor co-ordination in patients with Parkinson's disease (PD), multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) reflects degeneration in the dopminergic neurons in the substantia nigra and basal ganglia. Differential diagnosis is very difficult even using the most latest imaging methods. We wish to determine whether, functional magnetic resonance imaging (fMRI) can differentiate any difference in the motor activity in patients with idiopahtic parkinsonism.We are also interested to determine the effectiveness of dopaminergic therapy in the three groups.

Methods: Thirty two right handed patients and 8 healthy controls were recruited from the movement disorder clinic of our institute. Standard diagnostic and exclusion criteria were followed. Two fMRI scans were carried out at 1.5T (Magnetom Avanto, Siemens, Erlangen, Germany); one in the practically "off" state (i.e. after 12 hours of last dopa administration) and the other after 2 hours of dopa administration in the "on" state. Single-shot echo planar imaging was used for the functional MRI studies to study the blood oxygen level dependent (BOLD) effects in the whole brain (number of slices: 31, slice thickness: 4.0 mm; TR: 4000 ms, TE: 44 ms, FOV: 230mm, resolution: 128 × 128). Using a block design for fist clenching exercise, and SPM2. The Bold activation pattern was overlaid onto the 'mni' template using the Talairach and Tornoux co-ordinates. One way ANOVA ($p<0.001$, cluster threshold 5) was used for group analysis, while paired t-test was carried out for comparing the results during "on" and "off" states.

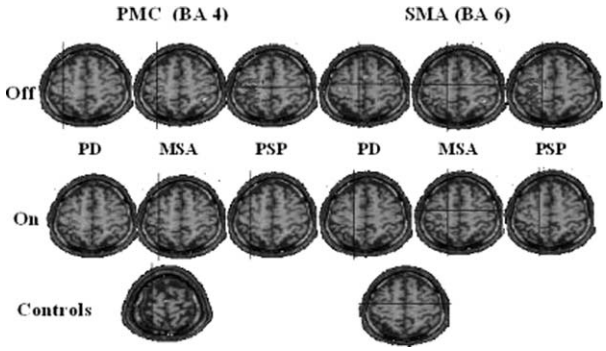

FIG. 2 (969).

Results: The activation clusters both for the on and off states for all the three disorders are summarised in the table above.

Conclusions: This study confirms the dopaminergic aided reversal of premotor/motor/parietal cortical hyperfunction in parkinsonism. Also distinct pattern of activation among the three types of parkinsonism might be of help in differential diagnosis.

970

Transcranial magnetic stimulation over the cerebellum in ataxic and non-ataxic patients with progressive supranuclear palsy

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Objective: To investigate cerebellar function in progressive supraclear palsy (PSP) patients with and without ataxia.

Background: PSP presents various signs and symptoms; among them, cerebellar ataxia is believed to be rare. However, some studies have reported early, marked cerebellar ataxia and its underlying mechanism remains to be investigated. The cerebellar inhibition (CBI) studied by paired-pulse transcranial magnetic stimulation (TMS) is used to assess the function of cerebellar efferent pathway, or dentatothalamocortical pathway. Because the dentate nuclei are degenerated in PSP, ataxia, if any, might be related to abnormality in the cerebellar efferent pathway and the extent of CBI might be different between PSP patients with and without ataxia.

Table 1. The clinical profile of Parkinsonian patients (PD. MSA. PSP) and controls and the respective brain activation pattern for the primary and supplementary motor area and cerebellum.

Group	Subjects	Age (yrs)	Disease Duration	Daily dopa intake (mg)	Stage of the disease	MMSE	UPDRS III	BOLD cluster count					
								BA 4		BA 6		Cerebellum	
								Off	On	Off	On	Off	On
PD	18 (11M/7F)	59.8±14.3	6.53±3.5	712.5±303.5	H & Y 1.7±0.61	27.2± 2.67	20.5±10.8	106	30	10	4	.	.
MSA	9 (7M/2F)	61.7±7.02	6.2±8.9	401.5±181.9	UMSARS 2.6±0.96	28.3 ± 1.8	22.0±8.8	32	26	0	0	.	.
PSP	5 (4M/1F)	64.6±8.1	2.96±0.9	215.6±141.2	PSP rating 3.0±1.0	25.5 ± 3.2	27.3±4.0	19	50	60	77	35	24
Controls	8 (5M/3F)	48.6±5.2	-	-	-	29.0 ± 1.0	-	0		10		0	

MMSE: Mini-mental State Examination; UPDRS: Unified Parkinson's Disease Rating Scale; UMSARS: Unified Multiple System Atrophy Rating Scale.;H&Y: Hoehn & Yahr staging sytem for PD; BA4: Primary motor cortex; BA6: Supplementary motor area.

FIG. 1 (969).

Methods: CBI was investigated in six PSP patients with ataxia, whose clinical presentations agreed with the National Institute of Neurological Disorders and Stroke and the Society for PSP, Inc. (NINDS-SPSP) criteria except that they showed marked cerebellar symptoms. We also studied 11 patients with PSP who fulfilled the NINDS-SPSP criteria, and ten healthy volunteers. For CBI, TMS over the cerebellum was followed by contralateral motor cortex stimulation at interstimulus intervals (ISIs) of 4—8 ms. CBI at each ISI was expressed as the ratio of the mean amplitude of motor evoked potentials (MEPs) elicited by paired-pulse paradigm to the average of those elicited by motor cortex stimulation alone.

Results: CBI was reduced in both PSP groups with and without cerebellar ataxia, and there was no significant difference between them.

Conclusions: CBI was consistently reduced in PSP patients, whether they presented with ataxia or not. This finding may reflect degeneration of the dentate nuclei in PSP patients. According to the fact that there was no significant difference between those with and without ataxia, we propose two possible reasons. One is that all PSP patients might have cerebellar dysfunction, but that it is clinically masked by some other symptoms such as rigidity or akinesia in some of them. The other is that the cerebellar afferent pathway dysfunction may mainly produce ataxia in some of PSP patients.

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Dysphagia as a presenting symptom of progressive supranuclear palsy

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Objective: To describe two cases where severe dysphagia was a presenting symptom of progressive supranuclear palsy (PSP).

Background: Dysphagia is more common as an early feature in PSP or multiple system atrophy than other causes of parkinsonism. However; to our knowledge, it has not been previously described as the presenting symptom of PSP.

Methods: We describe two cases of clinically probable PSP whose first presenting symptoms included severe dysphagia.

Results: Case 1- a 58 year old man with 17 years of insulin dependent diabetes developed severe dysphagia 2 days after onset of a mild upper respiratory tract illness. On exam he was very hoarse, had absent pinprick sensation in the left neck and lower face, and a left upper extremity action tremor. Serial MRI 5 days apart showed no evidence of stroke. He successfully weaned off tube feeds after one week. At 2-month follow-up, he had developed severe fatigue and pseudobulbar palsy. On exam, there were frontalis dyskinesias elicited during speech, hypokinetic vertical saccades, and bilateral kinetic tremor and bradykinesia. By 9 months, the dysphagia was essentially resolved, but he had developed a slowly progressive expressive aphasia. Case 2 - a 71 year old woman with 40 years of bipolar depression developed severe dysphagia, dysarthria, incontinence and postural instability. She was found to have a toxic lithium level, and had dramatic improvement of all symptoms except postural instability after lithium was discontinued in favor of valproic acid. Initial exam showed impaired vertical gaze and symmetric parkinsonism with marked postural instability. Head CT demonstrated significant bilateral fronto-temporal atrophy. At 6- and 12-month follow up, the dysphagia and dysarthria were markedly improved. Gait improved modestly after intensive physical therapy, though she remained unstable on pull Testing.

Conclusions: In the setting of severe physiologic stressors (including medical illness or drug toxicity), transient exacerbation of PSP symptoms such as dysphagia may occur. As a result, dysphagia may appear to be a presenting feature of the disease. With early diagnosis and supportive treatment, quality of life may be regained once the initial stressor is resolved.

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An analysis of cognitive and behavioural features of MSA-P and MSA-C patients

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Objective: We compared cognitive and behavioural characteristics in patients with multiple system atrophy (MSA) of the cerebellar (MSA-C) and parkinsonian (MSA-P) type.

Background: Current clinical research in MSA focuses on the evaluation of motor disability and autonomic dysfunction while the cognitive and behavioral status of patients has been only marginally explored.

Methods: In this multicenter study, we evaluated 39 MSA-P (mean age: 63.4±7.5 years; mean disease duration: 59±30 months; mean total UMSARS score: 55±13; M/F=19/20), and 22 MSA-C (mean age: 63.1±6,8 years; mean duration: 78±46 months; mean total UMSARS score: 44±12; M/F=12/10) patients. All patients underwent the following neuropsychological and behavioural assessment: MMSE, CPM_Raven, FAB, Digit Span, RAVLT, Attentive Matrices, GDS, NPI. Patients also completed quality of life measures: PDQ39 and EQ5 score.

Results: There were no significant differences between MSA subtypes in demographic and clinical characteristics with the exception of total levodopa equivalent doses (LEDDs), which were higher in MSA-P versus MSA-C patients (611±470 versus 137±206 mg; $p=0.000$). Cognitive and quality of life scores were not significantly different between both groups. Neuropsychiatric assessment revealed significant differences in the anxiety item that was worse in MSA-P (MSA-P: 2.65±4; MSA-C: 0.44±1; $p<0.05$).

Conclusions: Our results demonstrate a similar cognitive performance in the two MSA subtypes with a tendency towards greater anxiety scores in MSA-P patients.

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Blood-brain barrier impairment is functionally correlated with the clinical severity in patients of multiple system atrophy

S.-K. Song, Y.H. Sohn, S.-K. Lee, J.J. Lee, J.E. Lee, H.S. Choi, P.H. Lee (Seoul, Korea)

Objective: To evaluated the integrity of the blood-brain barrier (BBB) and the functional significance of BBB changes in patients with MSA.

Background: With identification of α–synuclein-positive glial cytoplasmic inclusions as a suitable marker at autopsy, multiple system atrophy (MSA) has been regarded as a unique entity within the spectrum of dligodendrogliopathy. However, the pathomechanisms undelying the initial trigger and aggravating factors responsible for disease progression remain unknown. The implication of BBB dysfunction has not been fully appreciated; however, this dysfunction may act as a modifier of disease pregression in neurodegererative disease.

Methods: We evaluated the integrity of the BBB and its functional significance in patients with MSA using the CSF/serum albumin index (CSF-AI) and the volume transfer coefficient (K^{trans}) in dynamic contrast-enhanced MRI.

Results: CSF-AI and K^{trans} values increased significantly in patients with MSA compared to the control. There were positive relationships between both CSF-AI and K^{trans} and clinical severity of MSA. K^{trans} in the periventricular white matter was significantly correlated with the volume of white matter hyperintensities among all subjects ($r=0.58$, $p=0.001$) and within patients with MSA ($r=0.58$, $p=0.019$), but not within controls ($r=0.42$, $p>0.05$). In addition, a significant positive correlation was detected between CSF-AI and K^{trans} ($r=0.81$, $p=0.002$). Multiple linear regression analysis showed

that only unified MSA rating scale (UMSARS) score was a significantly independent predisposing factor for CSF-AI ($\beta=0.193$, $p=0.04$).

Conclusions: Our data suggest that BBB dysfunction is related to the underlying nature of MSA and its dysfunction is closely coupled to disease severity.

974

Morphological differences between two subtypes of progressive supranuclear palsy on MRI: A voxel-based morphometric and diffusion tensor imaging study

K. Srulijes, A. Groeger, E. Dietzel, M. Nechyporenko, J. Godau, C. Maenz, D. Berg, W. Maetzler (Tuebingen, Germany)

Objective: To investigate whether magnetic resonance imaging (MRI) can be used to differentiate Richardson's syndrome (RS) from progressive supranuclear palsy-parkinsonism (PSP-P) in vivo.

Background: In post mortem studies severity and extent of pathology have been shown to differ between RS and PSP-P, the most common subtypes of PSP.

Methods: 17 PSP patients (10 RS, 7 PSP-P: mean disease duration 4.3 years) were examined on a 1.5 T whole-body MR scanner with the 8-channel head coil. After the localizer a 3D T1-weighted MPRage sequence (TE=3.93 ms, TR=2 s, TI=1.1 s, voxel size=$1\times1\times1$ mm^3) was used for the anatomical images to obtain voxel-based morphometry (VBM). Additionally, a diffusion tensor imaging (DTI) sequence with 12 diffusion encoding directions (b values=0, 800 s/mm^2, TE=94 ms, TR=11.6 s, voxel size=$1.8\times1.8\times1.9$ mm^3) was acquired to calculate the apparent diffusion coefficients (ADC) and fractional anisotropy (FA) maps. For the VBM calculation the SPM5 VBM toolbox was used.

Results: VBM revealed significant inter-group differences with increased grey and decreased white matter probability in RS compared to PSP-P in the midbrain, the primary motor cortices, and the right posterior cingulate gyrus as well as decreased grey matter and increased cerebrospinal fluid probability for the third ventricle. In addition, in RS patients the ADC values were elevated and the FA values reduced in the whole brain compared to PSP-P patients.

Conclusions: Statistical parameter mapping analysis can detect relevant morphological differences between RS and PSP-P patients. In the midbrain, the primary motor cortices, and the right posterior cingulate gyrus the results can be interpreted as shifts in the grey matter in RS patients due to stronger white matter atrophy. Additionally, the third ventricle was significantly larger in RS patients, which fits the atrophy results. The differences in the ADC and FA maps of the whole brains between the two groups indicate a more severe neurodegenerative process in RS and support the significant brain atrophy with a loss of white matter. This helps to differentiate in vivo the PSP subtypes RS and PSP-P and might explain different clinical findings.

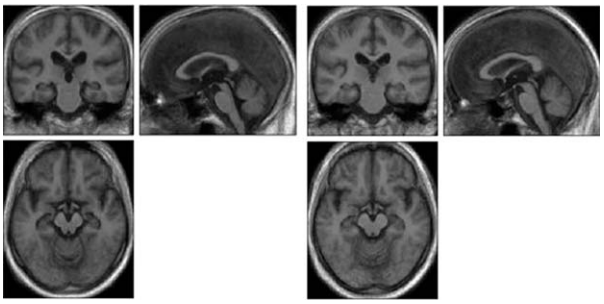

FIG. 1 (974). Mean T1w images of the RS group (left) and the PSP-P group (right) on the level of the midbrain show clearly the midbrain atrophy in RS patients.

975

In vivo demonstration of microstructural brain pathology in progressive supranuclear palsy: A DTI study using TBSS

M. Stamelou, M. Belke, H. Katja, U. Pilatus, K. Eggert, W.H. Oertel, S. Knake, G.U. Hoeglinger (Marburg, Germany)

Objective: To investigate brain microstructure in patients with probable progressive supranuclear palsy using a whole brain analysis of diffusion tensor imaging (DTI) data.

Background: Progressive supranuclear palsy (PSP) is a sporadic neurodegenerative disorder, presenting in the vast majority of cases clinically as Richardson's syndrome, an akinetic-rigid syndrome characterized by postural instability, vertical gaze palsy and frontal lobe dysfunction. In absence of reliable in vivo biomarkers, the definite diagnosis still relies on the neuropathological diagnosis. Therefore, a specific and sensitive identification of such a neurodegenerative process with a routinely available technique such as MRI could be of value for the early differential diagnosis and a detailed monitoring of disease progression.

Methods: We investigated brain microstructure in 13 patients with probable PSP-R at stage III or less and 10 age-matched controls using a whole brain analysis of DTI data. DTI images were analysed using tract-based spatial statistics, a hypothesis-free technique. Fractional anisotropy (FA), radial diffusivity (RD) and axial diffusivity (AD) were determined.

Results: Significant increases in FA ($p<0.0001$), an unspecific measure of microstructural tissue integrity, were found in the cerebellum and in the superior cerebellar peduncle bilaterally, in the fornix, the body of the corpus callosum and the olfactory region. Regional reductions in AD ($p<0.0001$), an indicator of altered axonal integrity, were observed in the pons, the right substantia nigra and the cerebellar white matter bilaterally. Significant increases in RD ($p<0.0001$), a potential measure of altered myelin integrity, occurred bilaterally in the superior cerebellar peduncle, the cerebellar white matter, the vermis of the cerebellum, the fornix, the body of the corpus callosum and the olfactory region. RD values in the superior cerebellar peduncle discriminated PSP patients and controls with high sensitivity (0.92) and specificity (1.0). The findings are supported by neuropathological studies.

Conclusions: Our data suggests the usefulness of this clinically available new technique as a possible tool for differential diagnosis.

976

Spatio-temporal dynamics of brain volume changes in patients with cortico-basal-degeneration

M. Suedmeyer, P. Pieperhoff, S. Groiss, L. Wojtecki, K. Zilles, K. Amunts, A. Schnitzler (Duesseldorf, Germany)

Objective: To longitudinally quantify individual spatio-temporal dynamics of brain volume changes in patients with corticobasal degeneration (CBD) as compared to age matched controls.

Background: CBD is a progressive neurodegenerative disorder comprising asymmetric hypokinesia and cortical sensory as well as motor dysfunction. The evolution of the neurodegenerative process in CBD is barely unknown.

Methods: Topographic distribution of cerebral atrophy as a sign of neurodegeneration was analyzed using a novel approach of deformation-field morphometry (DFM) analysis. Whole brain 3D-MR-scans of two patients suffered from early and advanced CBD stage and of six healthy controls were acquired longitudinally three to five times over periods of 19 to 26 months. Based on repeated registrations of MR images, maps of local volume ratio (LVR) changes were computed. These maps quantify the volume changes over time in each individual brain. LVR maps were superimposed with probabilistic maps of cytoarchitectonic areas and fiber tracts in order to associate the observed volume changes with the underlying microstructure of the brain. Patients and controls underwent detailed neurological follow-up examinations including Unified-Parkinson's-Disease-

Rating-Scale (UPDRS) Part-III, Florida Apraxia Screening Test (FAST), finger tapping and neuropsychological evaluation.

Results: Compared to healthy controls, longitudinal DFM analysis in CBD revealed significant progressive cortical atrophy within distinct spatially and functionally related areas. In early disease stage focus of asymmetric cortical degeneration comprised bilateral primary motor cortex (area 4), premotor area 6, primary somatosensory area 3, whereas in advanced CBD atrophy of the superior and inferior parietal lobules was more prominent. Local atrophy rates correlated significantly with corticospinal tract degeneration and motor impairment (UPDRS-III, finger tapping).

Conclusions: This is the first longitudinal demonstration of individually assessed topography of cortical atrophy rates in CBD patients in short time intervals, which shows distinct dynamics of fronto-parietal degeneration at different disease stages.

977

To subtype the protean clinical and analyze the MRI appearances of Wilson's disease (WD)–a two year prospective study at Indira Gandhi Government General Hospital & PGI–Pudhucherry. (IGGGH&PGI)

S.C. Thirunavukarasu, V. Sivasankari, A. Mukundan, S.D.T.J. Krishna, G.A. Ganesan, S. Paranjothi, V. Govindaraj (Pudhucherry, India)

Objective: To assess the protean clinical and radiological presentations of Wilson's disease.

Background: Wilson's disease is a neurometabolic disorder of autosomal recessive inheritance. It is one of the most common extrapyramidal syndrome with diverse clinical presentations. The MRI features of Wilson's disease is also diverse and does not follow a set pattern. Our aim of this study is to collect cases of Wilson's disease and subtype them clinically based on Marsden's clinical subtyping. We will also analyse the MRI features of Wilson's disease.

Methods: To screen all cases with extrapyramidal syndrome at IGGGH&PGI for Wilson's disease. Slit lamp for KF ring is done in all cases with extrapyramidal syndrome. If positive serum copper, serum ceruloplasmin and 24 hour urine copper is done. If serum ceruloplasmin is below 20mg/dl a diagnosis of Wilson's is made and other basic investigations are done for the patient. MRI brain is done for these patients.

Results: 8 cases of Wilson's disease were diagnosed out of 252 cases of patients presenting with extrapyramidal manifestations. The age group was between 13–35 out of which 5 were male and three were female. Pseudosclerotic form : 2. Dystonia predominant: 2. Parkinsonism extrapyramidal predominant : 2 Mixed : 1. Neuropychiatric form:1 MRI Features: Grey matter: Basal ganglia involvement:8. Mid brain:5. Thalamus:5. Cerebellum:3 Pons:2. White matter: 2 patients. Cerebellar peduncle hyperintensities. Pyramidal tract involvement and DRPLA hyerintensities. Both were involved in 2 patients and cerebellar peduncle was involved in one.

Conclusions: The conclusions which we were able to make was it is imperative to screen all patients with extrapyramidal syndrome for Wilson's disease. Wilson's disease has diverse neurological presentations. It fits into Marsden's clinical subtyping. Wilson's disease involves both grey and white matter. Classical face of giant panda is a rarity and we did not encounter in our study. The cub sign without the mother was seen in our patient. Degeneration in MRI is more widespread and may not correlate clinically in all patients.

978

Indian variant PSP-P: Clinical and quantitative MRI profile

R. Nehru, A. Batla, T. Vijay, J.B. Sharma, S.K. Puri (New Delhi, Delhi, India)

Objective: To study the clinical profile of Indian variant PSP-P and describe its imaging profile.

Background: PSP-P is now recognised as a distinct variant of PSP and is different from classic Richardson Syndrome and Parkinson's disease. We describe another clinical variant, Indian variant PSP-P.

Methods: Prospective study of 12 patients of PSP-P. Patients of PSP-P were identified based on previously described clinical profiles. MRI brain was done and mid sagittal mid brain diameters and ratio of mid brain area to pons area was calculated.

Results: All 12 patients had insidious onset asymmetric tremor, with a relatively slowly progressive course. Nuchal rigidity was present in all. Vertical supranuclear up gaze palsy with or without restriction of down gaze was present in all patients (in contrast to Western literature). All patients had apraxia of eye lid opening. Recurrent falls were not present early in the course of the disease, and were either absent or only occasional. Response to levodopa was better than PSP, moderately good and was often sustained for several years in some cases. MRI measures revealed a mean mid brain diameter of 13.71 mm and a midbrain area of 80.7 mm2 These values are in between previously reported measures for PD and PSP.

Conclusions: Our patients comprised the entire sample of PSP-P patients seen during the study period, and represent a population consistently and regularly seen by us. Our patients represent a distinct clinical variant: 'Indian variant PSP-P.' Pathological mechanisms involved appear to involve the midbrain, but such that might be different from Classic PSP.

POSTER SESSION 4

THURSDAY, JUNE 17, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-16:00
Authors Present: 13:30-15:00

QUALITY OF LIFE/CAREGIVER BURDEN IN MOVEMENT DISORDERS

979

Depression and quality of life (QOL) in Parkinson's disease: Preliminary results of a broad spectrum analysis in a non-demented Brazilian sample

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Objective: Access different aspects of motor and non-motor symptoms of Parkinson's disease (PD) and their impact in patients quality of life.

Background: Most clinical manifestations of PD, including motor and non-motor, are treatable by farmacological or non-farmacological interventions. Depression is a prevalent co-morbidity that affects up to 45% of PD patients. The clinical definition of depression in PD is complex and comprises features that might indicate future cognitive changes and may be used as a marker of negative impact in daily living activities.

Methods: A sample of 66 non-demented PD patients (diagnosed according to the Queen Square criteria) was submitted to fulfill the questionnaires World Health Organization Quality of Life-BREF (WHOQOL-BREF) and Beck depression inventory (BDI) (both versions previously validated to portuguese). The four WHOQOL-BREF domains: physical health (domain 1), psychological (domain 2), social relationship (domain 3) and environment (domain 4) were confronted with BDI scores by a linear regression analysis (pearson's correlation coefficient). Patients with mini mental state examination score below 25 points were excluded.

Results: All studied variables had a normal (Gaussian) distribution. We found a linear correlation between the domain 1 and BDI (r2=-0,57), domain 2 and BDI (r2=-0,49) and between domains: domain 1 and domain 2 (r2=0,63); domain 3 and 4 (r2=0,63).

Conclusions: This preliminary result suggests that depression has a significant impact in PD patients QOL, especially on physical and psychological domains. Other aspects of disease such as sleep disorders, time of disease, motor fluctuations, predominant symptom (tremor x rigidity), and its impact on patients QOL are under analysis.

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Results of a multi-national patient and physician survey on treatment satisfaction with current botulinum toxin treatment in focal dystonia

M. Fargel, E. Psaila (Rueckersdorf, Germany)

Objective: Assessment of the overall patient satisfaction with their current treatment scheme of focal dystonia using Botulinum toxin (BoNT) preparations in Canada, France, Germany and the USA and evaluation of preferences of patients regarding the BoNT treatment.

Methods: 180 cervical dystonia patients and 120 physicians in Canada, France, Germany and the USA were interviewed face-to-face regarding their BoNT treatments. Patients qualified for this survey if they underwent at least 2 complete treatment cycles before the survey and participating physicians had at least 3 years of experience with BoNT injections.

Results: Mean duration of focal dystonia was 7.5 years and patients received Botulinum injections for 3.8 years. 70 % of patients were between 46 and 75 years old. 46% of the patients were males. Mean interval between injections was 13.9 weeks. The QoL was as follows: 44% of patients had at least some difficulties moving around, 36% with washing/cleaning, 67% with carrying out daily activities, 87% had moderate to extreme pain and 62% were anxious/depressed. While 70% of physicians were satisfied with the efficacy, only 13% were satisfied with the disappearance of pain as well as increased patient satisfaction. Improvement that patients would like to see the most was "longer lasting efficacy" (28%). 70% of patients and 55% of physicians would prefer shorter injection intervals compared to those intervals in which the patients actually receive BoNT.

Conclusions: The results of the survey show that generally the patients are satisfied with BoNT therapy. However, the majority of patients and physicians would prefer shorter injection intervals of BoNT to improve the treatment effect.

981

Measuring quality of life in patients with Parkinson's disease using the McGill quality of life questionnaire

T.E. Gofton, H. Kumar, A. South, M. Speechley, M.S. Jog (London, Ontario, Canada)

Objective: In this study, the validity and reliability of internal consistency of the MQOL in a population of patients with Parkinson's disease (PD) was assessed.

Background: The McGill Quality of Life (MQOL) questionnaire is a tool originally developed for measuring quality of life (QOL) in palliative care patients. The MQOL assesses multiple domains affecting QOL including physical symptoms, psychological well being, physical well being, supports and more existential aspects of life.

Methods: 81 consenting patients with PD completed the MQOL, single item scale, UPDRS, PDQ-39 and SF-36. Scree plots and eigenvalues generated by factor analysis within the MQOL identified the most relevant factors. These factors represented subscales of the MQOL within this population. A principal components analysis showed the loading of individual items within the subscales. The validity of the MQOL in PD was established with a correlation analysis comparing the MQOL with the other validated tools.

Results: The mean age of participants was 65.18+/-8.43 years with a mean UPDRS of 14.58+/-5.51. Statistical factor analysis demonstrated that 4 factors exist within the MQOL in patients with PD. The four factors represent a physical well-being subscale, a physical subscale, a psychosocial subscale and a combined existential and support subscale.

Conclusions: The MQOL is both and acceptable and valid QOL assessment tool in PD. The advantage of the MQOL is that it measures contributors to quality of life, such as the combined existential and support subscales, which are difficult to measure with existing tools in PD.

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Measuring existential, psychological and physical contributors to quality of life in Parkinson's disease using the mcgill quality of life tool

T.E. Gofton, H. Kumar, M.S. Jog (London, Ontario, Canada)

Objective: This study used the MQOL to measure physical, psychological, existential and support influences on QOL in Parkinson's disease (PD).

Background: Previously established quality of life (QOL) assessment tools designed for use with patients living with PD focus primarily on physical symptoms and social supports. Other factors that influence QOL, including existential experiences, remain elusive. The McGill Quality of Life questionnaire targets such domains using a specifically designed set of questions as well as areas of free response.

Methods: Using the MQOL, a valid, reliable and acceptable tool in PD, 81 consecutive consenting patients with PD were evaluated. Both quantitative and qualitative analyses were used based on previously established methodology.

Results: The mean age of participants was 65.18+/-8.43 years. The total mean score on the MQOL was 7.29+/-1.58. The means of a single item scale (SIS) and the MQOL subscales were 6.9+/-1.94 (SIS), 7.03+/-2.21 (physical well being), 6.42+/-2.49 (physical), 7.69+/-2.02 (psychological) and 8.02+/-1.33 (existential and support).

Conclusions: Previously available QOL assessment tools validated for use in patients living with PD were strongly weighted towards physical symptoms. The MQOL substantially extends assessment of QOL in patients living with PD because it reveals that psychological and existential factors have a profound and equally important effect on the overall disease experience.

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Bone metabolism in Parkinson's disease

H. Ito, T. Sano, S. Hattori, T. Kamei (Chigasaki, Kanagawa, Japan)

Objective: To investigate the bone metabolism in Parkinson's disease (PD).

Background: There is a high incidence of hip fractures in PD patients and bone mineral density was reported to be decreased in PD patients, however, bone metabolism in PD patients has not been elucidated.

Methods: This was a prospective, open-trial study. We measured serum N-terminal telopeptide of type I collagen (NTx; 14 nMECE/l) and undercarboxylated osteocalcin (ucOC; normal value<4.5 ng/ml) in typical PD patients. We excluded patients who had already been treated with vitamin D3, vitamin K, calcium agents, bisphosphonates, and corticosteroid.

Results: 118 patients (45 men and 73 women; mean age 74 years, range 49 to 92 years) were enrolled and divided into two groups. Group 1 was 37 patients in Hoehn-Yahr stages 1 and 2. Group 2 was 81 patients in stages 3 to 5. NTx level elevated in both groups, how-

ever, it was higher in group 2 (mean 19.2 nMECE/l) than group 1 (mean 15.2 nMECE/l). Also, ucOC level elevated in both groups and it was higher in group 2 (mean 5.83 ng/ml) than group 1 (mean 4.62 ng/ml).

Conclusions: We confirmed that osteoporosis was common in PD patients. Both the increase of bone absorption and decrease of bone formation were commonly found in PD patients, especially in advanced stage.

984

Baseline characteristics of patients receiving botulinum toxin type A (BOTOX®) for approved therapeutic indications in the Canadian MOBILITY study: A large ongoing phase IV prospective observational cohort study

M. Jog, T. Wein, R. Beauchamp, R. Miller, M. Bhogal, S. Simonyi (London, Ontario, Canada)

Objective: The objective of this analysis is to describe the baseline characteristics of patients enrolled in a large ongoing study of BOTOX® for approved therapeutic indications.

Background: Botulinum toxin type A (BOTOX®) has numerous therapeutic indications in Canada including blepharospasm, 7th cranial nerve disorders, cervical dystonia, focal spasticity, cerebral palsy, and hyperhidrosis. Movement disorder specialists have extensive experience with the drug, but little is known about the impact of treatment on health utility.

Methods: Phase IV prospective observational cohort study in patients receiving BOTOX® for approved therapeutic indications in Canada. Patient demographic, diagnostic and treatment data are collected at baseline. Health-related quality of life is measured at baseline, week 4 and subsequent visits.

Results: 917 patients have been enrolled at 40 clinical sites to date. The retention rate is 94.5% and 69.7% of patients have returned the week 4 survey. Of 608 patients were included in this interim analysis 67% were female, 93% were Caucasian, and 13% were treatment-naive. Indications for BOTOX® include: adult focal spasticity (AFS), 27%; cervical dystonia (CD), 24%; hyperhidrosis (HH), 11%; 7th cranial nerve disorder (CND), 9%; cerebral palsy (CP), 6%; blepharospasm (BPS) 5%; and other, 18%. The mean age of treatment-naïve patients was younger than previously-treated patients (47yr vs 54yr) and the mean age varied with the indication: AFS, 56yr; CD, 57yr; HH, 35yr; CP, 26yr; BPS, 63yr. The mean duration of treatment in treated patients ranged from 14 months (HH) to 80 months (BPS). The median BOTOX® dose was 200U in both treatment-naïve and previously-treated patients with the highest median dose used to treat AFS (300U, range 100-900U) and the lowest to treat BPS (50U; range 15-125U).

Conclusions: This interim analysis provides an overview of the demographic characteristics of a diverse group of patients receiving BOTOX® for approved therapeutic indications. CD and blepharospasm are long established approved indications for the BOTOX®; however, AFS has emerged as an important indication for the drug in Canada.

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Botulinum toxin type A (BOTOX®) improves health utility in patients treated for approved therapeutic indications: Interim analysis of a large ongoing phase IV prospective observational cohort study (MDs on BOTOX® Utility-MOBILITY) in Canada

M. Jog, T. Wein, R. Beauchamp, R. Miller, M. Bhogal, S. Simonyi (London, Ontario, Canada)

Objective: The objective of this analysis is to describe the impact of BOTOX® on health utility after 4 weeks of treatment in a large ongoing study.

Background: Botulinum toxin type A (BOTOX®) is used extensively for numerous therapeutic indications, however little is known on its effect on health utility. The ongoing prospective MOBILITY study aims to measure the impact of BOTOX® on health utility with validated instruments.

Methods: Phase IV prospective observational cohort study in patients receiving BOTOX® for approved therapeutic indications in Canada (blepharospasm, 7th cranial nerve disorders, cervical dystonia, focal spasticity, cerebral palsy, hyperhidrosis). The SF-12v2 Health Survey and Global Rating Scale are administered at baseline, week 4 and at subsequent clinic visits. Physical component scores (PCS), and mental component scores (MCS) are derived from self-reported SF-12v2 and SF-6D data. In this interim analysis continuous data were analyzed by student's t-test and dichotomous data by Chi-square test.

Results: 917 patients are enrolled at 40 clinical sites with a 94.5% retention rate. 69.7% returned the week 4 survey. Of 608 patients included in the analysis 526 were receiving ongoing BOTOX® treatment; 82 were BOTOX®-naïve. Significant differences in self-reported SF-6D scores between baseline and week 4 ($p=0.05$ for continuous data; $p=0.0001$ for dichotomized data), and between baseline and week 4 on the MCS ($p=0.03$ as continuous data) are reported. Among the BOTOX®-naïve patients, there was a significant difference in SF-6D scores between baseline and week 4 ($p=0.03$ for continuous data; $p=0.018$ for dichotomized data). This trend was not significant among patients receiving ongoing therapy at baseline.

Conclusions: Interim analysis from the ongoing MOBILITY study reveals that significant improvements in health utility can be demonstrated in patients receiving BOTOX® for therapeutic indications. Health utility benefit was most pronounced in BOTOX®-naïve patients and in MCS score at 4 weeks, BOTOX® expected peak effect window. Further recruitment and long term follow-up and analyses are ongoing.

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Resilience in patients with Parkinson's disease

S.R. Kim, S.J. Chung, H.-W. Shin, M.S. Kim, S.J. Lee, M.C. Lee (Seoul, Republic of Korea)

Objective: The aims of this study was to investigate the level of resilience and related factors in patients with PD in Korea.

Background: Resilience is defined as the ability to bounce back or cope successfully despite substantial adversity. Originally, resilience was referred to as a positive personality trait whereas over the past decade resilience has been redefined as a dynamic modifiable process. Resilience is being increasingly studied in innovative ways among different diseases and diverse populations. However, the study of the resilience in Parkinson's disease (PD) patients has been rarely reported.

Methods: Between April 1, and August 20, 2009, we studied 148 PD patients who volunteered to be interviewed using structured questionnaires. Patient's data concerning demographics characteristics, social status, emotional status, and disease characteristics were obtained. The patients were assessed using the Resilience Scale (RS), Modified Beck Depression Inventory (BDI), and Spielburger's Anxiety Inventory.

Results: Sixty two male and 86 female patients were included. The mean age was 62.2 ($\pm$9.5) years and the mean age at onset was 52.4 ($\pm$11.8) years. The mean score of the Resilience Scale, BDI, anxiety score, and MMSE were 127.7 ($\pm$21.6), 12.9 ($\pm$9.3), 41.9 ($\pm$11.1), and 26.9 ($\pm$2.8), respectively. Among the demographic and social data, family income ($p=0.009$) and presence of leisure ($p=0.001$) were significantly correlated with higher RS score. Among the disease characteristics, the mean age at onset ($r=0.164$, $p=0.046$), disease duration ($r=-0.262$, $p<0.001$), and the treatment duration of levodopa ($r=-0.283$, $p<0.001$) were significantly correlated with RS score. In addition, the RS score was strongly correlated with BDI ($r=-0.531$, $p<0.001$) and anxiety score ($r=-0.572$, $p<0.001$). On stepwise regression analysis, the most important factor related to the RS score was anxiety score (adjusted $R^2=0.349$, p

<0.001), family income (adjusted R^2=0.386, p<0.005), and the treatment duration of levodopa (adjusted R^2=0.406, p=0.028).

Conclusions: The resilience in patients with PD was strongly associated with anxiety, economy status, and treatment duration of levodopa. Therefore, understanding of these factors is essential for improving resilience in PD patients and ultimately for effective treatment for PD.

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Quality of life in patients with Parkinson's disease: Translation and psychometric evaluation of the Iranian version of PDQ-39

M. Nojomi, Z. Mostafavian, G.A. Shahidi, C.J. DPhil (Tehran, Islamic Republic of Iran)

Objective: The aim of this study was to determine validity and reliability of Persian PDQ-39.

Background: Health related quality of life is considered to be an important outcome measure in studies involving patients with chronic neurological conditions such as Parkinson's disease. Disease specific patient reported outcome measures (PROMs) are increasingly used as primary end points in clinical trials of new treatments for such conditions. The most widely used disease specific PROM in PD is the 39 item Parkinson's Disease Questionnaire (PDQ-39).

Methods: Two hundred Parkinson's disease patients attending neurologic clinics of teaching hospitals were recruited. PD patients completed a translated version of the PDQ-39 after giving informed consent. Internal consistency reliability of the questionnaire was assessed by Cronbach's alpha coefficient. Reproducibility (test/retest reliability) was assessed across the 3-week interval using the intraclass correlation coefficient (ICC). To assess convergent validity, results on the PDQ-39 were correlated with those gained on the SF-36, a widely used generic outcome measure. Discriminate validity of questionnaire were assessed by comparing PDQ-39 scores and the severity and the duration of disease.

Results: A value of 0.93 (Cronbach's α) was gained for the summary score (PDQ-SI), indicating high levels of internal reliability. Alpha value of seven of the eight 8 domains was greater than 0.70. The intraclass correlation coefficient (ICC) ranged 0.47 to 0.90. The range of correlation coefficients between domains of SF-36 and PDQ-SI was -0.40 to -0.61. There was a statistically significant difference between severity of disease and mean scores of PDSI.

Conclusions: This study provides evidence that the Persian version of PDQ-39 is valid and reliable measure of quality of life in PD.

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Treatment satisfaction with current botulinum toxin treatment of post-stroke spasticity: Results of a multi-national patient and physician survey

E. Psaila, M. Fargel (Rueckersdorf/Nuremberg, Germany)

Objective: The satisfaction with the current Botulinum toxin (BoNT) therapy regimen among patients suffering from post-stroke spasticity and physicians and potential improvements of the therapy were assessed in a multi-national survey.

Methods: 125 patients and 120 physicians in Canada, France, Germany and the USA underwent face-to-face interviews (ca. 25 min.) regarding their current BoNT treatment and potential improvements of BoNT therapy. Patients qualified if they underwent at least 2 complete treatment cycles. Participating physicians must have had at least 3 years experience with Botulinum toxin injections.

Results: Patients suffered from post-stroke spasticity for an average of 3.8 years and received Botulinum injections for 2.0 years. 70 % of patients were between 46 and 75 years old. 46% of the patients were males. The mean interval between injections was 14.4 weeks. 76% of patients have at least some problems of moving around and also 92% have at least some problem carrying out their daily activities. 63% of patients are at least moderately depressed or anxious. 47% of physicians are not satisfied with the efficacy and patient response and only 11% and 18% are satisfied with the patient satisfaction and recovering mobility, respectively. 70% of patients and 55% of physicians would prefer shorter injection intervals compared to those intervals in which the patients actually receive BoNT. Also, physicians estimated that about 24% of patients would benefit from injection of higher doses than actually used. 42% of patients do not receive BoNT despite the fact that they would benefit from a BoNT treatment for post-stroke spasticity.

Conclusions: Although there is a general satisfaction with the BoNT treatment, patients and physicians would prefer shorter injection intervals and higher doses for the treatment of post-stroke spasticity.

POSTER SESSION 4

THURSDAY, JUNE 17, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-16:00
Authors Present: 13:30-15:00

RESTLESS LEGS SYNDROME

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MEIS1 as a potential mediator of the RLS-iron pathology

N. Silver, R.P. Allen, C.J. Earley (Baltimore, Maryland, USA)

Objective: Investigate the effects of iron deficiency on MEIS1 protein and the effects of decreased MEIS1 on mRNA expression of several iron management genes and on BTBD9 another important RLS-risk gene.

Background: Intronic variants in the gene MEIS1 have been associated with restless legs syndrome (RLS). These intronic variants lead to decreased MEIS1 mRNA and protein in RLS brain tissue and lymphoblastic cells. MEIS1 is important for development but also in adult mice is expressed in dopaminergic neurons of substantia nigra. Little has been done to understand its role in mature tissues or in the pathology of RLS. Since brain iron deficiency is considered a primary pathology in RLS, a fundamental question addressed in this study is whether or not there is a relation between MEIS1 and iron regulation that might explain at least in part it relation to RLS.

Methods: Two studies cultured THP-1 cells. First, to investigate decreased iron effects on MEIS1 expression cells were cultured for 24 hours with or without 25uM DFO. Second, effects of decreased MEIS1 message and protein expression on iron management were evaluated using 48-hour siRNA specific to MEIS1 compared to a control siRNA.

Results: iron chelation with DFO increased by 37% MEIS1 protein on Western blotting. Study 2: 48-hour inhibition of MEIS1 production increased transferrin receptor (TfR) mRNA by 35%, TfR2 mRNA by 146%, SLC40A1 (ferroportin) mRNA by 173%, and decreased hepcidin mRNA by 68%. BTBD9, another gene highly associated with RLS risk, was increased 91% with siRNA inhibition of MEIS1.

Conclusions: MEIS1 protein appears to be, in part, regulated by cellular iron status, while MEIS1 itself may also feedback to regulate some component of cellular iron management. Prior studies in RLS tissues have shown that MEIS mRNA and protein are decreased in those with the RLS-risk haplotype. The findings in study 2 above are remarkably similar to what we found in the human lymphocytes from RLS: increased iron importer (TfR) and increased iron exporter (ferroportin). Increased ferroportin may relate to the decreased hepcidin: decreased hepcidin increases ferroportin. These preliminary studies strongly support the role for MEIS1 in iron regulation and also in

the regulation of other genes associated with RLS risk. (Similar not identical abstract submitted to APSS Sleep2010).

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Evaluating a murine iron-deficiency (ID) model for RLS

E.L. Unger, R.P. Allen, C.J. Earley (Baltimore, Maryland, USA)

Objective: Determine the extent a selected iron-deficient (ID) murine strain matches the RLS phenotype

Background: A murine RLS model should produce biological, behavioral and dopaminergic response patterns matching the RLS phenotype. Dietary ID compared to control diet (CD) showed for one murine strain large decreases in ventral mid-brain iron (VMB) with little change in hemoglobin (Hgb) matching the well-established neurobiology of RLS. This strain was tested for RLS-like behavior matching 3 of the 4 diagnostic criteria for RLS, namely: decreased resting time (resting engenders RLS symptoms) with increased activity (activity relieves the RLS symptoms) in the home cage occurring during the last 2 hours of the active (dark) period (RLS symptom times) but NOT during the last 2 hours of the rest (light) period) (RLS protected time with few symptoms).

Methods: Home cage behavior was tested 3 months after post-weaning for mice maintained on either normal control diet (CD) or iron deficient (ID) diet (3–5 mcg/g iron). Study 1 measured the behaviors for 4 consecutive days comparing the ID and CD animals for the last 2 hours of the dark (active period) and the last 2 hours of the light (inactive period). Study 2 treated the ID mice with l-dopa (12.5 and 25 mg), the dopamine agonist quinpirole (0.5 and 1.0 mg) and saline given ip at 3 hours before the end of the active period. The RLS behaviors were evaluated for 3 hours after the treatment. There were 6-7 animals in each evaluation group. Activity was cumulated for consecutive 6-minute intervals. Rest was defined as a 6-minute interval without activity and a rest epoch was any consecutive 6-minute intervals without activity.

Results: The ID compared to CD animals in study 1 showed increased activity ($p=0.12$) with significantly ($p<0.02$) decreased resting time and resting epochs. All the dopamine treatments compared to placebo in study 2 served to significantly change toward normal all of the RLS-like behaviors for the first hour after treatment. Quinpirole showed the same effect for hour 2 after treatment.

Conclusions: This ID murine strain uniquely matches the biological, behavioral and dopaminergic response patterns of the RLS phenotype. It provides an animal model of RLS deserving further evaluation.

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Periodic leg movements during sleep in narcoleptic patients with or without restless legs syndrome

E. Antelmi, C. Franceschini, S. Vandi, R. Ferri, G. Plazzi (Bologna, Italy)

Objective: To analyze periodic leg movements during sleep's (PLMS) periodicity in narcolepsy with cataplexy (NC) patients with or without restless legs syndrome (RLS).

Background: Nocturnal sleep NC is usually disturbed by a numbers of events. Patients with NC have also a high number of leg movements during sleep significantly less periodic than those of patients with RLS; furthermore, RLS affects a significant proportion of individuals with NC. In this new study, we analyze PLMS in NC patients with or without RLS, with the hypothesis that they show different periodicity features.

Methods: We recruited 31 patients with NC; 8 patients (5 males, mean age 46.2 ± 16.24 years) were found to be affected by RLS (based on the four international criteria and on a frequency of 2 times/week) while the remaining 23 (13 males, mean age 40.2 ± 17.80 years) were not. PLMS were detected in the polysomnographic recordings of all patients and their number, duration, and time structure were analyzed by means of an approach particularly able to consider their periodicity.

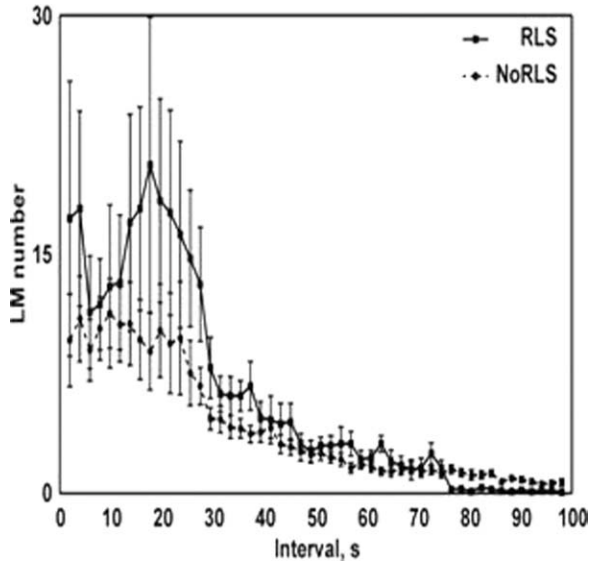

FIG. 1 (991). Distribution histogram of intermovement intervals in NC patients with or without RLS.

Results: PLMS index was found to be higher in NC patients with RLS than in those without (41.6 ± 22.15 vs. 25.5 ± 21.79, $p<0.047$). The distribution histogram of intermovement intervals also showed important differences between the two subgroups of patients. Subjects without RLS had a wide peak ranging from 2 to 24 s while patients with RLS showed a main peak at around 18 s, preceded by another peak at around 4 s (a distribution usually seen in patients with idiopathic RLS).

Conclusions: The results of this study confirm the initial hypothesis that RLS in NC is characterized by PLMS with a time structure very similar, if not identical, to that of PLMS in idiopathic RLS. Furthermore, these findings confirm the specificity of these features of PLMS for RLS an this latter finding may have practical consequences.

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Sonographic abnormalities of brainstem structures of restless legs syndrome: Comparison between idiopathic RLS and RLS in Parkinson's disease

J.S. Baik, J.H. Park, J.H. Lee (Seoul, Korea)

Objective: To investigate and compare the sonographic abnormalities in substantia nigra (SN) in patients with idiopathic RLS (iRLS), RLS in parkinson's disease (RLS-PD), idiopathic parkinson's disease (iPD) and healthy controls.

Background: RLS in PD (RLS-PD) has different clinical course comparing to idiopathic RLS (iRLS), for example, later onset, seldom proceeding PD onset. Transcranial sonography (TCS) is a neuroimaging method with the ability to provide data on various brain structures in its B-mode. Although several unique findings of TCS in movement disorders were reported already, for example, SN hypoechogenicity in patients with iRLS and hyperechogenicity in iPD, the TCS finding of RLS-PD is not reported yet.

Methods: Total 60 patients (41 iRLS, 19 RLS-PD) with RLS and 25 iPD patients from January 2007 to December 2008, who were visiting to Sanggye Movement Disorders Clinic, and 35 age-matched healthy controls were involved to this study. All patients underwent TCS by single independent expert blinded for the patients and control group. We measured the areas of SN hyperechogenicity and cal-

culated the SN hyperechogenicity ratio to the half areas of the midbrain at the same side.

Results: The mean age of the PD group (RLS-PD and iPD) was significantly older than that of the non PD group (iRLS and control) ($p<0.05$). In RLS group, the patients with RLS-PD were older than patients with iRLS (71.3±7.8 vs. 62.3±15.5 $p<0.05$). Comparing all groups, the area of echogenicity of the SN region in iRLS patients was significantly decreased compared with PD-RLS, iPD and control group ($p<0.0001$), the PD-RLS group demonstrated a significantly increased area of echogenicity compared with the control group ($p=0.007$) and iPD group ($p<0.0001$). However, there was no significant difference of echogenicity between PD-RLS group and iPD group ($p=0.11$). Seventy-four percent of patients with iRLS were found to have SN hypoechogenicity compared to 27% of RLS-PD patients and 16% of iPD patients ($P<0.001$).

Conclusions: we found that RLS-PD has a different sonological findings comparing to iRLS and different clinical findings comparing to iPD. To explain detail pathophysiological mechanisms of RLS-PD, we need to perform of more prospective studies of relationship between TCS findings and pharmacological treatments in RLS-PD patients.

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Safety and efficacy of long-term treatment with transdermal rotigotine in patients with idiopathic restless legs syndrome: A 12-month open-label extension study

H. Benes, D. Garcia-Borreguero, W. Oertel, A. Fichtner, E. Schollmayer, C. Trenkwalder, on Behalf of the SP791 Study Group (Schwerin, Germany)

Objective: To assess the safety and efficacy of long-term treatment with rotigotine in patients with restless legs syndrome (RLS) in a 12-month open-label (OL) extension trial (SP791 [NCT00498108]).

Background: Two independent double-blind placebo-controlled trials, SP790 (NCT00136045, 6-month pivotal trial) and SP794 (NCT00275236, 1-month sleep laboratory trial) showed transdermal rotigotine to be well tolerated and efficacious in RLS patients based on IRLS and CGI assessments, as well as PLM-Index in SP794. Previous analysis of the SP791 OL-extension data showed clinically relevant augmentation is uncommon with long-term rotigotine therapy.

Methods: Eligible patients completing the double-blind trials had their dose de-escalated. OL rotigotine treatment was titrated upwards and maintained at the patient's optimal dose (1, 2 or 3 mg/24h) for 12 months during surveillance for adverse events (AEs). Efficacy assessments included IRLS, RLS-6, CGI-1 and CGI-2.

Results: Of 341 patients entering the study, 91 (27%) discontinued, 58 (17%) due to AEs and 17 (5%) due to lack of efficacy. The most common AEs were application site reactions (33%), nausea (7%), fatigue (7%), nasopharyngitis (6%) and headache (6%). Mean daily dose at the start of maintenance was 2.08 mg/24h; after initial dose titration, 70% of patients required no further dose adjustment; 5% decreased and 24% increased their dose. At the end of maintenance, mean IRLS score was 10.6 (SD: 9.8; -17.0 points from baseline, SD: 10.2), 65% of patients were classified as IRLS responders (IRLS score reduced by ≥50%), 55% were IRLS remitters (IRLS score of ≤10 points) and 30% had no RLS symptoms (IRLS score of 0). Illness severity (assessed by CGI-1) improved to a less severe category (normal, borderline ill, or mildly ill) in 81% of patients and change in condition (CGI-2) was categorized as "very much improved" or "much improved" in 80%. Improvement in both nighttime and daytime symptoms was shown by RLS-6.

Conclusions: The favorable safety and efficacy profile of transdermal rotigotine shown in two double-blind trials was maintained for an additional year in this OL extension study at doses of 1, 2, or 3 mg/24h.

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Neuroanatomical aspect of the dopaminergic diencephalospinal pathway in the non human primate: Potential implications for restless legs syndrome

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Objective: The aim of this study was: 1. to determine the regional distribution of DA spinal receptors subtypes in non human primate spinal cord by using *in situ* hybridation (ISH), 2. to characterize the DA-containing neurons within the diencephalon which are known to project to the spinal cord by using a retrograde labeling technique. 3. to test the effect of the DA specific neurotoxin 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), used to model PD in experimental animals, on A11 neurons.

Background: Restless legs syndrome (RLS) involves abnormal limb sensations leading to severe sleep disruption. It has been suggested that RLS arises from dysfunction of the diencephalospinal dopaminergic (DA) pathway (A11) although its neuroanatomical and functional organization remains poorly known in the human and relatively uninvestigated in primate.

Methods: The ISH procedure was performed in macaca mulatta lumbar spinal cord (n=4) with 35S-labeled complementary RNA probes designed to recognize each DA subtype receptors. For retrograde labeling, the tracer Fluoro-Gold (FG) was stereotaxically and unilaterally injected into the C2-C6 dorsal aspect of the macaca mulatta spinal cord. Stereological count of hypothalamic A11 neurons and monoamines dosages by HPLC at spinal cord level were performed to assess the MPTP effects on the diencephalospinal pathway.

Results: ISH revealed that D2 and D3 subtypes are the most expressed DA receptors. The FG reached the DA neurons within the so-called A11 group but didn't target to any other DA neurons group. These neurons were located ventrally in the posterior hypothalamus adjacent to the periventricular region. MPTP systemic intoxication leads to about 50% of neuronal loss in A11 group compared to normal but DA levels remain unchanged at spinal level.

Conclusions: We conclude that the diencephalic A11 area is the sole dopaminergic group to project to the spinal cord in the non-human primate where it modulates sensory-motor integration through D2 and D3 receptor subtypes. This may explain the high potency of dopaminergic D2/ D3 agonists in the relief of RLS symptoms. This work was supported by the French association of patients with restless legs syndrome (A.F.J.R.S).

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Transcranial sonography in differential diagnosis of restless legs syndrome

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Objective: Aim of this study was to evaluate the usage of combined TCS/TCCS imaging in diferential diagnosis of idiopathic and secondary RLS.

Background: Restless legs syndrome (RLS) is one of the most common underdiagnosed neurological disorders, with prevalence of around 10% in general population. Also, non-idiopathic RLS is more frequently found in patients with anaemia. Recent transcranial sonography studies have shown that supstantia nigra (SN) hypoechogenicity apears to be the frequent finding in RLS, just as it is increased blood flow velocity in a. cerebri media (ACM), measured by TCCS, in anaemic patients.

Methods: Twenty patients with RLS symptoms (diagnosis was made according to IRLSSG criteria), ten patients with anaemia (hemoglobin values <12 g/dl) and RLS symptoms, and 20 controls underwent neurological and sonographic examination.

Results: Bilateral mean SN area measured on TCS was significantly lower in idiopatic RLS patients versus controls (0.09±0.01

cm^2 vs. 0.18±0,02 cm^2 ; p<0,01). Values of mean blood floow velocity measured in ACM by TCCS were also higher in RLS patients (123,24±7,33 vs 80,7±6,55; p<0,01) with anaemia, with normal finding of SN area.

Conclusions: TCCS in combination with TCS is a useful tool in diagnosing idiopathic RL syndrome, just as it is in differeating idiopathic from secundary RLS due to anaemia.

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A Brazilian multicenter prevalence study of restless legs syndrome in multiple sclerosis patients

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Objective: To assess the prevalence and severity of RLS in MS patients in relation to controls.

Background: Restless legs syndrome (RLS) is a frequent and often non-diagnosed neurological disorder. RLS can be divided into primary and secondary forms, the latter being classically associated with iron deficiency, pregnancy and renal failure. More recently, an intriguing association of RLS and multiple sclerosis (MS) has been the subject of a few publications.

Methods: Questionnaires on the presence and severity of RLS were applied to MS patients and controls in four large Brazilian cities. The present study was approved by the institutional Ethics Committees involved in the research. Patients and controls in use of medications known to influence symptoms of RLS were excluded.

Results: A group of 60 patients (46 F, 14 M, mean age 39.2±16.1 years; mean weight 67.6±12.3 kg) and a group of 120 controls (80 F, 40 M, mean age 39.1±16.12 years; mean weight 69.6±12.1 kg) were assessed for the presence and severity of RLS. MS duration was 9.2±7.9 years. Symptoms of RLS were identified in 55% of MS patients and 20% of controls [OR=4.89 (95% CI 2.4-9.6)]. The severity of the symptoms among controls with RLS was "mild" 51%, "moderate" 34%, "severe" 10% and "very severe" 5%. Among patients, the severity was rated as "mild" 18%, "moderate" 34%, "severe" 39%", "very severe" 9%. There was no correlation with disease duration and the presence and/or severity of RLS symptoms in MS patients. Regarding MS treatment, 58 patients were in regular use of immunomodulators. Patients in use of glatiramer acetate had a lower prevalence of RLS symptoms (3/13; 2.5%) than those in use of beta interferons (14/45; 31.1%) (OR=1.4 95%CI 0.3-6.1).

Conclusions: The prevalence of RLS in Brazilian control subjects was in accordance with previous reports. MS patients were five times more prone to RLS than healthy controls. The severity of RLS in MS patients (48% severe or very severe) was higher than that of controls (15% severe or very severe). The influence of immunomodulators on the presence of RLS symptoms is a matter for further investigation.

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Augmentation incidence during a 26-week controlled trial of pramipexole for restless legs syndrome

D. Garcia-Borreguero, B. Högl, C. Trenkwalder, L. Ferini-Strambi, W. Hening (Deceased), W. Poewe, S. Brenner, M. Sohr, S. Albrecht, R.P. Allen (Madrid, Spain)

Objective: To assess the incidence of augmentation during 26 weeks of double-blind pramipexole vs placebo for restless legs syndrome (RLS).

Background: Pramipexole is effective for RLS, but no controlled studies have lasted >12 weeks. Augmentation—RLS exacerbation attributed to an initially beneficial treatment—is perhaps the most clinically relevant complication of long-term dopaminergic RLS therapy.

Methods: For 26 weeks, RLS patients with pretreatment serum ferritin >30 ng/mL took double-blind optimized pramipexole (0.125-0.75 mg/d) or placebo. Assessments included International RLS Study Group Rating Scale (IRLS) score, and all patients kept symptom diaries. All cases meeting any of 4 predefined criteria for suspected augmentation were reviewed by an expert panel (blinded to treatment), which utilized standard diagnostic criteria for Augmentation (REF).

Results: Among 152 pramipexole and 149 placebo recipients treated for ≥4 weeks, and therefore eligible for augmentation diagnosis, 47 (30.9%) and 40 (26.8%) were referred for expert-panel review. For confirmed augmentation, the 6-month incidence was 14 cases (9.2%) on pramipexole vs 9 cases (6.0%) on placebo. Among these cases, the mean time to augmentation was 110±54.7 days on pramipexole vs 80.6±52.3 days on placebo (P=0.2143), and for pramipexole but not placebo, incidence increased with treatment duration, diverging from placebo for case emergence after week 12. However, treatment dosage showed no relation to confirmed-augmentation rate. Only 6 confirmed cases involved IRLS deterioration to a score worse than at baseline—4 cases (29% of 14) on pramipexole and 2 (22% of 9) on placebo.

Conclusions: The nonsignificant differences in augmentation rates between pramipexole and placebo indicate the difficulty to distinguish augmentation from natural fluctuations in RLS severity during the first months of treatment. Thus, studies should be longer than 6 months. Supported by Boehringer Ingelheim GmbH.

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Impact of neuropsychiatric comorbidity on treatment success in restless legs syndrome

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Objective: To prospectively assess treatment success in idiopathic RLS in the clinical setting and to elucidate demographical factors and comorbidities which may limit treatment response.

Background: Randomized controlled trials prove efficacy of dopaminergic, opiod and antiepileptic drugs in the treatment of restless legs syndrome (RLS). In contrast, epidemiological data suggest frequently insufficient RLS treatment in clinical practice.

Methods: 100 patients with idiopathic RLS (40% had never received RLS specific treatment) were examined at baseline and after 12 months. At baseline, treatment recommendations for RLS treatment were given to primary and secondary care physicians according to RLS therapy guidelines of the German Neurological Society. Outcome measures were reduction of RLS symptoms as measured by the International RLS Severity Scale (IRLS), improvement of quality of life as measured by the RLS quality of life instrument (RLS-QoL) and treatment satisfaction.

Results: After 12 months of guideline based treatment in the typical clinical setting, no statistically significant improvement of IRLS and RLS-QoL could be observed. However, treatment satisfaction was given in 40% of the patients (compared to 14% at baseline, p=0.002). Best predictor for treatment satisfaction was RLS-QoL improvement (Rho=0.74, p<0.001), which showed a negative correlation with neuropsychiatric comorbidity (r=-0.74, p<0.001), including somatoform disorders (prevalence 41%), chronic pain (32%), anxiety (20%) and major depression (16%). Other frequent comorbidities such as low serum ferritin (23%), essential tremor (11%) and cardiovascular disorders (40%) as well as demographical factors had no impact on treatment outcome. There was also no difference between intially untreated and pretreated patients.

Conclusions: It is essential to carefully assess and treat neuropsychiatric comorbidity along with RLS symptoms in order to achieve treatment satisfaction. Supportive treatment strategies such as psychotherapy and behavioural therapy should become an integral part of RLS therapy.

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Withdrawal incidence after a 26-week controlled trial of pramipexole for restless legs syndrome

B. Högl, D. Garcia-Borreguero, C. Trenkwalder, L. Ferini-Strambi, W. Hening (Deceased), W. Poewe, S. Brenner, M. Sohr, S. Albrecht, R.P. Allen (Innsbruck, Austria)

Objective: To assess the incidence of withdrawal after cessation of as much as 26 weeks of double-blind pramipexole vs placebo for restless legs syndrome (RLS).

Background: Pramipexole is effective for RLS, but no controlled studies have lasted >12 weeks, and none was designed to assess withdrawal—RLS exacerbation if treatment stops.

Methods: For 26 weeks, RLS patients with pretreatment serum ferritin >30 ng/mL took double-blind optimized pramipexole (0.125-0.75 mg/d) or placebo. Assessment tools included the International RLS Study Group Rating Scale (IRLS), which was administered at screening, at randomization, at end of treatment (without study-drug tapering), and 7±1 days afterwards. Withdrawal was defined as a ≥4 point increase (i.e., worsening) in the post-treatment score vs baseline (the higher of the patient's scores at screening and randomization).

Results: Among 321 patients, of whom 234 completed 26 weeks, the adjusted mean IRLS score change at end of treatment was –13.7 on pramipexole vs –11.1 on placebo ($P=0.0077$). Of 135 pramipexole recipients with no RLS therapy after their drug-stop date, 14 (10.4%) had a post-treatment increase (compared with baseline) of ≥4 points. Among them, 2 (10.5% of 19) had been on 0.125 mg/d, 5 (11.4% of 44) on 0.25 mg/d, 5 (14.3% of 35) on 0.50 mg/d, and 2 (5.4% of 37) on 0.75 mg/d. Of 133 placebo recipients with no RLS therapy after their drug-stop date, 2 (1.5%) had a post-treatment IRLS increase of ≥4 points.

Conclusions: Although withdrawal is generally considered to be most likely after high dosage, the frequency of post-treatment deterioration in the present trial was independent of dosage, and could thus be interpreted simply as loss of benefit after effective RLS treatment was abruptly stopped. Nevertheless, the treatment-group difference (10.5% vs 1.5%) suggests that pharmacodynamic mechanisms may be involved. Supported by Boehringer Ingelheim GmbH.

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Prevalence of secondary restless legs syndrome in Japan–rheumatoid arthritis

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Objective: The aim of study was to clarify the prevalence of secondary restless legs syndrome (RLS) in rheumatoid arthritis (RA).

Background: Prevalence of idiopathic RLS was regarded as low frequency in Asian people compared with Caucasoid. We tried to clarify whether or not secondary RLS prevalence was also low in Japanese people. Many condition were reported in secondary RLS, firstly we choose RA because our hospital is the national center for the allergic and rheumatoid disease in Japan.

Methods: Subjects: 256 patients with RA who accepted to participate with this study were medicated well in our out-patient clinic. Diagnosis of RA was made by diagnosed criteria several years ago. 259 cases were consisted of male 35, female 224, whose age were59.5+/-12.6 y/o (16~83). Duration of illness was 15.2+/-11.4 years. Methods: We used questionnaire methods. Questionnaire contains clinical diagnosis criteria and severity scores for RLS. Definition of RLS is according to the definition of the International RLS Group (1995). In this survey, patients were randomly chosen in our clinic in a certain month. After this survey, we checked all these patients' laboratory data, such as Hb and iron concentration in serum from the medical records and also whether or not accompanying the apparent polyneuropathy in the medical records.

Results: Twenty-three patients with RA were comorbid with RLS. So that crude prevalence was 8.8%. Background of patients with RA and RLS was not different from patients without RLS (age; 58.8+/-8.5y/o, duration of illness; 15+/-12years). However, RA with RLS was more common in male patients (male n=5 (16.7%), female n=18 (8.7%). There was no difference in Hb and iron concentration among them.

Conclusions: We previously reported prevalence of RLS with hemodialyzed renal failure was 32%. In this study, prevalence of secondary RLS comorbid with RA was 8.8%. We thought secondary RLS was not rare in Japan. We are now going to survey in bronchial asthma in our out-patients.

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Long-term safety and efficacy of rotigotine in patients with idiopathic RLS: 5-year results from a prospective multinational open-label follow-up study

B. Hogl, C. Trenkwalder, D. Garcia-Borreguero, R. Kohnen, W. Poewe, K. Stiasny-Kolster, L. Bauer, A. Fichtner, E. Schollmayer, W. Oertel, for the SP710 Study Group (Innsbruck, Austria)

Objective: To evaluate the safety and efficacy of rotigotine treatment in patients with moderate to severe idiopathic restless legs syndrome (RLS) over 5 years.

Background: Rotigotine is a transdermally applied D3/D2/D1 dopamine agonist, approved for the treatment of early and advanced Parkinson's disease (PD) and moderate to severe RLS in the European Union, and for early PD in the US.

Methods: This study (NCT00498186) was the prospective follow-up of a placebo-controlled phase IIb dose-finding trial (NCT00243217) with rotigotine in RLS patients. Patients were titrated to an optimal dose of rotigotine (0.5, 1.0, 2.0, 3.0, 4.0 mg/24h). Safety assessments included adverse events (AEs), and efficacy was measured by IRLS, CGI-1, CGI-2, and RLS-6. Quality of life was measured by QoL-RLS. Results from the final 5-year analysis are presented.

Results: 295 patients with a mean age of 58.3 years (66% female) entered the study, of whom 126 (43%) completed the 5-year follow-up. 89 patients (30%) discontinued the study prematurely due to an AE, and 31 (11%) due to lack of efficacy. Mean rotigotine dose was 2.43 mg/24h after initial titration, and 3.09 mg/24h at end of study. Most AEs were mild to moderate in intensity, the most common being application site reactions (58%), nasopharyngitis (19%), back pain (14%), nausea (12%), and fatigue (11%). Mean IRLS score was 27.8 at baseline, improving by 18.7 points to 9.0 at end of study. 59% of patients were classified as remitters (IRLS≤10), and 39% as symptom-free (IRLS=0). At the end of study, 85% of patients were in a less severe illness category (normal, borderline ill, or mildly ill as assessed by CGI-1) compared with 3% at baseline. Change in condition (assessed by CGI-2) was categorized as "very much improved" or "much improved" in 96% of patients. RLS-6 showed improvement for both nighttime and daytime symptoms; QoL-RLS also improved.

Conclusions: Long-term treatment with rotigotine was generally well tolerated. Efficacy remained stable in patients remaining on study drug over 5 years of follow-up.

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Where is the core of the volcano? The undetermined origin of primary restless legs syndrome

B. Isak, K. Agan, A. Pehlivan, K. Uluc, T. Tanridag, O. Us (Istanbul, Turkey)

Objective: The aim of this study was to investigate the involvement of small and large fiber sensory network in primary restless legs syndrome (RLS), on the basis of nerve conduction studies (NCS) and autonomic tests.

Background: An association between peripheral neuropathy and primary RLS was suggested since both of the conditions share common characteristics i.e., positive sensory symptoms, circadian changes and the length dependent pattern of symptoms and autonomic imbalances i.e., hypertension and heart disease.

Methods: Twenty seven (18 women and 9 men) patients with symptoms and signs of RLS were recruited according to the IRLSS (International restless Legs Study Group) criteria. Normal values were obtained from twenty six (20 women and 6 men) age- and sex-matched controls. The patients were evaluated with Neuropathy Symptom Profile (NSP) and Autonomic Symptom Profile (ASP) questionnaires and then both groups underwent conventional motor and sensory nerve conduction studies (NCS) and autonomic tests i.e., heart rate variation variability (HRVV), heart rate variability to deep breathing (i.e., expiration to inspiration ratio; E/I), heart rate variability to Valsalva maneuver, heart rate variability to standing up quickly (30/15 rate) and sympathetic skin responses (SSR).

Results: The patients suffered from neuropathic and autonomic complaints obviously. NSP revealed cramps (62.9%), tingling (70%), burning (55.5%) and ASP revealed orthostatic dizziness (66.6%), sexual problems (62.9%), secretion complaints (48.1 %) in RLS patients. However, there was no significant difference for NCS, heart rate variability tests and SSRs among patients and controls.

Conclusions: Since NCSs and the autonomic tests were within normal ranges, the complaints were considered to be the consequences of disorganisation in sensory integration, due to the dysfunction of the caudal diencephalic A11 group, rather than a neuropathic process. The cardiac autonomic imbalance possibly emerges as a consequence of arousal periods prior to or during the PLM episodes in sleep, but not due to autonomic neuropathy. The clinical picture of RLS, which was referred to the involvement of peripheral sensory network previously, could be attributed to the sensitization of the sensory and autonomic neurons due to dysfunction of caudal diencephalic A11 group.

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Neurophysiological approach to the complex organization in spine: A study on F-wave duration and cutaneous silent period in patients with primary restless legs syndrome

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Objective: The aim of this study was to define the restless legs syndrome (RLS) patients with the help of uncommon electromyographic parameters i.e., F-wave duration (FWD) and cutaneous silent period (CSP).

Background: Central sensitization is suggested to be one of the core mechanisms in the pathogenesis of RLS. FWD and CSP are considered to be influenced by the central excitability and/or diminished central inhibition due to central sensitization. The reflection of central sensitization on conventional electromyography was expected to emerge on the basis of the changes in the activities of motor neurons, i.e., the common components of CSP and F-wave pathways.

Methods: Twenty four patients of primary RLS were compared with thirty one age- and sex-matched controls. The subjects were evaluated with nerve conduction studies (NCS), F- wave parameters (minimum-maximum-mean latencies, chronodispersion, persistence, duration and the ratio of mean FWD to compound muscle action potential [CMAP] duration), CSPs (latency, duration and the ratio of durations from lower and upper extremities, respectively), expiration to inspiration ratio (E/I) and sympathetic skin responses (SSR).

Results: There was no significant difference between patients and controls for NCS, E/I and SSR. However, FWDs were prolonged and CSP parameters were shortened significantly in the lower extremities of the patient group ($P<0.0001$).

TABLE (1003). *Comparisons of the F-wave duration and Cutaneous Silent Period Parameters*

Abnormal FWD and CSP parameters	RLS (value ± SD)	Cnt (value ± SD)	P (RLS vs.Cnt)
Ul–FWD (ms)	12.65±1.15	11.13± 1.01	0.0001
Ul-FWD /CMAPdur(ms)	1.07±0.16	0.93±0.14	0.001
Tb-FWD (ms)	19.26± 2.36	15.10±1.71	0.0001
Tb-FWD/CMAP-dur(ms)	1.53±0.30	1.15±0.19	0.0001
TA CSP lat	110.13 ± 27.42	91.04 ± 14.25	0.001
TA CSP dur	25.25 ± 11.06	71.35 ± 20.04	0.0001
S.P.R.	0.45 ± 0.18	1.34 ± 0.33	0.0001

Ul, Ulnar; Tb, Tibial; Fdur, Fduration; ms, milliseconds; FWD /CMAP dur, F-wave duration/CMAP duration; CSP: Cutaneous silent period, APB: Abductor Pollicis Brevis, TA: Tibialis Anterior, lat: Latency, dur: Duration; SPR:Silent Period Ratio; RLS, Restless Legs Syndrome patients; Cnt, Control; SD, Standard Deviation.

These parameters in the lower extremities were highly sensitive for defining the patients ($P<0.0001$).

TABLE (1003). *Comparisons according to number of abnormal subjects*

Comparisons according to number of abnormal subjects	n (%)	n (%)	P (RLS vs.Cnt)
Ul–FWD Abnormal	4 (16,7%)	1 (3,2%)	0.156
Ul-FWD / CMAP dur Abnormal	6 (25,0%)	1 (3,2%)	0.035
Tb-FWD Abnormal	10 (41,7%)	1 (3,1%)	0.0001
Tb-FWD / CMAP dur Abnormal	15 (62,5%)	1 (3,1%)	0.0001
TA CSP lat Abnormal	7 (29.2%)	2 (6.3%)	0,030
TA CSP dur Abnormal	17 (70.8%)	0 (0%)	0.0001
S.P.R. Abnormal	22 (91.7%)	0 (0%)	0.0001

Ul, Ulnar; Tb, Tibial; Fdur, Fduration; ms, milliseconds; FWD /CMAP dur, F-wave duration/CMAP duration; CSP: Cutaneous silent period, APB: Abductor Pollicis Brevis, TA: Tibialis Anterior, lat: Latency, dur: Duration; SPR:Silent Period Ratio; number of subjects; RLS, Restless Legs Syndrome patients; Cnt, Control.

Conclusions: FWD and CSP parameters were found to be very sensitive for defining the patients with RLS. Since both the NCSs and the autonomic tests were in normal ranges, the abnormalities of FWD and CSP parameters were referred to dysfunction of different interneuron groups (i.e., Ib-interneurons and Renshaw cells) in the spine. Focusing on FWD and CSP should be helpful to define the RLS patients, in whom the conventional electrophysiological procedures are not helpful.

1004

Prevalence of restless legs syndrome in patients taking neuroleptic drugs

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Objective: To study the prevalence of restless legs syndrome (RLS) in patients taking neuroleptic drugs.

Background: RLS is a sensorimotor syndrome that responds dramatically to dopaminergic medications. Dopamine deficiency or dopamine dysfunction has been implicated as one of the factors involved in its pathophysiology.

Methods: Patients taking neuroleptic drugs were consecutively enrolled from psychiatry clinic of Chulalongkorn University Hospital and interviewed for RLS symptoms. RLS was diagnosed if the patient fulfilled all the four symptoms of the NIH-IRLSSG essential diagnostic criteria for RLS. Patients were excluded if they had a history of end-stage renal disease, peripheral neuropathy, spinal cord diseases, malignancy and Parkinson's disease or if they were pregnant.

Results: One hundred patients were interviewed. There were 51 males (51%) and 49 females (49%). Mean age was 43.44±13.32 years. Fifty-two patients (52%) were diagnosed with schizophrenia and 11 with bipolar disorder (11%). Mean disease duration was 10.1±8.674 years (n=97). Only one patient had symptoms consistent with RLS (1%). The patient was a 40 year old female with a diagnosis of depression for seven years. RLS symptoms started about four years after she started taking perphenazine. She had been taking 4 mg of perphenazine for six years, 60 mg of fluoxetine for four years and one mg of lorazepam for one-and-a-half years. She described having an uncomfortable, bothersome feeling in her legs which makes her feel like wanting to amputate her legs. These feelings would come on during periods of rest in the evening or at night. She had to walk around to relieve the symptoms. She had symptoms about once per week with mild to moderate severity. She did not report these symptoms to her psychiatrist. The patient felt that her depression had resolved so she stopped all the medicines by herself. After stopping the medicines, the symptoms still persisted but the frequency decreased to once per month with the severity remaining the same. The patient denied a blood test therefore serum ferritin level could not be checked. She lost to follow-up thereafter. There was no family history of RLS in her family.

Conclusions: The prevalence of RLS in patients taking neuroleptics in our study is 1%. A larger cohort and a longitudinal study is needed to confirm the result.

1005

Rotigotine reduced impairment of daily activities due to pain in patients with idiopathic restless legs syndrome

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Objective: To assess impairment of daily activities in patients with idiopathic restless legs syndrome (RLS) due to pain in arms and legs, and the effects of transdermal rotigotine, in a 6-month, double-blind, placebo-controlled study (SP790 [NCT00136045]).

Background: Pain is one of the sensory symptoms most frequently reported by patients suffering from RLS.

Methods: SP790 was a 6-month, double-blind study in patients with moderate to severe RLS. Patients were randomized to receive either placebo or rotigotine (1, 2, 3 mg/24hrs) by transdermal administration. Patient impairment of daily activities due to pain was assessed using Item 8 of the Quality of Life Questionnaire for RLS patients (QoL-RLS). At each visit, patients were asked to what degree pain in their arms or legs impaired their wellbeing or normal daytime activities. Potential answers ranged from "not at all" (0 points) to "extremely" (5 points).

Results: Of 458 patients randomized to treatment in this study, 456 (99.6%) were assessed using QoL-RLS Item 8 at baseline and 433 (94.5%) could be assessed at the end of maintenance/withdrawal visit (EoM). At baseline, 55.6% of the placebo-randomized patients had moderate to extreme pain, compared with 61.9% of patients randomized to rotigotine. At EoM, moderate to extreme pain was recorded for 38.2% of placebo-treated and 22.9% of rotigotine-treated patients. The mean value for pain (QoL-RLS item 8) decreased from 2.41 (SD: 1.61) to 1.85 (SD: 1.64) in the placebo group, and from 2.61 (SD: 1.54) to 1.39 (SD: 1.46) in the rotigotine group (p=0.0003, ANCOVA). The median change was 0 points in the placebo group, and -1 point in the rotigotine group.

Conclusions: In addition to a previously reported reduction in RLS symptoms as measured by the IRLS scale, and an overall improvement in the Clinical Global Impression, patients treated with transdermal rotigotine over six months showed significant improvement in initial impairment of wellbeing and daily activities due to RLS-related pain.

1006

Periodic limb movements in obstructive sleep apnea-hypopnea syndrome patients

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Objective: To explore the influence of the presence of Periodic Limb Movements (PLM) in the sleep architecture in Obstructive Sleep Apnea—Hypopnea Syndrome (OSAHS), and the possible link between both sides things.

Background: PLM and OSAHS are two frequent phenomenons in sleep, which often occur in the same patient. In OSAHS patients, the morbidity is from 8.1% to 48%.

Methods: Retrospective study of 229 consecutive diagnosis OSAHS patients (33 women and 196 men) were finally selected. PLM disorder was diagnosed if PLM index was higher than 5. According to this standard, 111 patients had only OSAHS, and the other 118 patients had both OSAHS and PLM. General information (age, sex, body mass index), sleep parameters (total time of sleep, percentage of sleep stages, rapid eye movement latency, sleep efficiency, Lowest SpO2,oxygen reducing index, apnea–hypopnea index, Index of periodic leg movements during sleep, Periodic leg movements with arousals) were calculated and compared between these two groups of observations. Descriptive statistics and nonparametric distribution techniques were used for analysis.

Results: The presence of PLM in OSAHS patients was less correlative only for an increase in stage 1 (15.5% vs 19.7%, $p<0.05$). After adjustment, for the potential confounders of age, sex, body mass index, and apnea-hypopnea index, an increased PLMI was associated with a higher sleep stages1(95%CI -0.22-1.85; P =0.04), but not with other indices of sleep quality.

Conclusions: In patients with OSAHS, the presence of PLM is less correlative.

1007

Prevalence of restless legs syndrome in parents of children with attention deficit/hyperactivity disorder

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Objective: To assess the prevalence of restless legs syndrome (RLS) in parents of children with attention deficit/ hyperactivity syndrome (ADHD).

Background: An association between ADHD and RLS has been previously proposed according to a possibly increased prevalence of RLS in ADHD children and the parents of these children, respectively.

Methods: Parents of at least two children with ADHD were assessed by using a recently validated self-administered 10-item RLS screening questionnaire (RLSSQ).

Results: The questionnaires of 291 parents of ADHD children (151 female; mean age 40.2±5.7 years) were analysed. The prevalence of RLS in these parents was 13.1% (n=38) and thus only slightly higher when compared with other assessments of the RLS prevalence in the German population. Furthermore there was no significant difference in the RLSSQ score between the parents of ADHD children w/o RLS (n=253) and a control group w/o RLS (n=187) (2.5±2.2 vs. 2.2±2.1, p=0.21).

Conclusions: Overall, these preliminary results do not support previous findings suggesting an increased prevalence of RLS (or RLS symptoms) in parents of ADHD children, but need to be supplemented by an assessment of the RLS prevalence in the general population according to the RLSSQ.

1008

Evidence for bilateral caudate nucleus involvement in PLMS: A case-study employing simultaneous EEG-EMG-fMRI

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Objective: To investigate the cerebral involvement in the pathophysiology of PLMS (periodic limb movements in sleep) using simultaneous EEG-EMG-fMRI recordings.

Background: PLMS are most frequently found in restless legs syndrome (RLS). The pathophysiology of RLS and PLMS in particular, is not well understood, despite many genetic, brain imaging and pharmacological studies. RLS is thought to be a disorder of the CNS. Most evidence so far suggests that subcortical inhibition is decreased, leading to reduced spinal and possibly cortical inhibition. Subcortical dopamine systems in particular, have been suggested as areas of primary dysfunction (dopaminergic hypothesis), largely because of the positive response to dopaminergic medication. The few existing neuroimaging studies suggest reduction of mean caudate and putamen D_2-receptor binding (^{18}F-DOPA PET in RLS patients) or involvement of brainstem nuclei (awake fMRI in PLMS patients, contrasting periods of unpleasant sensations with movement to periods with no symptoms or movements).

Methods: We used simultaneous EEG-EMG-fMRI to directly relate PLM during sleep to brain activation, while concurrently assessing sleep stage. One patient was able to sleep during scanning. This 44 year old male underwent polysomnography prior to scanning, indicating a PLM index of 110 (severe PLMS). During scanning, he suffered from PLM, involving right ankle dorsiflexion, approximately every 20 seconds, while sleeping (stage I-II). Brain activation was derived in an event-related design, for (awake) self-paced voluntary right ankle dorsiflexion as well as for involuntary PLM during sleep. Events were set at the onsets of EMG bursts after scanner artefact correction.

Results: Self-paced movements mainly resulted in activation of left thalamus and left primary motor cortex, whereas PLM during sleep were additionally associated with highly significant bilateral caudate nucleus activation.

Conclusions: This study provides the first direct evidence that the bilateral caudate nuclei are crucially implicated in the generation of PLMS. This is in line with the dopaminergic hypothesis concerning its underlying pathophysiology.

1009

Restless legs syndrome and periodic limb movements in patients after spinal cord injuries: Risk of symptoms being misinterpreted

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Objective: To evaluate the possibility of restless legs syndrome (RLS) and periodic limb movements (PLM) in patients with spinal cord lesions reporting insufficient effect of treatment for spasticity or neurogenic pain.

Background: Sensory and motor symptoms such as neurogenic pain and spasticity are frequently reported in patients with spinal cord lesions. These symptoms may not always be easily interpreted and in some cases the differential diagnosis of RLS and PLM may be suspected. RLS is characterized by uncomfortable sensations associated with an urge to move the legs that usually appears during evenings or during sleep. A clinical symptom that adds support to the diagnosis of RLS is PLM. PLM is reported in approximately 80 % of patients with RLS and consists of repetitive stereotypic involuntary movements with flexion of the hip, knee and ankle.

Methods: Some patients with insufficient effect of treatment for neurogenic pain and/or spasticity were referred to a clinician with special interest of RLS and PLM for evaluation and eventually treatment. Data from the cases were obtained retrospectively and reviewed.

Results: Four patients obtained treatment with pramipexole, initially 0,09-0,72 mg/day. Two had RLS and PLM, one RLS and one PLM. All four reported symptoms in lower extremities and one also in upper extremities. Three patients with remaining gait function reported RLS-score without/with treatment as follows: 32/11, 37/12 and 33/12. One patient with complete paraplegia (with incomplete RLS-score) reported 22/10. After a follow-up period of 16, 20, 43 respectively 49 months all four still reported excellent results. Two reported no increase in dose, one had increased from 0,09 to 0,18, one from 0,27 to 0,80 mg/day during follow-up.

Conclusions: In patients with spinal cord lesion complaining of involuntary movements or atypical sensations in lower extremities and with poor result of treatment for spasticity or neurogenic pain the possibility of RLS or PLM may be considered. In patients with spinal cord lesions sensory-motor symptoms due to RLS or PLM might not always follow normal patterns. Co-operation between the rehabilitation specialist and a clinician well experienced in RLS might be necessary. Our results indicate that further studies on the occurrence of RLS and PLM in this group of patients might be of value.

1010

Clinical characteristic of pediatric restless legs syndrome (RLS)

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Objective: To evaluate the clinical characteristics of restless legs syndrome (RLS) in children and to establish the treatment strategy of the disorder in this generation.

Background: RLS has been reported to occur even in children, but the awareness of the disorder is still limited not only in general population but also in pediatric medical practitioners or caregivers. In addition, consensus regarding the treatment of childhood RLS has not been established.

Methods: Consecutive 12 pediatric RLS patients under the age of 15 years who consulted three sleep disorder centers in Japan were included in this study. Diagnosis of RLS was confirmed by board certified sleep specialists based on the diagnostic criteria of NIH/IRLSSG consensus report. Onset age of RLS, family history of the disorder, iron status, polysomnographic findings and effectiveness of the medical treatment were investigated.

Results: Mean age of onset was 8.5 (SD 3.7) years. Growing pain was experienced in 17% of the patients and family history of RLS was found in 25% of the patients. Less than 50 ng/ml of serum ferritin level was observed in 58% of the patients. Of the 9 patients who underwent polysomnography (PSG), 22% of them had PLM index of more than five in PSG and 67% showed increased leg discomfort during suggested immobilization test (SIT). 9 patients were treated with pramipexole with the mean dose of 0.17 (SD 0.14) mg (rage 0.03-0.5mg). 4 of them required daytime dose for the daytime symptom during rest at classes. Most of the patients were treated successfully with pramipexole, but some of them experienced nausea with small dose.

Conclusions: Growing pain and family history of RLS were less prevalent in our patients compared with previous reports from the West. Treatment was mostly successful with dopamine agonist, but some pediatric patients required treatment for the daytime symptom so as to reduce the discomfort while sitting in their school classes.

1011

"Pure motor restless legs syndrome" mimicking myoclonus

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Objective: To report two cases of a proposed new entitiy "isolated motor restless legs syndrome".

Background: Restless legs syndrome (RLS) is predominately clinically defined by an urge to move the legs, a sensory component that is entirely subjective. Periodic limb movements of sleep accompany RLS in most cases but actual movements, whether while asleep or awake, are not part of the diagnostic criteria of RLS. No criteria for probable RLS or RLS that dose not meet all criteria exist. RLS

pathophysiology is incompletely understood but most data implicates spinal cord abnormalities.

Methods: We report two cases of elderly patients with moderate spinal pathology who were referred for myoclonus.

Results: Both cases had semi-rhythmic leg movements, mostly abduction, that partially improved while standing, but specifically denied any urge to move. (see video) One had failed more than 20 medications for a diagnosis of spinal myoclonus. The other had failed at least 5 medications for a similar diagnosis. These movements improved immediately and dramatically with a moderate dose of pramipexole, a dopamine agonists used for RLS. At 8 and 10 months, the efficacy is maintained with any adverse events. We propose that this "myoclonus" is actually the isolated motor component of RLS.

Conclusions: Physicians should consider dopamine agonist therapy in patients presenting with isolated involuntary leg movements. This may expand the phenotype of "restless legs syndrome". We propose the term "isolated motor restless legs syndrome".

1012

Prevalence and profile of restless legs syndrome in Parkinson's disease and other neurodegenerative disorders: A case-control study

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Objective: To determine the prevalence and profile of Restlesss Legs Syndrome (RLS) in idiopathic Parkinson's disease (PD), Progressive Supranuclear Palsy (PSP), multiple system atrophy (MSA) and Dementia with Lewy Bodies (DLB).

Background: There is an increasing evidence of the association of RLS with dysfunction of central dopaminergic neurotransmission seen in many neurodegenerative disorders. To the best of our knowledge there is no literature addressing the association of RLS with PD, PSP, MSA and DLB in a case-control pattern.

Methods: This was a prospective case-control study at National Institute of Mental Health & Neurosciences, Bangalore, India. Consecutive 187 patients with neurodegenerative disorders including PD (n=134), PSP (n=27), MSA (n=21) and DLB (n=5), clinically diagnosed by standard diagnostic criteria, were evaluated using International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria. Sleep disturbances were assessed by Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS). Exclusion criteria included non-ambulant state, severe cognitive and behavioral disturbances and current use of neuroleptics. Control group included 172 age and gender matched healthy subjects not related to the patients.

Results: The prevalence of RLS in patients was significantly higher than in controls (9.6% vs 2.9%; p=0.009). It was highest in PD (11.9%), equally affecting men and women, and low in the other disorders (MSA-4.8%, PSP-3.7%, DLB-0%). In PD the mean IRLSSG severity score was 15.8±6.4 and duration of RLS symptoms was 1.6±0.9 yrs. In 93.8% the symptoms followed onset of motor symptoms. All PD patients with RLS except one had only leg restlessness. There was no association between side of onset of motor symptoms and of RLS symptoms. The symptom frequency was usually 2-4 times/week over past one month. Comparison of PD patients with and without RLS did not show significant differences in mean age (55.9±11 vs 54.9±14.7 yrs), duration of motor symptoms (3.4±2.5 vs 4.8±3.5 yrs), H&Y stage (2.3±0.7 vs 2.2±0.6), UPDRS motor score (31.9±18.7 vs 31.4±16.2), PSQI (6.9±2.5 vs 5.7±3.6) and ESS (6.3±3.0 vs 5.4±3.9).

Conclusions: RLS was more commonly associated with PD than with MSA, PSP, DLB and healthy subjects. No specific disease characteristics of PD differentiated those with and without RLS.

1013

Phase-imaging study in restless legs syndrome

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Objective: Our aim was to use phase imaging to study brain iron content in patients with idiopatic RLS.

Background: The pathophysiology of idiopatic RLS is poorly understood. Observations point towards a role for the iron metabolism. Reduced brain iron in RLS is also suggested by MR studies that exploit the effect of iron on T2, T2* and T2', although with discrepant results. A recent technique, phase imaging, that measures the phase shifts in gradient-echo images may be a sensitive tool to quantify the iron content of the brain (1).

Methods: 11 idiopatic RLS patients (age 54±11, mean±SD) and 11 healthy volunteers (age 51±18) were studied in a 1.5 T scanner. Diagnostic criteria of the International Restless Legs Syndrome Study Group (IRLSSG) and IRLSSG rating scale for severity were used. Following published methods (1) a phase map was prepared. Regions of interest (ROIs) were selected (i) manually in structures known to accumulate iron (dentate and red nucleus, substantia nigra, basal ganglia) and (ii) automatically in whole brain. For whole brain ROIs, the 10th, 50th and 90th percentile of the filtered phase histogram were calculated, while for local ROIs, 25th and 50th percentiles only. Non-parametric tests were used.

Results: In the whole brain analysis, RLS patients showed lower phase dispersion, characterized by 10th and 90th percentile values of significantly smaller magnitude than in controls ($p<0.01$), while the median was no different. The 10th percentile of RLS patients correlated with disease duration ($r=0.60$, $p<0.05$). In the localized ROIs, differences were not significant although there was a clear trend.

Conclusions: Global brain iron content appears reduced in RLS patients compared to healthy subjects. Alterations were seen in both the 10th and the 90th percentile of the whole brain histogram where the extremes of image phase variation were reduced, due to reduced paramagnetic tissue content. Whole brain analysis was more sensitive than local ROI analysis, suggesting that this protocol may also be useful in all types of disease characterized by neurodegeneration with brain iron accumulation. **Reference** 1. Ogg RJ et al. *Magn Reson Imaging* 1999*;* 17:1141-8.

1014

Restless leg syndrome (RLS) by gender: The effects of hormones, life cycles and comorbidity in a female Sicilian cohort

R. Silvestri, I. Aricò, R. Condurso, G. Mento (Messina, Messina, Italy)

Objective: To evaluate RLS prevalence and clinical features by gender in a patient cohort diagnosed in a Sicilian sleep center.

Background: RLS prevalence in women is estimated nearly double than in males, with a high distribution during specific life cycles such as pregnancy and/or menopause. Furthermore, life and sleep quality, general health and mood are likely to be more disrupted in females.

Methods: All consecutive patients diagnosed with RLS in our sleep center from January 2007, according to the IRLS Diagnostic Interview (1995) were enrolled in this study. Data collection included: anthropometric data, physical/neurological examination, personal and familial history including comorbid disorders and treatment, iron status. Instrumental assessment: Epworth Sleepiness Scale (ESS), IRLS-RS (Allen et al., 2003), Pittsburgh Sleep Quality Index (PSQI), Hamilton Anxiety Rating Scale (HAM-A), Beck Depression Inventory (BDI), Short Form–36 2v health survey. Most patients also underwent a standard video PSG to assess objective sleep alterations.

Results: A total of 72 (46 F, 26 M), 8.3% of the total patients reporting to our center, were diagnosed with RLS. Among women, 17% had symptoms onset in pregnancy and 17% during menopause. No significant gender differences were found as far as age of onset, BMI, duration or severity of symptoms, ESS, objective PSP findings. However, a positive familial history with earlier onset was 7 fold higher in females versus males. All comorbid disorders were more represented in females with a significantly higher ratio of anxiety and mood disorders, migraines, diabetes, and sleep-related eating disorder (SRED). RLS secondary to iron deficiency (mean ferritin 7.9 μg/dl) was a specific F finding (32%). PSQI, BDI and HAM-A scores were significantly more affected in F. Response to dopaminergic treatment was stronger in M.

Conclusions: Gender severely affected symptoms, familial versus sporadic occurrence, comorbid disorder distribution and treatment response in our sample.

1015

Pediatric RLS: Diagnostic problems, co-morbidity and developmental impact in a Sicilian cohort

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Objective: To assess symptom onset duration and severity, comorbid disorders, sleep and behavioral impact in pediatric RLS patients in a Sicilian sleep center over the last 3 years.

Background: RLS in children and adolescents is a rare disorder (1,9%), often misdiagnosed and underreported. Nevertheless, it may severely affect sleep, cognition and behavior with grave consequences on daily life and development.

Methods: 17 patients, mean age 8,3 years, 16 M, diagnosed by the RLS diagnostic interview adjusted by pediatric criteria (ICSD-2) were assessed as far as RLS-RS severity (Allen et al., 2003), sleep interview, blood count, iron status and video polysomnography (PSG) to obtain standard sleep variables including periodic leg movements during sleep and wakefulness (PLMs and PLMw indexes).

Results: Symptoms had a mean onset at 8 years, mean duration of 17 months with mean IRLS-RS 19,7. Three children had a first relative affected. Mean ferritin was 44 μg/dl. All but 3 had co-morbid ADHD C type. Other comorbidities: migraine (2), dyslexia (4), language disorders (2), tics (1), bruxism (8), rhythmic sleep disorder (4), sleep apnea (3) disorders of arousal (7). All patients reported difficulties at initiating/maintaining sleep but no excessive daytime sleepiness. PSG indicated mean SL of 35 min, sleep efficiency of 7,5%, arousal index of 13.37 and PLMs and PLMw index respectively 27.50 and 44.1. Conner parental rating scale (CPRS) and sleep were significantly more affected in RLS+ ADHD children, showing an inverse correlation of ferritin with PLMw index. Moreover, video PSG enabled a definitive diagnosis in 8 children not diagnosable on the basis of the interview alone.

Conclusions: Pediatric RLS is not rare in a tertiary sleep center. It requires extensive parental/child interviews, highly enhanced by employing video PSG, especially in populations at risk such as ADHD and other developmental disorders to which RLS contributes in terms of dysfunctional load.

1016

Restless legs syndrome following peripheral trauma

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Objective: To report a case in which restless legs syndrome (RLS) started just after a peripheral trauma.

Background: RLS is defined by an uncomforble sensation in legs, that worsened with rest and it is an importante cause of impairment of sleep quality as patient has relieve with movements. The pathophysiology more acceptble involves abnormalities in dopamine pathways and impaired iron homeostasis. RLS can develop as a result of certain conditions or factors, peripheral neuropathy for example.The pathogenesis of RLS seems to involve more than one mechanism, which leads to restless legs as the final common pathway. Some movement disorders has been related after peripheral trauma, specially dystonia.

Methods: Case report: A 85-year-old-man seek our institution because of action and postural tremor, a clinical picture consistent with essential tremor (ET). During evaluation he complained of insomnia since he had a right tibia trauma. In fact he had insomnia because he started with uncomfortable alternating sensations in legs that reliefe with moving. On physic exam we observed action and postural tremor. We started pramipexol with complete resolution of RLS and primidon to ET with good response.

Conclusions: This case was atypical because of RLS just after peripheral trauma and the alternation phenotype. Possibly trigger of RLS in the case was damage of peripheral receptors.

1017

Is the restless legs syndrome (RLS) mediated by inflammatory and immunological mechanisms? RLS is associated with an increased prevalence of small intestinal bacterial overgrowth

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Objective: To determine the prevalence of Irritable Bowel Syndrome (IBS) and Small Intestinal Bacterial Overgrowth (SIBO) in restless legs syndrome (RLS).

Background: Patients with gastrointestinal (GI) diseases such as celiac disease and Crohn's disease have a high prevalence of Restless legs Syndrome (RLS). A meta-analysis indicates that 54% of patients with IBS have small intestinal bacterial overgrowth (SIBO). SIBO is suggested by a positive Lactulose Breath Test (LBT).

Methods: Thirty two RLS patients (23 F, 9 M avg age 52.7 yrs) were recruited from a newspaper and radio ad where the presence or absence of GI symptoms was neither encouraged nor discouraged. The presence or absence of IBS was determined and patients were submitted to LBT.

Results: The prevalence of IBS in our RLS population was 8/32=25% as compared to the prevalence of IBS in the general population from the literature of 6.7% (P =.0002). A positive LBT suggestive of SIBO was present in 21/32=65.6% of our RLS patients and in 3/28=10.7% of a normal population that we recruited where RLS and GI symptoms were excluded (18F, 10 M avg age 45.3 yrs). Assuming a false positive rate of 10.7%, a full 65.6 %-10.7%=54.9% of positive LBTs can be attributed to their association with RLS in an unselected population. There was an incomplete overlap of IBS and a positive LBT: 5 /8=62.5% of RLS patients with IBS displayed a positive LBT and 5/21=23.8 % of RLS patients with a positive LBT displayed IBS. More males than females were affected by a positive LBT in the RLS population (9/9=100% M versus 12/23=52.1% F). Age did not play a role in the distribution of positive LBTs and neither sex nor age played a role in the distribution of IBS in our RLS population. There was no correlation between serum ferritin levels, RLS severity or RLS duration and either a positive LBT or IBS.

Conclusions: Evidence of IBS and SIBO are common in RLS but there is not complete overlap. The high prevalence of SIBO in our RLS patients along with the fact that 75% of cases of secondary RLS are associated with inflammation suggests that RLS may be mediated through inflammatory or immunological mechanisms. Since inflammation is also associated with iron deficiency, these results are also in agreement with the iron deficiency hypothesis for RLS.

POSTER SESSION 4

THURSDAY, JUNE 17, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-16:00
Authors Present: 13:30-15:00

SPASTICITY

1018

Stiff person syndrome as the initial manifestation of systemic lupus erythematosus–case report

R.P. Munhoz, M.M. Moscovich, H. Fameli, L. Filla, H. Teive (Curitiba, Brazil)

Objective: Case Report.

Background: Stiff person syndrome (SPS) is a neurological disorder characterized by the presence of fluctuating muscle rigidity and spasms of the trunk and proximal body parts. SPS is believed to be

mediated by autoantibodies to glutamic acid decarboxylase (anti-GAD), limiting GABAergic activity and lowering the threshold for muscle spasms and other neuropsychiatric features.

Results: 48year-old woman with a history of painful thoracic lumbar paravertebral spasms that lasted for seconds, accompanied by severe pain. She felt fluctuating discomfort and rigidity in the cervical, thoracic and lumbar axial muscles, including scapular girdle, leading to persistent upright posture. Her muscles were normotrophic and tone was normal in the limbs but moderately increased in the axial muscles. Strength was normal and deep tendon reflexes were brisk, plantars were flexor. Cerebellar signs were absent.Fasting plasma glucose, hemoglobin A1C,creatinine, electrolytes, TSH and CK levels were normal; serology for infectious diseases was normal; plasma anti-GAD levels were 12.6 U/mL.CSF analysis, brain and spinal MRI were normal. Electromyography showed continuous activity of the lumbar paraspinal muscles. During investigation she developed photosensitive rash, metacarpo-phalangeal arthritis, fatigue and mild confusion. A rheumatologist requested inflammatory parameters: positive anti-double-stranded-DNA, anti-nuclear, anti-RP, anti-Scl-70 antibodies and IgM isotype of anticardiolipin antibodies titers; negative rheumatoid factor and mildly decreased C3 and C4 complement levels. Skin biopsy showed lymphocytic perivascular dermal infiltrates. The diagnosis of SLE was done. Treatment was initiated with oral prednisone, hydroxychloroquine, diazepam and baclofen. Intravenous immunoglobulin brought partial but significant relief of contractures.

Conclusions: Abnormal titers of a variety of antibodies have been described in SPS cases such as antiparietal cell, antinuclear, antithyroidal antibodies, Ri, Jo-1 antigens, ribonucleoprotein, and intrinsic factor. Most of these antibodies are also found in SLE. Our case reinforces the possibility of the pathological expression of a common immunogenetic background. Very strong association with HLA phenotypes, often associated with SLE, has also been observed in SPS.

1019

Post stroke arm spasticity–results of the German-Austrian prospective survey

H. Hefter, W. Jost, A. Reissig, J. Wissel (Duesseldorf, Germany)

Objective: To evaluate safety and efficacy of the treatment of patients with post stroke arm spasticity with botulinum toxin A (BoNT-A).

Background: Depending on the localisation of the lesion, different muscle groups are affected by the symptoms of stroke. The combination of these muscles constrains the affected arm in a specific posture or movement pattern. Five typical arm spasticity patterns can be distinguished and treatment recommendations for BoNT-A with respect to target muscles and doses have been drawn up based on these patterns.

Methods: This study was an observational, prospective, non-interventional study. Patients with post stroke arm spasticity requiring treatment to reduce muscle tone but with no fixed contractures of the upper limb were included.One treatment cycle was documented with assessments at baseline, an optional intermediate visit around week 4 and closing visit at approximately week 12. The pattern of spasticity, treatment goal, safety and efficacy were documented. The overall response and goal achievement was rated on a four point scale (non-responder, responder, good responder, best responder).

Results: 409 patients were included in this study, could be allocated to one of the five arm patterns and received Dysport in most cases according to the recommended injection scheme. The therapy goals were reduction of muscle tone (92.6%), support of physiotherapy (63.8%), increase in ROM (61.8%), reduction of pain (58.9%), ease of care (55.7%) and functional improvement in 17% of cases. The mean dose for most patients (97%) was between 700 and 800 MU Dysport. Most of the patients (84%) were classified as responder, good responder or best responder, only 16% of the patients were classed as non-responders.

Conclusions: The arm pattern classification and corresponding treatment recommendation is a helpful decision guidance for botulinum toxin treatment in patients with arm spasticity. A dose between 500 and 1000 MU Dysport for the treatment of post stroke arm spasticity seems to be adequate and safe.

1020

Efficacy of NT 201 (botulinum neurotoxin type A, free from complexing proteins) in the treatment of patients with upper limb spasticity

P. Kanovsky, M.P. Barnes, I. Pulte, P. Minnasch, S. Grafe, for the NT 201 Spasticity Study Groups (Olomouc, Czech Republic)

Objective: To evaluate the efficacy of NT 201 (Botulinum neurotoxin type A, free from complexing proteins) across clinical studies of patients with upper limb (UL) spasticity.

Background: NT 201 is a preparation of Botulinum neurotoxin type A free from complexing proteins, and its efficacy in the treatment of patients with UL spasticity has been examined in clinical studies of up to 89 weeks in duration.

Methods: Two prior studies investigated the efficacy of NT 201 in treating upper limb spasticity. In study 1, patients with UL post-stroke spasticity were randomised to receive up to 6 injections of NT 201 (maximum dose: 400 U). In study 2, patients with upper limb spasticity of various aetiologies received one treatment with NT 201 (20 U/ml or 50 U/ml; maximum dose: 400 U), with a 12-20 week follow-up. In both studies response rate ($\geq$1-point improvement on the Ashworth Scale and on the Disability Assessment Scale (DAS) at 4 weeks after injection) was measured. Study 1 also assessed the onset, duration, and waning of treatment effect.

Results: 340 patients with upper limb spasticity were enrolled. After one set of injections, Ashworth Scale and DAS response rates for each of the NT 201-treated muscle groups were consistently improved and statistically significant across the two studies. In study 1 this level of treatment response was maintained with repeated administration - for example, Ashworth Scale 66.3 - 75.5% response for wrist flexors after each injection in the extension phase of study 1. NT 201 led to significant improvements in the principal therapeutic target of DAS ($p \leq 0.0313$). In study 1 (double-blind phase), the median onset of treatment effect was 4.0 days, median waning of effect was 10.0 weeks, and median duration of effect was 12.4 weeks.

Conclusions: NT 201 has demonstrated consistent efficacy in the treatment of upper limb spasticity.

1021

Use of botulinum toxin in neurology: Experience of the neuroactive-neuromuscular blocking interdisciplinary service

C. Milani (Ribeirao Preto, Sao Paulo, Brazil)

Objective: To identify the demographic profile and the main therapeutic indications of the BT type A (Onabotulinumtoxin) in an interdisciplinary neuromuscular blocking service. Location: San Francisco Hospital of Ribeirao Preto, Ribeirao Preto city, Sao Paulo state, Brazil. Period: 2006-2009.

Background: The botulinum toxin (BT) is a biological product derived from the Clostridium botulinum, whose main action is to promote the release of acetylcholine in the neuromuscular junction and, consequently, temporary muscle relaxation. Since it was started its commercial use, there are more than twenty years, a large number of clinical conditions has its role of therapeutic indications in neurology and rehabilitation.

Methods: 108 patients assessed and subjected to at least one Onabotulinumtoxin application were studied. Age-related statistical data; sex; type of pathology; average total dose of BT-applied per session; subjective and objective assessment-powders; lock and key response time of BT-side effects were reviewed.

Results: The spasticity (primarily as a sequel of cerebral palsy and stroke) was the most frequent therapeutic indication of BT treatment, followed by hemifacial spasm. Other clinical conditions, such as idiopathic hyperhidrosis, blefarospasm and other various forms of distonias, were also found. For the vast majority of patients treated, the primary benefits were achieved, surpassing the possible side effects.

Conclusions: The BT demonstrates present safety and efficacy in various neurological diseases, with great potential for use in neurologic rehabilitation.

1022

Visual-induced startle reactions in a patient with stiff limb syndrome

P. Schestatsky, A. Dall Pizzol, L. Cabral, A.S. Schuh, M. Roriz-Cruz, F. Batistela, T.L. Monte, M.M. Bianchin, C.R.M. Rieder (Porto Alegre, Brazil)

Objective: To report visual-induced startle reactions in a patient with stiff limb syndrome.

Background: The stiff limb syndrome (SLS) is a rare condition characterized by focal muscle stiffness, painful reflex spasms and continuous motor unit activity as well as abnormal exteroceptive reflexes. One of the most fascinating findings of SLS patients is the reflex muscle spasm triggered by acoustic or tactile stimulation.

Methods: We report the case of a 74 year old woman with progressive stiffness of left leg that was not attributed to any known structural lesion. We performed a full clinical, laboratory and neurophysiological investigation in order to exclude other causes of leg stiffness.

Results: MRI of the brain and entire spinal cord, as well as general laboratory findings were unremarkable, including serum glutamic acid decarboxilase antibodies levels and cerebrospinal fluid parameters. However, during the electrophysiological studies, apart from classic findings of this entity, we noticed and filmed brisk muscle leg spasms induced by a visual cue.

Conclusions: This is the first description of visual-induced startle reactions in patients with SLS. This finding can shed some light on SLS physiopathology and illustrates the importance of neurophsyiological studies in patients with idiopathic increased muscle tone.

1023

Analysis of surgical intrathecal [*i.t.*] baclofen [ITB] implant results emphasizing revision surgery in a mixed pediatric/adult population

N. Roosen, Y. Awaad, K. McIntosh, M. Waines (Dearborn, Michigan, USA)

Objective: We retrospectively reviewed our recent revision surgery experience based upon 1) primary implants at our own institution [*"primary-implant-patients"*], and 2) operative revisions for cases originally implanted outside our institution [*"revision-only-patients"*].

Background: Increasingly, spasticity is managed with ITB using surgically implanted programmable pumps [Medtronic, Inc.]. ITB revision surgery unrelated to programmable pump end-of-life is not uncommon, requiring special attention during pre-, intra-, and post-operative management.

Methods: Since 2002 we treated 41 patients [21F/20M; 22 children (14F/8M) vs. 19 adults (7F/12M); 30 *"primary-implant-patients"*: 16 children (10F/6M) vs. 14 adults (5F/9M); 11 *"revision-only-patients"*: 6 children (4F/2M) vs. 5 adults (2F/3M)]. Clinical charts, operative and imaging reports were reviewed to evaluate reasons for revision surgery and diagnostic work-up requirements.

Results: Eight of 30 "*primary-implant-patients"* required 14 revisions and 7 of 11 *"revision-only-patients"* needed 13 procedures. Seven patients with slowly increasing baclofen-resistant spasticity had either 1) unsuspected pump-catheter connector defects [N=4] with a subcutaneously dislocated *i.t.* catheter [N=1], 2) an X-ray-documented pump-catheter connector defect [N=1] or 3) an X-ray-demonstrated fractured catheter with *i.t.* fragment [N=2] requiring laminectomy [N=1]. Injection studies revealed *i.t.* peri-catheter arachnoiditis [N=1; managed without laminectomy], and connector-related dye leakage [N=3]. Implant infections occurred in 4 cases [3 were multiply pre-operated]. Scintigraphy revealed occult CSF leakage [N=1]. Intrinsic pump failure was rare [N=1].

Conclusions: ITB, although very gratifying, has a high, predominantly technique-related complication incidence during implant life. Meticulous surgical technique, high clinical suspicion, appropriate work-up, and timely surgical management are emphasized to reduce surgical ITB complications.

1024

Surgical complications with intrathecal baclofen (ITB)–management experience in children (<16-years-old) and adults

N. Roosen, K.A. McIntosh, Y.M. Awaad (Wyandotte, Michigan, USA)

Objective: We reviewed our personal experience with ITB revision surgery to explore common etiological patterns related to revision procedures and to compare our results with published implant complication research.

Background: ITB administered by a programmable pump is increasingly popularized as a surgical management option for intractable spasticity and/or in case of unacceptable side effects of oral therapy. Surgical complications do occur, requiring specific diagnostic and revision procedures unrelated to routinely scheduled end-of-implant-life (EOL) revision surgery.

Methods: Since 2002 data on all patients with ITB-related operations by the presenting author was concurrently and prospectively collected. This data was reviewed for clinical information, diagnostics used, imaging results, intra-operative findings, revision intervention reasons, and revision outcomes.

Results: During 2002-2009 we treated 55 patients (27F/28M), including 23 children (14F/9M) and 32 adults (12F/20M). Primary diagnoses included cerebral palsy (CP), multiple sclerosis, myelopathy, idiopathic spasticity and others. We did the primary implant in 33 cases, whereas 22 patients had only revisions following their initial surgery at outside institutions. Eight of our own 33 primary implant patients required 15 revisions: mechanical catheter (N=4) or intrinsic pump (N=1) dysfunction, or other findings (N=10). A total of 22 revision procedures were necessary in 11 patients of the 22 revision-only cases; of these, 3 patients had more than 1 revision. Seroma was present in 3 of our 55 patients. Infection occurred in 4 patients, 3 of which had multiple revision procedures. Plain X-rays were not useful in 4 cases of unsuspected catheter tears. One patient with occult CSF leakage was diagnosed scintigraphically after a non-diagnostic contrast pump study by interventional radiology. One adult patient with CP had a very protracted and complicated course of persisting seroma effusions as well as recurring spinal fluid leakage episodes requiring multiple therapeutic interventions and ultimately implant removal. This will be illustrated in detail.

Conclusions: Our own ITB findings confirm previous literature on complication incidence and emphasize the need for careful surgical technique. Timely diagnosis and management of complications require an elevated index of suspicion.

1025

Juvenile parkinsonism due to a novel SPG 15 mutation

J. Schicks, M. Synofzik, H. Petrusson, P. Bauer, L. Schöls (Tuebingen, Germany)

Objective: To characterize and extend the phenotypic spectrum of hereditary spastic paraplegia 15 (SPG 15).

Background: Autosomal-recessive hereditary spastic paraplegias (arHSP) present with highly heterogeneous, complex phenotypes. It was recently shown that SPG 15 is the second most frequent cause of arHSP with mental retardation and thin corpus callosum (TCC) after SPG 11, but detailed descriptions of the phenotypic spectrum of SPG 15 are still rare. Typically, it is thought to present as an early onset HSP with severe progression of disease and mental impairment dominated by cognitive decline.

Methods: 3 siblings from the same Turkish cosanguineous family presenting with an unusual early onset parkinsonism were assessed by clinical and imaging investigations. Genetic analysis was performed by homozygosity mapping and consecutive sequencing analysis.

Results: In the eldest patient, parkinsonism presented during the very early stages of disease with severe akinesia, rigidity and moderate levodopa-response which progressively weakened. The initial resting tremor resolved after 5 years of disease. The other two patients displayed moderate hypomimia and bradykinesia. All three patients were affected with progressive spastic paraparesis which had initially occured at 18, 17 and 14 years of age, respectively, in association with mental retardation and sharp wave EEG-activity. Sensorimotor axonal neuropathy was present in only one of them. TCC with marked periventricular white matter changes was evident by MRI-scan. Genetic mapping revealed one homozygous locus (14q23.1-24.1) containing the ZFYVE26 gene which encodes SPG 15. Sequencing analysis detected a new homozygous mutation (IVS 29+1 G>T) in all three affected siblings.

Conclusions: Our results demonstrate that juvenile parkinsonism can be caused by SPG15 and, in fact, might even present as the inaugural symptom of disease. Moreover, it adds further evidence for a large phenotypic overlap between SPG15 and SPG 11, as the latter has also recently been identified as a potential cause of juvenile parkinsonism.

1026

The unexpected mutation frequency of *SPG4* gene in Chinese AD-HSP patients

L. Shen, Y. Wang, C. Chen, J. Du, Y. Luo, B. Tang (Changsha, Hunan, China)

Objective: To investigate the mutation frequencies of *SPG4* and *SPG3A* gene in AD and sporadic HSP patients in China.

Background: Hereditary spastic paraplegias (HSPs or SPGs) are a heterogeneous group of inherited neurodegenerative disorders characterized by slowly progressive spasticity and weakness of the lower extremities. Previous studies showed that approximately 20% of AD-HSP patients carried rearrangement mutation on SPG4 gene, however there was no frequency of AD-HSP patients with reaarrangement mutation investigated in Asia.

Methods: PCR and direct sequencing were carried out to detect the micro-mutation of *spastin* and *atlastin* gene in 22 AD-HSP patients and 44 isolated cases in China; MLPA technology and capillary electrophoresis were undertook to detect rearrangment mutation of *spastin* and *atlastin* gene in 22 AD-HSP patients.

Results: Five AD-HSP families and one sporadic case had micromutations on *SPG4* gene, and another five AD-HSP families carried rearrangment mutations of *SPG4* gene. We found 10 mutations on *SPG4* gene, which comprised of 1 missenses, 2 nonsenses, 2 micro-deletions, 1 micro-insertion, 3 exon deletions and 1 exon deletion/duplication, and five of them were novel. Most of SPG4 families presented "pure" spastic paraplegia, and one large pedigree represented marked gender difference of clinical signs and symptoms. One family and one isolated case had missense mutations on *SPG3A* gene, respectively. 1/2 missense mutations was novel. No rearrangement mutation of *SPG3A* gene was found in AD-HSP patients. Two SPG3A probands also presented pure spastic paraplegia, and the SPG3A family showed incomplete penetrance.

Conclusions: Approximately half of AD-HSP patients in Chinese Han nationality were identificated to carried *SPG4* or *SPG3A* mutation, and the frequency of rearrangement mutation of *SPG4* gene was higher than previous reports.

POSTER SESSION 4
THURSDAY, JUNE 17, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-16:00
Authors Present: 13:30-15:00

TICS/STEREOTYPIES

1027

Synchronization and continuation: Analysis of repetitive finger movements in patients with Tourette syndrome

L. Avanzino, A. Tachino, M. Bove, D. Martino, E. De Grandis, M. Mirabelli, E. Pelosin, E. Veneselli, G. Abbruzzese (Genova, GE, Italy)

Objective: To analyse the execution of finger opposition movements with and without external cues in patients with Tourette syndrome (GTS).

Background: GTS is a disorder characterized by vocal and motor tics. Abnormal functioning of the cortico-striato-cortical circuits may be pivotal in heralding tic symptomatology. In particular, the basal ganglia provide internal timing cues and this process may be impaired in movement disorders. We previously observed that GTS patients present abnormalities in executing finger opposition movements with an external cue.

Methods: 7 patients with GTS (mean age 12.8±2.75) and 12 age-matched normal subjects (NS) wore a sensor-engineered glove on their dominant right hand. They were asked to perform a sequence (SEQ) of opposition of the thumb to index, medium, ring and little finger, following an acoustic cue at 1, 1.5 and 2 Hz for 45 sec (synchronization: SYNC). After the acoustic cue was switched off, the subjects were asked to continue maintaining the same rate for other 45 sec (continuation: CONT). Inter tapping interval (ITI), Touch duration (TD) and percentage of correct sequences were analysed.

Results: During SEQ performance GTS patients executed less correct sequences than NS both in the SYNC and CONT phases (RM-ANOVA: GROUP $p<0.05$). While NS executed less correct sequences during CONT as compared to SYNC only at 2 Hz ($p<0.05$), GTS executed less correct sequences in the CONT phase at both 1.5 and 2 Hz ($p<0.05$). GTS patients showed, with respect to NS, an increase of TD ($p<0.05$) and a decrease of ITI ($p<0.05$) at all the rates both in the SYNC and CONT phases. Both GTS and NS presented a decrease of TD in the CONT phase respect to the SYNC phase ($p<0.05$) while ITI did not change.

Conclusions: GTS patients showed subtle alterations in the touching phase during repetitive finger movements with a lower number of correct sequences both when following an acoustic cue and when they did not rely on external cues. However, GTS patients executed the motor task worse in the CONT phase than in the SYNC phase suggesting a greater reliance than NS on external cues. These results suggest a dysfunction in the mechanisms of volitionally driven switching between fine motor tasks in GTS.

1028

Double-blind controlled randomized study of the use of levetiracetam to treat tics in children and adolescents with Tourette syndrome

Y.M. Awaad, A.M. Michon, S. Minark, T. Rizk (Riyadh, Saudi Arabia)

Objective: To evaluate the effects of Ievetiracetam on motor and vocal tics, behavior and school performance in children and adolescents with tics and Tourette syndrome.

Background: Some drugs currently used to treat tics have drawbacks, including the risk of side effects such as tardive dyskinesia. Therapeutic options with better safety profiles are needed. Leve-tiracetam is an antiepileptie drug with atypical GABAcrgic effects that might be beneficial for this indication.

Methods: 24 patients, age 6-18 years with tics and Tourette syndrome were enrolled in this prospective, double- blinded placebo randomized study for 8 weeks. Each group had 12 patients. The initial starting dose of levetiracetam was 250 mg/d. The dosage was titrated over 3 'weeks to 1,000 to 2,000 mg/d. Clinical out-comes were assessed with the Clinical Global Impression Scale, Yale Global Tie Severity Scale, and Revised Conners' Scale.

Results: 10 out of 12 patients in the Levetiracetam group showed improvements based on all of the scales used and 4 patients improved with regard to behavior and school performance. 2 patients dropped out. 9 patients out of 12 patients in the placebo group showed no improvement, one patient showed a great placebo effect, and 2 patients dropped out of the study. Levetiracetam was generally well tolerated. 2 patients discontinued because of exaggeration of pre-existing behavioral problems.

Conclusions: Levetiracetam may be useful in treating tics in children and adolescents. Given its established safety profile, levetiracctam is a candidate for additional evaluation.

1029

Sensitivity to sensory stimuli is a common feature of Tourette syndrome, and is not a result of reduced detection threshold

B.A. Belluscio, M. Hallett (Bethesda, Maryland, USA)

Objective: To define the subjective experience of sensory sensitivity in Tourette syndrome (TS), and to test specific aspects of sensory processing that could potentially explain the heightened sensitivity.

Background: Altered sensory perception may be an important aspect of TS. As documented in several studies, most TS patients describe their tics as actions produced to gain relief from an ongoing feeling of discomfort. Interviews have also revealed that patients often have exquisite sensitivity to specific external stimuli, including lights, sounds, smells, and touch. It is not known, however, how wide-spread this sensitivity is, and whether is it due to enhanced detection or altered processing of input.

Methods: We recruited 20 TS subjects and 20 age-matched healthy control subjects, to whom we administered a survey regarding reactions to sensory and emotional input. In these same subjects, we then tested their threshold for detecting olfactory and tactile stimuli. Finally, we assessed each subject's perception of intensity for stimuli just above threshold.

Results: Our results confirm that, compared to controls, TS subjects are significantly more likely to experience a heightened sensitivity to stimuli across all modalities as well as to emotions. This was in marked contrast to our finding that the threshold for detection of olfactory and tactile stimuli did not differ significantly between TS subjects and healthy volunteers. Interestingly, when presented with near-threshold stimuli, TS subjects most often used the lowest range of the intensity scale to rate them, in contrast to controls, who often used the moderate range.

Conclusions: Together, these data indicate that the subjective sense of sensitivity to which most TS subjects ascribe is not due to either enhanced detection or to increased perception of intensity of faint stimuli. It remains possible that the experience of sensitivity derives from the way in which sensory input is filtered, which will be the focus of our future work.

1030

Quantitative wearable monitoring of Tourette motor tics

M. Bernabei, E. Preatoni, M. Mendez, L. Piccini, M. Porta, M. Sassi, D. Servello, G. Andreoni (Milano, Italy)

Objective: The aim of this study was to design, apply and evaluate a novel automatic method for monitoring and quantifying motor-tics caused by the Tourette Syndrome (TS).

Background: The evaluation of TS is currently carried out through clinical examination or patient reports based on a self-assessment of tic disorder. Both the former and the latter have strengths and weaknesses: patients' reports are subjective and may be substantially different from the physician's evaluation; clinical scores are a semi-quantitative measure depending on examiner opinion and experience.Goetz et. al. introduced a new method to evaluate symptom severity for TS through a video-based tic rating scale.

Methods: Now we explore and propose the possibility to quantitatively measure the occurrence and the severity of tics through a wearable systems based on 3D MEMS (MicroElectro-Mechanical Sensor) sensor.

Results: Sensitivity, specificity, accuracy of the tic recognition algorithm manifested mean values that ranged between 75.8 and 80.8 %. The agreement study showed that automatic detection tended to overestimate the number of tic occurred. Though, it appeared this may be a systematic error due to the different tic recognition systems. Furthermore there was substantial concurrency with the gold standard in estimating the severity indexes.

Conclusions: The proposed methodology gave promising performances in terms of automatic motor-tics detection and classification in a standard clinical context. This may provide physicians with a quantitative aid for TS assessment and monitoring. Further efforts are needed to improve the system qualities for its application to everyday long term monitoring of TS motor disorders.

1031

Dystonic tics in patients with primary tics disorders

J. Damasio, M.J. Edwards, A. Alonso, P. Scwingenschuh, K.P. Bhatia (London, United Kingdom)

Objective: To characterize the phenomenology of dystonic tics (DT) in primary tics disorders (PTD).

Background: Tics are involuntary, stereotyped movements or vocalizations, which can be voluntarily suppressed. Typically motor tics are clonic (brief jerky movement, lasting milliseconds), however DT (slow and temporarily sustained movements, producing briefly maintained abnormal postures1) have also been noticed in patients with PTD. Scarce information exists about the latter.

Methods: DT were defined as a single tic with a sustained spasm lasting over 3 seconds. We found 14 patients from our database of 50 with PTD, and present their clinical features after analyzing medical records and videos.

Results: 13 out of 14 patients were male. 13 out of 14 had dystonic and clonic tics and 1 had DT. 8 had the diagnosis of chronic motor tics, 3 of Gilles de la Tourette syndrome and 3 of adult onset Tourettism. Mean age of tics onset was 21.6±18.0 years. In 5 patients the first manifestation were DT, and in 9 clonic tics. When known (5 out of 9), the mean interval between clonic and DT was 6.6±13.1 years. The identified DT by semiology were: torticollis (6), retrocollis (3), laterocollis (1), anterocollis (1), head tilt (2), blepharospasm (4), sustained eyebrow elevation (1), upward gaze deviation (1), jaw opening (1), sustained shoulder elevation (4). Obsessive-compulsive disorder and attention-deficit hyperactivity disorder were present in 4 each. 4 patients had family history of tics, 3 of psychiatric diseases and 2 of tremor. 11 patients were treated with botulinum toxin; 7 had also been treated with oral drugs. 3 remained without any treatment. Dystonic tics didn't respond well to oral drug treat-

ments, but all patients had a moderate to good response to botulinum toxin.

Conclusions: We believe that DT are underrecognized in clinical practice. As expected, these patients were predominantly males, with a higher age of tics onset than the described for PTD. The most frequent DT involved the cervical region, eyes and shoulder. Botulinum toxin was the most effective treatment in all treated patients. References 1–Jankovic J, Stone L. Dystonic tics in patients with Tourette's syndrome. Mov Disord. 1991;6(3):248-52.

1032

Motor and vocal tics and their association with ADH among children in Ulaanbaatar

U. Dashdorj, B. Tserensodnom, B. Jigjidsuren (Ulaanbaatar, Mongolia)

Objective: Objective: The aim of this study was to determine the childhood clinical association tic with ADHD in different age groups.

Background: A tic is a stereotyped repetitive involuntary movement or sound frequently preceded by premonitory sensations or urges (David Shprecher et al.,2009).ADHD is sometimes associated to other important neurological problems such as behavioral disorders, tics or headaches, and may occasionally be related to epilepsy (Mulas F et al., 2004).

Methods: This study investigated the tic and their association with ADHD among children aged 7-16 years primary and secondary schools of BayanZurkh District, Ulaanbaatar. A representative school based sample of 4648 first nine graders was recruited using a multistage sampling method (Questionnaire the Conners'Parent and Teacher Rating Scales).

Results: Depending on the sample characteristics 0.13-1% all children had tic. Boys outnumbered girls by 4:1. Motor and vocal tics who aged 7-11 years 61,9%, 12-16 years was diagnosed 38,1%. Results showed that rates motor complex tic, inattention, school problem, middle insomnia, aggressive behavior increased with age. Whereas bruxism, night terror and vocal tic decreased with age.

Conclusions: Tic and ADHD have most often been comorbid disorders among children in BayanZurkh District. Boys with tic and ADHD more often than girls, suffer from comorbid disorders.

1033

Cortical excitability in Tourette patients–differential effects of voluntary movements and median nerve stimulation

S. Franzkowiak, B. Pollok, K. Biermann-Ruben, J. Paszek, G. Thomalla, A. Muenchau, A. Schnitzler (Duesseldorf, Germany)

Objective: To investiagate to what extent cortical excitability is altered in GTS patients by means of event-related desynchronization (ERD) and event-related synchronization (ERS).

Background: Gilles de la Tourette syndrome (GTS) is a neuropsychiatric disorder characterised by multiple tics. The pathophysiology of GTS is associated with a dysfunction of the basal ganglia possibly yielding cortical excitability changes. Accordingly, in GTS-patients alterations of motor cortex (M1) excitability have been evidenced. Furthermore, sensory processing might be altered in GTS-patients causing increased sensitivity to sensory stimulation. During voluntary movements and sensory stimulation a typical pattern of ERD and ERS occurs. ERD has been associated with an increased excitability of the sensorimotor cortex, whereas ERS may represent cortical deactivation.

Methods: In a first study, 11 GTS-patients and 11 control subjects performed a self-paced finger movement task. In the second study an electrical stimulation was applied to the median nerve of 12 GTS-patients and 12 control subjects. During both tasks neuromagnetic activity was recorded using a 122-channel whole-head magnetoencephalography system. Temporal spectral evolution was calculated for the alpha (8 - 12 Hz) and beta (13 - 24 Hz) frequency band, respectively.

Results: In the movement task, ERD at beta frequency was significantly increased in the contralateral hemisphere in GTS-patients before and during movements. The ERS following movement termination was significantly increased in the ipsilateral M1 and was inversely correlated with tic severity. In contrast, after median nerve stimulation ERD and ERS of the somatosensory cortex in both hemispheres were significantly reduced in GTS-patients at alpha-frequency.

Conclusions: Our data provide evidence for a pattern of increased activation followed by increased inhibition during voluntary movements. We speculate that the increased activation of contralateral M1 might be related to tic generation whereas increased inhibition of ipsilateral M1 might reflect compensatory activity to suppress tics. The reduced alpha modulation after median nerve stimulation might represent an adaptive mechanism of the somatosensory cortex to inhibit sensory input.

1034

Autism stereotypies in Allan-Herndon-Dudley syndrome

A.D. Gika, A.J. Hulse, D. Josifova, G. Baird, T.J. Hedderly (London, United Kingdom)

Objective: To present a patient with an SLC16A2/MCT8 gene mutation and a clinical phenotype previously not reported in AHDS.

Background: Allan-Herndon-Dudley syndrome (AHDS) is an X-linked learning disability (XLLD) syndrome caused by mutations in the SLC16A2/MCT8 gene and associated with characteristic thyroid function test (TFT) abnormalities.

Methods: Case study and video recording of a patient with an SLC16A2/MCT8 gene mutation and an unusual clinical phenotype.

Results: A male aged 15 years, presented aged 3 years with developmental delay and tremor. Perinatal history was unremarkable. Investigations including brain magnetic resonance imaging (MRI) were normal except for low thyroxine with normal TSH for which he was commenced on thyroxine treatment. His diagnosis was revisited at the age of 15 years. He has severe learning difficulties and a communication disorder while his motor skills are preserved. Detailed multidisciplinary assessment revealed features of autism spectrum disorder although formal diagnostic criteria were not met. Examination revealed florid abnormal movements including dystonic tremor and a variety of stereotypies. Additionally he has mild unusual facial features. Neurometabolic investigations and repeat brain MRI were requested. TFTs while off thyroxine treatment revealed consistently elevated free triiodothyronine with low thyroxine and normal TSH, a profile which is characteristic for AHDS. Screening of the SLC16A2/MCT8 gene showed two previously unreported de novo sequence changes ([c.680T>A]+[c.680T>G]) affecting the same nucleotide. Further genetic studies are planned.

Conclusions: Previously reported patients with AHDS exhibit a dystonic movement/motor disorder and profound learning disability with absent speech associated with delayed myelination on neuroimaging. Our patient has a less severe neurological phenotype which is characterised by stereotypies and severe learning difficulties. Although the sequence changes in SLC16A gene have previously not been reported, the thyroid profile is characteristic of AHDS indicating their effect on gene expression. We suggest an expanding clinical spectrum for AHDS and emphasise the importance of triiodothyronine measurement as a screening test for SLC16A2/MCT8 gene mutations in cases of XLLD.

1035

Stereotypies and repetitive motor behavior in patients with Alzheimer's disease who present spared vs. impaired executive functioning

E. Gleichgerrcht, A. Chade, M. Roca, T. Torralva, F. Manes (Capital Federal, Buenos Aires, Argentina)

Objective: To evaluate the severity of neuropsychiatric symptoms in patients with early Alzheimer's disease (AD) who present impaired executive functioning.

Background: Patients with AD have major deficits in memory, but cognitive symptoms may further expand to other domains, including language, visuospatial abilities, attention, and executive functions. Some authors have proposed an AD subgroup of patients characterized by their early impairment on executive functioning. Such "dysexecutive" AD group seems to differ from patients diagnosed with AD but who present no executive dysfunction, also, in terms of their frequency of psychiatric symptoms (e.g. delirium). Nonetheless, little research has been conducted concerning the behavioral disturbances in this subgroup of dysexecutive AD patients.

Methods: Thirty patients with early (CDR $\leq$ 1) AD diagnosis were assessed with a battery of executive tasks and clustered into groups depending on whether they showed impaired (IEF: z score<-2 on two or more executive tasks) or spared (SEF: z score<-2 on one or none of the tests)executive functioning. Their closest relatives or caregivers completed the Cambridge Behavioral Inventory (CBI) which assesses behavioral symptoms grouped into 13 categories. The frequency of behavioral disturbances was compared between SEF and IEF patients.

Results: A significant difference was found between SEF and IEF in terms of the frequency of stereotypies and repetitive motor behavior (U=1.0, p=0.019). As well, significant differences were found between the groups on executive tasks with strong motor components, while no performance differences were observed in the case for verbal tasks of executive function.

Conclusions: The presence of stereotypies could be associated with a dysexecutive profile in AD patients, therefore affecting cognitive performance, especially executive functions. These results shed light on the role of frontal circuitry in the expression of motor symptoms in AD.

1036

Aripiprazole use in TS: A two year retrospective experience in 27 patients

J.J. Juncos, G.J. Revuelta (Atlanta, Georgia, USA)

Objective: To evaluate the clinical efficacy and tolerability of aripiprazole in treating motor and phonic tics in patients with Tourette syndrome (TS).

Background: Observational studies have suggested that the atypical antipsychotic, aripiprazole, may be useful in the treatment of tics, and possibly mood and anxiety disorders associated with TS. Compared to other antipsychotics, aripiprazole has a unique in vitro mechanism of action as a dopamine D2 and serotonin 5-HT(1A) partial agonist, and a serotonin 5-HT(2A) antagonist.

Methods: This was a retrospective chart review on the use of aripiprazole in 27 patients with TS [mean age ($\pm$SEM) 20$\pm$11 yrs] followed for 24$\pm$5 months [range 1-48]. Aripiprazole was titrated to clinical effect on tics [range 1-30 mg/d; mean dose 10$\pm$2 mg/d]. Using intent to treat, chart data was reviewed and scored independently at baseline and at time of last observation by a movement disorders fellow (GR) using clinical global improvement (CGI) scales for tics, OCD and ADHD and a Worst Tic Intensity Scale.

Results: Of the 27 patients, 24 (89%) had co-morbid OCD and 19 (70%) had ADHD. Ten stopped aripiprazole, seven due to lack of efficacy and 3 due to intolerance. Seventeen are still on it. Using all data, Tic CGI-Severity improved from 4.6$\pm$0.2 to 3.6$\pm$0.2 (p <0.001), and worst tic intensity from 69$\pm$4 to 41$\pm$5 (p<0.001). Sixteen patients were much improved or better, 3 minimally improved and 8 unchanged or worse. OCD CGI scores improved slightly whereas ADD CGI did not. Intolerance was most often due to akathisia at doses between 5-15 mg/d.

Conclusions: These results are encouraging given the positive responses in a large proportion of subjects previously refractory to other antipsychotics. The conclusions are tempered by the uncontrolled, open-label nature of the observations. However, the prolonged follow up makes it more difficult to dismiss the findings as placebo responses. Reliance on CGI scores comes at the loss of the fine grain characterization of the clinical response that is possible with more detailed rating scales. Nonetheless, the results are consistent with others in the literature suggesting that aripiprazole may be beneficial in the treatment of tics and anxiety symptoms in TS. These findings inform and justify controlled clinical trials of aripiprazole in TS.

1037

Major determinants of psychosocial and occupational disability in adult Tourette syndrome

D.G. Lichter, S.G. Finnegan (Buffalo, New York, USA)

Objective: To determine clinical factors contributing to psychosocial and occupational disability in adult Tourette syndrome (TS).

Background: The determinants of psychosocial disability in adult TS are less well characterized than in juvenile TS.

Methods: Clinical conditions contributing most to problems at home, socially and at work were assessed in 66 adult TS patients, aged 36.9+/-13.5 yrs, followed at a University-based clinic for 8.2+/-6.2 yrs. Methods included clinical interview, review of clinical records, and use of the Yale Global Tic Severity Scale (YGTSS), Yale-Brown Obsessive Compulsive Scale, Clinical Global Impression Scales and the Global Assessment of Functioning (GAF) scale. DSM-IV criteria were used for psychiatric diagnoses except for ADD, where proposed DSM-V criteria were applied. Relationships of individual rating scale scores with the GAF score and other clinical and demographic variables were assessed.

Results: Tics caused some difficulties in some areas of functioning for 41 (62%) patients and were associated with clear or major psychosocial problems in 21 (32%), although coprolalia and troublesome self-injurious behaviors occurred in only 4 (6%) and 3 (4.5%) cases respectively. OCD caused at least moderate disturbance in social or occupational functioning in 11 (17%) and milder disturbance in 27 (41%) patients. Other clinically significant conditions included non-OCD anxiety disorders, depression, ADD, bipolar disorder, rage attacks, learning disorders, psychosis and RLS. Previous or current substance use disorder (SUD) was an important or critical co-morbid condition in 15 (23%) patients. Neither patient age, gender, nor family history of tics/OCD predicted pattern or severity of tics or comorbid disorders. Mean GAF scale score was 65.5+/-9.8. In a stepwise regression analysis, two factors contributed significantly to variance of the GAF score: YGTSS score (34.4% of variance: F ratio 27.7, P<0.0001); and a history of SUD (7.5% of variance: F ratio 3.7, p=0.006).

Conclusions: Despite the general tendency for tics to ameliorate in adulthood, and the frequency of comorbid psychiatric disorders, tic severity remains the primary factor contributing to global psychosocial and occupational disability in adults with TS. SUD may significantly complicate the clinical course and has been under-recognized as an important comorbid disorder in adult TS.

1038

Is it a tic? Twenty seconds to make a diagnosis

J. Paszek, B. Pollok, K. Biermann-Ruben, K.R. Mueller-Vahl, V. Roessner, G. Thomalla, M.M. Robertson, M. Orth, A. Schnitzler, A. Muenchau (Duesseldorf, Germany)

Objective: To determine how long it takes to distinguish between a tic in patients with Gilles de la Tourette syndrome (GTS) and spontaneous movements in healthy controls.

Background: Tics are sudden, repetitive movements (motor tics) or sounds (phonic tics). They are the hallmark of GTS. Single tics are difficult to distinguish from voluntary movements. In fact, movement kinematics of tics, e.g. anticipatory force adjustments during grip tics, are indistinguishable from normal movements. This implies that it may be difficult to identify a tic in isolation but easier on the basis of its occurrence in time.

Methods: We presented either short (3 seconds) or longer (20 seconds) video clips showing tics of GTS patients or spontaneous movements of healthy controls to two GTS experts with the instruction to decide whether presented movements were tics or not.

Results: Diagnostic accuracy was 46(/81)% for 3-second and 73(/96)% for 20-second clips. Diagnostic accuracy was higher for 20-second clips compared to 3-second clips in rater I (df=1, χ=6.12, p=0.020) but not in rater II (df=1, χ=1.3, p=0.300).

Conclusions: The main finding is that it is more difficult to distinguish a single tic from a single spontaneous movement than a series of tics from a number of spontaneous movements. These data support the hypothesis that tics are not abnormal movements per se but physiological movements with abnormal appearance in time and context.

1039

Pitfalls in deep brain stimulation for treatment-refractory Tourette syndrome

D. Servello, M. Sassi, S. Defendi, A. Brambilla, M. Porta (Milano, Italy)

Objective: To retrospectively evaluate our experience in deep brain stimulation (DBS) treatment for patients affected with Tourette Syndrome (TS) and refractory to conservative and invasive traditional and innovative therapies.

Background: Since November 2004, a total number of 40 patients have been treated at our Functional Neurosurgery Unit at the IRCCS Galeazzi for therapy-refractory Tourette Syndrome (TS).

Methods: Postoperative evolution of the clinical picture has been put into association with the preoperative clinical picture and considerations concerning the indication criteria has been posed. In particular, compliance of the patient and of the caregivers of the patient has been evaluated in correlation with the adverse events and complications that have been reported during follow-up.

Results: Complications to be referred to specific features of TS and of the complex social dynamics of these patients have been demonstrated, together with limits of the DBS procedures that have to be borne in mind when indicating DBS for a patient with refractory TS. A deeper evaluation of the patient and of the patient's family can forecast compliance to treatment. Considering the frequent need for parameters regulation demanded by some of the patients, distance from the hospital must also be considered. On the other hand, this usually leads to a difficulty towards more prompt evaluation of the patients, and subsequently in our series a rather high incidence of infection or adverse reaction (the surgical wounds) was observed, in some cases due to insufficient compliance and compulsive urge of the patient to touch the scars. Finally, disregulation of the stimulating parameters and the need for further adjustments was documented in our series, thus aggravating the compliance problem because of the need for more frequent modification of the stimulating parameters.

Conclusions: A multidisciplinary team is mandatory to properly evaluate all the possible complications that can issue in these complex patients. In particular, even if the indication to treatment is correct and the patient might have a positive result from DBS per se, all of these logistical complications have to be addressed and discussed.

POSTER SESSION 4

THURSDAY, JUNE 17, 2010
LOCATION: SAN TELMO ROOM, LOBBY LEVEL

All posters available for viewing: 9:00-16:00
Authors Present: 13:30-15:00

TREMOR

1040

Clinical features that best differentiate patients with adult onset dystonic tremor from tremulous Parkinson's disease

C. Lonngren, T. Maggs, V. Gontu, N. Bajaj (Nottingham, United Kingdom)

Objective: To review clinical videos of patients with adult onset dystonic tremor (AODT) versus those with tremor dominant Parkinson's disease (TDPD) to see which clinical features best differentiate these two clinical entities.

Background: It is likely that a significant proportion of the 5-15% cases of SWEDDS (subjects without evidence of dopaminergic deficit) recruited for recent clinical trials with anti-parkinsonian drugs have tremulous syndromes other than TDPD. Recently it has been highlighted that at least some of these SWEDD patients may have AODT. AODT patients can have many of the cardinal parkinsonian features including rigidity, tremor and bradykinesia although true fatiguable bradykinesia is uncommon.

Methods: Clinical review of 34 AODT and 31 TDPD patients with reference to the Queen Square brain bank criteria (QSBCC) for PD and the clinical features suggestive of AODT. Clinical diagnoses were made in all cases on the basis of [^{123}I] FP-CIT SPECT, response to dopaminergic agents for all TDPD cases (and many AODT cases) and long term (3 year) follow-up. Statistical analysis was carried out using SPSS for Windows v17.0.

Results: Dystonic features in the hands (Little finger hyperextension, [p=0.055; AODT: 44%; TDPD: 22%]; thumb hyperextension [p=0.01; AODT: 38%; TDPD: 12.5%]), head tremor (p=0.016, AODT 24%; TDPD 3%), myoclonic flurries (p=0.03, AODT 22%; TDPD 3%) and family history of tremor (p=0.017, AODT 56%; TDPD 24%) favoured AODT whilst stooped posture (p=0.028, AODT: 19.4%; TDPD 51.7%], pill-rolling tremor (p=0.022; AODT 3%; TDPD 24%), dependent tremor on walking (p=0.01; AODT: 17.5%; PD: 64.5%), reduced arm swing (p=0.04, AODT: 70%; PD: 90%), flexed arm posture (p=0.036; AODT:3%; TDPD 29%) and bradykinesia (p=0.004; AODT: 70%; PD 97%) were most predictive of TDPD.

Conclusions: AODT can be difficult to differentiate clinically from TDPD despite rigorous use of the QSBBC. In this study, bradykinesia, pill-rolling tremor, stooped posture, reduced arm swing with flexed arm posture and dependent tremor on walking were the strongest predictors of TDPD and dystonic features of the hand, head tremor, myoclonic flurries and family history of tremor favoured AODT. It is also notable that both parkinsonian features and dystonic features occurred frequently in AODT and TDPD populations.

1041

The influence of age in essential tremor

N. Cinar, S. Sahin, T. Okluoglu, S. Karsidag (Istanbul, Turkey)

Objective: The aim of this study was to assess the clinical features of Essential Tremor (ET) in different age groups.

Background: ET is one of the most common, often heritable neurological disorder with a prevalence ranging from 0.4% to 5%.The

cerebellar and thalamocortical circuits may play a major role in the pathophysiology of ET.

Methods: We evaluated 35 patients, 22 men and 13 women fulfilling the clinical criteria for diagnosis of ET. The patients were divided into three groups according to age at onset of ET symptoms (younger than 30 (Grup I; n:10), 30-60 (Group II; n:11) and older than 60 (Group III; n:14) years old). The patients were clinically examined according to Fahn–Tolosa scale (FT) including spiral drawing task and hand tremor was studied with surface electromyographic recordings. The tremor's frequency and mean amplitude were assessed with visual inspection of the records. All of the patients were not taking any medication for tremor.

Results: Mean age of men and women were 59,7±20 years and 65,8±16 years respectively. There was no statistically significant difference amoung the three groups for tremor frequency and amplitude. Spiral drawing task was higher in Group II and Group III than Group I ($p=0.04$, $p=0.002$). Also total score of FT scale was significantly higher in Group II and Group III than Group I ($p=0.02$). Correlation analysis test is performed and our data indicated a significant positive correlation between age and both spiral drawing task and total score of FT scale ($p<0.0001$).

Conclusions: Several studies have indicated that the cerebellum plays an important role in the generation of tremor in ET patients. Although there was no statistically significant difference for the tremor frequency and amplitude, It is worth noting that spiral drawing task and total score of FT scale were higher in the middle and old age group. The present study showed an interactive effect of aging on hand coordination and fine motor skills in essential tremor patients. Age related degenerative changes in the cerebellum may be more appearent in these patients and may play an important role on quality of life.

1042

Holmes tremor in a HIV positive patient worsened by immune recovery inflammatory syndrome (IRIS)

R.B. Correa, F.R. Schmidt, F.M.L.C. Silva, F.H.R. Costa, A.L.Z. Rosso, D.H. Nicaretta, J.P. de Mattos, S.A.P. Novis (Rio de Janeiro, Brazil)

Objective: To describe a HIV positive patient with Holmes tremor worsened by IRIS and the remarkable recovery after therapy with steroids.

Background: IRIS is seen within a broad spectrum of HIV-related opportunistic infectious diseases and autoimmune disorders in patients who had been given HAART. The clinical features described in the literature associated with IRIS are paresia, paresthesia, behavioral disorders, headache, tremor and ataxia.

Results: Case report: A 41-year-old woman presented with esophageal candidiasis and then she was found to be positive for HIV. A month later she complained of headache and tremors. On examination she had mild rest, postural and action tremor mainly on the left side, discreet ataxic gait, pyramidal signs and hypoesthesia on the left side, multidirectional nystagmus, right abducens and bilateral peripheral facial palsy. She had a CD4 count of 32 cells/μl and a viral load >500,000 copies/ml. Brain MRI showed a T2 and Flair high signal from the right thalamus to the medulla oblongata with no contrast enhancement. The images were considered non-specific. CSF was normal and negative for anti-JC virus. She was treated iniatially with stavudine, lamivudine and lopinavir/ritonavir. Three months later the tremor had worsened, she was unable to walk without assistance or stay with her eyes opened because of the great intensity of the head tremor. She developed tetraparesis and excessive somnolence. The CD4 count was 264 cells/μl and the viral load 38,837 copies/ml. Brain MRI showed multiple scattered bilateral subcortical lesions with high signal in T2 and Flair. The older lesion had grown in volume compared with the previous exam. A brain biopsy failed to reveal features of Progressive multifocal leucoencephalopathy. The clinicoradiological features were speculated to be HIV encephalopathy associated with IRIS. Oral prednisone 60 mg/day, topiramate 200 mg/day and clonazepam 1.5 mg/day were started with moderate improvement of the symptoms. The HAART regimen was switched to D4T, 3TC and efavirenz. One year from the HIV diagnosis the patient has only moderate postural and action tremor on the right arm.

Conclusions: To our knowledge this is the first report of a patient with Holmes tremor aggravated by IRIS.

1043

Percentage of essential tremor patients for whom front-fine medications have been discontinued

N.L. Diaz, E. Louis (New York City, New York, USA)

Objective: To determine the percentage of ET patients for whom front-line medications have been discontinued and the reasons for discontinuation.

Background: Treatment options for essential tremor (ET) are limited. There are only two front-line medications, propranolol and primidone. Although small treatment trials have examined the efficacy of front-line medications in tremor reduction, an overall survey of the effectiveness of pharmacological management has not been undertaken in a large sample of ET cases.

Methods: A computerized billing database at the Neurological Institute of New York, Columbia University Medical Center, was used to identify patients with the ICD diagnostic code 333.1 who were seen in the past five years. Five hundred were randomly selected for further review. Clinical charts were retrospectively reviewed using a structured data abstraction form that included items on demographics, tremor history and usage of all ET medications.

Results: 260 had ET (mean age=63.4±17.9 years); the remainder had other diagnoses (e.g., dystonia, enhanced physiological tremor, Parkinson's disease). 177/260 (68.1%) had taken one or more medications for ET. Of these 177, 53 (29.9%) had taken >4 medications, 31 (17.5%) had taken >5 medications, and 3 (1.7%) had taken >10 medications (mean=2.8±2.0). 127/260 (48.8%) had taken propranolol. Of these 127, 69 (54.3%) had discontinued it (37.5% because it was ineffective and 16.8% because of side effects). 131/260 (50.4%) had taken primidone. Of these 131, 82 (62.6%) had discontinued it (27.4% because it was ineffective and 35.1% because of side effects). 172/260 (66.2%) had taken either primidone or propranolol. Of these 172, 75 (43.6%) were taking neither anymore, 10 (5.8%) were taking both, and the remainder were taking one or the other.

Conclusions: Approximately two thirds of all ET patients had taken one or both of the two frontline medications yet nearly one-half of those who were treated were no longer on either medication. A higher proportion of patients stopped primidone due to side effects whereas it was more common for propranolol to be stopped due to lack of efficacy. This study suggests that there is a sizable proportion of ET patients who have failed treatment with both of the front-line medications. These data underscore the paucity of adequate pharmacological options for ET.

1044

Disappearance of essential tremor after stroke

M.J.-M. Dupuis, F.L.A. Evrard, J.G. Philippe, P.R. Gaetane, L.G. Oliver (Ottignies Louvain La Neuve, Brabant, Belgium)

Objective: To report and interpret lesions involved in strokes interrupting essential tremor (E.T.).

Background: 10 cases of strokes with disappearance of E.T. after stroke recovery have been reported; they concern various locations.

Methods: We report 4 other cases of E.T. disappearance after stroke.

Results: The 4 strokes are respectively located in the pons, the posterior limb of internal capsule, the cortico subcortical peri-rolandic structures and the cerebellum. In the litterature these 4 locations and thalamus are reported.The cortico subcortical stroke induced

only transitory E.T. disappearance, in contrast to deep strokes; one case of pontine lacune has a 1O years follow-up without E.T. controlaterally.

Conclusions: The locations of strokes interrupting E.T. are heterogenous but nevertheless all these cases could be interpreted as concerning afferent and efferent connections between the cerebral cortex and the cerebellum.

1045

Essential tremor across diagnostic and/or categorical assessment

S.G. Echebarria Mendieta (Las Arenas - Getxo, Bizkaia, Spain)

Objective: To increase methodological ascertainment in subjects-sampling, considering new designs across samples and subsets added to tremor plus neurologic signs.

Background: Recent developments in Essential tremor and historical/traditional standpoints (considering hereditary and benign essential tremor definitions) may be disclosed according to distinguishing views in diagnostic-methodologic sampling (genetic burden) respect to descriptive-nosologic clues (tremor plus other movement disorders association).

Methods: Searching of ETM1, ETM2, 6p loci and DRD3 variant series (literature). Approaching and grouping methods with Parkinson's disease/Essential Tremor (PD/ET) office-based clinical series (traditional studies).

Results: Grouping criteria in typical District and Movement Disorders Clinical-office between PD/ET subsets show a comparative reliability with grouping methods in genetic forms of ET (Charcot-Marie-Tooth + ET and neurosensorial hearing loss/hydrocephalus/ulcus/migraine associations) (A category). Levels of distinction between typical ET and persistent tremor ; dystonia and head dyskinesias associated tremor show descriptive definitions.

Conclusions: New perspective of ET as a diagnostic methodological group may be defined with association - signs tool and/or genetic associative/non-associative tools.

1046

Risk factors for perioperative complications in deep brain stimulation surgery for tremor

J. Fang, E. Presant, F. Phibbs (Nashville, Tennessee, USA)

Objective: To identify preoperative risk factors for the development of perioperative complications of deep brain stimulation surgery for tremor.

Background: Essential tremor is a common movement disorder that can be treated with medications or surgery. Deep brain stimulation targeting the ventral intermediate nucleus of the thalamus is often effective in medication refractory cases. However, surgery can be complicated by perioperative neurological deficits that may interfere with the surgery itself or with followup. This study is intended to analyze preoperative risk factors affecting deep brain stimulation surgery.

Methods: A retrospective chart review was performed on all patients undergoing deep brain stimulation surgery for tremor over a three-year period. The incidence of perioperative complications such as somnolence, dysarthria, or other neurological deficits was recorded. Possible risk factors for complications such as age, tremor severity, and cognitive deficits (Wisconsin Card Sort, Boston Naming Test, and Verbal Comprehension Index) were examined using Fisher's Exact Test.

Results: Fifty-eight charts were identified. Eight patients experienced perioperative complications of somnolence or prolonged neurological deficit such as dysarthria. Age showed a statistically significant association with complications. Using age less than sixty-five versus age over seventy-five, the p value was 0.0123. No other significant association was identified between any of the preoperative characteristics. All patients appeared to benefit in terms of tremor reduction from surgery.

Conclusions: Age over seventy-five appears to predispose tremor patients to perioperative complications of deep brain stimulation. However, since these complications do not necessarily lead to long-term deficits, deep brain stimulation can still be effective in elderly persons. Elderly patients may require a longer period for recovery from deep brain stimulation.

1047

Neuropathic tremor with response to rituximab

C.V. Garcia Mendez, J.C. Giugni, V. Silva, R. Diez, A. Cueto, R.J. Giannaula (Buenos Aires, Argentina)

Objective: To evaluate the response to the monoclonal antibody rituximab in a patient diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP) and neuropathic tremor.

Background: Neuropathic tremor is the kind of tremor observed in the context of peripheral neuropathy, characterized for being both postural and intentional, irregular, with a variable frequency between 4 and 11 Hz. Not every neuropathy displays tremor. It is more commonly found in demyelinating neuropathies. No specific treatment is available for this unusual variant of tremor.

Methods: 28 year-old, female, with a previous history of autoimmune thyroiditis, Sjogren Syndrome, autoimmune anemia and CIDP with poor response to treatment with immunoglobulin and steroids. She developed moderate rest, postural and severe intentional tremor, which was diagnosed as neuropathic tremor. Treatment was started with different drugs (levodopa, clonazepam, propranolol, phenobarbital, gabapentin) with poor outcome. Later, she was diagnosed with systemic erythematous lupus with nephropathy and received a rituximab therapy.

Results: After treatment with the monoclonal antibody rituximab, the patient's systemic disease and tremor improved significantly: tremor at rest disappeared, and the postural and intentional types improved more than 90%.

Conclusions: In patients with neuropathic tremor, where treatment is difficult, improvement of the underlying cause could be a valid therapeutic choice. The monoclonal antiboby rituximab should be taken into account for these cases. Poster presented at the XLVI Argentine Congress of Neurology. Mar del Plata, Argentina. October 14-October 17, 2009.

1048

Electrophysiological correlates of lithium tremor

D. Haubenberger, G.J. Lopez, B. McElroy, E. Considine, M. Hallett (Bethesda, Maryland, USA)

Objective: To characterize electrophysiological characteristics of lithium induced postural tremor in patients with SCA1.

Background: Tremor is one of the most prominent side effects of chronic lithium therapy. Up to 65% of patients under lithium have been reported to exhibit tremor, which is commonly described as postural and kinetic tremor, in the frequency range of 8-12Hz, resembling enhanced physiological tremor. Here, we assess whether the hypothesis of lithium tremor as enhanced physiological tremor can be proven electrophysiologically.

Methods: As part of the NIH safety trial on lithium in SCA1, tremor physiology studies were conducted at multiple timepoints throughout the trial. Nine subjects (5f; mean age 51.7), who participated in all study visits per protocol were included in the analysis. Both hands were studied while patients were sitting upright with both arms supported on armrests with hands extended forward parallel to the ground, without weights and after addition of 1pound per hand. Accelerometry was recorded bilaterally from the back of the hands in the z-axis, as well as surface EMG over wrist flexors and extensors. Per patient, a total tremor power score was calculated from 2-min recordings per condition by averaging the power at the spectral tremor frequency peak of both hands. Tremor power was normalized to baseline. The main study outcome parameters were the

change of tremor power and frequency between baseline and the visit ON lithium, 1 month after wash-in.

Results: Total normalized tremor power ON lithium increased significantly compared to baseline (mean 1.64, 95%CI 0.72-2.52; p=0.38; Wilcoxon Signed Rank Test). Mean frequencies in the unweighted condition did not differ between baseline and ON (baseline R hand 6.5Hz, LH 6.2Hz; ON RH 6.6Hz, LH 6.2Hz). In the weighted condition, there was a significant drop in frequency in both hands at baseline as well as during ON. In both hands, at both visits, the mean reduction of frequency was 1.9Hz (each $p<0.005$; paired samples t-test).

Conclusions: Already at baseline, patients exhibited a fine amplitude postural tremor consistent with physiological tremor. On lithium, the increase in tremor power as well as the unchanged finding of a predominant mechanical tremor component, with the lack of a central component, supports the hypothesis of lithium tremor being an enhanced physiological tremor.

1049

Is the central component of physiologic tremor a positive predictive factor for the incidence of a pathologic tremor

H. Hellriegel, I. Petrovic, F. Pawlas, G. Deuschl, J. Raethjen (Kiel, Germany)

Objective: Evaluation of electrophysiological changes in physiologic tremor in the course of 12 years.

Background: As mechanical resonance at the eigenfrequency caused by motor units firing at this frequency, physiologic tremor (PT) is mainly a peripheral phenomenon. However, there is a central component of physiologic tremor. And it has been suggested that pathologic tremor may develop out of this central component of PT.

Methods: We included 10 healthy subjects with EMG synchronization suggestive for a central component of their physiologic tremor and 10 subjects without this electrophysiological feature. Tremor was recorded by accelerometers placed on the dorsum of the hands and by bipolar surface- EMG of the forearm flexors and forearm extensors. Tremor was recorded under rest condition, postural condition and postural condition with 1000g weights on the dorsum of the hands. The duration of each tremor recording was 30 seconds. For each condition one measurement was taken in 1996, the second measurement in 2008. Spectral analysis of the rectified EMG and accelerometric data was performed. Tremor frequency and total power as a measure of tremor amplitude was calculated.

Results: None of the subjects reported the incidence of a notable and disabling tremor. In the Fahn, Tolosa, Marin tremor scale, performed 2008, subjects were rated in a range between 1–4 of 144 points. A two factorial analysis of variance including measurements for the factors time (first measurement 1996, second measurement 2008) and group (central component–no central component) was performed for tremor total power and showed no significant changes of tremor total power over time and no differences between both groups for the different conditions: rest (p=0,303) posture (p=0,769) and load with 1000g weights (p=0,914).

Conclusions: There is no evidence that subjects with a central component of physiologic tremor are more likely to develop pathological tremor in the course of time.

1050

The effects of transcranial magnetic stimulation on electromyographic characteristics in primary writing tremor patients

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Objective: To study effects of Transcranial Magnetic Stimulation (TMS) on the electromyographic (EMG) characteristics in patients with typical task-specific Primary Writing Tremor.

Background: Primary writing tremor (PWT) is a type of task-specific tremor in which tremor predominantly occurs and interferes with handwriting. EMG in PWT patients is characterized by 5-7-Hz tremor during the acts of writing and drawing. TMS could be used to influence-reset cortical structures involved in generation of tremulous activity associated with writing task.

Methods: We studied changes in frequency content (dominant frequency peak–DFP and mean power frequency–MPF) in abductor pollicis brevis muscle of the dominant hand in 6 PWT patients during a task-specific act (writing that induced tremor in the affected hand - Wr) and unspecific voluntary contractions of the same hand, while adopting writing-like position, of intensity matching that developed during writing and during strong near maximal voluntary contraction. In addition, cross spectra (CS) of the initial amplitude spectra of EMG preceding TMS and immediately after TMS induced silent period (SP) were computed. TMS, set at 1.2 X resting motor threshold, was delivered over the vertex.

Results: The DFP (5-7 Hz) was present in amplitude spectra of EMG signals both before TMS and after TMS induced SP in all conditions. However, the amplitude of DFP was significantly higher during Wr condition than in both voluntary contraction conditions. TMS did not have significant effect on the DFP, which remained unchanged after TMS-induced SP as compared to DFP obtained immediately before TMS. Accordingly the CS dominant frequency component was preserved during Wr. The CS dominant frequency component was not present in voluntary contractions conditions.

Conclusions: The tremor dominant component was expressed only during writing emphasizing the task-specific nature of PWT. TMS did not reset tremor in PWT patients suggesting complex organization of central, intracortical structures involved in the generation of PWT.

1051

Holmes' tremor or rubral tremor, description of 5 cases

E.R. Lopez (Chillan, Nuble, Chile)

Objective: Describe the characteristics of a group of patients with mesencephalic or rubral tremor.

Background: It's an irregular tremor, of which the frequency is less than 5Hz. It's not a tremor in repose, but one of which the intensity increases with posture and even more with intention. The tremor is caused by the injury of the dentatorubrothalamic tracts along with nigrostriatal dopaminergic fibers. Therefore, when in presence of this kind of tremor it is necessary to perform a neuroimaging test to appraise the possibility of a mesencephalic structural injury.

Methods: Patients with tremor diagnosis from August 2007 to July 2009 are checked in order to find the principal characteristics of the tremor. The ones that fit into the criteria of a rubral tremor are selected.

Results: Out of 238 cases of tremor, 32 of them where in repose and related to parkinsonism, 186 were essential and 15 had no clear-cut characteristics. Of this, it is determined that 5 of the cases fit into the clinical characteristics of the rubral tremor. The average age of the patients is 54 years old, Four of them female and one male. Three of the cases had not been diagnosed nor studied. Brain MRIs were performed, presenting three cases of multiple ischemic injuries including the diencephalon and brain stem; one case of demyelinating injuries of Multiple Sclerosis and one with a normal MRI. Several therapeutic schemes were used with no success, leaving all of the patients with use of Clonazepam at night-time as a tranquilizer.

Conclusions: Rubral tremor is infrequent and its characteristics are not easily acquainted, most of the time, believed to be other kind of tremor and not being considered the implications of its detection.

1052

Cognitive and motor functional activity in nondemented community-dwelling essential tremor cases

E.D. Louis, J. Benito-Leon, S. Vega-Quiroga, F. Bermejo-Pareja (New York City, New York, USA)

Objective: We (1) compared functional level in essential tremor (ET) cases vs. controls, assessing functional activities that are cognitively-based (e.g., remembering appointments) and those that are dependent upon both motor and cognitive factors (e.g., writing checks), and (2) determined whether lower mini mental status test scores in ET cases have a functional correlate.

Background: Many investigators have observed mild cognitive deficits in ET yet the functional significance of these deficits is unclear. Also, there are very few data in which functional activity in ET has been divided into cognitively-based activities vs. motor-based activities.

Methods: In a population-based study of people >65 years in central Spain (NEDICES), a 37-item version of the Mini-Mental State Examination (37-MMSE) and an 11-item version of Pfeffer Functional Activities Questionnaire (FAQ) were administered to nondemented ET cases and controls.The FAQ includes six functional activities that are cognitively-based (e.g., keeping track of current events, remembering appointments, greeting appropriately) and five activities that are based on both cognitive and motor factors (e.g., writing checks and balancing a checkbook, making coffee).

Results: FAQ was 55.5% higher (i.e., lower function) in 208 cases than 3,616 controls (2.8±4.8 vs. 1.8±4.2, $p<0.001$). Cases reported more difficulty (i.e., higher FAQ scores) with FAQ items that were cognitive measures ($p<0.001$) as well as FAQ items that were both cognitive-motor in nature ($p<0.001$). 37-MMSE score was lower in cases than controls (27.9±5.8 vs. 29.3±5.4, $p=0.002$). In cases, lower 37-MMSE was associated with more difficulty on both cognitively-based and cognitive-motor-based FAQ items ($p<0.001$).

Conclusions: In this large, population-based study, ET cases had more functional difficulty than did similarly-aged controls. Furthermore, this functional difficulty was not only observed with regards to tasks that were cognitive-motoric in nature but also extended to tasks that were primarily cognitive in nature. Among cases, lower cognitive test scores were associated with more reported difficulty with both motor and cognitively-based functional activities, indicating that lower cognitive test scores in ET, rather than being inconsequential, have a clear clinical-functional correlate.

1053

Neurophysiologic tremor analysis in patients with non-parkinsonian tremors

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Objective: To evaluate electrophysiologically patients with non parkinsonian tremors.

Background: Tremors present commonly in neurology OPD. Apart from parkinsonian tremor, non parkinsonian tremors eg. essential tremors, exaggerated physiological tremors, drug induced, rubral, dystonic tremors are seen. ET is one of the most common movement disorders. Surface EMG(SEMG) can be used to electrophysiologically evaluate such tremors.

Methods: 22 patients with non- parkinsonian tremors were studied. Tremors were clinically grouped and tremor rating scale (TRS) applied. All subjects underwent surface EMG analysis. EMG burst patterns that were observed were synchronized, mixed and alternate patterns. In patients with clinically probable ET,the results were compared with the criteria laid down by the MDS consensus statement for concordance.

Results: 22 Patients with non parkinsonian tremors were studied.-There were 59.1% males and 40.9%females. Age of the studied group ranged from 14-76 with mean age of 40.63yrs.Essential tremor was the most common non-parkinsonian tremor found in our study (59.1%) followed by psychological and rubral tremor (9.1%).3 Types of Burst activity in EMG analysis were seen in our study namely synchronized, mixed and alternating pattern.76.9% clinically probable ET showed classical synchronized EMG burst pattern (p-0.011) with mean frequency of 9.69±3.06 Hz. 40.9% patients had high frequency tremors (≥10z).The TRS score in ET was 11.46±3.21.

Conclusions: Essential tremor can be differentiated from enhanced physiological tremor using synchronized surface EMG Burst pattern. Such a differentiation clinically alone is difficult. The abnormalities noted were largely the classically described patterns.

1054

Botulinum toxin A injections are an effective treatment of essential head tremor

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Objective: To evaluate the efficacy of botulinum toxin type A in essential head tremor.

Background: Botulinum toxin is widely used in the treatment of blepharospasm, cervical dystonia, latyngeal dystonia, certain task-specific dystonias, and hemifacial spasm. Open-label trials regarding the use of botulinum toxin in tremor have indicated a favorable response in a variety of tremors. We hypothesize that botulinum toxin A also improves the intensity of essential head tremor.

Methods: We examined in open-label study the effects of botulinum toxin type A in 14 patients with essential head tremor. Each subject received 5 to 12 treatments approximately 3 months apart, into sternocleidomastoid, trapezius, and splenius capitis muscles. A subjective questionnaire of treatment effectiveness was administered using a scale from 1 to 5, with 1 being no effect and 5 being complete resolution of symptoms. The subjects were assessed before each treatment and 2, 4, and 8 weeks after injections. Botulinum toxin (Botox) was reconstituted using sterile normal saline (without preservative) to a concentration of 100 U/ ml, and 30 U was injected into each sternocleidomastoid muscle, 40 U into each splenius capitis, and 30 U into each trapezius without EMG guidance.

Results: All patients in this series experienced improvement in their head tremor with intramuscular Botox treatments. Advers events included neck muscle weakness was observed in 2 patient and was short in duration and completely reversible.

Conclusions: We conclude that botulinum toxin A may be useful for patients with essential head tremor.

1055

Parkinsonian features in essential tremor patients

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Objective: To determine the frequency of parkinsonian features in patients with Essential Tremor (ET) and (2) to describe demographic and epidemiological data of patients diagnosed with ET.

Background: Although ET and Parkinson's disease (PD) are considered distinct disorders, there is overlap in some clinical features. Functional neuroimaging suggests that some ET patients have dopaminergic deficit. The reported risk of parkinsonism in essential tremor patients varies from being unchanged to 35 times higher than expected.

Methods: Retrospective study of medical records (n=60) from a Movement Disorders Outpatient Clinic at the University Hospital of the Federal University of Sergipe in Aracaju–Sergipe–Brazil.

Results: The sample was composed of 33 males and 27 females, 50% caucasian and 50% non-white. The mean age was 58.6 (SD 21) years, the mean age at onset of ET was 47,6 (SD 21) years, and the mean ET duration was 10,9 (SD 9) years. Forty patients had family history of tremor, and six patients had family history of parkinsonism. It was observed arm tremor in 56 patients. Six patients presented parkinsonian features, four with hypertonia (mean duration 3,25 years) and three with bradykinesia (mean duration 4 years). Gait

instability was observed in 11 patients. Twenty-five patients had hypertension as comorbidity, and 35 presented psychiatric symptom, such as depression, anxiety or panic syndrome.

Conclusions: Our data suggest that (1) parkinsonian features were not common in patients with ET. Therefore, they should be considered during evaluation and treatment of ET. (2) Gait instability was considerably frequent in our sample. (3) High percentage of patients presented psychiatric symptoms.

1056

Tremor profile of a movement disorder clinic

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Objective: A retrospective study of all the patients presented to the movement disorder clinic over 7 years to analyse the profile of tremor in the area, the actual clinical diagnosis, the management and the follow-up.

Background: Tremor is one of the common presenting symptoms in the movement disorder clinic and commonly confused with extrpyramidal disorders in clinical practice. Though tremors are one of the diagnostic criteria's of Parkinson's disease, one third of Parkinson's disease patients remain tremor free through the course of their disease.

Methods: We analysed case notes of all patients are referred to the movement disorder clinic run by a single specialist. Their demographic profile, final clinical diagnosis, treatment and follow-up data were collected from online interactive database used for Movement Disorder Clinic.

Results: 137 patients, 61 males and 76 females. Age range 41-92yrs, mean age 71 yrs. Most common diagnosis was central/essential or intentional tremors constituting about 67% of all referrals (93/137). We grouped central and intentional tremors together because clinically it is difficult to differentiate between these two due to their kinetic nature. Other diagnoses were drug induced tremors, restless legs syndrome, isolated head tremor, dystonia, myoclonus, Parkinson's disease. 75% patients received treatment. About 66% of the total treated patients were on primidone (25%%) or on beta blockers (41%). Primidone was tried initially in 38% patients as a first line therapy, 18% of them did not tolerate. It was used as a second line in 2 patients. Propranolol was used as first line therapy in 35% patients; 5.5% had termination of therapy. Propanolol was a second line drug in 2 patients in our follow up. About 5% were on topiramate and another 5% needed multiple drugs to control their tremors. Other drugs used in our patients are benzodiazepines anti parkinsonian drug (rotigotin/pramipexole/ropinirole) for RLS. Our patients have had a mean follow up for about 22 months.

TABLE 1 (1056). *Diagnotic labels of Tremor*

Essential/Central/intentional tremors	93	67%
Drug induced	12	8.7%
RLS	10	7.3%
Isolated Head Tremor	7	5.1%
Myoclonus	5	3.6%
Othersvascular Parkinsonism, dystonic movement disorders, isolated tongue tremors and tremors of neuropathic origin.	9	6.5%
Parkinson's disease	1	0.7%

Diagnosis, Total numbers, Precentage of patients.

Conclusions: Workload of Patients with Tremor in Movement disorder clinic is considerable and treatment results are variable. Longer follow up of these patients are justified for successful management of their symptoms and and Diagnosis. Approximately 20% patients need second line; unable to tolerate first line treatment or need combination treatment. Follow up of these patients till symptom control is advisable.

1057

Hand tremor in dystonic patients

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Objective: Background: Hand tremor is a relatively frequent sign in focal dystonia, but so far there are very few studies concerning tremor asymmetry in dystonic patients (DP).

Background: Objectives: To assess clinical characteristics of tremor in DP.

Methods: Methods: 27 DP were included: 12 with torticollis and 15 with blepharospasm. Severity of dystonic symptoms and disability were assessed by Toronto Scale in torticollis and by Jankovic Rating Scale in blepharospasm. Severity of hand tremor was assessed by Simple Tremor Severity Scale and disability by Tremor Functional Scale. Results: In clinical assessment tremor was found in 12 DP (45%). 9 DP (40.7%) with torticollis and 13 DP (48%) with blepharospasm. The tremor was more spread in the left hand in 15DP (60%), and in 12 DP (40%) in right hand. Symmetrical tremor occurred in 13.7% of DP: 9.8% with torticolis and 3.9% with blepharospasm. Asymmetrical tremor occurred in 25.5% of DP: 9.8% with torticolis and 15.7% with blepharospasm. Asymmetrical tremor was significantly more frequent in right hand then left one ($p=0,0008$). The groups with symmetrical and asymmetrical tremor did not differ in sex or age. There were no significant differences in Tremor Functional Scale in both groups.

Conclusions: Conclusions: In our group of patients, asymmetrical tremor in DP is more frequent than symmetrical one, predominating in the right hand. Further investigation concerning evaluation of tremor intensity and its amplitude, must be done.

1058

Validation of TremAn–a tool for analysis of tremor frequency from video recordings

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Objective: A validation study of TremAn in comparison with accelerometry.

Background: A precise measure of tremor frequency can be obtained using accelerometers or electromyography. These methods are, however, cumbersome and impractical for routine clinical use. As an alternative, we have proposed a method of tremor frequency analysis based on common video recordings - TremAn (1).

Methods: We examined 20 patients with essential tremor (ET) (5 F, mean age 57.5±17.5, range 19-81, ET duration 24.3±15.9 years, Fahn-Tolosa score 26.9±13.5) and 4 volunteers (2 F, mean age 33±10.7) without clinical features or family history of tremor. Acceleration and video sequences were acquired in four standardized positions of the upper limbs. Triaxial accelerometers were placed on the back of the subjects' hands. Frequency distribution of the 3D accelerometric signal was computed as the sum of the power spectral densities (PSD) obtained for every component of the 3D signal. Spatial tremor amplitude was estimated by dividing the power under the tremor peak detected in the interval 3.5-12Hz by square of the angular frequency of the peak. Video sequences were processed using TremAn, with the image intensity from the selected area collected over time as a one-dimensional periodic signal. The frequency being measured was based on the Fourier transform power spectrum.

Results: Altogether, 368 sequences of video and accelerometric recordings were analyzed, including 312 samples from ET patients and 56 from healthy controls. Periodic signals were absent in all healthy controls and in 147 ET patient samples, where the accelerometric amplitudes were 0.25±0.14mm (range 0.06-0.79mm). Periodic signals were detected and their frequency assessed in 165 samples. A close correlation ($r=0.93$) was found between the frequencies measured by accelerometry and and by TremAn (see example in Figure 1).

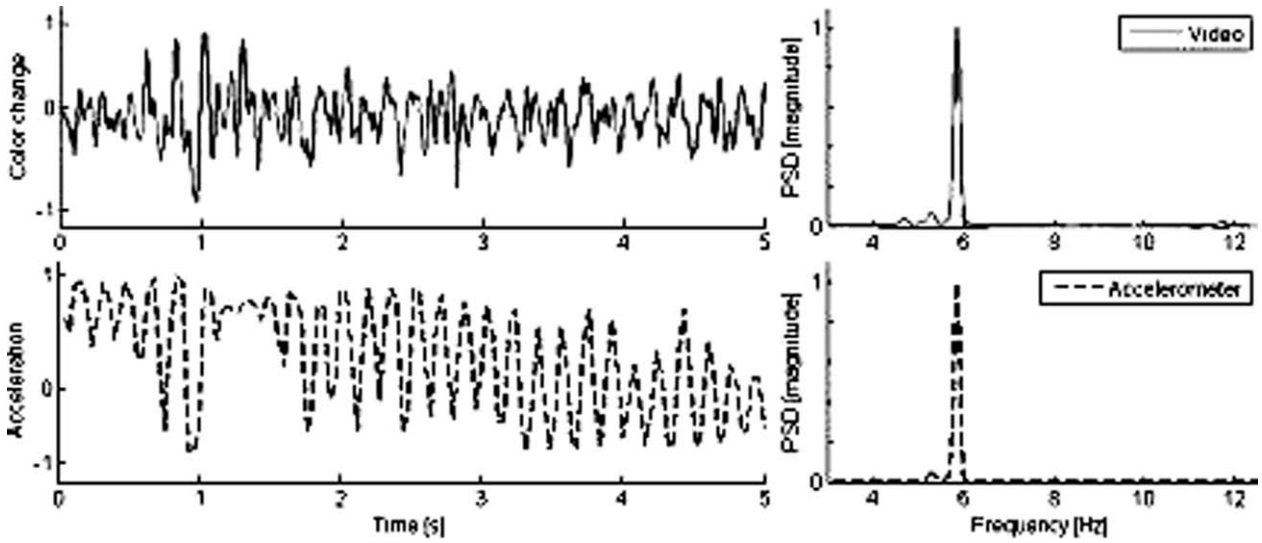

FIG. 1 (1058). Raw signals and corresponding frequency spectra of tremor in a patient with ET.

Conclusions: TremAn has been shown to effectively analyze the frequency of tremor, in close correlation with the results of accelerometry. (1) Uhrikova Z et al. Mov Disord. in press, DOI:10.1002/mds.22904.

1059

Thalamic and subthalamic dbs for essential tremor: What is the optimal location of the electrode

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Objective: To assess the location of contacts yielding the best result in DBS for Essential Tremor (ET).

Background: At present DBS in the ventrolateral thalamus (Vim) is the golden standard in the treatment of ET. DBS in the posterior subthalamic area (PSA), including Zona incerta and prelemniscal radiation, has recently demonstrated promising results.

Methods: 43 patients (19 Vim/24 PSA) were included in this non-randomized sequential study. 70% were males and the mean age 59.4±16 years. Evaluation, using the Essential Tremor Rating Scale (ETRS), was done before, and one year after surgery concerning PSA, and after a mean time of 66±38 months concerning Vim. The patients were tested before, and after surgery, off and on stimulation, with optimized stimulation settings. Each contact was further evaluated using standardized settings concerning the effect in the treated arm; items 5/6 and 10-14. The location of each contact in relation to the anterior and posterior commissures was determined from postoperative CT images and then plotted onto the horizontal sections in the Schaltenbrand atlas in order to determine their neuroanatomical position.

Results: Total ETRS for the whole group was before surgery 45.8±11.5. Total ETRS was on unilateral stimulation reduced by 48% in the Vim group and by 58% in the PSA group. Tremor/function in the treated hand, was improved by 67% in the Vim-group and 92% in the PSA-group. In the Vim group the contacts yielding the best result on total ETRS, were found to be located in PSA in 40 % and in Vim in 32% of the patients. In the PSA group the optimal location was found to be in PSA (55%) Vim counted for 12.5%. In several cases the location could not be determined. When looking specifically at the contacts achieving an improvement in hand fuction/tremor of more than 90% only 3 such were seen in the Vim group, all located in the Vim (mean coordinates X=13±1.4, Y=-1.8±0.5 and Z=4.1±0.3.) In the PSA group no less than 33 contacts achieved this level of tremor reduction and of these 59% were clearly located in the PSA (X=12±1.8, Y=-5.8±1.6 and Z=-1.7±2.6).

Conclusions: In this population contacts located in the PSA gave superior alleviation of tremor regarding both totalt tremor scores as well as scores for the treated hand.

1060

Neurophysiological evidence for cerebellar dysfunction in neuropathic tremor

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Objective: To investigate if cerebellar function is abnormal in patients with immune-mediated neuropathy who have tremor compared to those without.

Background: The pathophysiology of neuropathic tremor remains largely unexplored. We aimed to establish whether there is evidence of abnormal cerebellar function in patients with tremor associated with immune-mediated neuropathy compared to those without tremor, using the classic eyeblink conditioning paradigm. This paradigm at short intervals is dependent on the olivo-cerebellar circuit and does not require cerebral and/or basal ganglia activation.

Methods: Eyeblink conditioning was performed by pairing an auditory tone (conditioning stimulus-CS) with a supraorbital nerve stimulus (unconditioned stimulus-US) with a delay interval of 400 ms in 3 age-matched groups: 8 patients with an immune-mediated neuropathy with tremor (5 CIDP, 2 MMNCB, 1 IgMPN), 6 patients without tremor (4 CIDP, 2 IgMPN) and 9 healthy controls. Conditioning consisted of 7 learning blocks of 11 trials (9 trials were CS-US pairs, 1 US only, 1 CS only), followed by 2 extinction blocks. EMG bursts were regarded as conditioned eyeblink responses (CRs) if latency was >200 ms after the CS but before the US. For CS only trials, EMG bursts occurring 200–600 ms after the CS were considered CRs.

Results: Comparing CRs produced per block, patients with neuropathic tremor had a significantly lower rate of CRs as the blocks progressed compared to neuropathy patients without tremor and healthy controls. Latencies of CRs, spontaneous blink rates and "alpha blinks" were not significantly different between the three groups.

Our results indicate an abnormality of associative learning in this group of patients with neuropathic tremor.

Conclusions: This study provides neurophysiological evidence for functional changes in the olivo-cerebellar pathway of patients with immune-mediated neuropathy associated with a tremor compared to those without tremor. Further work needs to be done to determine if these changes are primary or secondary in nature.

1061

Clinical presentation of SWEDDS with abnormal olfaction

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Objective: To evaluate the clinical presentation of patients with a clinical diagnosis of PD who had dopamine transporter scans without evidence of dopaminergic deficiency (SWEDDs) and hyposmia.

Background: Recent data suggests that SWEDDs patients have UPSIT scores in the range of controls and subjects with dystonic or essential tremor. We have identified a subgroup of SWEDDs who present with hyposmia and we sought to explore their clinical phenotype.

Methods: We examined 41 patients who had presented as PD but had a normal FP-CIT scans and were followed for an average of 3 years without clinical worsening. The University of Pennsylvania Smell Identification Test (UPSIT) was interpreted according to published data for the United Kingdom[1]. Clinical features were assessed by examination (tremor in posture and in rest, in one or in both sides, and systematic analysis of free drawn Archimedes spirals[2]) or self-report (age of onset, side of tremor at the start of disease, family history of parkinsonism or tremor, difficulties to roll in bed, symptoms of REM sleep behavioural disorder, worsening with stress, response to dopaminergic therapy).

Results: Of the 41 SWEDDs 17 (41.5%) presented with olfaction in the range compatible with PD. See clinical characteristics in Table1. Standardized videos of 9 of these 17 patients had been analyzed by two blinded movement disorder specialists: a false positive diagnosis of PD was made in 3/9 (33%) by one specialist and 2/9 (22%) by the other specialist, with 2 of the patients being diagnosed as PD by both.

TABLE (1061). *Clinical features*

	UPSIT in control range	UPSIT in PD range	significance
UPSIT-mean(SD)	30.5 (3.6)	17.9 (5.8)	p<0.001 (t-test)
Sex-N(%) female	12 (50%)	12 (70%)	p=0.2 (X2 test)
Age-mean(SD)	63.8 (13.1)	71.1 (6.7)	p=0.04 (t-test)
Age of onset-mean(SD)	46.3 (18.3)	56.8 (13.1)	p=0.06 (t-test)
Disease duration-mean(SD)	15.1 (3.1)	13.1 (3.2)	p=0.6 (t-test)
Start of tremor in both sides-N(%)	10 (46%)	2 (9.1%)	p=0.07 (X2 test)
Presence of postural tremor-N(%)	22 (95%)	15 (88%)	p=0.6 (X2 test)
Presence of rest tremor-N(%)	10 (43%)	6 (40%)	p>0.9 (X2 test)
Family history for tremor-N(%)	10 (43%)	5 (31%)	p=0.5 (X2 test)
Family history for PD-N(%)	6 (26%)	2 (13%)	p=0.4 (X2 test)
Difficulty to roll in bed-N(%)	5 (22%)	4 (24%)	p>0.9 (X2 test)
REM sleep BD-N(%)	6 (26%)	3 (18%)	p=0.7 (X2 test)
Positive response to ethanol-N(%)	7 (37%)	3 (38%)	p>0.9 (X2 test)
Positive response to dopaminergics-N(%)	9 (56%)	6 (40%)	p=0.5 (X2 test)
Archimedes Spiral coefficient-mean(SD)	0.36 (0.49)	0.42 (0.51)	p=0.7 (t-test)

Conclusions: SWEDDs with low UPSIT scores were older than SWEDDs who had UPSIT in the control range. There are trends towards older age of onset and unilateral onset of tremor in these patients. It is of note that in this cohort of SWEDDs, a higher than expected proportion of hyposmic subjects was found; this cohort also presents a high number of false positive diagnosis by movement disorder specialists. Given the normal scans, mean disease duration >10 years, and the follow-up without deterioration, it is unlikely that these patients have PD but further long term follow up and pathological examination of such cases would be of great interest. *References: [1]Mov Disord. 2009;24(8):1144-53. [2]Assessing tremor severity: a clinical handbook. London: Smith-Gordon 1993.*

1062

Orthostatic tremor: Is it really benign? A review of 33 cases

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Objective: To identify clinical characteristics that indicates disease severity in patients with orthostatic tremor (OT).

Background: OT is a rare condition characterised by feeling unsteady when standing manifested by high frequency leg tremor. Due to its rarity little is known about the impact on quality of life (QoL) and its natural history.

Methods: We reviewed medical records of 33 patients with neurophysiologically confirmed OT from The Alfred Hospital Movement Analysis Laboratory. All patients were posted a questionnaire to evaluate clinical characteristics. 23 patients responded and were evaluated further by interview to establish factors that cause disability and response to medications (0=none, 1=mild, 2=moderate, 3=good and 4=excellent).

Results: 82 % (27/33) of the cohort were female, mean age of onset was 61 years (range 10-84) and mean symptom duration was 12 years (range 1-47). Family history of OT was present in 2/23. 57% (13/23) had isolated orthostatic tremor, 6 had associated restless leg syndrome and 5 had essential tremor. Mean response to treatment was mild (mean 1.1, median 2, range 0-4). 12 patients (52%) had no benefit from medications. Clonazepam was the most commonly prescribed medication (13/23), and improved symptoms in 77% (mean response 1.7, median 2, range 0-4). 43 % of all patients (10/23) required a mobility aid; mean time from disease onset to first use of mobility aid was 3.2 yrs (range 0.5-7). Excluding the patient with juvenile onset OT (onset age 10 yrs), patients using a mobility aid were older (mean 78 years) and had later age of onset (mean 71 yrs) than those not needing a mobility aid (mean 70 yrs, t-test p=0.007; onset 59 yrs, t-test p=0.01). Despite most patients experiencing at least moderate unsteadiness only 13% (3/23) fell in the previous 3 months.

Conclusions: Women with OT were significantly more likely to be referred to our Laboratory than men, supporting previous studies identifying gender differences in OT. Clonazepam appeared to provide a moderate benefit in less than half of patients. Older patients and those with a later age of onset were more likely to require a mobility aid suggesting a greater impact on QoL than in younger patients. A scale to assess the impact of OT on QoL would be of benefit to better quantify disability and disease progression.

1063

Essential tremor: Factors influencing the quality of life

S. Telarovic (Zagreb, Croatia)

Objective: To analyze the effect of essential tremor (ET) upon the quality of life and the contributing factors.

Background: The most frequent of all hyperkinesias, ET, although of benign course and prognosis, can substantially reduce the patient's quality of life.

Methods: The investigation included 89 patients with ET, who were followed-up in the out-patient unit for movement disorders and

fulfilled the decisive criteria for the diagnosis of ET (Consensus Statement of The *Movement* Disorder Society 1998, and the Washington Heights-Inwood Genetic Study of Essential Tremor Criteria). Along with detailed case history and clinical examination, the investigator and the patient fulfilled during three visits several complex questionnaires (translated to Croatian): Tremor scale (TS), Tremor Assessment Form (intensity of tremor, interference with daily activities, drawing of the Archimedean spiral, etc.), as well as the Fahn-Tolosa-Marin Tremor Rating Scale and the Quality of Life in Essential Tremor Questionnaire (QUEST).

Results: The mean age of the examinees (M=51, F=38) was 52.1±4.3 years (18-82). The mean duration of ET was 8.4±3.7 years (5-21). The QUEST/30 analysis showed in 79.77% examinees markedly disrupted quality of life due to ET, which in 64.04% of the patients interfered in various degrees with everyday chores. Sex and the duration of ET did not show significant correlation with the level of disturbed quality of life, while more pronounced degree and tremor intensity (TS≥3), more marked affection of the dominant arm, younger life age (<50) and employment were in positive correlation with the aggravated quality of life.

Conclusions: ET significantly reduces the quality of life in the majority of patients, particularly in younger ones and those still working. Such patients, besides treatment, require interdisciplinary medical and non-medial support as well.

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"Bag tremor" as a type of task-specific isometric tremor

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Objective: We describe 10 patients with "bag tremor", a task-specific isometric tremor that develops only when holding a bag with the arm extended.

Background: Isometric tremor is an action tremor that results from a muscle contraction against a rigid stationary object. It has been associated with either essential tremor (ET) or Parkinson's disease (PD).

Methods: Descriptive study of 10 patients visited in a Movement Disorders Clinic. All patients were visited because of complaints of hand tremor that was elicited while holding a heavy bag with the arm extended. Complete clinical and demographic data were recorded. DAT-SPECT and neurphysiological study (accelerometer and EMG) was performed in all participants.

Results: Bag tremor (BT) was the only complain in 8 patients, and it was the main complain in two patients with additional slowness of movement or rest tremor. BT started at 68±8 years and was mostly unilateral (7 left, 2 right). At first visit, 2 patients accomplished criteria for PD, 7 were diagnosed of ET by the presence of bilateral and symmetric postural tremor with no rigid-akinetic syndrome, and use of clebopride led to the diagnosis of drug-induced tremor in one patient. DAT-SPECT was abnormal only in the two patients with a clinical diagnosis of PD. After a mean follow-up of 6.5±2.5 years, BT in ET remained stable, mildly improved with dopaminergic treatment in PD, and resolved after withdrawal of clebopride. It was mildly disabling in all patients. Motor symptoms in both PD patients followed a slow progression and showed a tremor-dominant phenotype.

Conclusions: The presence of BT appears as a task-specific tremor that seems to be more associated with ET. Its association with PD could be a marker of good prognosis.

1065

Is botulinum toxin treatment useful in patients with tremor

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Objective: To evaluate the efficacy and safety of Botulinum toxin type A (BTXA) injections in patients with hand and arm tremor.

Background: There are controversial data concerning on the effect of the therapy with BTXA in patients with tremor disorders and this therapy is considered less effective compared to dystonia or spasticity although it can be beneficial in selected patients.

Methods: Thirty five patients with the tremor of the arms with an unsatisfactory medical therapy or with unacceptable side effects were treated during last 6 years using BTXA. Essential tremor (ET) was the reason of treatment in 16 cases; parkinsonian tremor (PT) had 17 patients. Two patients had other type of tremor. Mean age in the time of the first injection was 67 years (39- 87), 15 women a 20 men. Self-rating numeric scale and handwritten spiral analysis were used for evaluation. Overall 206 applications were done using EMG guidance with mean dose of 44 unit of Botox® (25-100) or 227 unit of Dysport® (120- 400) per one arm. Repeated bilateral injections were used in 15 cases, 20 persons underwent the therapy of one extremity. The majority of patients with ET had bilateral therapy (11 persons), the patients with PT had mainly unilateral injections (15 cases).The most frequently injected muscles were extensor digitorum communis, pronator teres, and flexor digitorum superficialis.

Results: The average improvement referred by patients was 55%, the reduction of the tremor by spiral drawing was in most cases 1 point (maximal improvement 2 points). The mean time of the improvement was 10 weeks, adverse events (mostly transient mild weakness) were found in 19% of all injections. The treatment was non-effective (les then 20% during 2 consecutive applications) in 24% of patients: in 7 patients from 16 with ET, but only in one from 17 with PT (p=0.016, Fisher's exact test).

Conclusions: The treatment using BTXA should be considered in patients with arms tremor. This therapy is probably more useful in patients with the parkinsonian type of tremor comparing with the patients with essential tremor.

1066

Direct evidence for central oscillators underlying neuropathic tremor

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Objective: To evaluate whether cortical and thalamic oscillators contribute to neuropathic tremor.

Background: Neuropathic tremor (in absence of other tremor conditions) was assumed to result from defective afferent input deregulating cerebello-thalamo-cortical motor integration and thereby contributing to tremor.

Methods: A 76 year old female with IgM paraproteinaemic neuropathy developed postural and action tremor refractory to medical treatment. Bilateral deep brain stimulation of the ventral intermedial thalamus (Vim-DBS) was performed. Tremor-related synchronization (coherence) between Vim, motor cortex (M1), and muscles (M. extensor digitorum, M. flexor digitorum) was assessed (i) preoperatively, (ii) intraoperatively, and (iii) four days after surgery in both rest and tremor conditions. Directionality and time delay of information flow were assessed by directed transfer function (DTF) and phase analysis. Stimulation effects (130Hz) on tremor and corticomuscular coherence were tested and the patient was followed for 12 months (Tremor Rating Scale, CADET-Score).

Results: Vim-DBS reduced tremor (59%) and improved functionality in daily activities (31%, CADET-A). Corticomuscular coherence between M1 and contralateral muscle during tremor was present at tremor frequency (4Hz) in conditions without stimulation (absent at rest), but completely suppressed by Vim-DBS. Coherence was also significant in the tremor frequency between Vim and ipsilateral M1, Vim and contralateral muscle, but non-significant between Vim and contralateral M1. Information flow was directed from M1 to Vim (7ms delay). Flow was bidirectional between M1 and muscle (M1 to muscle: 10ms; muscle to M1: 32ms) and between Vim and muscle (Vim to muscle 9ms, muscle to Vim 19ms).

Conclusions: Our study provides direct evidence of central oscillators in neuropathic tremor and substantiates the concept of central feed-forward processing in deafferentiation tremor.

1067

Orthostatic tremor: A review of 40 cases

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Objective: To evaluate the clinical characteristics, associated features, and treatment response of a large orthostatic tremor (OT) series seen over a 22-year period.

Background: OT was described in 1984 by Heilman as unsteadiness on standing accompanied by a 13 to 18 Hz tremor of the legs. OT is a rare condition and its relationship to essential tremor and Parkinson's disease has not been clearly established.

Methods: We reviewed the medical records of 40 patients seen at the Baylor College of Medicine Parkinson's Disease Center and Movement Disorders Clinic between 1987 and 2009 who fulfilled the diagnostic criteria for OT.

Results: The mean age at onset was 60.1 years (range 32-77 years) and 21/40 (53%) were men. A family history of tremor was noted in 21/40 (53%) patients. 2/40 patients reported a family history of OT, although these relatives were not examined at our center. 34/40 (85%) had primary OT with (n=25) or without (n=9) an associated postural arm tremor. We found that 6/40 (15%) had OT plus additional neurological features including 1 with Parkinson's disease and restless legs syndrome, 2 with parkinsonism, 1 with ataxia, and 1 with hemifacial spasm. One patient was diagnosed with dementia with Lewy bodies preceded by OT for 20 years. Follow-up data was available for 28/40 patients and averaged 53.3 months (range 1 to 196 months). Treatment response was modest and inconsistent, averaging 1.1 (0=no improvement to 3=complete resolution). In 9/28 cases OT worsened over the follow-up period. Medications found to be most effective for treatment of OT included clonazepam, propranolol, gabapentin, pregabalin, primidone, carbidopa/levodopa, valproic acid, and phenobarbital. One patient recently underwent thalamic deep brain stimulation (DBS) surgery.

Conclusions: In our population of OT patients, a slightly higher proportion of men had OT and postural hand tremor was a frequent finding. Over half of our patients had a family history of tremor, but a family history of OT was uncommon. Additional neurological features were seen in the minority of patients and we report possibly the first case of dementia with Lewy bodies associated with OT. Our series is of similar size as the largest series of OT reported in the literature and contributes to understanding the clinical characteristics of this rare disease.

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