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Poster Session 1

Caregivers, employment, and healthcare utilization

P001
Caregiver's burden in multiple sclerosis is higher in Mexican population

R Llorens-Arenas[1], L Nuñez-Orozco[1]
[1]*CMN 20 de Noviembre, Neurology, Mexico, Mexico*

Background: According to previous studies, 25% of caregivers of chronically ill patients have been reported to suffer some degree of burden. Latin caregivers experience caregiving as less challenging than Caucasians. Factors influencing burden include scholarship of the caregiver, relationship with the patient, motor and cognitive decline of the disease. To date there are no studies addressing the issue in Mexican caregivers of multiple sclerosis patients.
Objectives: To describe the prevalence and predicting factors of caregiver burden in multiple sclerosis within a Mexican population.
Methods: 99 Caregiver-patient pairs were recruited during scheduled office visits. Demographic data was recollected. Zarit Burden Interview (ZBI) was administered to caregivers and Expanded Disability Status Scale (EDSS) was calculated in each patient.
Results: Some degree of caregiver burden was found in 60.6%, being moderate or severe in 31.1%. The "Impact of caregiving" subdimension accounted for most weight of the construct. The median patient disability according to the EDSS was 5.5. Variables predicting caregiver burden were EDSS ($p < 0.001$, CI 95% 0.09-0.21), daily hours of caregiving ($p < 0.001$, CI 95% 0.81-0.91) and incomplete high-school for caregivers ($p = 0.030$, CI 95% 0.01-0.79). Daily hours of caregiving also predicted each subdimension of the ZBI independently. Kolmogorov-Smirnov test was used to determine the goodness of fit of the normal distribution of the interval variables. A likelihood ratio test was performed comparing the complete model with a reduced one including only the predicting factors, obtaining a significant $p = 0.0014$ for 6 degrees of freedom.
Conclusions: Caregiver's burden prevalence was much higher than reported previously. In fact, even moderate or severe burden were higher than the overall burden described in other studies. Predicting factors were similar to those found in previous reports. Considering the higher prevalence of caregiver burden found, it is possible that the study sample was underestimated. If this is so, there's a chance that two more variables (Age of caregiver and Months spent as caregiver) could have reached significance providing the sample was enlarged. According to the results, neurologists should implement supporting measures for caregivers, addressing the time they spend with their patients.

Future research should focus in other patient's variables and cultural environment.

P002
How do MS patients' sickness absence and disability pension trajectories develop over time? A nationwide cohort study of 3 543 MS patients

P Tinghög[1], K Alexanderson[1], M Wiberg[1], J Hillert[1], C Björkenstam[1]
[1]*Karolinska Institutet, Stockholm, Sweden*

Background: Multiple sclerosis (MS) generally occurs during the most productive period of life, and sickness absence (SA) and disability pension (DP) is common.
Objectives:

1) Characterize MS patients' SA/DP trajectory from five years before to five years after diagnosis and compare this with matched controls,
2) Explore if the progression of MS patients' SA/DP trajectories are associated with socio-demographics.

Methods: This population-based cohort study contains 3 543 Swedish residents aged 24-57 that were diagnosed with MS in 2003-2006 and 17 715 matched controls. Individuals with MS were followed, with regard to annual net days of SA and DP, from 5 years before until 5 years after diagnosis (t-5 - t5). Matched controls were followed over an equivalent time period. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated with General Estimation Equations (GEE) using a negative binominal distribution. A piecewise GEE model was fitted to evaluate if socio-demographics influenced the progression of MS patients' SA/DP trajectories at three distinct time periods, i.e., t-5 - t-1, t1- t1 and t1 - t5. Differences of SA/DP progression were assessed by examining the interactions between socio-demographics and time.
Results: MS patients mean SA/DP days increased gradually between t-5 to t-1 (46 to 77) followed by a sharp increase (t1, 136), after which only a marginal increase was observed (t5, 145). Matched controls had less SA/DP days at all studied years, although the difference increased over time from an adjusted OR of 2.01 (1.93-2.08) to an adjusted OR of 5.00 (4.82-5.18) at t5. Men with MS had a sharper increase in SA/DP days during the period before diagnosis, i.e. t-5 - t-1, adjusted OR 1.05 (1.01-1.09). A lower educational level was associated with a less marked SA/DP progression, OR 0.94 (0.88-0.99) around the time of diagnosis t1- t1, while the reverse scenario was detected during the time period that followed, t1 - t5, OR 1.10 (1.04-1.16).
Conclusions: Individuals with MS have a markedly higher risk for SA/DP than matched controls even 5 years before diagnosis.

Underlining of author represents the presenting author in each abstract

P003

Knowledge and attitude towards multiple sclerosis in Turkey

<u>S Canbaz Kabay</u>[1,2], H Ozışık Karaman[2], S Ayas[1], E Mestan[1], M Çetiner[1]

[1]Dumlupınar University Faculty of Medicine, Department of Neurology, Kutahya, Turkey, [2]Çanakkale 18 Mart University Faculty of Medicine, Department of Neurology, Çanakkale, Turkey

Background: Multiple Sclerosis is an inflammatory, autoimmune and neurodegenerative disease which effects young adults. The patients have many social problems. In many countries especially ın developing ones, there are little knowledge about the disease and its course in the community. So that the patients may be lack of social support during their lives.
Objectives: The aim of this study was to investigate the perception of Multiple Sclerosis in Turkey, in an eastern city Kütahya.
Methods: The Survey of multiple sclerosis patients, their relatives and control group on the Knowledge, Attitudes, and Behavior Regarding the Disorder was used and included questions on descriptive characteristics, familiarity with multiple sclerosis(MS), attitudes toward MS, and understanding of MS.
Results: 71 MS, 46 relatives of MS patient and 40 control group included in the study. The control group were consisted of the people which had no MS diagnose or no relatives or friends with MS. Mean age of the MS patients, relatives and control group were 37yr (min19-max56), 40yr(min19-max66), 39(18-67), respectively. In the MS patient and relative groups; 10(14%) and 4(8:7%) of them concealed the diagnosis from other people. Both the patient and relatives groups had knowledge about the symptoms of the disease; however in the control group 30 (75%) people had no idea about the disease or the symptoms or about the etiology. Of the patients 61(85.9%) had no social problems, while 5(7%) had been fired of their work and 3(4.2%) had stigmatization. But from the control group 15 (37.5%) people thought that MS patients were stigmatized or having social problems in the society.

The number of participants who would allow their child marrying someone with MS was significantly higher in MS patient group than control group (p < 0.05). Of the patient and relatives groups 4(%5.6) and 6(%13) had decided to use alternative herbal medicine in addition to medical treatment, respectively.
In the control group 7(17.5%) of them thought not to employ a MS patient, while 27 (67%) of them thought to employ a MS patient for only easy works.
Conclusions: Although understanding of MS was favorable in MS patients and in relatives of MS patients, it wasn't well understood in the community. Educating the community about MS and personal contacts must be the major strategies against understanding MS patients and their social problems.

P004

Early loss of working capability in a Swiss cohort of patients with multiple sclerosis

<u>O Findling</u>[1], M Baltisberger[1], CP Kamm[1], HP Mattle[1], J Sellner[2,3]

[1]Inselspital, University Hospital Bern and University of Bern, Neurology, Bern, Switzerland, [2]Christian-Doppler-Klinik, Paracelsus Medical University, Neurology, Salzburg, Austria, [3]Klinikum rechts der Isar, Technische Universität München, Neurology, München, Germany

Background: Diagnosis and disability associated with multiple sclerosis (MS) have far reaching implications on the patient's private and professional life. Notably, MS patients experience some of the highest rates of unemployment among individuals with severe and chronic disabilities.
Objectives: To assess working capability and employment status in a cohort of Swiss patients with MS.
Methods: A cross-sectional study was conducted over a period of 12 months among patients treated at the outpatient clinic for MS at the Inselspital, a tertiary care hospital at the University of Bern, Switzerland. The paper-based questionnaire inquired about details of current employment and impact of MS-related disability on working capability. The survey was supplemented by clinical data derived from the most recent medical report.
Results: The questionnaire was handed out to 644 patients and returned by 449 (68%). Individuals above the retirement age (n=44) were excluded. A total of 405 patients (women 266, 66%) with a mean age of 44 years (range 18-64), median EDSS of 3.0 (range 0-8.5) and median disease duration of 12.4 years (range 1-43) were subjected to further analysis. Full-time employment was declared by 108 patients (27%, median EDSS 2.0 (0-6.5), mean age 40.8 y (19-62), median disease duration 10.5 y (range 1-43) women 58 (54%)). A total of 104 patients (26%, median EDSS 3.0 (1.0-7.0), mean age 45 y (26-63), mean disease duration 12.4 y (range 1.7-34.0) women 68 (65%)) had scaled down to part-time work because of disease-related issues. Complete inability to work was reported by 110 patients (27%, median EDSS 5.0 (1-8.5), mean age 48 y (25-65), median disease duration 16.0 y (range 3.2-43.0) women 73 (66%)). 83 patients (21%) were not employed but reported other reasons than MS (mostly care for children, household).
Conclusions: Our data further corroborate the toll this disorder takes on the life of the patients and caregivers early in the course and despite emerging treatment options. Only less than one-third of the patients in a cross-sectional cohort of Swiss MS patients with mostly mild impairment were fully employed. Part-time work is common despite limited disability. Further efforts need to be taken in order to develop measures to preserve and regain working capability. Moreover, studies aimed to assess potential gender-and education-related inequalities are warranted.

P005

Profile of social participation of multiple sclerosis adults in Québec city

<u>N Lacroix</u>[1,2], N Boucher[1,2], P Villeneuve[2]

[1]Université Laval, CIRRIS (Center for Interdisciplinary Research in Rehabilitation and Social Integration), Quebec, QC, Canada, [2]Université Laval, School of Social Work, Quebec, QC, Canada

Background: Many studies have presented the physical and psychological consequences of chronic degenerative diseases such as multiple sclerosis (MS). Only a few studies have focused on the impact on social participation. Our observations suggest that social roles seem more affected than activities of daily living (ADLs).
Objectives:

1) Describe the social participation of people living with MS, and
2) determine what personal factors may influence it.

Methods: Participants were recruited via a local MS organization. Data were collected through telephone interviews using

questionnaires. Social participation was evaluated using the Assessment of Life Habits (LIFE-H), which quantifies the level of difficulty and support required to carry out various life habits. The Participation and Activity Limitation Survey (2006) was used to collect additional data regarding participation in employment. Socio-demographic and disease-related variables such as type of MS, years since diagnosis and self-evaluation of the presence and importance of symptoms were also documented.

Results: Of the 90 participants (74.4% female, age 23-78, median = 53.2), 62.2% had relapsing remitting MS, 11.1% had primary progressive, and 23.3% had secondary progressive. The LIFE-H results showed that social roles (mean = 7.5) were more affected than ADLs (mean = 8.7). The most affected area of social participation were Recreation (49.4%), Employment (43.0%), Mobility (32.2%), Fitness (22.2%), and Interpersonal relationships (12.4%). Symptoms with the most important perceived impact were fatigue (59.3%), leg weakness (40.4%), bladder dysfunction (33.3%), heat sensitivity (31.3%), and balance problems (31.0%). Multiple linear regression analyses showed the following significant (p < 0.05) relationships with social participation categories:

1) balance problems and leg weakness explained variance in Mobility scores,
2) depression and sexual problems in Interpersonal relationship scores, and
3) leg weakness and cognitive changes in Leisure scores.

Conclusions: These findings show that, if it's possible to correlate most perceived impact of the symptoms with life habits accomplishment, when put in multiple linear regression, only few emerge as significant. Interaction seems more important than individual disease-related factors. These outcomes suggest that some other factors, like work status, might be as important as individual disease-related factors for the accomplishment of daily activities and social roles.

P006

Determinants of stigma experienced by patients suffering from multiple sclerosis. A Hellenic population study

M Anagnostouli[1], S Katsavos[1], A Artemiadis[1], M Zacharis[1], P Argirou[1], I Theotoka[2], F Christidi[1], I Zalonis[1], A Rombos[1], I Liappas[2], E Stamboulis[1]
[1]Medical School of National and Kapodistrian University, 1st Dept of Neurology, Athens, Greece, [2]Medical School of National and Kapodistrian University, 1st Dept of Psychiatry, Athens, Greece

Background: Multiple Sclerosis (MS) is a disease with substantial socioeconomic impact among its sufferers. 'Disease burden' as perceived by MS patients, cannot be accurately evaluated by the single use of disability scales, like the Expanded Disability Status Scale (EDSS). Co-evaluating stigma assessment tools may be useful towards this direction. The term 'stigma' is used to describe the amount of social isolation-reject experienced by a patient due to his medical condition.

Objectives: Aim of this study was to investigate the main determinants of stigma among Hellenic MS patients.

Methods: We used a sample of 299 MS sufferers that visited the Outpatient Clinic of our Hospital. The data collected concerned demographic elements, habits, disease-derived variables (EDSS,

disease subtype, imaging etc), as well as the Stigma Scale for Chronic Illness (SSCI) questionnaire. Statistical processing included univariate analysis, and variables significant below p=0.05 were assessed further in multiple regression models. Principal component analysis confirmed two independent stigma measuring factors (internal: coming from the inner self - external: coming from the social environment). SSCI's reliability was satisfactory (Cronbach's alpha = 0.923).

Results: Mean age of patients was 43.2 years and mean disease duration was 12 years. Female sex was predominant (67.2%), while the relapsing-remitting disease subtype was the most frequent (70%). The majority of patients were married (59.2%) with children (58.2%), and active workers (55.2%). 45.2% of them had received tertiary level education. Any type of social support (family, friends, social structures) was present in 92% of cases. Age, disease duration, EDSS score, disease subtype, occupational status and social support could explain the variability of 24.5%, 22.4% and 20.5% of the total, internal and external stigma respectively. Higher EDSS scores and lower social support correlated with higher total, internal and external stigma (p< 0.0001 and p=0.01 respectively), independently of all other factors.

Conclusions: Surprisingly, despite the ongoing economical crisis in Greece, occupational status had much lower influence than disability and social support in total stigma formation. Lower social support had also lower influence in external than internal stigma, fact that maybe reflects the stable Hellenic social solidarity. Other aforementioned demographic and laboratorial parameters, did not seem to further influence stigma.

P007

A 10-year longitudinal study of use of and satisfaction with health care in a population-based sample of people with MS

C Chruzander[1,2], S Johansson[1,2], L Widén Holmqvist[1,2], K Gottberg[3], U Einarsson[2], C Ytterberg[1,2]
[1]Karolinska Institute, Neurobiology, Care Science and Society, Stockholm, Sweden, [2]Karolinska University Hospital, Department of Physiotherapy, Stockholm, Sweden, [3]Karolinska Institutet, Neurobiology, Care Science and Society, Division of Nursing, Huddinge, Sweden

Background: People with multiple sclerosis (PwMS) use a large amount of health care services with hospital care and primary care in parallel and many departments and services involved. Several studies have demonstrated that PwMS are unsatisfied with several areas of health care services. For the purpose of improving health care services for PwMS it is important to investigate their satisfaction with care in a long-term perspective.

Objectives: The aim of this 10-year follow-up of a population-based sample of PwMS was to explore the use of health care in a long-term perspective (10 years). An additional aim was to explore the satisfaction with health care services from the perspective of the PwMS over 10 years.

Methods: This study was based on a 10-year follow-up of a population-based study in Stockholm (n=166). Home visits were used to collect data on personal and disease-specific factors, functioning and satisfaction with health care. Data on use of total outpatient health care (including primary care and outpatient hospital care) and inpatient health care were obtained from the computerised register of the Stockholm County Council.

Results: A total number of 35 984 outpatient contacts were registered from baseline to the 10-year follow-up of which 65% were registered in primary care and 35% in hospital outpatient care. Contacts with nurses composed 47% (n=11 019) of the total number of contacts in primary care. A total number of 4108 days were registered for inpatient hospital care; mean 22 days per PwMS, range 0-302 days. Seventy-one percent of the PwMS were satisfied with the efficacy/outcome of primary care at both baseline and at the 10-year follow-up. There was a significant increase in the proportion of PwMS who were satisfied with the efficacy/outcome of hospital out-patient care, from 75% to 85%.

Conclusions: Preliminary results demonstrate that primary care constitute a large portion of the total care used and that a third of the PwMS express that they are unsatisfied with the outcome/efficacy of primary care. Further analyses are needed to explore which factors are associated with the use of health care.

P008

Differences in health care utilization over 10 years between people with MS who entered a nursing home and those who did not

M Finlayson[1], RA Marrie[2], GS Finlayson[3], O Ekuma[2], D Jiang[2]
[1]Queen's University, Kingston, ON, Canada, [2]University of Manitoba, Winnipeg, ON, Canada, [3]Manitoba Centre for Health Policy, Winnipeg, ON, Canada

Background: People with MS often require increasing amounts of physical care over time. For approximately 5-10% of people with MS, care needs may lead to nursing home (NH) entry. Understanding longitudinal patterns of health care utilization (HCU) may offer opportunities to identify individuals at risk of NH entry, which may inform interventions to prevent or delay this outcome.

Objectives: To compare the 10-year trajectories for three annualized indicators of HCU between people with MS who entered a NH and those who did not.

Methods: Population-based, de-identified claims data from the Population Health Research Data Repository at the Manitoba Centre for Health Policy were used for this case-control analysis. Applying a validated algorithm we identified all Manitobans with MS between 1984 and 2012. From this pool, cases were identified (nursing home entrant at any point since 2005). Cases were matched to controls (not resident in a nursing home since 2005) by age, sex, geographic region, and date of first demyelinating disease claim. The HCU trajectories for ambulatory physician visits, number of prescriptions, and hospital days were generated using semi-parametric group-based trajectory approaches. The Bayesian Information Criterion (BIC) was used to select the best model together with theoretical considerations. The trajectories displayed changes in HCU for each annualized HCU indicator over time for both groups.

Results: 226 cases and 896 controls were identified, for a total of 1122. The average age of the cases was 48.35 (SD=13.25) and 44.91 for the controls (SD=11.58). The percentage of females for the cases was 64%, and for the controls, 61%.

For ambulatory physician visits, the 10-year trajectories were similar across the cases and controls up until the 9th year, when the cases experienced an increase in visits in the year before NH entry.

Days in hospital remained relatively stable over time for controls but began to increase at year 5 for cases with a more marked increase in the two years prior to NH entry.

For the number of prescription medications, the 10-year trajectories for the controls saw increases of 1-3 prescriptions versus 1-7 prescriptions for cases.

Conclusions: The HCU trajectories of people with MS who enter a NH may be different from those who do not enter a NH. In the next phase of the study, potential moderators and mediators of these trajectories will be evaluated.

P009

Multiple sclerosis relapses: economic impact of oral high-dosecorticosteroids

D Veillard[1], C Beauchamp[1], E Le Page[2], G Edan[2]
[1]Rennes University Hospital, Epidemiology and Public Health, Rennes, France, [2]Rennes University Hospital, Neurology, Rennes, France

Background: Introducing oral treatment for multiple sclerosis (MS) relapses should improve its accessibility, patients quality of life and consistently minimize the therapy-related costs. We conducted a prospective study (COPOUSEP Trial - ClinicalTrials.gov Identifier: NCT00984984) evaluating simultaneously the clinical effectiveness and the treatment strategy-related costs of per os (PO) versus intravenous (IV) corticosteroids.

Objectives: To analyse cost-effectiveness (COA) of PO versus IV high-dose corticosteroids in MS relapses treatment during the 3 months after treatment start and to estimate the economic impact of oral treatment at home.

Methods:

- Patients inclusion and exclusion : cf COPOUSEP trial
- Points of view : societal and health insurance perspectives
- Primary endpoint : Incremental Cost-Effectiveness Ratio (ICER): cost for one more patient improved by the treatment
- Time horizon: 28 days after the beginning of treatment for the main analysis and 90 days for the second analysis
- Acquisition of data : Direct costs (medical, non-medical) and indirect costs are collected by loading patients' data from the French national health insurance database linked to the national hospital discharge database[1]
- Costs valuation : Medical costs are recovered from the rate of reimbursement for health insurance and patient financial contribution for medical costs. Indirect costs are valued by the method of human capital (productivity loss) from daily allowance reimbursed by health insurance. Non-medical costs are valued at average cost of an equivalent resource on the market (replacement cost) taking into account frequency and duration.
1 http://www.ameli.fr/fileadmin/user_upload/documents/SNIIRAM_database_at_a_glance.pdf

Results: : 178 patients were included for medico-economic study (89 in the IV group and 89 in the PO group). Their characteristics are similar in both group (age: 35.36 years for the IV group vs 35.20 for the PO group, sex : 25.8 % men in each arm, at least one concomitant treatment beginning the day of inclusion or later: 91.8 % in each arm).

Clinical trial results are now available (cf Dr E Le Page abstract). Economic analysis is being process. Following results, will be available in June: total costs, part of each item of expenditure, average cost per patient in each treatment group, and globally ICER (cost per patient improved).

Conclusions: We will show an improved cost-related and quality of life benefit from introducing oral high-dose MP in the treatment of MS relapses.

P010

Treatment patterns and budget impact of dalfampridine in multiple sclerosis: a retrospective claims database analysis

S Palli[1], M Sidovar[2], M Grabner[1], A Guo[2]
[1]HealthCore, Inc., Wilmington, DE, United States, [2]Acorda Therapeutics, Inc., Ardsley, NY, United States

Background: There are limited real-world data on treatment patterns associated with dalfampridine extended release tablets (D-ER; fampridine outside the US), 10 mg twice daily, for improvement in walking in patients with multiple sclerosis (MS).

Objectives: To describe patient characteristics and to evaluate treatment patterns and budget impact of D-ER initiators in a large commercially-insured US population.

Methods: This retrospective observational study used the HealthCore Integrated Research Database[SM] consisting of administrative claims data from a geographically diverse US population. Inclusion criteria were: patients with ≥1 D-ER claim from 1/1/2010-2/29/2012, but no prior D-ER claims (index date = earliest fill date); age ≥18 years; ≥2 distinct pre-index MS-related medical or pharmacy claims; ≥12 months continuous pre-index (baseline period) and ≥12 months continuous post-index enrollment; and no prior claims for stroke, Parkinson's disease, brain neoplasm/abscess, tendonitis, or cerebral palsy. Demographics and comorbidities were assessed at baseline. Patients were followed for 1 year to evaluate adherence (medication possession ratio, MPR) and persistence (days between index date and either discontinuation or last fill date). Budget impact was calculated as cost per member per month (PMPM) over available follow-up of D-ER patients within the database of 20.3 million members.

Results: A total of 938 patients were identified with a mean age 51.5 years, with 69.6% female, 65.8% treated by neurologists, and 65.5% with Preferred Provider Organization coverage. Quan-Charlson Comorbidity Index score was 0.6 (±1.1). Gait abnormality was the most frequent disorder (30.1%) followed by abnormal involuntary movements (8.9%) and lack of coordination (8.1%). The most prevalent disease-modifying therapies included interferon-beta-1a (28.8%) and glatiramer acetate (24.2%). In this cohort of D-ER initiators, 78.3% had ≥2 fills and 82.6% of the patients were adherent to D-ER with MPR ≥80%. Mean persistence was 181.1±137.4 days. Preliminary budget impact of D-ER was estimated at $0.013-0.026 PMPM.

Conclusions: This analysis is the first of its kind to evaluate treatment patterns and budget impact of D-ER in a real-world patient population with MS. In this cohort of first time D-ER users, the majority were adherent to therapy and the budget impact is likely to be small.

P011

Greater cost savings associated with disability improvement in patients treated with alemtuzumab versus interferon beta-1a

L Steinman[1], V Herrera[2], M Selzer[3], Q Zhang[4], DH Margolin[3], on behalf of the CARE MS II Investigators
[1]Stanford University School of Medicine, Stanford, CA, United States, [2]Express Scripts, Waldwick, NJ, United States, [3]Genzyme, a Sanofi Company, Cambridge, MA, United States, [4]Sanofi R & D, Bridgewater, NJ, United States

Background: Alemtuzumab is approved in over 30 countries for the treatment of relapsing-remitting multiple sclerosis (RRMS). In the phase 3 CARE-MS II study, alemtuzumab demonstrated superior efficacy vs subcutaneous interferon beta-1a (SC IFNB-1a) with a reduction in the risk for relapse and rate of sustained accumulation of disability in RRMS patients who relapsed on a prior therapy. Disability is an important factor contributing to the cost burden of MS.

Objectives: To compare costs associated with disability improvement or worsening with alemtuzumab vs SC IFNB-1a in the CARE-MS II trial.

Methods: CARE-MS II (NCT00548405) was a 2-year trial in which patients with active RRMS who relapsed on prior therapy were randomized to receive 2 annual courses of alemtuzumab 12 mg (n=426) or SC IFNB-1a 44 μg 3 times weekly (n=202). The Expanded Disability Status Scale (EDSS) was used to assess an improvement or worsening in disability, defined as a ≥0.5-point decrease or increase, respectively, from baseline EDSS score. Costs associated with disability change over 2 years were assessed by:

1) disability costs associated with EDSS score distribution at the study end, and
2) net change in disability costs from baseline weighted by probability of EDSS improvement or worsening from baseline EDSS score.

Yearly disability costs adjusted for inflation were estimated and the United Kingdom (UK) disability cost estimates were applied as a sensitivity analysis.

Results: Mean age was 35 years, with 67% female and baseline mean EDSS score of 2.7. Alemtuzumab-treated patients had significantly improved EDSS scores vs those on IFNB-1A (45.5% vs 29.7%, respectively, p< 0.001). Proportion of patients with no change in EDSS score was similar between both treatment groups (30%). Yearly disability costs per patient associated with EDSS status at study end were lower for alemtuzumab ($9,828) relative to IFNB-1a ($10,359). After accounting for baseline EDSS scores, the net change in disability costs per patient associated with EDSS improvement or worsening for alemtuzumab was -$1,117 vs +$3,216 for IFNB-1a. Findings were cross-verified and consistent with disability costs estimated using the UK data.

Conclusions: Lower disability costs per patient and reduced net disability costs in alemtuzumab- vs IFNB-1a-treated patients suggest that patients with RRMS may incur lower healthcare costs associated with improvements in EDSS and reduced clinical relapses with alemtuzumab therapy relative to IFNB-1a.

P012

Economic burden of multiple sclerosis: a systematic review of the literature

AO Ashaye[1], S Cadarette[1], ET Kinter[2]
[1]Evidera, Lexington, MA, United States, [2]Biogen Idec Inc., Cambridge, MA, United States

Background: Multiple Sclerosis (MS) is a debilitating disease associated with significant neurological disability and increased use of healthcare services, medications, and informal care. Additional burdens on society, the healthcare system, caregivers, and patients can cause productivity losses due to short- and long-term absences from work, time lost from work and leisure, and early retirement.

Objectives: To summarize evidence relating to the economic burden in relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and other forms of progressive MS and to evaluate costs associated with levels of disability in MS as measured by the Expanded Disability Status Scale (EDSS).

Methods: Comprehensive systematic searches were conducted in MEDLINE, Embase, and the National Health Service Economic Evaluation Database (NHS EED) for relevant articles published between January 2003 and November 2013 using pre-defined Medical Subject Heading and free-text terms. Proceedings of relevant scientific meetings were also hand-searched. Articles underwent two rounds of screening by independent researchers. Data were extracted by one investigator and validated by a second, independent investigator.

Results: Fifty-six studies reporting direct (medical and non-medical), indirect, or intangible costs conducted in Europe (41), North America (5), South America (6), Australia (1), and Asia (3) were included. The majority of studies estimated cost from a societal perspective. Direct costs were mainly driven by medication costs, followed by cost of procedures and visits to healthcare providers. Indirect costs consisted mainly of productivity losses due to short- and long-term absences from work, and early retirement due to MS. Similarly, total costs were driven by medication costs and disease severity. Relapses were also associated with increased total cost. Direct, indirect, and total costs increased with higher levels of disability as measured by EDSS score. All cost components varied by country, reflecting variations in practice patterns, and also by MS type; costs were much higher for SPMS than for primary progressive MS or RRMS.

Conclusions: MS is associated with significant economic burden. Total, direct, and indirect costs increase with increasing disease severity and during relapses. MS costs vary by geographical location. Treatments which reduce relapses and delay disability progression could reduce the overall costs of MS to patients and the healthcare system.

P013

Cost-effectiveness of alemtuzumab vs subcutaneous interferon beta-1a for treatment of active relapsing-remitting multiple sclerosis: payer perspective

C Celestin[1], GR Cutter[2], AJ Coles[3], A Reimers[4], DH Margolin[1], on behalf of the CARE-MS I and II Investigators
[1]Genzyme, a Sanofi Company, Cambridge, MA, United States, [2]University of Alabama at Birmingham, Department of Biostatistics, Birmingham, AL, United States, [3]University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom, [4]Genzyme, a Sanofi Company, Stockholm, Sweden

Background: Alemtuzumab is approved in over 30 countries for treatment of relapsing-remitting multiple sclerosis (RRMS). Alemtuzumab demonstrated superior efficacy over subcutaneous interferon beta-1a (SC IFNB-1a) and manageable safety in RRMS patients (treatment-naive or who relapsed on a prior therapy). Given increasing constraints on health care resources, there is a need to evaluate the relative value of alemtuzumab compared with a commonly accepted therapy for treatment of RRMS.

Objectives: To compare the cost-effectiveness of alemtuzumab vs SC IFNB-1a in active RRMS patients in Sweden.

Methods: In the Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis (CARE-MS) studies, RRMS patients (treatment-naive [CARE-MS I (NCT00530348)] or who relapsed on prior therapy [CARE-MS II (NCT00548405)]) were randomized to alemtuzumab 12 mg/day intravenously on 5 consecutive days at baseline and on 3 consecutive days 12 months later, or SC IFNB-1a (44 μg 3 times weekly). A cohort-based Markov model based on School of Health and Related Research model was used to estimate incremental costs and benefits. The model tracks patients as they progress through a series of disability states, using a 1-year cycle length. Costs and quality-adjusted life-years (QALYs) per patient were calculated based on time in each Expanded Disability Status Scale state, relapse incidence, adverse events, and treatment duration. The outcomes reported include incremental costs in Swedish krona (SEK) per QALY gained, incremental costs per life-year (LY) gained, and incremental costs per relapse avoided. A societal perspective was taken with a lifetime time horizon using data from CARE-MS I and II trials.

Results: Alemtuzumab is more effective and less costly than SC IFNB-1a across all outcomes in RRMS patient populations, which is important to payers. Alemtuzumab was associated with a total cost saving of SEK 291,634 and additional QALY gain of 0.46 and 0.09 LY gain in treatment-naive patients. In patients who relapsed on prior therapy, alemtuzumab was associated with a total cost saving of SEK 834,561 and additional QALY gain of 1.14 and 0.17 LY gain. In RRMS patients, alemtuzumab treatment was associated with a total cost saving of SEK 735,544 and additional QALY gain of 1.01 and 0.16 LY gain.

Conclusions: Alemtuzumab is projected to be both cost-saving and more effective when compared with high-dose, high-frequency interferon in active RRMS patients in Sweden from a payer perspective.

P014

Sources of income for individuals with multiple sclerosis: a nationwide population-based study in Sweden

M Wiberg[1], E Friberg[1], K Alexanderson[1], M Stenbeck[1], A Norlund[1], J Hillert[1], P Tinghög[1]
[1]Karolinska Institutet, Stockholm, Sweden

Background: Multiple sclerosis (MS) is associated with labour market marginalization, but there is limited knowledge about MS-patients' sources of income.

Objectives: Gain knowledge on MS patients' earnings and social benefits compared to others.

Methods: From all residents in Sweden aged 21-64 years in 2010 (n=5,318,764), those with a MS-diagnosis (n=13,935) were compared to a matched reference group (n=69,825) using nationwide registers. Income from Earnings, Disability pension (DP), Sickness absence (SA), Disability allowance, Unemployment benefits, and Social welfare were analysed for all as well as stratified by socio-demographics and year since MS diagnosis. A two-part regression model was used to estimate the percentage difference in the grouped incomes between the MS-patients and the matched reference group.

Results: For both MS patients and the matched reference group, the largest proportion of their income was obtained from earnings followed by DP and SA benefits. MS patients and the matched reference population had equivalent amounts of incomes from social welfare, but the MS patients had lower earnings and unemployment benefits and higher income from disability allowance, DP and SA. The MS patients diagnosed in 2010 had 16% lower earnings than the matched reference group, while MS patients diagnosed before 2005 had 39% lower earnings. Corresponding figures regarding benefits were 30% and 132% higher for MS patients. Further, the matched reference group's earnings peaked in ages 45-54 whereas the MS patients income peaked in ages 35-44. On average, the total income (all types of incomes aggregated) was 15% lower among MS patients compared with the matched reference group.

Conclusions: The results indicate that MS patients are overrepresented, in relative and absolute terms, with regard to health-related benefits and have lower levels of earnings. The redistribution welfare systems appear to financially compensate the MS patients considerably; in line with the intent of the Swedish social redistribution systems.

P015

Prevalence of complications in hospitalized multiple sclerosis patients among different age groups: national perspective

AA Patel[1], M Dave[2], S Lahewala[3], S Arora[4], S Mehta[5], A Badheka[6], V Jani[7]

[1]*Icahn School of Medicine at Mount Sinai, New York, NY, United States,* [2]*Houston Methodist Hospital, Houston, TX, United States,* [3]*Mount Sinai Hospital, New York, NY, United States,* [4]*Mount Sinai St. Luke's, New York, NY, United States,* [5]*Saint Louis University, Saint Louis, MO, United States,* [6]*Detroit Medical Center, Detroit, MI, United States,* [7]*Michigan State University, East Lansing, MI, United States*

Background: Multiple Sclerosis (MS) is a neurological disorder without any clinical findings that are unique to MS. But MS is associated with episodes of transient loss of varied CNS functions, long term complications and comorbid conditions.

Objectives: This study is aimed to examine the prevalence of various complications according to different age groups in hospitalized MS patient during 2001 -2011.

Methods: We queried the Healthcare Cost and Utilization Project's NIS for 2001-2011 using ICD-9-CM diagnosis code, 340 (primary or secondary diagnosis) for MS. Data for complication was extracted using ICD-9-CM diagnosis codes (377.30, 311, 599.0, 596.54, 401.9, 507, 345, 038) for both primary and secondary outcomes. We used Cochran-Armitage trend test to compare age groups. The NIS is the largest all payer dataset which represents 20% of all the hospitals and all analyses were performed using the designated weighting to minimize bias.

Results: 283,213 patients were hospitalized with MS as primary or secondary diagnosis during 2001-2011, which is national representative of 1,393,298 (weighted) patients. Overall prevalence of optic neuritis (1.6%), urinary tract infection (UTI)(25.2%), unspecified hypertension (HTN)(30.2%), aspiration pneumonia(3.6%), depressive disorder (14.1%), neurogenic bladder (10.6%), septicemia(10.1%), epilepsy(3.6%). After age groups stratification prevalence of optic neuritis was highest (11.5%) in 0-18 age group and was declining with increasing age (p< 0.001). Prevalence of UTI, HTN and aspiration pneumonia were increasing with age being highest (35.2%, 43.3% and 6.0% respectively) in age group of >70 (p< 0.001), while prevalence of depressive disorder was increasing with age being highest (16.1%) in age group 50-59 and then declining with age (p< 0.001). Prevalence of neurogenic bladder and septicemia were increasing with age being highest (13.4% and 10.5% respectively) in age group 60-69 and then decreased in age group >70 (p< 0.001). Prevalence of epilepsy was also increasing with age being highest (4.1%) in age group 40-49 and then decreasing with age (p< 0.001).

Conclusions: Our analysis concludes that prevalence of complications in MS hospitalized patients is highly variable in different age groups. Prevalence of optic neuritis and epilepsy were more in younger patients of MS while other complications like neurogenic bladder, UTIs, aspiration pneumonia, septicemia and depressive disorder were higher in old age patients.

P016

Brain MRI lesions and atrophy are associated with employment status in patients with multiple sclerosis

S Tauhid[1], R Chu[1], R Sasane[2], BI Glanz[1], M Neema[1], JR Miller[1], G Kim[1], JE Sigornivich[3], BC Healy[1], T Chitnis[1], HL Weiner[1], R Bakshi[1]

[1]*Harvard/BWH, Boston, MA, United States,* [2]*Novartis Pharmaceuticals, East Hanover, NJ, United States,* [3]*Analysis Group, Boston, MA, United States*

Background: The compromised ability to perform occupational functions is a common difficulty for multiple sclerosis (MS) patients. This impaired level of performance can frequently lead to unemployment.

Objectives: We investigated the link between brain MRI findings and employment status in MS.

Methods: 100 CLIMB study MS patients completed a Work Productivity and Activity Impairment (WPAI) questionnaire (general health version) and brain MRI using the same protocol at 1.5T. The WPAI survey measured employment status, absenteeism, presenteeism (impairment during work), overall work impairment, and daily activity impairment. Patients who reported "working for pay" were classified as employed while those "temporarily not working but looking for work", "not working or looking for work due to age", and "not working or looking for work due to disability" were considered not employed. The patients also underwent an examination to assess Expanded Disability Status Scale (EDSS). Brain T1 hypointense lesion volume (T1LV) and T2 hyperintense LV (T2LV) were expert-quantified using an edge-finding tool. To assess a lesional destructive capability, we

calcualted the ratio of T1LV to T2LV (T1/T2) for each subject. To assess whole brain atrophy, we measured normalized brain parenchymal volume (BPV) from 3D T1-weighted images using SIENAX.

Results: The mean (SD) age was 45.5 (9.7) years and disease duration was 12.1 (8.1) years; 75% were women, 76% had relapsing-remitting MS, and 76% were working for pay. T1LV, T1/T2, and EDSS score were higher and BPV was lower in the not employed group vs. the employed group (Wilcoxon rank-sum tests, p< 0.05). Age, disease duration, and T2LV did not differ between groups (p>0.05). In a multivariable logistic regression model adjusting for age, gender, and disease duration, higher T1LV was associated with a lower chance of working for pay (p< 0.05). Pearson correlations showed that EDSS was associated with activity impairment (p< 0.05). However, disease duration, age, and MRI variables were not correlated with activity impairment or other items of the WPAI (all p>0.05).

Conclusions: Brain MRI lesions and atrophy are associated with employment status in MS. Among lesion measures, their destructive potential as assessed by the overall T1 hypointense burden and the proportion of T2 hyperintense lesions showing T1 hypointensity is most relevant.

P017

Treatment patterns and cost in multiple sclerosis - a cross-sectional study from Slovakia

V Donath[1], M Ondrusova[2]
[1]F.D.Roosevelt Teaching Hospital, Neurology, Banska Bystrica, Slovakia, [2]Pharm-In, Bratislava, Slovakia

Background: Currently, MS treatment focuses on preventing relapses and delaying disability progression. Therefore, comprehensive economic costs in individual EDSS states can only be assessed by evaluating MS treatment patterns in real clinical practice.

Objectives: The main objective of the cross-sectional study from MS patients 'medical records was to measure the resource utilization and the direct costs associated with health-care management of MS in Slovakia and to provide a basis for cost-effectiveness evaluations.

Methods: The cross-sectional study consisted of two steps. In the first step descriptive epidemiological indicators of 2,552 MS patients were analyzed in 27 MS-centers. In the second step all types of health-care services were analyzed in 152 patients (followed-up in 2011-2012) from 34 MS centers (geographically from whole the Slovak Republic) and the costs were assessed for the year 2013. Patients complying with inclusion criteria were included in the study randomly. Continuous variables were calculated using standard descriptive statistics methods.

Results: As EDSS increased, a growing number of patients are hospitalized and hospitalization costs increased. The highest one-year hospital costs were found at EDSS 7 (€822). 30% of patients were hospitalized due to a relapse with the average hospital stay 9.3 days (ranging between 1-20 days with the median 8 days). The cost of relapse including admission to hospital was €752.86. Medical devices cost were highest at EDSS 8 (€897). The most patients treated with DMT were found at EDSS 2 (97%). The most expensive DMT measured as cost per patient was fingolimod (€ 24,758), while the cheapest was glatiramer acetate (€ 8,659). The

highest annual costs per DMT patient were seen at EDSS 4 (€ 13,026). As the EDSS number rised, the number of MRI examinations falled. The highest MRI cost was seen at EDSS 2 (€ 548). The total annual cost per patient varied from € 963 to € 14,175, depending on EDSS. The highest cost was found at EDSS 4.

Conclusions: This cross-sectional study determined the average annual direct cost per MS patient to be € 9,199. As the EDSS number increased, DMT costs falled and the costs of medical devices rised.

P018

Multiple sclerosis and variation in health utilities: a systematic review of the literature

AO Ashaye[1], S Cadarette[1], ET Kinter[2]
[1]Evidera, Lexington, MA, United States, [2]Biogen Idec Inc., Cambridge, MA, United States

Background: Multiple sclerosis (MS) is a debilitating disease associated with significant neurological disability. Disability in MS is commonly measured by the Kurtzke Expanded Disability Status Scale (EDSS), a clinician-based neurological impairment rating scale. Scores range from 0 to 10 and higher scores indicate greater disability.

Objectives: Comprehensive systematic literature reviews were conducted to summarize the evidence relating to the health utility impact of RRMS, secondary progressive MS (SPMS), and other forms of progressive MS. Evidence on the utilities associated with different levels of disability in MS as measured by the EDSS was also evaluated.

Methods: Using pre-defined Medical Subject Heading (MeSH) and free-text terms, systematic searches were conducted in MEDLINE, Embase, and NHS EED databases for relevant articles published between January 2003 and November 2013. Proceedings of relevant scientific meetings were also hand-searched. Citations returned from the searches underwent two rounds of screening by independent researchers based on predefined inclusion/exclusion criteria. The first round was based on titles/abstracts, while the second round was based on full texts of articles meeting the inclusion criteria. Data were extracted by one investigator and validated by a second, independent investigator.

Results: Twenty-seven studies reporting health utilities associated with health states of MS met the inclusion criteria for the review. The majority of studies (26 studies) elicited preference via the European Quality of Life Five Dimensions (EQ-5D) questionnaire, a generic preference elicitation instrument; one study used the Health Utilities Index-3 (HUI-3). There was an inverse relationship between utilities and EDSS scores; no trend was noted for geographical location. Mean utility scores ranged from 0.80 to 0.88, 0.49 to 0.70, 0.38 to 0.58, and -0.03 to 0.1 for patients with EDSS scores of 0-1, 3, 6, and ≥8, respectively. Some patients valued their health states as worse than death as reflected by the negative utility scores.

Conclusions: MS negatively impacts health utilities which decrease significantly with increasing neurological disability. Relapses were also associated with decreases in utility scores. There appears to be no differential effect of MS type and geographical location on health utilities. Treatments for MS that delay disability progression may allow a patient to remain in a better health state utility longer.

P019

Cost of MS - patients´ burden in Norway

BO Svendsen[1], K-M Myhr[2], NG Torkildsen[1], T Smedal[1], L Boe[1], JH Aarseth[1]

[1]Haukeland University Hospital, Department of Neurology, Bergen, Norway, [2]University of Bergen, Department of Clinical Medicine, Bergen, Norway

Background: Multiple sclerosis (MS) often implies a high burden of the disease to the patients and reduces quality of life. The disease has major health economic impact on society, but MS also imposes costs on the patients themselves. The magnitude of these costs has not been investigated.

Objectives: The objective of this work was to estimate the annual cost (in 2013), as well as estimate the long term cost of multiple sclerosis to patients in Norway.

Methods: Information on disease related economic burden was gathered through a postal survey to all MS-patients in Hordaland County, Norway. The postal survey was sent to all persons (n=) 965, who had received a definite MS-diagnosis according to the Poser or McDonald´s criteria who were alive at the end of 2013.

Results: 27 questionnaires were returned because of unknown adressees, and 5 persons were reported recently dead. Of the remaining 933, 562 responded.

The average annual (2013) total, indirect plus direct, economic cost to patients was € 11,337. Indirect economic cost, loss of income, accounted for 63 %. Remodelling of houses, € 1,590, constituted the most important direct economic cost - patients´ payment for resources used due to the disease. Direct economic cost was close to identical for females and males. Indirect economic cost was close to 10 % higher for males, mainly due to higher salaries before diagnosis. Over a period of 30 years, the present value of the average annual total economic cost amounted to € 258,986 when a 2 % discount rate was used to adjust for differential timing of costs. In general, costs inceased with progressive disease severity, and patients with a rapid disability progression had a much higher cost than patients that progressed more slowly. For patients among the 10 % with the most rapid progression, the present value of the 30-year annual total economic costs from disease onset might easily exceed € 410,000 and be expected to come close to € 600.000 in extreme cases. For patients among the 10 % with the slowest progression expected present value ranged from € 29,000 to € 97,000.

Conclusions: The cost of MS to the patients is a significant part of the burden of the disease for all patients, especially patients with severe forms of the disease. This, patient centered, information should be important to health politicians who are to decide on allocation of resources to treatment and research on the disease, and on economic support to patients with MS.

P020

Updates from the *Sonya Slifka longitudinal multiple sclerosis study* and the *comprehensive analysis of the direct and indirect costs of MS* study

SL Minden[1]

[1]Brigham and Women's Hospital, Harvard Medical School, Psychiatry, Boston, MA, United States

Background: The National Multiple Sclerosis Society´s (NMSS) *Sonya Slifka Longitudinal Multiple Sclerosis Study (Slifka)* began in 2000 to study change in demographic and disease characteristics, quality of life, use and cost of health services, and treatment, economic, and psychosocial outcomes among a generally representative sample of almost 2,200 individuals with multiple sclerosis (MS) in the United States (US). A second cohort of nearly 2,500 patients was added in 2007.

A Comprehensive Analysis of the Direct and Indirect Costs of MS (MS Costs) was designed to produce detailed estimates of the types, amounts, and costs of health services used and health-related purchases made by individuals with MS.

Objectives: To report the most recent findings from the *Slifka* and *MS Costs* studies.

Methods: Both cohorts were randomly sampled from NMSS mailing lists with broad outreach for newly-diagnosed patients. Participants kept daily logs of health service use and spending. These data, with demographic and disease updates, were collected by computer-assisted telephone interviews every 6 months through 2010. The 2009 wave (n=2,361) provides event-based data on use and costs of services (inpatient, emergency, day hospital, physician, rehabilitation, mental health, alternative; tests, treatments, procedures; paid/unpaid home care) and types and costs of purchases (DMTs; prescription drugs; home/vehicle modifications; equipment/supplies; transportation). Our multidisciplinary team of clinicians, economists, health services and policy researchers are producing bi- and multivariate statistics for service use and purchases and estimating their cost. We mapped patient-reported procedures to standardized billing codes and assigned Medicare prices and estimated medication prices using national average Medicaid reimbursements. Unpaid home care was valued at the rates paid for equivalent services by other participants in their communities. Lost earnings from unemployment were estimated by comparing occupations and incomes to Census Bureau data.

Results: Findings produced through April 2014 will be presented at the Consortium of Multiple Sclerosis Centers meeting in Dallas. Additional and new findings produced through August will be presented In Boston.

Conclusions: The cross-sectional and longitudinal data from these studies will advance understanding of demographic, disease, and care characteristics, health service use, unmet needs, and the financial burden of MS in the US.

P021

Improving clinical outcomes and healthcare resources utilization in multiple sclerosis: a Portuguese hospital perspective

D Viriato[1], J Carrasco[1], J Fonseca[1], R Pacheco[1]

[1]Novartis Farma - Produtos Farmacêuticos S.A., Porto Salvo, Portugal

Background: Treatment of Multiple Sclerosis (MS) is associated with significant clinical and economic burden. In Portugal there are about 2,694 patients treated with interferon beta (IFNB) and it is estimated that 30.4% are poor responders (disability progression of ≥1 point in EDSS scale) and can benefit from second-line treatment. Fingolimod treatment costs are an obstacle to treatment escalation, despite the fact that early initiation of fingolimod may impact favorably on long-term clinical outcomes.

Objectives: This analysis aimed to assess if the early switch from IFNB to fingolimod impacts MS clinical outcomes and promotes better resource utilization in a Portuguese hospital perspective.

Methods: TThis analysis was based on the annualized relapse rate of TRANSFORMS phase III trial extension. A cost-effectiveness model was developed to calculate the cost per relapse avoided with 4.5 years of continuous treatment with fingolimod (early treatment) versus 1 year of treatment with IFNB followed by a 3.5 years of treatment with fingolimod (delayed treatment). A Portuguese hospital perspective was adopted addressing only direct costs: drug, monitoring and relapses' treatment. Drug costs were based on Portuguese list prices, while the unit cost of each complication was obtained from the Diagnosis Related Groups tariff. The costs of relapses were derived from the Portuguese literature.

Results: Assuming there are 819 patients treated with IFNB that are poor responders, the early treatment with fingolimod resulted in more relapses avoided when compared with delayed treatment with fingolimod (2,211 versus 1,843) - an additional 369 relapses avoided. The early treatment with fingolimod led to an increase of drug acquisition costs, but reduced cost associated to monitoring and relapses' treatment. The total costs were 86,380,820€ for early treatment versus 79,257,091€ for delayed treatment. This represents an average incremental investment of 1,933€ per patient per year. The early strategy resulted an incremental cost effectiveness ratio of 19,358€ per relapse avoided when compared with the delayed strategy.

Conclusions: Under the Portuguese hospital perspective, early treatment with fingolimod is expected to result in better clinical outcomes associated with a more efficient healthcare resources allocation.

P022

The economic cost of a multiple sclerosis relapse

K O'Connell[1], SB Kelly[1], E Fogarty[2], M Duggan[1], L Buckley[1], M Hutchinson[1], C McGuigan[1], N Tubridy[1]
[1]St Vincents University Hospital, Dublin, Ireland, [2]National Centre for Pharmacoeconomics, St James' Hospital, Dublin, Ireland

Background: Multiple sclerosis (MS) commonly affects young adults and can be associated with significant disability resulting in considerable socioeconomic burden for both patient and society.

Objectives: The aim was to determine the direct and indirect cost of an MS relapse.

Methods: This was an prospective audit composed of medical chart review and patient questionnaire. Relapses were stratified into 3 groups: low, moderate and high intensity. Age, gender, MS subtype, disease duration, expanded disability status scale (EDSS), disease modifying therapy (DMT) use and employment status were recorded. Direct costs included GP visits, investigations, clinic visit, consultations with medical staff, medication and admission costs. Indirect costs assessed loss of earnings, partner's loss of earnings, childcare, meals and travel costs.

Results: Fifty-three patients had a clinically confirmed relapse. Thirsteen were of low intensity; 23 moderate intensity and 17 high intensity with mean costs of €503, €1395 and €8862 respectively. Those with high intensity episodes tended to be older with higher baseline EDSS ($p < 0.003$) and change in EDSS ($p < 0.002$). Direct costs were consistent in both low and moderate intensity groups

but varied with length of hospital stay in the high intensity group. Loss of earnings was the biggest contributor to indirect costs. A decision to change therapy as a result of the relapse was made in 23% of cases, further adding to annual MS related costs.

Conclusions: The cost of an MS relapse is dependent on severity of the episode but even low intensity episodes can have a significant financial impact for the patient in terms of loss of earnings and for society with higher annual MS related costs.

P023

MS disease severity does not affect patient or clinician satisfaction with clinic visits when using the FILMS quality of life assessment

S Koster[1], M Wesson[2], M Kirk-Junior[1], V Nolan[3], E Fox[4], L Mayer[4], E Frohman[5], G Remington[5], A Courtney[5], L Jehle[3], J Cooper[3]
[1]Jordan Research & Education Institute, Berkeley, CA, United States, [2]Kaiser Permanente, Oakland, CA, United States, [3]Alta Bates Summit Medical Center, Berkeley, CA, United States, [4]Central Texas Neurology Consultants, Round Rock, TX, United States, [5]UT Southwestern Medical Center at Dallas, Dallas, TX, United States

Background: The Functional Index for Living with Multiple Sclerosis (FILMS) was developed to facilitate collection of Quality of Life (QoL) information from Multiple Sclerosis (MS) patients.[1] [2]The FILMS Instrument has proven to be easy to administer and interpret in clinic setting. [3]

Objectives: To determine whether patient's clinician rated disease severity influenced the patients' or clinicians' overall satisfaction with clinic visits when the FILMS Quality of Life questionnaire was used.

Methods: Patients (n=93) and clinicians (n=4) at 3 MS practices completed two clinic visits 3-6 months apart. Visit 1 was conducted per clinic routine. Visit 2 included the FILMS instrument. Patient and clinician perception of visit quality was assessed at the end of each of the visits using a 1-5 Likert scale. Clinicians rated patient disease severity using a 1-5 Likert scale at visit 1. For the purpose of this analysis disease severity was classified as mild-moderate (1-3) and severe (4,5). Odds Ratios (OR) and McNemar's test for correlated populations was done comparing correlation between clinician rated disease severity and patient and clinician perception of visit quality with the two visits.

Results:

Patient perception: Overall patient satisfaction for the visits was not correlated with clinician rated disease severity. All 9 patients with severe disease responded that they were satisfied with both visits 1 and 2. 76 patients with mild disease had greater odds of being satisfied with visit 2 (FILMS) and not satisfied with visit 1 (no FILMS) however this correlation did not prove to be statistically significant (p=0.69)

Clinician Perception: Clinicians' satisfaction with visits when FILMS was not used and when FILMS was used was not correlated with patient disease severity. Clinicians were more likely to be satisfied with the visit when FILMS was used whether the patient's disease severity was rated mild (p=0.0002) or severe (p=0.01).

Conclusions: We submit that using an easy to administer and easy to interpret QOL instrument such as FILMS during routine clinic practice increases patient and clinician satisfaction and helps to

better address QoL concerns of MS patients regardless of disease severity.

P024

People with multiple sclerosis unmet perceived needs point toward a personalised intervention

M Ponzio[1], P Zaratin[1], C Vaccaro[2], MA Battaglia[3]
[1]Italian Foundation of Multiple Sclerosis, Scientific Reseach Area, Genoa, Italy, [2]Fondazione CENSIS, Rome, Italy, [3]University of Siena, Department of Physiopathology, Experimental Medicine and Public Health, Siena, Italy

Background: The effects of multiple sclerosis (MS) are wideranging, having an impact on physical, psychological, and social well-being. It is a complex condition which requires a careful management of treatment and has profound influences on people life who are affected. Community-based studies are required to accurately describe the supportive services needed by people with MS (PwMS).

Objectives: Within this strategy the Italian MS Society promoted this study to evaluate the present needs and future expectations to enhance the management of PwMS.

Methods: A total of 1,235 PwMS, attending neurology outpatient clinics, rehabilitation units, MS Society local branches, participated in a cross-sectional study. The questionnaire used was specifically developed by a multi-disciplinary team. Subgroups of the subjects as the sickest patients (EDSS≥7) and newly diagnosed were built with the aim to better specify the results.

Results: The 'Psychological difficulties of accepting and living with MS' was the most frequent problem declared (62.9%), higher for newly diagnosed subjects (70.6%). Following the 'Practical difficulties to integrate and live in a society with many barriers' (22.9%) and 'To keep alive social relations and friendships' (23.0%) were both more relevant for subjects with higher disability levels. Similarly, we observed distinct, unmet needs reported by the subjects with different characteristics as well as financial and psychological support were reported primarily by newly diagnosed subjects, while the architectural barriers in public places, personal assistance, and transportation were reported by the sickest patients. Finally, among the services to be enhanced and improved, the rehabilitation, transportation, and homecare service were more frequent in the sickest patients while the MS clinical centres, financial and psychological support in newly diagnosed subjects.

Conclusions: The MS population is a heterogeneous population as a result of different difficulties and needs perceived according to the clinical stage and disability degree. Focusing on individual patient needs is a prerequisite for a patient-centred approach, which also means engaging patients in healthcare decision making as much as possible. These findings suggest that personalised treatments could provide the basis for improving and changing the access and coordination of community services and to drive policymakers towards the development of an MS-specific and personalised taking charge.

P025

A health resource utilization in Thai patients with idiopathic inflammatory demyelinating central nervous system disorders

C Chanatittarat[1], S Siritho[2,3], N Prayoonwiwat[2], U Chaikledkaew[1], P Pasogpakdee[4]

[1]Social and Administrative Pharmacy Excellence Research (SAPER) Unit, Pharmacy, Mahidol University, Bangkok, Thailand, [2]Division of Neurology,Siriraj Hospital, Bangkok, Thailand, [3]Bumrungrad International Hospital, Neurology Dept., Bangkok, Thailand, [4]Sriphat Medical Center, Chiang Mai University, Chiang Mai, Thailand

Background: Increasing awareness of Thai patients with Idiopathic Inflammatory Demyelinating Central Nervous System Disorders (IIDCDs) such as neuromyelitis optica (NMO) and multiple sclerosis (MS) causes higher prevalence of the diseases over the past decade. However its impact on patients including financial status, debilitating condition and care-giver burden has never been systematically explored.

Objectives: To measure economic burden and health care utilization of IIDCDs categorized in each disease and at its level of disability.

Methods: A cross sectional study of 275 patients with IIDCDs who attended at the two MS clinic during September 2011 to March 2014 were interviewed for direct non-medical (DNM) in patients or their caregivers related to hospitalization (HP) (e.g., food, traveling, facility modification (FM), informal care cost (IF) and other alternative treatment) and indirect cost (IC). Then direct medical cost (DMC) of 169 patients besides demographic data and 5 year disease burden alongside the study was retrospectively reviewed in one center. All expenses were adjusted to 2014 years using consumer price index and US exchange rate of 32.58 Baht. Descriptive analysis was undertaken.

Results: The mean age at time of diagnosis, disease duration and EDSS in MS (n=99) and NMO (n=151) was 38 and 41 years, 7.4 and 5.2 years, 3.8 and 3.8, respectively. An average number of outpatient visits was 3.4 times a year. Patients spent 12 hours and accompanied by one family member per visit. Annually expenses per patient based on DNM cost, IF cost, FM was \$US2,224 (95% CI: 1,826-2,621), \$US1,165 (95% CI: 884-1,147), \$US283 (95% CI: 133-434), respectively. HP was \$US618 (95% CI: 522-713), while annual total IC was \$US31,628 (95% CI: 26,028-37,228). The annual DMC for outpatient visit (n=169) was \$US1,766 (95% CI: 1,432-2,100) and DMC for inpatient was \$US3,824 (95% CI: 3,215-4,537).There was no significant difference between MS and NMO in DMC regardless of EDSS. However, each disease demonstrated more utilization in patients who had less EDSS than those with higher EDSS (p<0.001). Interestingly, DNM in patients with either MS or NMO contributed to be 41% of the Gross National Income which emphasized that it was an important explicit burden.

Conclusions: Economic burden of Thai IIDCDs both in MS and NMO demonstrated high resources utilization and cost. Further economic evaluation is warrant to guide decision maker how to best deal this disease for patients.

P026

The impact of persistence with therapy on hospitalization and emergency room visits in the US among patients with multiple sclerosis

A Farr[1], S Curkendall[2], E Yu[3], N Thomas[3]
[1]Truven Health Analytics, Life Sciences, Cambridge, MA, United States, [2]Independent Consultant, Bend, OR, United States, [3]Genentech, San Francisco, CA, United States

Background: Among patients with multiple sclerosis (MS), few studies have examined the association between persistence with disease modifying therapies (DMT) and healthcare utilization.

Objectives: Compare the likelihood of hospitalization and emergency room (ER) visits in the USA between patients with MS who were persistent vs. non-persistent with DMT.

Methods: This retrospective analysis was conducted with Truven Health Marketscan® Commercial and Medicare Supplemental Databases, containing de-identified administrative claims for inpatient and outpatient medical and outpatient pharmacy services. Patients with ≥1 claim with a diagnosis of MS (*International Classification of Diseases,* Ninth Edition 340) and ≥2 claims for a single DMT (natalizumab, intramuscular interferon beta-1a, subcutaneous interferon beta-1a, interferon beta-1b, glatiramer, fingolimod) between 1/1/2009 and 12/31/2011 were included in the study sample. The date of the first DMT claim was defined as the index date and the type of DMT was defined as the index drug. Patients were required to be ≥18 years old and to be continuously enrolled for ≥6 months prior to index date with no claims for index drug and for ≥12 months following the index date. Non-persistence measured during the 12 months following index date was defined as a gap of >60 days without index drug "on hand." The presence of a hospitalization or an ER visit during the 12-month follow-up was captured. Odds ratios for hospitalization and ER visit comparing persistent and non-persistent patients were estimated using logistic regression and controlling for demographic and clinical characteristics.

Results: The study sample comprised 16,218 patients with MS. The average age of the sample was 44.5 years (SD 10.8) and 77.1% were female. The majority of the sample (79.9%) had no claim for another type of DMT during the 6 months prior to the index date. During the 12-month follow-up period, 35.3% of patients were non-persistent with their index drug, 10.0% had a hospitalization, and 24.9% had an ER visit. Persistent patients had significantly decreased likelihood of hospitalization (adjusted odds ratio [AOR]=0.50, 95% confidence interval [CI] 0.45-0.56) and of an ER visit (AOR=0.65, 95% CI 0.60-0.69).

Conclusions: Patients with MS in the USA who were persistent with DMT therapy during the year following initiation had decreased likelihood of hospitalization and ER visits.

P027

National estimates on the prevalence and characteristics of medicare patients using treatments for multiple sclerosis and related symptoms in the USA

S Chahin[1], X Yu[2], AL Pengxiang[2], N Dahodwala[1], J Doshi[2]
[1]University of Pennsylvania, Department of Neurology, Philadelphia, PA, United States, [2]University of Pennsylvania, Department of Medicine, Philadelphia, PA, United States

Background: Treatment for Multiple Sclerosis (MS) and related symptoms has become increasingly complex. Little is known about the use of disease modifying therapy (DMT) and the impact of symptomatic treatment nationally in the United States (US).

Objectives: To estimate the prevalence of DMT and symptomatic treatment use among US Medicare beneficiaries (government-based insurance plan for all individuals over the age of 65 or severely disabled) with MS, and identify factors associated with DMT use.

Methods: We used 5% Medicare claims of 2010 to identify MS cases. Cases were defined as having at least one inpatient or outpatient claim for MS (ICD-9 340).

We linked individuals with their prescription drug claims through Medicare Parts B & D. Logistic regressions were used to identify factors associated with DMT use.

Results: Out of 4711 cases with MS, 1567 (33%) were on a DMT. The majority of cases were treated with Glatiramer Acetate (43%), followed by Interferon beta-1a (36%), Interferon beta-1b (13%), and then Natalizumab (12%).

Cases most commonly received symptomatic treatment for pain (80%), followed by spasticity (57%), seizures (42%), tremor (27%), incontinence (25%), fatigue (14%), cognitive dysfunction (8%) and gait dysfunction (4%).

After adjustment for potential confounders including age and socioeconomic status, individuals≤ 65 years old were more likely to be treated (Odds Ratio (OR) 2.77 p< 0.001) compared to individuals 65-69 years-old. Individuals receiving treatment for gait dysfunction, fatigue or urinary incontinence were more likely to be on DMT (OR 3.06, 2.07, and 1.52, respectively; p< 0.001).

Within the treated subgroup, younger age and fatigue treatment were associated with use of Interferon beta-1a, Glatiramer acetate and Natalizumab (OR 1.9-3.66, p< 0.001 and OR 1.37 - 1.7, p≤0.01, respectively). Treatment for incontinence was associated with Interferon beta-1b and Natalizumab use (OR 1.41 -1.85, p≤0.03). Treatment for gait dysfunction was associated with Glatiramer acetate and Natalizumab use (OR 2.46 - 3.35, p< 0.001).

Conclusions: Among a national sample of Medicare beneficiaries with MS, the majority of patients were not on DMTs. Younger individuals were more likely to be treated. Treatment of concurrent fatigue, incontinence and gait dysfunction could reflect a more active disease as evidenced by increased DMT use, notably natalizumab, among these cases.

P028

MS with versus without relapse - the economic perspective in the PEARL study

SV Vormfelde[1], S Seibert[1], T van Lokven[1], S Ortler[1], S Moser[1], A Fuchs[1], T Ziemssen[2]
[1]Novartis Pharma GmbH, Nuremberg, Germany,
[2]Universitätsklinikum Karl Gustav Carus, Dresden, Germany

Background: The PEARL study (**P**rosp**E**ctive ph**A**rmacoeconomic coho**R**t eva**L**uation) focusses on real world aspects of providing health care for MS patients in Germany.

Objectives: Here we focus on employment, hospitalization and rehabilitation. We compare patients with a relapse in the first study year (ACTIVE group) to patients without a relapse in the first study year (INACTIVE group).

Methods: PEARL is a non-interventional study in 1705 patients with relapsing remitting multiple sclerosis (RRMS). PEARL collected pharmacoeconomic and clinical data for 24 months. Of 1705 patients, 1214 patients used injectable interferon and 491 patients injected glatiramer acetate.

In the first study year, 411 patients relapsed at least once (**ACTIVE group, "A"**); 1294 patients did not relapse (**INACTIVE group, "I"**). Mean MS-duration was 5.1 and 5.2 years in ACTIVE and INACTIVE patients, respectively. The mean annual relapse rate

was 1.4 and 0.1 relapses/year over the two year period, respectively. ACTIVE patients switched drug and discontinued therapy more frequently (A: 30% and 35%, I: 12% and 18%).

Results: Employment declined only in the ACTIVE group during the two year period (A: 58%→53%, I: 61%→61%). ACTIVE patients permanently reduced working hours more often (A: 7%→5%, I: 6%→2%), and to a lower fraction of full employment (A: 50%→35%, I: 53%→56%). ACTIVE patients continuously felt their work productivity suppressed by MS, while INACTIVE patients recovered over time (A: 2.2→2.3, I: 2.1→1.7, 0-10 rating scale).

MS-related sick leave was more frequent among ACTIVE patients even in the quarter before the study began, throughout the two years and up to the last quarter (A: 33%→18%, I: 18%→8%, [of patients/quarter]). Sick leave duration per sick leaving patient declined over the two years comparably in both groups (A: 21→14 d, I: 22→14 d).

More ACTIVE patients were hospitalized prior to the study, throughout and up to the end of the study (A: 7.1%→3.3%, I: 4.0%→1.2%, [of patients/quarter]). Duration of hospitalization due to MS declined less in ACTIVE patients (A: 7.2→6.4, I: 9.8→4.5, [days/hospitalization]).

Rehabilitation stays were more often in ACTIVE patients declining over the two years and assimilating among groups (A: 2.7%→1.4%, I: 1.8%→1.0%, [of patients/year]). Duration of rehabilitation was comparable among groups and over time (A: 30→24, I: 25→28, [days/stay]).

Conclusions: Relapsing patients remain less productive in the year following a relapse. Strong relapse prevention may reduce such costs.

P029

Impact of improved adherence to disease-modifying therapies on healthcare resource utilization and medical costs for patients with multiple sclerosis

S Yermakov[1], M Davis[1], M Calnan[1], M Fay[2], B Buckley[2], S Sarda[3], MS Duh[1], R Iyer[3]

[1]Analysis Group Inc, Boston, MA, United States, [2]Biogen Idec Inc., Weston, MA, United States, [3]Biogen Idec Inc., Cambridge, MA, United States

Background: Adherence to disease modifying therapy (DMT) is suboptimal in many patients with multiple sclerosis (MS). Prior studies have shown MS patients with high DMT adherence have better health outcomes and lower costs than non-compliant patients. However, no study has examined the effects of improving DMT adherence on medical cost offset.

Objectives: This study estimated the effect of DMT adherence on healthcare resource use and cost outcomes for patients with MS. The impact of improving adherence on the same outcomes was modeled overall and within patient subgroups.

Methods: A retrospective analysis was conducted using OptumHealth Reporting & Insights employer claims database on MS patients (≥2 diagnoses of ICD-9-CM 340) initiating DMT from 1/1/2002 through 3/31/2012. Direct medical costs (paid amounts to providers for services or drugs, excluding payments for DMTs), indirect costs (disability payments to employees and workloss costs to employers), and resource use were analyzed in the 6 months prior to initiation of any DMT (baseline period) and

up to 3 years after initiation (follow-up period). Adherence to any DMT was measured by proportion of days covered (PDC). Multivariate regression analyses were used to estimate the effect of PDC on follow-up period outcomes, controlling for baseline characteristics. The estimated model was used to predict the change in utilization and costs associated with a 10 percentage point improvement in PDC.

Results: 1,538 patients met the selection criteria (baseline age 43.6 years, 63% female). PDC had a statistically significant effect on direct medical and indirect work productivity costs, workloss days, and likelihood of an inpatient stay or emergency visit at 1, 2, and 3 year follow-up periods (all p< 0.01). A 10 percentage point improvement in PDC was estimated to reduce direct costs by 4%, indirect costs by 3-4%, workloss days by 3-7%, likelihood of an inpatient stay by 13-19%, and likelihood of an emergency visit by 8-19%, depending on the follow-up period. The impact on the likelihood of an inpatient stay or emergency visit increased with the length of the follow-up period. In the first year, the decrease in direct costs associated with a 10% improvement in adherence was greater for patients with PDC≥0.8 (10%), men (6%), and patients not on disability in the baseline period (5%).

Conclusions: Improved adherence to DMTs is associated with lower medical and indirect costs, reduced workloss days, and decreased inpatient stays and emergency visits for MS patients.

P030

Application of the RAND/UCLA method to explore the appropriateness of current and emerging treatments for relapsing-remitting multiple sclerosis

HJ Stoevelaar[1], F Barkhof[2], T Berger[3], D Centonze[4], C Papeix[5], A Tourbah[6], T Ziemssen[7]

[1]Ismar Healthcare, Centre for Decision Analysis and Support, Lier, Belgium, [2]VU University Medical Center, Department of Radiology, Amsterdam, Netherlands, [3]Innsbruck Medical University, Clinical Department of Neurology, Innsbruck, Austria, [4]U.O.C. Neurologia, Department of Neuroscience, Rome, Italy, [5]Salpêtrière Hospital, Department of Neurology, Paris, France, [6]CHU de Reims, Department of Neurology, Reims, France, [7]University Clinic Carl Gustav Carus, Department of Neurology, Dresden, Germany

Background: The therapeutic arsenal for patients with relapsing-remitting multiple sclerosis (RRMS) is rapidly expanding. Over the last few years, several disease-modifying treatments (DMTs) have been introduced, and new medications are expected to be approved in the near future. All established and novel DMTs have specific efficacy-safety profiles, and treatment choice requires individual balancing of benefits (e.g. decreased relapse rate, delayed disability progression) versus potential safety risks.

Objectives: To develop a comprehensive model for weighing benefits and risks of DMTs in relation to specific patient characteristics.

Methods: The RAND/UCLA Appropriateness Method (RUAM) was used to systematically assess the appropriateness of available and novel DMTs for a variety of clinical scenarios. A treatment was considered appropriate when the expected benefits largely exceeded the potential risks. A panel of 12 European experts in MS individually judged the appropriateness of 10 treatment regimens (including no/deferred treatment) for hundreds of clinical

scenarios, using a 9-point scale. Scenarios were combinations of several patient characteristics such as treatment history, disease activity status (a.o. number of relapses and new T2 lesions in the last year), disability progression (EDSS increase), and presence of MS-related and unrelated co-morbidities. The panel process consisted of 2 individual ratings rounds and 3 panel meetings to prepare the scenarios and to discuss the results. Based on the median panel score and extent of agreement, for each scenario an appropriateness statement was calculated (appropriate, inappropriate, uncertain).

Results: Agreement (≥ 75% of ratings in the same section of the 9-point scale) increased from 32% to 45% in the second round. Appropriateness outcomes showed logical patterns, with DMT escalation being the underlying concept, and disease activity/ inflammation and disability progression as the most important determinants of treatment choices and switches. Results between the two rounds showed that ratings are highly sensitive for new scientific evidence and regulatory changes.

Conclusions: The RUAM proved to be a valuable approach to weigh the benefits and risks of established and novel DMTs for RRMS at the level of individual patients. Periodic review of the results in light of new scientific evidence and regulatory approval is mandatory.

P031

Presenteeism and quality of life between MS patients and healthy workers

A Ferreira[1], AM Passos[1], <u>MR Neves</u>[1], C Sousa[2], MJ Sá[2]
[1]Instituto Universitário de Lisboa (ISCTE-IUL), Business Research Unit, Lisboa, Portugal, [2]Hospital de São João, Porto, Portugal

Background: In recent years there has been a growing interest in the study of quality of life (QoL) in patients with multiple sclerosis (MS). However the study of QoL and well-being in patients with MS in the workplace is a totally unexplored area of research. Presenteeism is the behavior of being present at work with a physical or psychological state that limits the capacity to produce. The symptoms associated with health problems (e.g. depression, anxiety) are responsible for a significant and undeniable reduction of job performance.

Objectives:

(1) To compare productivity in spite of both presenteeism and QoL of individuals with and without MS
(2) To analyze the influence of psychological antecedents of depression and anxiety on productivity in spite of presenteeism and QoL of MS patients.

Methods: A total of 63 subjects with MS and 109 subjects without MS were examined with the *BDI*, the *BSI* (anxiety subscale), the Stanford Presenteeism Scale and the subscale of Fatigue of *Hamburg Quality of Life Questionnaire in Multiple Sclerosis*. The MS group had none-to-moderate levels of impairment in EDSS (0-3.5).

Results: Results showed that subjects without MS had more QoL than MS patients [$t_{(110)} = 2,03$, $p < .05$] .We found no significant differences for productivity in spite of presenteeism (SPS-6). A regression analysis was performed to analyze whether depression and anxiety symptoms predicted QoL and productivity in spite of

presenteeism in subjects with and without MS. Data showed that anxiety decreases the QoL of workers without MS ($\beta = -.412$, $p < .01$), whereas depression symptoms decrease the QoL in subjects with MS ($\beta = -.692$, $p < .001$). We also found that depression decreases productivity in spite of presenteeism in subjects with and without MS ($\beta = -.412$, $p < .01$; $\beta = -.461$, $p < .05$, respectively).

Conclusions: Results indicate that QoL is lower for workers with MS thus. Hence, QoL can be increased toward more efficient HR practices, enhanced work designs and more flexible schedules, promoting a better balance between family and work-life. Our results also showed that MS has no significant impact on productivity as a physical health problem. Despite this, there is evidence that depression is the higher predictor of lower QoL in MS patients, whereas anxiety is the most significant predictor for subjects without MS. According to our study, the strategy for both groups must be different, considering depression is the main factor for the MS patients, whereas anxiety is the critical variable for subjects without MS.

P032

Patterns of use of tests to monitor disease activity among patients with relapsing remitting multiple sclerosis in the United States and Europe

P O'Meara[1], S Narayanan[2], J White[3], J Chan[3], S Gabriele[3]
[1]Ipsos Healthcare, New York, NY, United States, [2]Ipsos Healthcare, Columbia, MD, United States, [3]Ipsos Healthcare, London, United Kingdom

Background: Progression of symptoms among Relapsing Remitting Multiple Sclerosis (RRMS) patients (pts) may necessitate active disease management (DM). Data on patterns of use of different tests to monitor disease activity/progression among RRMS pts in Europe (EU) and the United States (US) is lacking.

Objectives: To assess the patterns of use of tests to monitor disease activity/progression in RRMS in the EU and US, based on pt disease severity.

Methods: A multi-center retrospective chart-review study of MS pts conducted in EU (UK/France/Germany/Italy/Spain) and US to collect de-identified data on diagnosis, clinical status and DM approaches. Healthcare providers (HCPs; 94% neurologists) were screened for duration of practice (>=3yrs) and pt volume (>=15 MS pts/month (mo.)) and recruited from a large panel to be geographically representative in each country. Medical charts of next 10 consecutive MS pts were selected by each HCP. RRMS pt data was analyzed.

Results: 2433 eligible RRMS pt charts were abstracted by 365 HCPs (EU/US: N-265/100; mean neurology practice duration-17/21yrs; mean # of pts seen per month-66/62). In EU/US, pt mean age: 37/41yrs, female: 67%/70%, currently treated: 85%/88%, currently with mild:moderate:severe disease: 60%:34%: 5%/67%:29%:3%. Top-5 tests used to monitor RRMS varied between the regions - overall as well as by pt disease severity (EU/ US: % pts): Neurological exam: overall-83/88, mild-80/89, moderate-87/86, severe-91/90; Gadolinium (Gd) Magnetic Resonance Imaging (MRI): overall-62/71, mild-57/71, moderate-69/71, severe-77/70; T2 MRI: overall-62/73, mild-59/74, moderate-66/70, severe-64/75; T1 MRI: overall-53/62, mild-51/64, moderate-55/58, severe-59/70; Expanded Disability Status Scale (EDSS): overall-86/29, mild-87/29, moderate-86/30, severe-80/35.

% with unknown Gd-enhanced lesions were (EU/US): overall-33/40, mild-37/42, moderate-29/37, severe-17/25. % with unknown T2 lesions were (EU/US): overall-33/35, mild-34/36, moderate-32/34, severe-17/20. UK HCPs reported disproportionately more pts with unknown Gd-enhanced (70%) and T2 lesions (66%).

Conclusions: Besides neurological exam and EDSS, MRI testing is widely used and its use increased with increasing disease severity (EU only); % pts with unknown lesions decreased correspondingly. Still, one-third of patients had unknown lesions (with UK reporting two-thirds), warranting further scrutiny on practice patterns to optimize available therapeutic choices and alleviate disease burden.

Clinical outcome measures

P033
Video-based paired-comparison ranking: a validation tool for fine-grained measures of motor dysfunction in multiple sclerosis

J Burggraaff[1], M D'Souza[2], J Dorn[3], C Kamm[1], P Tewarie[1], P Kontschieder[4], C Morrison[4], T Vogel[3], A Sellen[4], M Machacek[3], P Chin[5], A Criminisi[4], F Dahlke[3], L Kappos[2], B Uitdehaag[1]
[1]VU University Medical Center, Amsterdam, Netherlands, [2]University Hospital Basel, Basel, Switzerland, [3]Novartis Pharma AG, Basel, Switzerland, [4]Microsoft Research, Cambridge, United Kingdom, [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States

Background: Measurement instruments used in the neurological examination, including the Expanded Disability Status Scale (EDSS), cannot report small changes in patient performance that may be needed to evaluate the clinical course of neurological diseases and the efficacy of treatment. For a more reliable and sensitive assessment of disability in multiple sclerosis (MS) we are developing the ASSESS-MS system, which relies on the automated image analysis algorithm of defined recorded movements. To validate a more sensitive tool, a method to capture clinical judgement in a more discriminatory manner than ordinal scales is required. Therefore, we investigate the ability of experienced neurologists to evaluate motor dysfunction in MS patients via video-based paired comparisons.

Objectives: To assess whether video-based paired comparisons of patient movements allow a reliable and finer-grained capture of clinical judgment of motor dysfunction in MS, than commonly used measurement instruments.

Methods: Thirteen experienced neurologists were presented with pairs of video recordings of MS patients (EDSS 1-7) performing standardized movements like the finger nose test (FNT) and movements based on activities of daily living (ADL), such as drinking from a cup. The clinicians were asked to compare patients' performance, evaluating as worse, equal or 'judgement not possible, because of confounding factors'. The pairwise comparisons were evaluated and mapped onto a continuous scale using the Bradley-Terry-Luce (BTL) model, a commonly applied model in the analysis of paired comparison data. The results were analysed for intra- an interrater reliability and were correlated with the matching EDSS subscores.

Results: The paired gradings were significantly correlated with the matching subscores (e.g. Kendall's tau for FNT was 0.5 with $p < 0.01$) and allowed to discriminate between patients, even in those with the same EDSS subscore. Internal reliability, which characterizes rater consistency, was above 90%, and short-term test-retest reliability was ~90%. Further results will be presented.

Conclusions: Paired comparisons of video-captured defined movements of MS patients appear to reliably capture neurological judgment of motor dysfunction. By providing finer-grained differentiation, gradings based on paired comparisons may serve as an improved external validation in the development of more sensitive (automated) outcome measures.

P034
eEDSS - an electronic capturing of standardized neurological assessments with real time feedback as a tool to improve consistency. A validation study

M D'Souza[1], O Yaldizli[1], B Gersbach[2], D Vogt[3], R John[4], A Papadopoulou[1], E Lucassen[1], M Menegola[1], M Andelova[1], F Dahlke[5], L Kappos[1]
[1]Universitiy Hospital Basel, Neurology, Basel, Switzerland, [2]Definition12, Basel, Switzerland, [3]University Hospital Basel, Clinical Trial Unit, Basel, Switzerland, [4]Claudiabasel GmbH, Basel, Switzerland, [5]Novartis Pharma AG, Basel, Switzerland

Background: The Expanded Disability Status Scale (EDSS) is the most widely used disability-rating scale in multiple sclerosis (MS), but has been criticized for its low reliability. To improve reliability a standardized version of the EDSS (Neurostatus) was established over the last two decades and is used in most major clinical studies including many of the pivotal trials for approval of MS drugs.

Objectives: To further improve EDSS reliability, we developed the electronic capturing and real time feedback EDSS (eEDSS), an algorithm-based evaluation performed with a tablet computer (iPAD). eEDSS provides immediate feedback, based on the Neurostatus definitions, indicating inconsistencies in the scoring of parts of the neurological examination, functional systems (FS), Ambulation-Score (AS) and EDSS. The final decision on the correct scores remains with the physician who can overrule the algorithm. Here we compared results obtained with the standardized EDSS paper-version (pEDSS) and the eEDSS.

Methods: Three certified EDSS raters who received training in the use of the eEDSS examined 100 MS patients with varying degrees of neurological deficits. Each patient was assessed twice. The first rater began with using the pEDSS and then switched to the eEDSS after seeing a third of the study population. In parallel the second EDSS rater assessed the same patients an the same day using the eEDSS and switched accordingly. The same principle was used for the third EDSS rater. pEDSS and eEDSS were compared for the frequency of inconsistencies in the assignment of the FS, AS and EDSS, using generalized mixed-effects-models and the exact McNemar-test.

Results: Inconsistencies in FS assessments where much more likely to occur when pEDSS was used compared to eEDSS (OR [95% CI] = 2.538 [1.397 - 4.613]). This was also the case for EDSS relevant FS inconsistencies (OR[95% CI] = 4.134 [1.453 - 11.757]). Inconsistencies were much more likely to occur for patients with low EDSS scores (≤ 3.5) than for those with high EDSS scores (> 3.5) (OR[95% CI] = 5.324 [1.192 - 23.770]).

Conclusions: In this randomized comparison the algorithm-based eEDSS was superior to the paper version, in providing consistent assessments. By reducing noise the eEDSS should have a positive impact on quality and power of clinical trials.

P035

Infrared depth sensor based automated classification of motor dysfunction in multiple sclerosis - a proof-of-concept study

M D'Souza[1], J Burggraaf[2], C Kamm[2], P Tewarie[2], P Kontschieder[3], J Dorn[4], C Morrison[3], T Vogel[4], A Sellon[3], M Machacek[4], P Chin[5], A Criminisi[3], F Dahlke[4], B Uitdehaag[2], L Kappos[1]

[1]University Hospital Basel, Neurology, Basel, Switzerland, [2]VU University Medical Center, Neurology, Amsterdam, Netherlands, [3]Microsoft Research, Cambridge, United Kingdom, [4]Novartis Pharma AG, Basel, Switzerland, [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States

Background: The Expanded Disability Status Scale (EDSS) is the most frequently used scale to rate disability in multiple sclerosis (MS) and an important outcome measure in clinical trials and daily care. However, it has a relatively low inter-rater and intra-rater reliability. To improve assessment of disability in MS patients, we developed an automated image analysis algorithm using advanced machine learning techniques, which classified movements recorded non-invasively with an infrared depth sensor (Kinect).

Objectives: To test classification performance of the automated image analysis algorithm on depth sensor recordings of six defined movements. To understand the dominant features in the movements identified by the automated image analysis algorithm in a medical context.

Methods: Six pre-defined movements from standardized neurological assessments, covering upper and lower extremities and trunk, as well as a movement typical of activities of daily living (drinking from a cup), were recorded in 72 MS patients and 102 healthy volunteers. For all patients a standardized EDSS-assessment, Nine-Hole-Peg-Test, and the Symbol Digit Modalities Test were performed and documented. Movement information was extracted directly from the depth sensor recordings, pre-processed and analysed by the bespoke automated image analysis algorithm. The built-in skeleton algorithm was not used. We evaluated the outcome with Dice scores, conservative estimates for classification accuracy that penalize misclassification.

Results: We were able to quantify the motor dysfunction of 72 MS patients in six pre-defined and recorded movements that cover the upper body, trunk, and lower body. Each movement was correctly classified with a Dice score of at least 80%, supporting the validity of the approach. Average sensitivity/specificity scores were 80-90%. The bespoke automated image analysis algorithm identified movement properties with highest discriminative power, which may help facilitate training of neurologists.

Conclusions: The infrared depth sensor recording technique with bespoke automated image analysis algorithm enables a reliable and sensitive quantitative assessment of motor dysfunction in MS patients. With a finer classification to capture different degrees of movement disability in future, this approach may improve the evaluation of disability and disease progression in MS.

P036

The squares test as a measure of hand function in multiple sclerosis

J Gielen[1], J Laton[1], J Van Schependom[1], PP De Deyn[2,3,4], G Nagels[1,5,6]

[1]Free University of Brussels, NEUR, Brussel, Belgium, [2]University of Antwerp, Institute Born-Bunge, Antwerp, Belgium, [3]University Medical Center, Alzheimer Research Center Groningen, Groningen, Netherlands, [4]ZNA Middelheim, Neurology, Antwerp, Belgium, [5]Université de Mons, Service d'Orthopédagogie Clinique, Faculté de Psychologie et des Sciences de l'Education, Mons, Belgium, [6]National MS Center, Melsbroek, Belgium

Background: Hand function is commonly impaired in Multiple Sclerosis (MS). There exists no effective treatment and symptoms rarely remit. It is commonly evaluated with the nine-hole peg test (9HPT), which is part of the MS Functional Composite (MSFC). The MSFC is often used as an outcome measure in clinical trials in MS. Although the 9HPT was favoured over other tests for inclusion in the MSFC, new measures should be tested as potential replacements. The squares test (ST) was designed by Annett as a group test for hand skill assessment. In its creation, care was taken to avoid the use of a cumbersome apparatus and it had to be easy to score. The ST has not yet been evaluated for use in the MSFC.

Objectives: We want to evaluate the usage of the squares test in evaluating hand function. We will compare test scores of the ST with those of the 9HPT in patients and examine the reliability of the ST results in a test-retest group.

Methods: Both tests were performed, according to the MSFC manual, by a group of 37 MS patients, a matched control group of 18 healthy volunteers and a group of 49 healthy test-retest (TRT) controls. The MS patients were divided into groups according to their Expanded Disability Status Scale (EDSS) score. EDSS scores ranged from 3-8.

Statistical analyses were performed in R and MATLAB.

Results: The 9HPT scores showed low to high correlation with the ST scores. Correlation was equal to 0.63, 0.50 and 0.28 (p< 0.0001, p=0.034 & p=0.05) for the patient, control and TRT groups respectively. In the total group of 104 subjects, correlation was high (r=0.84, p< 0.0001), and moderate in a group consisting of only the 67 healthy volunteers (r=0.51, p< 0.0001).

The 49 TRT controls were re-evaluated with the ST within four weeks of the first assessment. The correlation between these two measures was good (r=0.67, p< 0.0001). The average difference between the two measurements was 11.5 % ± 10.2 of the baseline value.

Conclusions: The ST is a reliable test of hand function. It is a brief and easy to administer paper-and pencil-test that can be used in a broad EDSS range. It has a high test-retest correlation, and correlates highly with the 9HPT. The ST is simpler and shorter to perform than the 9HPT, and it is more closely related to daily activities like writing. In addition, no material apart from pen and paper is needed, and a record of the test is easily kept. Therefore the ST is a candidate to be used in composite measures of MS related functional deficits for clinical practice and trials.

P037

Influence of method of analysis on responsiveness to change of an IRT score of global disability derived from NARCOMS performance scales

E Chamot[1], AR Salter[2], I Kister[3], GR Cutter[2]
[1]University of Alabama at Birmingham, Epidemiology, Birmingham, AL, United States, [2]University of Alabama at Birmingham, Biostatistics, Birmingham, AL, United States, [3]New York University, Neurology, New York, NY, United States

Background: We recently used item response theory (IRT) methodology to derive a patient-reported scale of global neurological disability from North American Research Committee on Multiple Sclerosis (NARCOMS) Performance Scales (PS). In a cross-sectional setting, the IRT scale was found superior to the traditional sum scale. In a longitudinal context, changes on several external measures of disease activity and progression were associated with changes in IRT-estimated PS score that were in the expected directions, but rather small.

Objectives: To determine the extent to which a "latent change" one-step statistical analysis strategy (direct longitudinal IRT modelling of observed responses to PS across occasions) and the "conventional" two-step strategy (estimation of IRT scores from patients' responses to the PS at each occasion, followed by separate conventional longitudinal analysis of score estimates) yield different estimates of responsiveness in PS IRT score when comparing changes on the new measure with changes on external anchor measures, including (1) self-evaluation of change in overall MS symptoms since last survey; (2) employment status; and (3) Patient Determined Disease Steps (PDDS).

Methods: Each single-item PS assess perceived disability in 1 of 11 neurological domains. Conventional and latent change analyses of responsiveness assessed associations between within-person changes on the anchors and changes in PS IRT score. Participants were NARCOMS volunteers enrolled in 2003-2008 who had at least a follow-up immediately after enrollment and at 5 years of follow-up. Data consisted of the first three consecutive biannual updates that assessed the particular anchor of interest.

Results: Sample size ranged from 1435 persons (employment status analysis) to 2207 persons (PDDS analysis). Cohen's d effect sizes expressed in fraction of baseline PS IRT score variance were consistently much larger when estimated with the latent change approach than with the conventional approach. For instance effect size for "worse/much worse symptoms since last survey" was +0.22 (95% CI, +0.13, +0.31) with the former approach and +0.05 (95% CI, +0.01, +0.08) with the latter approach. Response shift did not play any role in these differences.

Conclusions: In this study, direct IRT modeling prevented bias known to occur with conventional two-step analysis strategy. Our finding may apply to analysis of other MS outcomes.

P038

Assessment of upper extremity function using the manual dexterity component of the multiple sclerosis performance test: validation of novel metrics

F Bethoux[1], D Schindler[2], J Alberts[2], D Miller[1], S Rao[3], J-C Lee[4], D Stough[1], C Reece[3], B Mamone[1], R Rudick[1]
[1]Cleveland Clinic, Mellen Center for MS Treatment and Research, Cleveland, OH, United States, [2]Cleveland Clinic, Biomedical Engineering, Cleveland, OH, United States, [3]Cleveland Clinic, Center for Brain Health, Cleveland, OH, United States, [4]Cleveland Clinic, Quantitative Health Sciences, Cleveland, OH, United States

Background: Impairment of upper extremity (UE) function is a frequent consequence of multiple sclerosis (MS). The MS Performance Test (MSPT) is an Ipad®-based neurological performance assessment tool designed to simulate the MS Functional Composite (MSFC). The 9-Hole Peg Test (9-HPT) assesses UE function within the MSFC. The Manual Dexterity Test (MDT) is the component of the MSPT simulating the 9-HPT. Preliminary data showed that the MDT demonstrates favorable psychometric characteristics compared to the 9-HPT. The MDT allows the computation of novel metrics, in addition to the total time needed to complete the test.

Objectives: To explore the performance characteristics of novel metrics derived from the MDT.

Methods: The 9-HPT and the MDT were administered in MS patients (MS) and age- and gender-matched healthy controls (HC) during two sessions on the same day. Two modalities of the MDT were used: "Dish MDT" (the 9 pegs are removed one by one from a dish and returned to the dish), and "Row MDT" (the pegs are removed from a row and returned to a dish). Novel metrics on the MDT included the total peg insertion time, total peg removal time, and peg-to-peg variability during insertion and removal (coefficient of variation=CV). The Expanded Disability Status Scale (EDSS) and MS Performance Scales (MSPS) were administered to assess MS-related disability.

Results: 51 MS (age 46.2(10.1) years, 78.4% women, symptom duration 12.1(9.1) years) and 49 HC subjects (age 45.7(10.7) years, 73.5% women) were included in the analysis. Test-retest reliability was satisfactory (concordance correlation coefficients: 0.721 to 0.953). Both the average insertion and removal times on the Dish and Row MDT differentiated between MS and HC (p 0.003 to < 0.001, Cohen's d 0.65 to 0.93). Peg-to-peg variability was not significantly different between MS and HC. Both the insertion and removal times were strongly correlated with total MDT time and 9-HPT time (Pearson correlation coefficients: 0.71 to 0.93). Patterns of correlation with disease duration, EDSS, and MSPS were comparable to those of the total MDT time and 9-HPT.

Conclusions: In this cross-sectional study, the insertion and removal times on the MDT exhibited similar performance characteristics to the total MDT time and 9-HPT, suggesting that the test could be reduced to only one phase without compromising its clinical usefulness. Longitudinal studies are needed to confirm these findings.

Clinical trials

P039

Improvement in MRI outcomes across subgroups with alemtuzumab versus interferon beta-1a in treatment-naive relapsing-remitting multiple sclerosis

X Montalban[1], DL Arnold[2,3], E Fisher[4], DH Margolin[5], J Palmer[5], on behalf of the CARE-MS I Investigators

[1]Edifici Cemcat, Vall d'Hebron University Hospital and Research Institute, Barcelona, Spain, [2]NeuroRx Research, Montréal, QC, Canada, [3]Montréal Neurological Institute, McGill University, Department of Neurology and Neurosurgery, Montréal, QC, Canada, [4]Cleveland Clinic, Department of Biomedical Engineering, Cleveland, OH, United States, [5]Genzyme, a Sanofi Company, Cambridge, MA, United States

Background: In the CARE-MS I (NCT00530348) trial in treatment-naive patients with active relapsing-remitting multiple sclerosis (RRMS), alemtuzumab proved superior to subcutaneous interferon beta-1a (SC IFNB-1a) with respect to relapse rate, reduction in magnetic resonance imaging (MRI) lesion activity, and brain volume loss over 2 years.

Objectives: Investigate MRI outcomes in CARE-MS I patient subgroups stratified by baseline demographic and disease characteristics.

Methods: In the 24-month, phase 3, head-to-head CARE-MS I study, patients were randomized to receive alemtuzumab 12 mg/day intravenously on 5 days at baseline and on 3 days 12 months later, or SC IFNB-1a 44 µg 3 times weekly. Annual cranial MRI was analyzed blinded to treatment. Treatment effects on gadolinium (Gd)-enhancing, new/enlarging T_2-hyperintense and new T_1-hypointense lesions, and brain volume loss (brain parenchymal fraction [BPF] change) over 2 years were analyzed for subgroups stratified by: gender, age, race, geographic region, baseline Gd-enhancing lesion activity, T_2 lesion volume and BPF, highly active disease (≥2 relapses in the year prior to randomization and ≥1 Gd-enhancing lesion at baseline), baseline Expanded Disability Status Scale (EDSS) score, disease duration, and relapses in prior 2 years. Odds ratios (ORs) were calculated by logistic regression (covariate adjustment for baseline lesion count).

Results: In most patient subgroups, alemtuzumab (n=376) significantly reduced the risk (p< 0.05) of Gd-enhancing lesions (OR range: 0.20-0.43), new/enlarging T_2 lesions (OR range: 0.29-0.52), and new T_1 lesions (OR range: 0.24-0.43) vs SC IFNB-1a (n=187) at Month 24. Atrophy measured by BPF was reduced with alemtuzumab vs SC IFNB-1a in all subgroups at Month 24; this treatment difference was significant in all cases (p< 0.01) with the exception of the Latin America and EU regions, likely due to small subgroup size. Alemtuzumab was superior to SC IFNB-1a across all MRI measures in most subgroups including patients who at baseline had: Gd-enhancing lesion activity (p≤ 0.01), median T_2 lesion volume ≥4.117 cm³ (p< 0.01), highly active disease (p< 0.01), and EDSS score ≥2.0 (p< 0.01).

Conclusions: Significant benefits of alemtuzumab vs SC IFNB-1a were observed on MRI lesion activity and brain volume loss in most examined subgroups of treatment-naive RRMS patients. These findings support the superior efficacy of alemtuzumab over SC IFNB-1a in RRMS and demonstrate the robustness of treatment effects across various subgroups.

P040
MRI outcomes in patients with early multiple sclerosis treated with teriflunomide: subgroup analyses from the TOPIC phase 3 study
JS Wolinsky[1], P Truffinet[2], D Bauer[3], AE Miller[4], for the Investigators of the TOPIC Study and the MRI-AC in Houston, TX

[1]University of Texas Health Science Center at Houston, Houston, TX, United States, [2]Genzyme, a Sanofi Company, Chilly-Mazarin, France, [3]Sanofi, Bridgewater, NJ, United States, [4]Icahn School of Medicine at Mount Sinai, New York, NY, United States

Background: Teriflunomide is a once-daily oral immunomodulator approved for relapsing-remitting multiple sclerosis (MS). TOPIC (NCT00622700) is a phase 3 study that evaluated the efficacy and safety of teriflunomide in patients with a first clinical episode suggestive of MS and a magnetic resonance imaging (MRI) scan showing ≥2 T2 lesions ≥3 mm in diameter. The primary endpoint in TOPIC was met, showing that teriflunomide 14 mg significantly reduced the risk of relapse determining conversion to clinically definite MS by 42.6% vs placebo (P=0.0087).

Objectives: To report results of a post-hoc analysis of the treatment effects of teriflunomide 14 mg on MRI activity in patients by gender, age, and baseline MRI status.

Methods: A total of 614 patients were randomized and treated to once-daily treatment with teriflunomide 14 mg, teriflunomide 7 mg, or placebo for up to 108 weeks. MRI scans were performed at screening, 12, 24, 48, 72, and 108 weeks, and were processed at a central MRI analysis center. Patients treated with teriflunomide 14 mg were analyzed by the following subgroups: gender, age (< or ≥31 years), baseline total lesion volume (TLV; < or ≥5 mL), and baseline number of gadolinium (Gd)-enhancing lesions (0 or ≥1).

Results: Baseline characteristics were well balanced across the treatment groups; the mean TLV was 8.66 mL and 31.4% of patients had at least one Gd-enhancing lesion. Overall, teriflunomide 14 mg significantly reduced TLV increase from baseline vs placebo at all time points (each P< 0.05). At 108 weeks, the least-squares (LS) mean difference in TLV was significantly in favor of teriflunomide 14 mg vs placebo (LS mean difference -0.091; P=0.0374). The number of Gd-enhancing lesions per post-treatment scan was significantly reduced (0.40 vs 0.95 with placebo), with a relative risk reduction of 58.5% (P< 0.001). The benefits of teriflunomide 14-mg treatment on the number of Gd-enhancing lesions per scan were consistent across all subgroups. The positive effects on TLV were observed in subgroups of teriflunomide-treated patients defined by age, baseline TLV, and number of Gd-enhancing lesions at baseline. Although there was some statistical evidence of a greater effect in females, it was not consistent across time, and the male subgroup was quite small for comparison.

Conclusions: Teriflunomide 14 mg had a generally consistent beneficial effect on TLV and number of Gd-enhancing lesions per scan in subgroups of patients defined by gender, age, and baseline MRI status.

P041
Effect of laquinimod on gray matter and white matter atrophy in relapsing-remitting multiple sclerosis: analysis of the BRAVO phase III trial
K Nakamura[1], TL Vollmer[2], T Gorfine[3], V Knappertz[4,5], DL Arnold[6]

[1]McGill University, Montreal, QC, Canada, [2]University of Colorado, Aurora, CO, United States, [3]Teva Pharmaceutical Industries, Netanya, Israel, [4]Teva Pharmaceutical Industries, Frazer, PA, United States, [5]Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany, [6]NeuroRx Research, Montreal, QC, Canada

Background: Laquinimod (LAQ) is an oral immunomodulator under development for the treatment of MS. LAQ reduced whole brain atrophy rate in both the ALLEGRO and BRAVO phase III trials, as well as gray matter (GM) and white matter (WM) atrophy rates in the ALLEGRO trial.

Objectives: This study investigated the treatment effect of LAQ on the rates of GM and WM atrophy in the BRAVO trial.

Methods: RRMS patients were randomized to LAQ, intramuscular interferon beta-1a (IFN), or placebo (PLC). The percent change in GM and WM volumes on MRI were measured at year 1 and year 2 with respect to baseline using pairwise Jacobian integration (PJI). PJI nonlinearly aligns a pair of scans from baseline and follow-up and calculates the mean Jacobian determinants of the deformation field, which represent atrophy or growth at each voxel. We calculated the treatment effect as the difference in the unadjusted means between the active and PLC arms divided by the mean PLC value. For p-values, we used ANCOVA with baseline covariates of categorical Gadolinium-enhancing lesion counts (≥ 1 or 0), T2 lesion volume, and corresponding normalized tissue volume. The rate in the second year was calculated from year 1 and 2 values.

Results: The unadjusted mean (SD) percent changes in GM volume from baseline to year 1 were -0.609 (0.829) for PLC (n=383), -0.797 (0.859) for IFN (n=396), and -0.298 (0.774) for LAQ (n=371), and from baseline to year 2 were -1.196 (0.902), -1.340 (0.988), and -0.865 (0.940) for PLC, IFN, and LAQ, respectively. Similarly, WM mean (SD) percent changes were -0.452 (0.921), -0.542 (1.171), and -0.274 (1.020) for year 1; and for year 2, -0.793 (1.310), -0.954 (1.445), and -0.670 (1.311) for PLC, IFN, and LAQ, respectively.

There was a significant treatment effect of LAQ on GM atrophy (51% at year 1 and 28% at year 2, both p< 0.001) compared with PLC. The IFN group showed worsening of 31% (p=0.004) at year 1 and 12% at year 2 (p=0.075). The treatment effect of LAQ on WM atrophy was 39% (p=0.001) at year 1 and 15% (p=0.015) at year 2, compared with PLC. The IFN group was not statistically different from PLC in WM rates at year 1 (p=0.488) and year 2 (p=0.239). The rates of atrophy in the second year for GM and WM in LAQ and IFN were not different than PLC.

Conclusions: LAQ showed significant reduction of GM and WM atrophy compared with PLC between baseline and year 2, without evidence of "pseudoatrophy," consistent with findings in ALLEGRO.

P042

Peginterferon beta-1a may improve recovery following relapses: data from the 2-year ADVANCE relapsing-remitting multiple sclerosis study

BC Kieseier[1], TF Scott[2,3], SD Newsome[4], SI Sheikh[5], S Hung[5], X You[5], B Sperling[5]

[1]Heinrich-Heine University, Department of Neurology, Düsseldorf, Germany, [2]Alleghany General Hospital, Department of Neurology, Pittsburgh, PA, United States, [3]Drexel University College of Medicine, Department of Neurology, Pittsburgh, PA, United States, [4]Johns Hopkins School of Medicine, Department of Neurology, Baltimore, MD, United States, [5]Biogen Idec Inc., Cambridge, MA, United States

Background: At Year 1 of the Phase 3 ADVANCE study, it was evident that the significant reduction in risk of sustained disability progression (SDP) observed in relapsing-remitting multiple sclerosis (RRMS) patients treated with subcutaneous peginterferon beta-1a (PEG-IFN; 125 µg every 2 weeks [Q2W]) versus (vs) placebo (relative 54% reduction in risk of 24-week confirmed SDP) may be partially due to greater recovery following relapses (RfR). Furthermore, approximately half of patients with SDP in Year 1 of ADVANCE did not have a preceding relapse.

Objectives: To determine whether PEG-IFN Q2W treatment improved RfR vs placebo in year 1, and over 2 years of the ADVANCE study, via analyses of risk of experiencing 24-week SDP following a relapse.

Methods: During Year 1 of ADVANCE, 1512 RRMS patients were randomized (1:1:1) to placebo or PEG-IFN 125 µg Q2W or Q4W. After Year 1, placebo patients were re-randomized to PEG-IFN 125 µg Q2W or Q4W for Year 2, while active arms continued the same dosing regimen. SDP due to incomplete RfR was defined as onset of 6-month SDP (≥ 1.0- or ≥ 1.5-point increase in Expanded Disability Status Scale score, from baseline scores of ≥ 1.0 or 0.0, respectively, confirmed after 24 weeks) within 180 days after a relapse. Post-hoc analyses were conducted based on Year 1 and over 2 year results, grouped by Year 1 treatment assignment.

Results: Of the 1512 patients who received study drug, n=67 experienced SDP associated with relapses, while n=76 experienced SDP not associated with relapses. Over 2 years, significantly fewer patients in the Q2W group experienced SDP associated with relapses versus those switched to PEG-IFN from placebo (n=10 vs n=30; p=0.0010). Fewer patients experienced a relapse with SDP on Q2W (n=6) versus those on placebo during Year 1 (n=24), representing a 75% reduction (p< 0.001). Following a recent relapse during Year 1, a significantly lower proportion in the Q2W group (6.7%) had SDP vs the placebo group (17.4%; relative risk reduction 61% [p=0.0207]). Similar results were seen over 2 years when comparing those on Q2W with those who switched to PEG-IFN from placebo.

Conclusions: The combination of an overall reduction in risk of relapses and a higher chance of avoiding disease progression from experiencing any relapses, resulted in an overall 75% risk reduction (p< 0.001) of a patient experiencing 24-week confirmed disability progression caused by a relapse for PEG-IFN Q2W vs placebo in Year 1.

P043

Efficacy and safety of alemtuzumab in patients with relapsing-remitting MS who relapsed on prior therapy: four-year follow-up of the CARE-MS II study

H-P Hartung[1], DL Arnold[2], JA Cohen[3], AJ Coles[4], EJ Fox[5], E Havrdova[6], KW Selmaj[7], DH Margolin[8], J Palmer[8], P Oyuela[8], MA Panzara[8], DAS Compston[9], on behalf of the CARE-MS II Investigators

[1]Department of Neurology and Center for Neuropsychiatry, Heinrich-Heine University, Düsseldorf, Germany, [2]Department of Neurology and Neurosurgery, Montréal Neurological Institute, McGill University, Montréal, QC, Canada, [3]Mellen Center and Department of Biomedical Engineering, Cleveland Clinic, Cleveland, OH, United States, [4]University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom, [5]University of Texas Medical Branch, Round Rock, TX, United States, [6]Department of Neurology, First School

of Medicine, Charles University, Prague, Czech Republic,
[7]Medical University of Łódź, Department of Neurology, Łódź,
Poland, [8]Genzyme, a Sanofi Company, Cambridge, MA, United
States, [9]Department of Clinical Neurosciences, University of
Cambridge, Cambridge, United Kingdom

Background: Alemtuzumab is approved in over 30 countries for
relapsing-remitting multiple sclerosis (RRMS). The phase 3
CARE-MS II study in patients with active RRMS who relapsed on
prior therapy showed alemtuzumab had superior efficacy over
subcutaneous interferon beta-1a (SC IFNB-1a) and manageable
safety over 2 years; 3-year follow-up showed durable efficacy of
alemtuzumab, with only 20% of patients receiving a third annual
treatment course.
Objectives: To examine 4-year efficacy/safety of alemtuzumab
patients and 2-year efficacy/safety of patients who switched from
SC IFNB-1a to alemtuzumab.
Methods: In the 2-year CARE-MS II study (NCT00548405),
patients with active RRMS who relapsed on prior therapy received
alemtuzumab (12 mg/day intravenously [IV] on 5 consecutive
days and on 3 consecutive days 12 months later) or SC IFNB-1a
(44 μg 3 times/week). In the extension study (NCT00930553),
alemtuzumab-treated patients received as-needed retreatment (12
mg/day IV on 3 consecutive days) ≥1 year apart or permitted use
of approved disease-modifying therapy (DMT), on evidence of
relapse or magnetic resonance imaging activity. Former SC
IFNB-1a patients received 2 alemtuzumab courses in the
extension.
Results: The extension enrolled 393 (93%) eligible patients from
the core study alemtuzumab arm. Through 4 years, 68% of these
patients received only 2 annual courses, while 24% and 7%
received 1 or 2 additional courses, respectively, and < 5% of
patients received another DMT during the extension. Twenty-five
patients discontinued from the study, none due to adverse events
(AEs). Among patients who received SC IFNB-1a in the core
study, 146 (83%) entered the extension, 131 (90%) of these
patients received 2 courses of alemtuzumab. There were 7 with-
drawals in the crossover group during the 2-year extension, 1 due
to an AE. Efficacy and safety data will be reported for Year 2 of
the extension for the alemtuzumab cohort (Years 3 and 4 of alem-
tuzumab exposure) and for the crossover cohort (Years 1 and 2 of
alemtuzumab exposure).
Conclusions: The majority of patients who received 2 courses of
alemtuzumab during the core study after relapsing on prior treat-
ment did not require further treatment during the 2-year extension
period; few sought alternative therapies or withdrew from the
study. Among former SC IFNB-1a patients who received alemtu-
zumab during the extension, the majority received both treatment
courses and remained in the study; few sought treatment with
other therapies.

P044
Alemtuzumab improves quality of life in relapsing-remitting multiple sclerosis patients who relapsed on prior therapy: 3-year follow-up of CARE-MS II

T Moreau[1], DH Margolin[2], L Kasten[3], B Singer[4], on behalf of
the CARE-MS II Investigators
[1]Burgundy University, Dijon University Hospital, Dijon, France,
[2]Genzyme, a Sanofi Company, Cambridge, MA, United States,

[3]PROMETRIKA, LLC, Cambridge, MA, United States, [4]MS
Center for Innovations in Care, St. Louis, MO, United States

Background: Alemtuzumab is approved in over 30 countries for
the treatment of relapsing-remitting multiple sclerosis (RRMS).
In CARE-MS II (NCT00548405), alemtuzumab had superior effi-
cacy compared with subcutaneous interferon beta-1a (SC
IFNB-1a), with manageable safety. Alemtuzumab-treated patients
had significant improvements in multiple aspects of quality of life
(QoL) from baseline (BL) to Year 2, and QoL scores were signifi-
cantly higher than those of the SC IFNB-1a arm.
Objectives: To examine QoL outcomes at Year 3 in alemtuzumab-
treated patients who relapsed on a prior therapy.
Methods: CARE-MS II was a 2-year, phase 3 trial in patients with
RRMS who relapsed on prior therapy. Patients randomized to
alemtuzumab 12 mg/day received intravenous infusions on 5 con-
secutive days at BL and on 3 consecutive days 12 months later.
Patients could be retreated as-needed with alemtuzumab in an
ongoing extension study (NCT00930553). QoL was measured
every 6 months using the following instruments: Functional
Assessment of Multiple Sclerosis (FAMS; scale 0-176 for total
score); Medical Outcomes Study 36-Item Short-Form Survey
(SF-36; scale 1-100; healthy population mean=50; administered
annually in the core study); and EuroQol in 5 Dimensions visual
analog scale (EQ-5D VAS; scale 0-100). Higher scores represent
better QoL. Change from BL was analyzed by the Wilcoxon one-
sample signed rank test. Worsening and improvement on the
SF-36 physical component summary (PCS) and mental compo-
nent summary (MCS) were defined as a ≥5-point decrease and
increase from BL, respectively.
Results: 435 patients were treated with alemtuzumab 12 mg in the
core study, 393 entered the extension study, and 80 received alem-
tuzumab re-treatment. FAMS total score was significantly
improved from BL to Year 3 (119.1 vs 124.8; p< 0.0001), with
significant improvements on 5 of 6 subscales. Mean SF-36 PCS
score rose from BL to Year 3 (42.7 vs 44.7; p< 0.0001) as did
mean MCS score (44.9 vs 46.5; p=0.042), corresponding with
improvements on 6 of 8 SF-36 subscales. Compared with BL,
Year 3 PCS and MCS scores were stable or improved in 82% and
73% of patients, respectively. Mean EQ-5D VAS was also
improved from BL to Year 3 (70.1 vs 73.0; p=0.0045).
Conclusions: Overall sustained improvement in physical, mental,
and emotional aspects of QoL were observed through 3 years in
alemtuzumab-treated patients who relapsed on a prior therapy,
even though most patients received only 2 alemtuzumab treatment
courses.

P045
Larger treatment effects in early multiple sclerosis: a meta analysis of randomized trials

A Signori[1], MP Sormani[1]
[1]University of Genoa, Health Sciences, Section of Biostatistics,
Genoa, Italy

Background: In recent years post-hoc analyses of clinical trials
were conducted to determine the efficacy of disease-modifying
treatments in Multiple Sclerosis (MS) across specific patient sub-
groups. However, single clinical trials are not powered to detect
subgroups specific treatment effects, and no baseline factors

emerged in previous analyses indicating subgroups of patients with higher treatment effects.

Objectives: To evaluate whether there are subgroups of relapsing-remitting (RR) MS patients that are more responsive to treatments taking advantage of the increased power coming from a meta analytic approach.

Methods: We systematically searched all published randomized clinical trials in RRMS reporting a subgroup analysis, that is, an assessment of the treatment effect in different subgroups of patients defined according to baseline characteristics (sex, age, baseline Expanded Disability Status Scale (EDSS), relapse history, previous treatments, presence of Gadolinium enhancing lesions (Gd+) and T2 lesion volume on the baseline MRI scan). Treatment effect was assessed on two endpoints: the annualized relapse-rate (ARR) and the disability progression according to sustained increase of EDSS score. The analysis was made independent from the specific overall treatment effect size by rescaling the treatment effect in each subgroup to the overall treatment effect size, and reporting the subgroup effect as a relative contribution to the treatment specific effect. The subgroup specific treatment effects were combined in a meta-analysis weighted by the inverse of variance.

Results: Six trials including a total of 6693 RRMS patients were included in the meta-analysis. Pooled treatment effects on ARR resulted to be significantly higher in younger subjects (p< 0.0001), in patients with lower baseline EDSS (p=0.013), in patients with baseline Gd+ activity (p< 0.001) and with a trend for patients with high T2 lesion load (p=0.091). A similar scenario was detected for pooled effects on disability progression with an higher effect in younger patients (p = 0.015) and in patients with baseline Gd+ activity (p = 0.019). For both endpoints no differences of treatment effect were detected among groups defined by different gender, relapse history or history of previous treatment.

Conclusions: This study shows in a formal way that in RRMS, higher treatment effects are associated to characteristics of an earlier (age and EDSS) and more active (Gd+ and T2 activity) disease.

P046

Evaluating the effect of teriflunomide in subgroups defined by prior treatment: pooled analyses of the phase 3 TEMSO and TOWER studies

MS Freedman[1], D Dukovic[2], M Benamor[3], P Truffinet[3], L Kappos[4]
[1]University of Ottawa and the Ottawa Hospital Research Institute, Ottawa, ON, Canada, [2]Sanofi, Bridgewater, NJ, United States, [3]Genzyme, a Sanofi Company, Chilly-Mazarin, France, [4]University Hospital Basel, Basel, Switzerland

Background: Teriflunomide is a once-daily oral immunomodulator approved for relapsing-remitting multiple sclerosis (MS). The TEMSO (NCT00134563) and TOWER (NCT00751881) phase 3 studies had similar designs and patient populations that allowed data pooling. In the main pooled analyses, teriflunomide 14 mg significantly reduced annualized relapse rate (ARR) and risk of disability progression vs placebo; the 7-mg dose significantly reduced ARR. The two teriflunomide doses had similar, manageable safety profiles. Pre-trial use of disease-modifying therapies (DMTs) may suggest higher baseline disease activity in some study patients.

Objectives: To assess the consistency of teriflunomide treatment effect on ARR and disability progression across patient subgroups defined by prior MS treatment.

Methods: Adult patients with relapsing forms of MS (N=2251) were randomized 1:1:1 to receive teriflunomide 14 mg, 7 mg, or placebo, for 108 weeks (TEMSO) or for 48 weeks after the last patient randomized (TOWER). Post hoc pooled analyses of ARR and 12-week confirmed disability progression were performed according to patient subgroups defined by prior MS treatment: >1 prior DMT; 1 prior DMT; and no prior DMT.

Results: Baseline characteristics were generally well balanced among treatment groups. Mean time since diagnosis of MS ranged from 4.4 years (no prior DMT) to 7.3 years (>1 prior DMT). Mean time since most recent relapse ranged from 5.6 months (no prior DMT) to 6.4 months (>1 prior DMT).

Teriflunomide 14 mg generally demonstrated efficacy vs placebo across the patient subgroups for ARR and risk of disability progression; there were no significant treatment-by-subgroup interactions. Relative risk reductions for ARR with teriflunomide 14 mg vs placebo were 46.7%, 27.7%, and 35.9% for >1 prior DMT, 1 prior DMT, and no prior DMT, respectively; corresponding hazard rate reductions for risk of disability progression were 78.6%, 46.6%, and 17.4%. A more robust effect was observed on disability progression with teriflunomide 14 mg versus teriflunomide 7 mg, whereas similar results were observed on ARR with both doses.

Conclusions: These pooled subgroup analyses show a consistent treatment effect of teriflunomide 14 mg across subgroups defined by pre-trial therapy, and confirm the clinical efficacy of teriflunomide.

P047

The effects of age and gender on brain volume in FREEDOMS, FREEDOMS II and TRANSFORMS phase 3 studies

E-W Radue[1], JS Wolinsky[2], D Tomic[3], DA Häring[3], P Chin[4], F Barkhof[5]
[1]University Hospital Basel, Medical Image Analysis Centre, Basel, Switzerland, [2]University of Texas Health Science Center at Houston, Department of Neurology, Houston, TX, United States, [3]Novartis Pharma AG, Basel, Switzerland, [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States, [5]VU Medical Centre, Image Analysis Centre, Amsterdam, Netherlands

Background: Analysis of brain volume (BV) in patients with relapsing-remitting multiple sclerosis (RRMS) in fingolimod clinical trials revealed relationships between variables such as MRI lesions, disability progression and whole BV change, but few studies of large datasets have examined the impact of age and gender on BV loss in RRMS.

Objectives: To examine the effect of age and gender on normalized BV (NBV) at baseline (BL) and on percentage BV change (PBVC) from BL to end of study (EOS) across the three phase 3 trials of fingolimod (2-year FREEDOMS and FREEDOMS II; 1-year TRANSFORMS).

Methods: 'Structural Image Evaluation, using Normalization, of Atrophy' (SIENA) was used to assess PBVC from BL to EOS, and cross-sectionally at BL (SIENAX) to assess NBV. In a statistical

model selection process using multiple regression models, the independent associations of several BL variables with NBV and PBVC were tested. For NBV, these variables were: age; gender; duration of MS; number of relapses 1 or 2 years before the study; disability score (Expanded Disability Status Scale [EDSS] or MS Functional Composite [MSFC]); Gd+ lesion count; T2 lesion volume; and T1-hypointense lesion volume. The same variables and NBV were tested as covariates for PBVC, with treatment as a fixed variable. Variables were ranked by importance in each trial, and the highest ranking were used to define the final model, if selected in all three trials.

Results: Age correlated most strongly with NBV across the three trials, closely followed by BL T2 lesion volume. Disability score (MSFC or EDSS) and duration of MS also correlated with NBV. NBV was slightly greater in women than men in FREEDOMS (respectively, 1518.3 cm^3 vs 1505.8 cm^3; p=0.0167) and FREEDOMS II (1530.3 cm^3 vs 1493.5 cm^3; p< 0.001), but not in TRANSFORMS (1526.4 cm^3 vs 1524.3 cm^3; p=0.6592); gender was excluded from the final regression model because of its poor rank across trials. Age and gender did not predict PBVC in any trial. The best BL predictors of PBVC were treatment, T2 lesion volume and Gd+ lesion count.

Conclusions: Age, T2 lesion burden, MS disease duration and disability status were important determinants of NBV. Between-gender differences in BV were minimized by the normalization process in SIENAX; at BL, NBV was similar in men and women. Regardless of age, men and women were equally affected by BV loss. Compared with controls, fingolimod treatment reduced BV loss in all three studies irrespective of age or gender.

P048
Follow-up data from the Mirror study: a dose-ranging study of subcutaneous ofatumumab in subjects with relapsing-remitting multiple sclerosis

PS Sorenson[1], ST Kavanagh[2], DJ Austin[3], RA Grove[4], MC Lopez[5], JM Tolson[6], SA Van Meter[7], A Bar-Or[8]
[1]Copenhagen University Hospital, Rigshospitalet, Department of Neurology, Copenhagen, Denmark, [2]GlaxoSmithKline, Clinical Statistics, Neurosciences, Research Triangle Park, NC, United States, [3]GlaxoSmithKline, Clinical Pharmacology, Stockley Park West, United Kingdom, [4]GlaxoSmithKline, Clinical Statistics, Neurosciences, Stockley Park West, United Kingdom, [5]GlaxoSmithKline, Stiefel Global Clinical Dev US, Research Triangle Park, NC, United States, [6]GlaxoSmithKline, RD Projects Clinical Platforms & Sciences, Research Triangle Park, NC, United States, [7]GlaxoSmithKline, Neurosciences Therapy Area Unit, Research Triangle Park, NC, United States, [8]McGill University and McGill University Health Center, Montreal Neurological Institute and Hospital, Montreal, QC, Canada

Background: Studies have demonstrated the benefits of anti-CD20 monoclonal antibody treatments in relapsing-remitting multiple sclerosis (RRMS). This study investigated the safety and efficacy of four subcutaneous ofatumumab (OFA) dosing regimens in subjects with RRMS. Upon completion or discontinuation of a 24-week treatment phase, subjects entered a 24-week follow-up phase, during which they did not receive treatment but were further monitored for B-cell repletion, safety and MRI lesion activity.

Objectives: To assess subject safety, persistence of MRI lesion suppression and B-cell repletion over the course of a 24-week follow-up phase, subsequent to a 24-week treatment phase.

Methods: 232 subjects were randomized to one of 5 treatment groups: placebo (PBO), OFA 3mg q12w, OFA 30mg q12w, OFA 60mg q12w, or OFA 60mg q4w. At week 12, the end of the PBO-controlled phase, the PBO group received a single OFA 3mg dose.

Results: 231 subjects received at least one dose of treatment. Of these, 221 (96%) subjects entered the 24-week follow-up phase; 212 (92%) subjects completed and 9 (4%) subjects prematurely withdrew. The most common reason for withdrawal was withdrawal of consent.

During the 24-week follow-up phase, the most common adverse events (AEs) were related to infections, observed in 25% of subjects across treatment groups. There was no evidence of a relationship between dose and the incidence or severity of AEs. Twelve serious adverse events (SAEs) were reported by 9 subjects with no SAE reported by more than one subject; no cases of progressive multifocal leukoencephalopathy or opportunistic infections were observed.

Assessment of efficacy data showed that the MRI lesion suppression seen during the 24-week treatment phase persisted through week 48 for the OFA treatment groups. As of the week 48 visit (equivalent to 36 weeks post-last dose for all groups except 60mg q4w, for which it was 28 weeks post-last dose), B-cell repletion (defined as ≥ baseline level or ≥ 0.11 GI/L) had been achieved by 46% of PBO/3mg-treated subjects, 35% of 3mg q12w-treated subjects, 40% of 30mg q12w-treated subjects, 33% of 60mg q12w-treated subjects, and 19% of 60mg q4w-treated subjects.

Conclusions: These results support further study of the safety and efficacy of OFA in longer term studies in subjects with RRMS. Repletion of B-cells following cessation of treatment was dose and regimen dependent; all treatment groups had started to replete by week 48.

P049
Safety, tolerability and efficacy of Boswellic acids in relapsing-remitting multiple sclerosis - the SABA proof-of-concept trial

KH Stürner[1], J-P Stellmann[1], F Paul[2], J Dörr[2], R Martin[3], C Heesen[1]
[1]University Medical Center Hamburg-Eppendorf, Institute for Neuroimmunology and Multiple Sclerosis Research (INIMS), Hamburg, Germany, [2]Charité Universitätsmedizin Berlin, NeuroCure Clinical Research Center (NCRC), Berlin, Germany, [3]University Hospital Zürich, Department of Neuroimmunology and MS Research, Zürich, Switzerland

Background: Orally available drugs exhibiting a safe and favourable side effect profile for the treatment of relapsing-remitting Multiple Sclerosis (RR-MS) are of high interest for patients and treaters. Boswellic acids (BAs), the main biologically active compound of frankincense, are orally available and known to exhibit anti-inflammatory activities. Clinical trials with frankincense extracts in rheumatoid arthritis showed very good tolerability and good efficacy in restraining inflammation, while the effect of BAs in RR-MS is unknown so far.

Objectives: We perform a Phase IIa bicentric open-label baseline-to-treatment study with the standardized frankincense extract

BOSWELAN® to test the safety, tolerability and efficacy of BAs in RR-MS patients.

Methods: The study is conducted under GCP. One major inclusion criteria is the presence of at least 2 new Gadolinium-enhancing (Gd+) lesions in monthly MRI during a 3-month screening phase. Treatment is initiated by an individualized dose finding to identify the highest well tolerated BOSWELAN® dose for each patient. Primary outcome is the number of new Gd+ lesions in monthly MRIs between months 5 and 8 of the treatment phase compared to 4 screening MRIs.

Results: 80 patients were screened at two centers to include 37 patients in the SABA trial. 6 patients terminated early due to non-compliance with the study protocol (n=3) or did start licensed immunotherapy because of relapse activity (n=3). Until now 23 patients have reached the primary endpoint of the treatment phase (month 8). Boswellic acids were very well tolerated at the highest dose of 4800mg per day which is the treatment dose for the majority of study patients (87%). There were no changes of laboratory parameters, in particular no changes in blood cell counts or liver enzymes due to the intake of BAs. Adverse events (AEs) were primarily mild (59% of all AEs) or moderate (39% of all AEs) and comprised predominantly gastrointestinal symptoms within the first four weeks (dose escalation phase). These declined almost completely to baseline frequencies afterwards. MRI disease activity was reduced by 63,8% in the number of new Gd+ lesions and by 62,4% in the number of new T2 lesions between screening and treatment phase (p < 0.05).

Conclusions: Up to now BOSWELAN shows a very good safety profile and high patient acceptance. Together with MRI results of the ongoing study a randomized placebo-controlled phase 2 trial in RR-MS seems justified to further evaluate BAs as a novel treatment option in RR-MS.

P050

Modeling dose-PK-lymphocytes relationship under siponimod (BAF312) treatment to infer time to immune reconstitution

C Sarr[1], M Savelieva[1], G Ette[1], C Petry[1], E Legangneux[1], E Wallström[1]
[1]Novartis Pharma AG, Basel, Switzerland

Background: Siponimod (BAF312) is an orally administered sphingosine 1-phosphate receptor (S1P)-1,5 modulator, being developed for the treatment of secondary progressive multiple sclerosis (MS). The therapeutic effects include prevention of circulating effector lymphocyte infiltration to the central nervous system.

Objectives: Characterize the relationship between siponimod pharmacokinetics (PK) properties and the pharmacodynamic (PD) effects on lymphocytes dynamics in healthy volunteers (HV) and MS patients including inter-patient variability, and to generate inferences regarding time required to recovery at targeted market dose (2 mg daily).

Methods: A PK/PD modeling approach was used to characterize link between individual dosing history, PK profiles, and lymphocytes dynamics through an indirect-response model on a log scale. Data from a total of 490 individuals from 6 phase I studies in HVs and 1 placebo-controlled phase II study in patients with relapsing-remitting MS were split into two datasets for model building (five

studies) and qualification (two studies). Inter-individual variability (IIV) was defined as log-normal distribution and residual variability as additive. Covariates tested were weight, age, gender, MS (yes/no) and ethnicity. Qualification of the model involved multiple levels of scrutiny; starting by standard goodness of fit and including assessment of the predictability of the model on the building dataset and on the qualification dataset.

Results: This PK/PD modeling approach characterizes the effect of siponimod on lymphocytes dynamics. The maximal effect was estimated at 83% inhibition (I-max). The concentration necessary to reach 50% of the maximal effect (IC50) was estimated at 4.86 ng/ml. After treatment discontinuation from 2 mg at steady-state, median time needed to recover lymphocyte levels to $0.6X10^9$/L, $1.5X10^9$/L and 90% of the baseline, are approximately 1, 5, and 6 days respectively. Clinically significant covariates were a gender effect on IC50, disease impact on baseline lymphocytes, and baseline effect on elimination rate (K-out). Overall, qualification and predictability of the model was acceptable.

Conclusions: For the first time, the relationship between siponimod doses and their impacts on lymphocytes dynamic has been characterized in HV and MS patients. Lymphocyte recovery time may be relevant for vaccinations, severe infections, therapy switch and other situations requiring reversal of pharmacodynamic effects.

P051

Brain MRI results of DECIDE: a randomized, double-blind trial of DAC HYP vs. IFNβ-1a in RRMS patients

DL Arnold[1,2], L Kappos[3], E Havrdova[4], K Selmaj[5], A Boyko[6], M Kaufman[7], H Wiendl[8], J Rose[9], S Greenberg[10], E Demirhan[11], M Sweetser[11], K Riester[11], J Elkins[11]
[1]NeuroRx Research, Montreal, QC, Canada, [2]McGill University, Montreal, QC, Canada, [3]University Hospital, Basel, Switzerland, [4]First School of Medicine, Charles University, Prague, Czech Republic, [5]Medical University of Lodz, Lodz, Poland, [6]Moscow Multiple Sclerosis Center, Moscow, Russian Federation, [7]Carolinas Medical Center, Charlotte, NC, United States, [8]University of Münster, Münster, Germany, [9]University of Utah Medical School, Salt Lake City, UT, United States, [10]Abbvie Biotherapeutics Inc, Redwood City, CA, United States, [11]Biogen Idec, Cambridge, MA, United States

Background: The humanized IgG1 monoclonal antibody daclizumab high-yield process (DAC HYP) is specific for CD25 (the alpha subunit of the human high-affinity interleukin-2 receptor). A previous randomized trial showed a 79% reduction in new Gd+ lesions at 52 weeks for DAC HYP 150mg once-monthly compared with placebo in patients with relapsing-remitting multiple sclerosis (RRMS).

Objectives: To determine the impact of DAC HYP versus interferon β-1a (IFNβ-1a) treatment on brain MRI activity in RRMS patients.

Methods: DECIDE is a randomized, double-blind, double-dummy, active-controlled, Phase 3 study. Patients were randomized 1:1 to subcutaneous (SC) DAC HYP (150 mg) once every 4 weeks or once weekly intramuscular (IM) IFN β-1a (30 mcg) for 96 to 144 weeks. The number of new or newly-enlarging T2 hyperintense lesions and total number and volume of new T1 hypointense, T2 hyperintense, and gadolinium-enhancing (Gd+)

lesions and change in whole brain volume over 96 weeks were measured by brain MRI. Treatment differences were evaluated using negative binomial regression model (number of new or newly-enlarging T2 hyperintense lesions at 24 weeks and 96 weeks) and proportional odds model (the number of new Gd+ lesions at 24 weeks and 96 weeks).

Results: A total of 1841 randomized patients were treated with either DAC HYP or IFN β-1a. At baseline, the mean number of T2 lesions was 50.5 (range 0 to 239) and < 1% of patients had 0, 7% between 1 to < 10, 38% between 10 to < 40, and 53% ≥40 T2 lesions. The mean (SD) baseline number of Gd+ lesions was 2.1 (5.9) and 44% of patients had ≥1 Gd+ lesions. Final MRI results will be presented.

Conclusions: The DECIDE study provides an assessment of the effect of DAC HYP on brain MRI activity in RRMS patients, as compared to IFN β-1a.

P052

Effect of bismuth subsalicylate on gastrointestinal events associated with delayed-release dimethyl fumarate: a double-blind, placebo-controlled study

C von Hehn[2], C Tornatore[1], J Li[2], TS Ma[3], J Walsh[2], J Zambrano[2]
[1]Department of Neurology, Georgetown University Hospital, Washington, DC, United States, [2]Biogen Idec, Inc., Cambridge, MA, United States, [3]PharmStats, Ltd., Escondido, CA, United States

Background: Delayed-release dimethyl fumarate (DMF) demonstrated efficacy and safety in relapsing-remitting multiple sclerosis in Phase 3 studies. Gastrointestinal (GI) events were common adverse events (AEs) associated with delayed-release DMF.

Objectives: Evaluate the effect of bismuth subsalicylate on GI events in healthy volunteers receiving delayed-release DMF in an 8-week, double-blind, placebo-controlled study.

Methods: Subjects were randomized 1:1 to receive bismuth subsalicylate (524 mg) or placebo 30 minutes prior to delayed-release DMF (120 mg twice daily [BID] for 7 days; 240 mg BID thereafter) in Weeks 1−4. All subjects received delayed-release DMF alone in Weeks 5−8. Subjects were prompted to record information about GI events daily using an eDiary device and two numerical rating scales, and returned to the study site at Weeks 2, 4, 6, and 8 for safety assessments.

Results: 175 subjects were enrolled, including 88 and 87 in the bismuth subsalicylate and placebo groups, respectively. One subject in each group discontinued due to GI AEs. The incidence of eDiary-reported GI events was highest in Week 1 and the prevalence of GI events declined thereafter. In Weeks 1−4, in the bismuth subsalicylate vs the placebo group, the incidence of overall GI events was 69.3% vs 68.6% and of acute GI events was 70.5% vs 68.2%; these rates are comparable to those seen in a previous study employing daily prompted self-report of GI events. The incidences of flatulence (38.6% vs 50.6%) and diarrhea (36.4% vs 48.2%) were lower in the bismuth subsalicylate group vs the placebo group, as were the mean worst severity scores for flatulence (1.1 vs 1.8; LS mean difference [95% CI]: 0.7 [0.1, 1.3]) and diarrhea (1.0 vs 1.6; LS mean difference [95% CI]: 0.6 [0.0, 1.2]. Percentages of subjects reporting worst severity scores of "severe" and "extreme" were lower in the bismuth subsalicylate group vs the placebo group for flatulence (severe, 1.1% vs 5.9%; extreme, 0% vs 0%), diarrhea (severe, 1.1% vs 9.4%; extreme, 0% vs 0%), upper abdominal pain (severe, 0% vs 8.2%; extreme, 0% vs 1.2%), indigestion (severe, 0% vs 3.5%; extreme, 0% vs 1.2%), and vomiting (severe, 1.1% vs 1.2%; extreme, 0% vs 1.2%). The duration of and percentage of days with individual acute GI events were comparable between groups.

Conclusions: Coadministration of bismuth subsalicylate with delayed-release DMF significantly reduced the severity and numerically reduced the incidence of flatulence and diarrhea.

P053

Comparable clinical and MRI efficacy of glatiramer acetate 40mg/mL TIW and 20mg/mL QD: results of a systematic review and meta-analysis

G Cutter[1], JS Wolinsky[2], G Comi[3], D Ladkani[4], V Knappertz[5,6], A Vainstein[7], N Sasson[7], O Khan[8,9]
[1]University of Alabama at Birmingham, Birmingham, AL, United States, [2]University of Texas, Health Science Center at Houston, Houston, TX, United States, [3]San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy, [4]Teva Pharmaceutical Industries, Petach Tiqva, Israel, [5]Teva Pharmaceutical Industries, Frazer, PA, United States, [6]Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany, [7]Teva Pharmaceutical Industries, Netanya, Israel, [8]Multiple Sclerosis Center, Wayne State University School of Medicine, Detroit, MI, United States, [9]Sastry Foundation Advanced Imaging Laboratory, Wayne State University School of Medicine, Detroit, MI, United States

Background: The GALA study in RRMS showed the safety and efficacy of glatiramer acetate (GA; Teva Pharmaceutical Ind.) 40mg 3 times weekly (TIW) vs. placebo (PBO). A systematic review and meta-analysis was performed to generate a robust estimate of the treatment effects of GA 20mg once-daily (QD) from PBO-controlled studies, and indirectly compare them with those of GA 40mg TIW.

Objectives: To assess the comparability of the GA 40mg TIW and GA 20mg QD efficacy profiles.

Methods: A systematic review for meta-analysis resulted in four eligible PBO-controlled studies with GA 20mg QD. Individual and aggregated meta-analyses to reach an overall estimate of GA 20mg QD treatment effect on annualized relapse rate (ARR) and number of new T2 lesions were performed. Risk ratios (RRs) from individual patient data were determined by negative binomial regression with treatment, baseline EDSS score, and number of relapses in the 2 years before entry as fixed effects, and study as a random effect in the model. A study-by-treatment interaction term was also included. For aggregate analyses, RRs were estimated using inverse variance for fixed effects and DerSimonian and Laird method for random effect. Statistical adjustments/weighting were used to account for differences in study designs, sizes, and drug exposure. The RRs for GA 20mg QD vs. PBO were descriptively compared with RRs for GA 40mg TIW vs. PBO in GALA for the same endpoints.

Results: GA 20mg QD showed ARR reductions of 28% vs. PBO in pooled individual patient data (RR=0.72, 95%CI 0.56, 0.93; *p*=.0112) and 30% in aggregate data (RR=0.70, 95%CI 0.60, 0.81; *p*< .0001). In GALA, the ARR was reduced by 34% with GA 40mg TIW vs. PBO (RR=0.66, 95% CI 0.54, 0.80; *p*< .0001).

Confidence intervals (CIs) for RRs of GA 20mg QD vs. PBO and GA 40mg TIW vs. PBO on ARR substantially overlapped, indicating similarity of GA 40mg TIW effect to that of GA 20mg QD. GA 20mg QD reduced new T2 lesions by 43% vs. PBO (RR=0.57, 95% CI 0.39, 0.81; p=.002) while in GALA, the GA 40mg TIW reduction was 35% (RR=0.65, 95%CI 0.55, 0.78; p< .0001). The RR CI for GA 40mg TIW was wholly contained within that of GA 20mg QD, suggesting a similar treatment effect on new T2 lesions.
Conclusions: In lieu of direct comparison, meta-analyses of data from large, prospective, well-designed and controlled trials support the similar efficacy of GA 40mg TIW and GA 20mg QD for reducing relapses and new T2 lesions in patients with RRMS.

P054

Switching from interferon β-1a IM to laquinimod: safety and efficacy results from the BRAVO study extension

TL Vollmer[1], N Ashtamker[2], Y Sidi[2], D Ladkani[3], T Gorfine[2], PS Sørensen[4]
[1]University of Colorado, Aurora, CO, United States, [2]Teva Pharmaceutical Industries, Netanya, Israel, [3]Teva Pharmaceutical Industries, Petach Tiqva, Israel, [4]Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Background: The BRAVO study assessed the efficacy, safety, and tolerability of laquinimod 0.6 mg vs. placebo in a double-blind design, with a reference arm of IFN β-1a IM (Avonex®) in a rater-blinded design. At the end of the core study, all patients were eligible to enter the open-label (OL) extension period of treatment with laquinimod 0.6 mg/day.
Objectives: To examine the safety and efficacy of switching from IFN β-1a IM to laquinimod.
Methods: Relapses and safety were assessed in patients who were initially treated with IFN β-1a IM and switched to laquinimod. Scheduled visits occurred every 6 months.
Results: No worsening in annualized relapse rate (ARR) was noted in 352 of 447 patients (78.7%) who switched from IFN β-1a IM to laquinimod during the extension. Cumulative ARR at the end of year 4 was maintained at 0.26. Comparison between patients who entered the extension versus those who terminated the core study early or chose not to continue to the extension (n=95) showed no differences in baseline demographics and disease characteristics. During the extension phase, 28 patients (8.0%) discontinued treatment due to withdrawn consent, and 10 (2.8%) due to an adverse event (AE). Serious AEs occurred in 20 subjects (5.7%), similar to the rate during the core study. Each event was reported in a single subject. Most AEs showed decreased incidence in the extension relative to the core study. An expected decrease in IFN β-1a IM known adverse drug reactions (ADRs) was noted, including thyroid-related (1.4% to 0.3%) and febrile and influenza-like AEs (61.4% to 7.4%). Increases in laquinimod ADRs were noted, including gastrointestinal (9.7% to 12.5%) and musculoskeletal (12.5% to 16.5%), but to a lesser degree when compared with the placebo group during the core study.
Conclusions: In the ensuing 2 years following the switch from IFN β-1a IM to laquinimod, the ARR remained stable. AEs following the switch showed the expected pattern of reduction in IFN β-1a IM related AEs and increase in laquinimod related AEs, with no new unexpected events.

P055

Effects of a very low fat, plant-food-based diet on fatigue in multiple sclerosis: report of a pilot trial

V Yadav[1,2], G Maracci[1,2], E Kim[1,2], R Spain[1,2], M Cameron[1,2], S Overs[3], A Lewis[1], J McDougall[4], J Lovera[5,6], C Murchison[1], DN Bourdette[1,2]
[1]Oregon Health & Science University, Neurology, Portland, OR, United States, [2]Portland Veterans' Affairs Medical Center, Neurology, Portland, OR, United States, [3]Novant Medical Group, Charlotte, OR, United States, [4]McDougall Research and Education Foundation, Santa Rosa, CA, United States, [5]Louisiana State University, Neurology, New Orleans, LA, United States, [6]Lsu, Neurology, Neurology, LA, United States

Background: Despite use of disease modifying therapies, poor quality of life in MS patients can be a significant management issue. Fatigue remains one of the most disabling symptoms of MS and effective treatment options remain limited.
Objectives: To assess the effects of a very low-fat, plant-food-based diet (< 10% of calories from fat) on fatigue and quality of life measures in relapsing remitting multiple sclerosis (MS) patients.
Methods: We conducted a randomized-controlled, rater-blinded, 1-year duration, study with subjects assigned to a very low-fat, plant-food-diet (diet) or wait-listed (control) group. Study outcomes: changes over one year in fatigue as measured by Fatigue Severity Score (FSS) and short version of Modified Fatigue Impact Score (MFIS) and quality of life by the SF-36 Score. Medications were unchanged during the trial.

Changes in blood lipids by nuclear magnetic resonance spectroscopy, blood insulin, C- reactive protein and 25 hydroxy vitamin D levels were assessed.
Results: 61 subjects with relapsing remitting MS [diet -32 (including 6 drop outs); control - 29 (including 2 drop outs)]; median age 41 (range 24-55), mean disease duration 5.3 (range 0.8-14.7), and mean EDSS 2.5 (range 0-4.5) were randomized. Linear regression indicated significant improvement in the diet group over the control group in the monthly change of fatigue as measured by FSS (monthly change compared to controls: -0.572 points/month; t=-2.40, p=0.017) and abbreviated MFIS (monthly change compared to controls: -0.277; t=-3.45, p< 0.001). There was a trend of improvement in the SF- 36 Mental score with the diet group showing an monthly score increase of 0.223 compared to controls (1.79 t-stat, p=0.075). Benefits on the fatigue measurements were observed within a month of beginning the intervention diet and were sustained at the same improved level throughout the year. Compliance based on monthly Food Frequency Questionnaire was excellent: Total fat intake of ~15% of calories in diet vs. ~ 40% in control. Results of changes in the fasting blood lipids, blood insulin and 25 hydroxy vitamin D levels will be presented.
Conclusions: A very-low fat, plant-food-based diet demonstrated significant improvement in fatigue and showed trends for improvement in mental health quality of life in the subjects over one year duration compared to controls. Studies with a larger sample size and longer follow-up are needed.

P056

Results from a randomized double-blind crossover study comparing oral L-carnitine versus placebo for the treatment of fatigue in multiple sclerosis

J-C Ouallet[1], D Laplaud[2], S Wiertlewski[2], M Debouverie[3], S Pittion[3], C Lebrun-Frenay[4], M Cohen[4], P Cabre[5], S Jeannin[5], D Brassat[6], G Chêne[7], J Asselineau[7], A Saubusse[8], D Djigo[8], J Chateauraynaud[8], B Brochet[8]

[1]Service de Neurologie, Hôpital Pellegrin CHU de Bordeaux, Bordeaux, France, [2]Service de Neurologie, Université de Nantes, Nantes, France, [3]CHU de Nancy, Service de Neurologie, Hôpital Central, Nancy, France, [4]CHU de Nice, Service de Neurologie, Hôpital Pasteur, Nice, France, [5]CHU de Fort-de-France, Service de Neurologie, Hôpital Pierre Zobda-Quitman, Fort-de-France, Martinique, [6]CHU de Toulouse, Service de Neurologie, Hôpital Purpan, Toulouse, France, [7]CHU de Bordeaux, Université de Bordeaux, Unité de Soutien à la Recherche Clinique et Épidémiologique du CHU de Bordeaux, Bordeaux, France, [8]CHU de Bordeaux, Service de Neurologie, Hôpital Pellegrin, Bordeaux, France

Background: There is no validated therapeutic strategy available to date in the treatment of Fatigue in MS. L-carnitine has been studied in some clinical trials but no placebo-controlled randomized study has been conducted to provide a reliable estimation of this drug's effect.

Objectives: To evaluate the efficacy and safety of L-carnitine versus placebo in the treatment of fatigue in patients with MS.

Methods: A randomized placebo-controlled multicenter double-blind crossover study was designed comparing L-carnitine treatment (2g oral solution, twice daily) versus placebo. Over a total of 9 months period, two 3 months periods with trial treatment were separated by a wash-out period of 3 months. ClinicalTrials.gov Identifier: NCT01149525.

Eligible MS patients were affected of fatigue for more than 3 months with global score on Modified Fatigue Impact Scale (MFIS)>45%.The primary outcome measure was the global score on the 21 item MFIS. Secondary outcome measures included the Fatigue Severity Scale (FSS), Fatigue Visual Analogic Scale (VAS), physical dimension scale of MFIS, and the SEP59 Quality Of Life scale (derived from the MSQOL-54, validated in French). Free carnitine and acyl-carnitine serum dosages were scheduled at baseline and at the end of study. A mixed linear regression model was used to assess the effect of the treatment and the treatment-period interaction.

Results: 59 patients were randomized to receive first L-carnitine treatment or placebo and 57 were analyzed on an intention-to-treat basis. Mean age was 45, 74% were women, and median EDSS was 3. At inclusion mean MFIS score was 71.3% (standard deviation [SD] 15.5) and mean FSS was 6.1 (SD 0.8). Adherence to study treatments was good and no significant unexpected adverse event was reported throughout the study. There was no difference in L-Carnitine treatment efficacy versus placebo for the primary end-point (-0.22 points, 95% confidence interval (95%CI)=[-5.80;5.36], p=0,94) and for any of the secondary end-points (FSS: -0.10 points, 95%CI=[-0.45;0.24], p=0,55; Except for VAS: 1.43 points, 95%CI=[0.22;2.65], p=0.02, in favor of placebo).

Conclusions: In this double-blind placebo-controlled trial, Oral L-Carnitine is not effective to treat MS fatigue at the global population level. Further evaluation of patients with carnitine deficiency is ongoing.This study confirms the fact that patient not deficient in carnitine doesn't need any supplementation.

P057

Delayed-release dimethyl fumarate and disability assessed by the multiple sclerosis functional composite: integrated analysis of DEFINE and CONFIRM

G Giovannoni[1], R Gold[2], L Kappos[3], DL Arnold[4], A Bar-Or[4], NC Kurukulasuriya[5], M Yang[5], SP Sarda[5]

[1]Queen Mary University of London, Blizard Institute, Barts and the London School of Medicine and Dentistry, London, United Kingdom, [2]St. Josef Hospital, Ruhr University, Bochum, Germany, [3]University Hospital, Basel Neurology, Basel, Switzerland, [4]McGill University, Montreal Neurological Institute, Montreal, QC, Canada, [5]Biogen Idec Inc., Cambridge, MA, United States

Background: Delayed-release dimethyl fumarate (DMF) demonstrated efficacy on clinical and radiological measures and an acceptable safety profile in patients with relapsing-remitting multiple sclerosis (RRMS) in the Phase 3 DEFINE and CONFIRM studies.

Objectives: Describe the effect of delayed-release DMF on the Multiple Sclerosis Functional Composite (MSFC), a multidimensional tool to assess disability, in a post hoc integrated analysis of DEFINE and CONFIRM.

Methods: Eligibility criteria included age 18-55 years, RRMS diagnosis (McDonald criteria), and EDSS score 0-5.0. Patients were randomized and received treatment with placebo (n=771), delayed-release DMF 240 mg twice (BID; n=769) or three times daily (TID; n=761), or glatiramer acetate (GA; n=350; reference comparator; CONFIRM only), for up to 2 years. The MSFC includes three components: Timed 25-Foot Walk (T25FW; measures walking speed), 9-Hole Peg Test (9-HPT; measures upper extremity function and dexterity), and Paced Auditory Serial Addition Test (PASAT-3; measures cognitive function). Positive change in the MSFC composite z-score indicates improvement. The analysis included patients receiving placebo or delayed-release DMF 240 mg BID (currently the approved dosing regimen in all regions).

Results: Statistically significant improvements with delayed-release DMF compared with placebo were seen on the MSFC composite z-score as well as each of the individual components of the MSFC. From baseline to 2 years, the mean (median) change in the placebo group vs the delayed-release DMF BID group was -0.053 (0.023) vs 0.054 (0.075) on the MSFC composite z-score (P=0.0001); -0.286 (-0.022) vs -0.088 (-0.013) on the T25FW (P=0.0351); 0.003 (0.012) vs 0.047 (0.054) on the 9-HPT (P=0.0112); and 0.123 (0.088) vs 0.178 (0.175) on the PASAT-3 (P=0.0016).

Conclusions: Compared with placebo, delayed-release DMF demonstrates improvement on the MSFC, indicating that DMF-treated patients did well on the measures of patient functioning that are relevant in MS.

P058

The efficacy of teriflunomide is evident before steady-state plasma concentrations are reached

JS Wolinsky[1], D Dukovic[2], P Truffinet[3], L Kappos[4], for the investigators of the Phase 2 Proof-of-Concept, TEMSO,

TOWER and TOPIC Studies, and the MRI-AC in
Houston, TX

[1]University of Texas Health Science Center at Houston,
Houston, TX, United States, [2]Sanofi, Bridgewater, NJ, United
States, [3]Genzyme, a Sanofi Company, Chilly-Mazarin, France,
[4]University Hospital Basel, Basel, Switzerland

Background: Teriflunomide is a once-daily oral immunomodulator approved for the treatment of patients with relapsing-remitting multiple sclerosis (MS). The teriflunomide clinical development program includes four monotherapy placebo-controlled studies. Teriflunomide has consistently demonstrated significant clinical and magnetic resonance imaging (MRI) benefits, and has a well-characterized safety profile. With both doses (14 mg and 7 mg), plasma accumulation of teriflunomide occurs slowly, with steady-state levels reached in 3-3.5 months. Analyses of data from the first few months of clinical trials enable estimates of the timing of onset of treatment effects.

Objectives: To assess the timing of onset of efficacy of teriflunomide through examining the relationships between pharmacodynamic (PD) effects, efficacy, and plasma concentration.

Methods: Integrated data from the TEMSO (NCT00134563) and TOWER (NCT00751881) pivotal phase 3 studies were used to model the pharmacokinetic (PK)/PD profile of teriflunomide and assess the relationship of plasma concentration to efficacy. Plots of Nelson-Aalen estimates of mean cumulative relapses over time based on integrated TEMSO/TOWER data were used to observe the timing of onset of the teriflunomide treatment effect on relapse. Data on effect on MRI outcomes were analyzed, as available, from 6 weeks in the phase 2 study (NCT01487096) and from 12 weeks in the TOPIC phase 3 study (NCT00622700). For cell counts, blood samples were taken at randomization, every 2 weeks for 24 weeks, then every 6 weeks until treatment end.

Results: Using the integrated data, PK/PD modeling showed that efficacy of teriflunomide was evident before plasma concentrations reached steady-state levels. Nelson-Aalen estimates of the mean functions for the number of relapses showed early separation of the teriflunomide 14-mg and 7-mg curves and the placebo curve, within 6 weeks of starting treatment. In the phase 2 study, combined unique active lesions (UALs) were reduced at 6 weeks with teriflunomide vs placebo; differences were significant at 12 weeks. In TOPIC, total lesion volume and UALs were reduced at 12 weeks with teriflunomide 14 mg vs placebo. Neutrophil and lymphocyte counts decreased within 6 weeks.

Conclusions: Findings from the teriflunomide clinical development program support the understanding that after initiating treatment, the effects of teriflunomide 14 mg on relapses, MRI outcomes, and laboratory parameters are evident before plasma concentrations have reached steady-state levels.

P059
Five-year follow-up of delayed-release dimethyl fumarate in relapsing-remitting multiple sclerosis: MRI outcomes from DEFINE, CONFIRM, and ENDORSE

NC Kurukulasuriya[8], DL Arnold[1,2], RJ Fox[3], R Gold[4],
E Havrdova[5], L Kappos[6], T Yousry[7], D MacManus[7],
R Zhang[8], M Yang[8], V Viglietta[8]
[1]NeuroRx Research, Montreal, AB, Canada, [2]Montreal
Neurological Institute, McGill University, Montreal,

AB, Canada, [3]Mellen Center for Multiple Sclerosis Treatment
and Research, Cleveland Clinic, Cleveland, OH, United States,
[4]St. Josef Hospital, Ruhr University, Bochum, Germany,
[5]Charles University, Department of Neurology, First Faculty of
Medicine, Prague, Czech Republic, [6]University Hospital, Basel
Neurology, Basel, Switzerland, [7]University College London
Institute of Neurology, Queen Square Multiple Sclerosis Centre,
NMR Research Unit, London, United Kingdom, [8]Biogen Idec
Inc., Cambridge, MA, United States

Background: Delayed-release dimethyl fumarate (DMF) demonstrated efficacy and safety in patients with relapsing-remitting multiple sclerosis (RRMS) in the 2-year, Phase 3 DEFINE and CONFIRM studies. ENDORSE is an ongoing, 5-year, dose-blind extension study of DEFINE/CONFIRM evaluating the long-term safety and efficacy of delayed-release DMF.

Objectives: To report integrated magnetic resonance imaging (MRI) outcomes with delayed-release DMF from DEFINE, CONFIRM, and ENDORSE.

Methods: In ENDORSE, patients randomized in DEFINE/CONFIRM to delayed-release DMF 240 mg twice (BID) or three times daily (TID) continued the same dosage. Patients randomized to placebo (PBO) or glatiramer acetate (GA) were re-randomized 1:1 to delayed-release DMF 240 mg BID or TID. Brain MRI scans were obtained yearly in ENDORSE, in the MRI cohort of patients. Although data were collected for both the twice- and thrice-daily DMF regimens, results are presented only for those patients receiving the approved, twice-daily dosage. Efficacy was analyzed (June 12, 2013 cutoff) by parent/extension study arm: BID/BID, PBO/BID, and GA/BID.

Results: Of the 982 MRI cohort patients who completed DEFINE/CONFIRM, 350 were dosed in ENDORSE (n=206 [BID/BID], 96 [PBO/BID], and 48 [GA/BID]). Among patients continuing delayed-release DMF (BID/BID) during the second year in ENDORSE, 68% were free of new/enlarging T2 lesions, 76% were free of new T1-hypointense lesions, and 88% were free of gadolinium-enhancing lesions. For patients switching from PBO to delayed-release DMF (PBO/BID), no new/enlarging T2 lesions were observed in 33% of patients during the second year on PBO in DEFINE/CONFIRM and 73% of patients during the second year on delayed-release DMF in ENDORSE.

Conclusions: Reduced frequency of new MRI lesions is maintained over 4 years among patients continuing delayed-release DMF therapy. After switching from PBO to delayed-release DMF, patients demonstrated MRI outcomes similar to those observed with delayed-release DMF in DEFINE/CONFIRM. Together with clinical efficacy and an acceptable safety profile, these results support the potential for delayed-release DMF as a long-term treatment option for patients with relapsing MS. Updated 5-year follow-up data are presented.

P060
Effect of teriflunomide on lymphocyte and neutrophil counts: pooled analyses from four placebo-controlled studies

G Comi[1], MS Freedman[2], L Kappos[3], AE Miller[4], TP
Olsson[5], JS Wolinsky[6], M Benamor[7], D Dukovic[8], P
Truffinet[7], PW O'Connor[9]
[1]University Vita-Salute San Raffaele, Milan, Italy, [2]University of
Ottawa and the Ottawa Hospital Research Institute, Ottawa, ON,

Canada, [3]University Hospital Basel, Basel, Switzerland, [4]Icahn School of Medicine at Mount Sinai, New York, NY, United States, [5]Karolinska Institute, Stockholm, Sweden, [6]University of Texas Health Science Center at Houston, Houston, TX, United States, [7]Genzyme, a Sanofi Company, Chilly-Mazarin, France, [8]Sanofi, Bridgewater, NJ, United States, [9]University of Toronto, Toronto, ON, Canada

Background: Teriflunomide is a once-daily oral immunomodulator approved for relapsing-remitting multiple sclerosis (MS). Teriflunomide is known to decrease the proliferation of stimulated lymphocytes via inhibition of dihydroorotate dehydrogenase activity that is required for de novo pyrimidine synthesis.

Objectives: To assess lymphocyte and neutrophil counts in pooled data from the placebo-controlled phase 2 (NCT01487096) and phase 3 TEMSO (NCT00134563), TOWER (NCT00751881), and TOPIC (NCT00622700) studies.

Methods: Patients with relapsing MS were randomized to receive once-daily teriflunomide 14 mg (n=1002), 7 mg (n=1045), or placebo (n=997). Blood samples were collected at randomization, every 2 weeks for 24 weeks, then every 6 weeks, and at treatment end.

Results: Mean baseline lymphocyte and neutrophil counts were similar across groups. Small reductions in mean lymphocyte/neutrophil counts were seen in patients receiving teriflunomide; mean counts remained within the normal range for most patients (lymphocytes, $1\text{-}4\text{x}10^9/\text{L}$; neutrophils, $2.5\text{-}7.5\text{x}10^9/\text{L}$). Mean (standard deviation [SD]) lymphocyte count reductions at Week 48 were: 14 mg, -0.27 $(0.45)\text{x}10^9/\text{L}$; 7 mg, -0.20 $(0.45)\text{x}10^9/\text{L}$; placebo, 0.01 $(0.50)\text{x}10^9/\text{L}$. Mean (SD) neutrophil count reductions at Week 48 were: 14 mg, -0.66 $(1.72)\text{x}10^9/\text{L}$; 7 mg, -0.41 $(1.57)\text{x}10^9/\text{L}$; placebo, -0.13 $(1.69)\text{x}10^9/\text{L}$. Decreases in mean values occurred within the first 12 weeks (lymphocytes) or 6 weeks (neutrophils) of treatment and stabilized thereafter. Lymphocyte and neutrophil count decreases returned to normal in the majority of patients before end of treatment. Protocols specified that patients with neutrophil counts $< 1\text{x}10^9/\text{L}$ were to discontinue treatment permanently. Eleven (1.1%; 14 mg), eight (0.8%; 7 mg), and one (0.1%; placebo) patients discontinued due to neutropenia or neutrophil count decrease as per the protocol requirement. Neutropenia serious adverse events (SAEs) were infrequent, as reported in seven (0.7%; 14 mg), two (0.2%; 7 mg), and three (0.3%; placebo) patients; there were no lymphopenia SAEs. No evidence of a link between neutrophil or lymphocyte count decreases and infection was observed.

Conclusions: Consistent with results from individual trials, pooled data from four studies of teriflunomide in patients with MS show small, reversible effects on lymphocyte and neutrophil counts. Limited impact on immune cell numbers without an associated increase in infection risk suggests teriflunomide is an immunomodulator with a minimal effect on immunity.

P061

Consistent effect of laquinimod on relapse-related and disability progression-related endpoints

<u>G Comi</u>[1], TL Vollmer[2], L Kappos[3], X Montalban[4], T Gorfine[5], N Sasson[5], V Knappertz[6,7]
[1]San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy, [2]University of Colorado, Aurora, CO, United States, [3]Clinical Research and Biomedicine, University Hospital Basel, Basel, Switzerland, [4]Hospital Universitari de

la Vall d'Hebron, Barcelona, Spain, [5]Teva Pharmaceutical Industries, Netanya, Israel, [6]Teva Pharmaceutical Industries, Frazer, PA, United States, [7]Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany

Background: Once-daily oral laquinimod 0.6mg has demonstrated efficacy in reducing relapse and disability-based outcomes. The effects of laquinimod on 3- and 6-month confirmed disability progression (CDP) are consistent, larger than expected based on relapse-related outcomes, and substantiated by a treatment effect for reducing brain tissue volume loss.

Objectives: To explore the potential influence of different baseline demographic and disease severity on the efficacy profile of laquinimod in the pooled phase III ALLEGRO and BRAVO data set.

Methods: Laquinimod treatment effects vs. placebo in subgroups of patients based on gender, age, baseline EDSS score (≤ 3 and > 3), baseline GdE T1 lesions (Y/N), and number of relapses in the 2 years prior to screening, as well as for patients with and without prior exposure to disease-modifying therapies for MS, were assessed. Additionally, impact of disease activity prior to inclusion (relapse rate) or at baseline (GdE T1 lesions), defined as 2 or more relapses in 1 year prior to screening, 2 or more GdE T1 lesions, and 2 or more relapses in the year prior to screening with GdE T1 lesions were assessed.

Results: The treatment effect on relapse rate was consistent for all defined subgroups even if effects sometimes varied in magnitude. The pronounced laquinimod treatment effect on time to 3- and 6-month CDP was also consistent among all subgroups tested. For example, for patients with EDSS score ≤ 3 or > 3 at entry, relapse rate reductions (RRR) were 20% and 25%, respectively, and reductions in 6-month CDP were 40% and 53%, respectively. For patient subgroups defined as having had 2 or more relapses in the year prior to screening with GdE T1 lesions, vs. those who did not, the RRRs were 30% and 20%, respectively, and reductions of 6-month CDP were 43% and 46%, respectively.

Conclusions: Observed laquinimod treatment effects are consistent across all subgroups studied. A substantial treatment effect on CDP was observed in patients with more advanced disability at baseline.

P062

Clinical efficacy of laquinimod 0.6mg once-daily in worsening relapsing-remitting multiple sclerosis defined by baseline EDSS over 3

<u>TL Vollmer</u>[1], G Comi[2], L Kappos[3], X Montalban[4], G Cutter[5], JR Steinerman[6], N Sasson[7], T Gorfine[7], V Knappertz[6,8]
[1]University of Colorado, Aurora, CO, United States, [2]San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy, [3]Clinical Research and Biomedicine, University Hospital Basel, Basel, Switzerland, [4]Hospital Universitari de la Vall d'Hebron, Barcelona, Spain, [5]University of Alabama at Birmingham, Birmingham, AL, United States, [6]Teva Pharmaceutical Industries, Frazer, PA, United States, [7]Teva Pharmaceutical Industries, Netanya, Israel, [8]Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany

Background: In patients (pts) with relapsing remitting MS (RRMS) who have demonstrated disease worsening and have

already reached an EDSS over 3, additional confirmed disability progression (CDP) would be more detrimental to everyday activities than progression from lower EDSS steps. Laquinimod, with its efficacy profile indicating a more pronounced effect on disability-related outcomes, could be an option for the treatment of this pt group.

Objectives: To determine the clinical efficacy profile of LAQ 0.6mg vs. PBO in the subgroup of RRMS pts in the phase III ALLEGRO and BRAVO studies with baseline (BL) EDSS scores over 3.

Methods: Pooled data from ALLEGRO and BRAVO pts (N=1990) were used in this *post hoc* analysis. Endpoints included ARR; time to CDP (defined as an increase from BL in EDSS score of ≥1 point if BL EDSS is ≤5, or of ≥0.5 point if BL EDSS >5), sustained for 3 or 6 months; and Multiple Sclerosis Functional Composite (MSFC). MRI endpoints included brain atrophy, measured percent brain volume change (PBVC), and cumulative numbers of gadolinium-enhancing (GdE) and new T2 lesions at months 12 and 24.

Results: Overall, 655 pts (33%; LAQ n=328, PBO n=327) had BL EDSS >3; mean (SD) BL EDSS was 4.1 (0.7). One-fourth (24.9%) had received prior MS treatment. Compared with the EDSS ≤3 subgroup, pts with BL EDSS >3 were older (mean age 41.3 vs. 36.5 years), had longer disease duration (5.2 vs. 3.7 years), and lower brain volume (1547 vs. 1601 cm^3) at BL. In the subgroup of RRMS pts with BL EDSS >3, LAQ significantly reduced ARR (25%, *p*=.012), 3-month CDP (40%, *p*=.0083), 6-month CDP (53%, *p*=.0009), and MSFC worsening (mean z-score difference of 0.25, *p*=.0009). Improvement on the MSFC was driven by a 59% improvement with LAQ on the T25FW component vs. PBO in these pts. LAQ also significantly reduced PBVC (adjusted mean Tx difference 0.39 [95%CI 0.21, 0.58]; *p*<.0001), and cumulative number of new T2 lesions (rate ratio 0.75 [95%CI 0.59, 0.96]; *p*=.021) vs PBO. The effect on cumulative number of GdE lesions was not statistically significant in this subgroup (rate ratio 0.83 [0.61, 1.13]; *p*=0.24).

Conclusions: Laquinimod demonstrated significant benefits in relapse, disability, ambulation, and MRI outcomes in patients with worsening MS who had reached an EDSS over 3 at baseline.

P063

The POPARTMUS French-Italian multicentric trial of postpartum progestin and estradiol in multiple sclerosis: MRI findings

F Durand-Dubief[1,2], M El-Etr[3], I Ionescu[1], L Bracoud[4], F Cotton[2,5,6], H Merle[1], C Cornu[7], B Frangoulis[1], L Remontet[8], N Bossard[8], L Durelli[9], E-E Baulieu[3], C Confavreux[1,6,10], S Vukusic[1,6,10], for the Investigators of the POPARTMUS Study

[1]Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, Neurologie A et Fondation Eugène Devic EDMUS pour la Sclérose en Plaques, Bron Cedex - Lyon, France, [2]CREATIS-LRMN, UMR 5220 CNRS & U 1044 INSERM & Université de Lyon, Villeurbanne, France, [3]INSERM, Le Kremlin-Bicêtre, France, [4]Bioclinica, Lyon, France, [5]Service de Radiologie - CHU Lyon, Centre Hospitalier de Lyon Sud, Pierre Bénite, France, [6]Université de Lyon, Lyon, France, [7]Hôpital Cardiologique Louis Pradel, Hospices Civils de Lyon, Centre d'Investigations Cliniques, Bron Cedex - Lyon, France, [8]Service de Biostatistique des Hospices Civils de Lyon, Lyon, France,

[9]University of Torino, Torino, Italy, [10]Centre des Neurosciences de Lyon, INSERM 1028 et CNRS UMR 5292, Equipe Neuro-Oncologie et Neuro-Inflammation, Lyon, France

Background: Women are affected by multiple sclerosis (MS) mainly in their childbearing years and the risk of relapse is particularly increased during the first trimester postpartum. POPARTMUS (NTC00127075) was a multicentric, randomized, double-blinded, placebo-controlled trial of progestin and estradiol, administered immediately after delivery for 12 weeks in 203 women with relapsing MS. Results showed no protective effect of sexual steroids on relapse rate after delivery and on the occurrence of new MRI lesions. Currently very few longitudinal MRI data are available in the MS literature to characterize this particular period in a woman's life.

Objectives: To describe MRI findings in the 28 women included in the MRI subgroup.

Methods: 28 patients out of 203 underwent the MRI follow-up. Inclusion and randomization took place before the end of the 36th week of amenorrhea. Neurologic evaluation and MRI acquisition were scheduled at week 36 of amenorrhea and at weeks 4, 8, 12 and 24 after delivery. MRI scans were assessed by a single neuro-radiologist blinded to group treatment and patient ID. The number of active MRI scans was assessed. A follow-up MRI was defined as active if presenting at least one new lesion (eg. new or growing T2 lesions and/or Gadolinium-enhanced T1 lesions (T1Gd) lesions, compared to previous timepoint). The cumulative number of new lesions was measured at each MRI timepoint. The volume of T2 and T1Gd lesions was also reported.

Results: 18 of the 28 women had at least one active MRI after delivery with no significant difference between treated and placebo groups. Mean cumulative number of new lesions was 21.9 in the treated group and 19.4 in the placebo group at week 12 and 27 vs 24.7 at week 24. Mean cumulative number of T1Gd lesions was 12.7 in the treated group and 8.2 in the placebo group at week 12, and 13.8 vs 10.1 at week 24. Mean volumes of T2 lesions were 10161.6, 9356.7, 9649.1 and 7967.1 mm^3 in the treated group versus 13434.1, 14596.9, 15506.5 and 16312.4 mm^3 in the placebo group at weeks 4, 8, 12 and 24 respectively. Mean volumes of T1Gd lesions were 626.1, 293.7, 251.2 and 28.2 mm^3 in the treated group versus 172.2, 165.1, 126.0 and 133.2 mm^3 in the placebo group at weeks 4, 8, 12 and 24 respectively.

Conclusions: MRI data confirm the absence of efficacy of sexual steroids in the POPARTMUS study. Nevertheless, this MRI cohort of postpartum MS women is unique and will be further investigated. Pooled post-hoc analysis will include brain atrophy and diffusion-weighted imaging.

P064

Long-term efficacy of delayed-release dimethyl fumarate in newly diagnosed patients with RRMS: an integrated analysis of DEFINE, CONFIRM, and ENDORSE

R Gold[1], G Giovannoni[2], JT Phillips[3], RJ Fox[4], A Zhang[5], NC Kurukulasuriya[5]

[1]St. Josef Hospital, Ruhr University, Bochum, Germany, [2]Queen Mary University of London, Blizard Institute, Barts and the London School of Medicine and Dentistry, London, United Kingdom, [3]Baylor Institute for Immunology Research, Multiple

Sclerosis Program, Dallas, TX, United States, [4]Cleveland Clinic, Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland, OH, United States, [5]Biogen Idec Inc., Cambridge, MA, United States

Background: Delayed-release dimethyl fumarate (DMF) demonstrated efficacy and safety in the 2-year, Phase 3 DEFINE and CONFIRM studies across a broad range of patients with relapsing-remitting multiple sclerosis (RRMS). ENDORSE is an ongoing, 5-year, dose-blind extension study evaluating the long-term safety and efficacy of delayed-release DMF.

Objectives: Report long-term clinical outcomes with delayed-release DMF in newly diagnosed patients from DEFINE, CONFIRM, and ENDORSE.

Methods: In ENDORSE, patients randomized in DEFINE/CONFIRM to delayed-release DMF 240 mg twice (BID) or three times daily continued on the same dosage. Patients randomized to placebo (PBO) or glatiramer acetate (GA) were re-randomized 1:1 to delayed-release DMF 240 mg BID or TID. Efficacy was analyzed (June 12, 2013 cutoff) by treatment arm in the parent study. Only results for delayed-release DMF 240 mg BID in ENDORSE are reported, as this represents the approved maintenance dosage in the United States and European Union. The GA arm was excluded from the parent analysis of newly diagnosed patients in DEFINE and CONFIRM. "Newly diagnosed" was defined as diagnosed within 1 year prior to parent study entry and either treatment naive or previously treated with corticosteroids alone. BID/BID patients remaining on study received at least 4 years of continuous delayed-release DMF treatment (2 years parent study, 2 years ENDORSE); those remaining on study who switched from PBO (PBO/BID) received at least 2 years of delayed-release DMF treatment (ENDORSE only).

Results: The newly diagnosed population included 144 BID/BID and 85 PBO/BID patients (median [range] treatment duration: 4.1 [0.6-5.7] and 3.9 [0.5-5.6] years, respectively). Over the entire observation period, the annualized relapse rate (ARR) (95% confidence interval [CI]) in the newly diagnosed population was 0.142 (0.11, 0.19) in BID/BID and 0.175 (0.12, 0.26) in PBO/BID. The Kaplan-Meier estimated proportion of patients with confirmed 24-week disability progression (95% CI) was 0.148 (0.07, 0.29) in BID/BID and 0.205 (0.13, 0.31) in PBO/BID.

Conclusions: After 4 years median follow-up, sustained treatment with delayed-release DMF demonstrated a strong effect on ARR and disability progression in newly diagnosed RRMS patients. Together with an acceptable safety profile, these findings support the potential for delayed-release DMF as a valuable long-term treatment option in this population and are consistent with the beneficial effects of early treatment.

P065
Efficacy of delayed-release dimethyl fumarate for RRMS in prior interferon users in the DEFINE and CONFIRM studies

Ó Fernández[1], G Giovannoni[2], RJ Fox[3], R Gold[4], JT Phillips[5], M Okwuokenye[6], A Zhang[6], NC Kurukulasuriya[6]

[1]Hospital Regional Universitario, Málaga University, Department of Neurology, IBIMA (Instituto de Investigación Biomédica de Málaga), Málaga, Spain, [2]Queen Mary University

of London, Blizard Institute, Barts and the London School of Medicine and Dentistry, London, United Kingdom, [3]Cleveland Clinic, Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland, OH, United States, [4]St. Josef Hospital, Ruhr University, Bochum, Germany, [5]Baylor Institute for Immunology Research, Multiple Sclerosis Program, Dallas, TX, United States, [6]Biogen Idec Inc., Cambridge, MA, United States

Background: Delayed-release dimethyl fumarate (DMF) improved relapse outcomes and was associated with an acceptable safety profile in the 2-year Phase 3 DEFINE and CONFIRM studies.

Objectives: To report the effects of delayed-release DMF on annualized relapse rate (ARR) in patients with relapsing-remitting multiple sclerosis (RRMS) from DEFINE and CONFIRM who had received prior interferon (IFN) treatment.

Methods: Eligibility criteria included age 18-55 years, RRMS diagnosis, and Expanded Disability Status Scale (EDSS) score of 0-5.0. Patients were randomized to receive delayed-release DMF 240 mg twice (BID) or three times daily, placebo, or subcutaneous glatiramer acetate (reference comparator; CONFIRM only) for up to 96 weeks. Prior IFN users were defined as patients previously treated with any IFN beta-1a or beta-1b therapy (Avonex, Betaseron, or Rebif) only. The adjusted ARR at 2 years was based on negative binomial regression, adjusted for baseline EDSS (≤2.0 vs >2.0), age (< 40 vs ≥40 years), region, and number of relapses in the year prior to study entry. Results from patients treated with delayed-release DMF 240 mg BID (currently the approved dosage in all regions) are reported.

Results: The integrated intent-to-treat population included 771 placebo and 769 delayed-release DMF patients, of whom 169 and 172 patients, respectively, were prior IFN users. In the prior IFN users, the ARR (95% confidence interval [CI]) at 2 years was significantly decreased with delayed-release DMF BID (0.215 [0.164, 0.282]) versus placebo (0.378 [0.300, 0.475]) (rate ratio of DMF BID vs placebo [95% CI]: 0.568 [0.406, 0.795]; p=0.0010). The ARR at 2 years in prior IFN users was similar to that in the overall ITT population (0.19 with delayed-release DMF BID, 0.37 with placebo; p< 0.0001). Additional analyses, including results by number of prior IFN treatments, will be presented.

Conclusions: Delayed-release DMF BID improved relapse outcomes in patients with RRMS who only received prior treatment with IFN. The ARR in those subjects was similar to that in the overall study population.

P066
Long-term follow-up of the safety of delayed-release dimethyl fumarate in RRMS: interim results from the ENDORSE extension study

C Pozzilli[1], JT Phillips[2], RJ Fox[3], K Selmaj[4], R Zhang[5], M Novas[5], MT Sweetser[5], R Gold[6]

[1]Sapienza University of Rome, Rome, Italy, [2]Baylor Institute for Immunology Research, Multiple Sclerosis Program, Dallas, TX, United States, [3]Cleveland Clinic, Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland, OH, United States, [4]Medical University of Lodz, Lodz, Poland, [5]Biogen Idec Inc., Cambridge, MA, United States, [6]St. Josef Hospital, Ruhr University, Bochum, Germany

Background: The efficacy and safety of oral delayed-release dimethyl fumarate (DMF) was demonstrated in patients with relapsing−remitting multiple sclerosis (RRMS) in the Phase 3 DEFINE and CONFIRM studies. ENDORSE is an ongoing, 5-year, dose-blind extension study evaluating long-term safety and efficacy.

Objectives: To report safety outcomes from ENDORSE, investigating the longer-term effects of delayed-release DMF.

Methods: Patients randomized to delayed-release DMF 240 mg twice (BID) or three times daily (TID) in DEFINE/CONFIRM continued on the same dosage in ENDORSE. Patients randomized to placebo (PBO; DEFINE/CONFIRM) or glatiramer acetate (GA; CONFIRM) were re-randomized 1:1 to delayed-release DMF 240 mg BID or TID. Adverse events (AEs) were analyzed according to treatment arm in the parent/extension study: BID/BID, TID/TID, PBO/BID, PBO/TID, GA/BID, and GA/TID.

Results: As of the June 12, 2013 data cut, mean follow-up in each group in the safety population was as follows: BID/BID (n=501), 30.9 mo; TID/TID (n=501), 30.5 mo; PBO/BID (n=249), 27.9 mo; PBO/TID (n=248), 26.7 mo; GA/BID (n=118), 25.5 mo; and GA/TID (n=119), 23.3 mo. A total of 445 patients (435 continuers) had been exposed to delayed-release DMF BID, and 427 patients (416 continuers) had been exposed to delayed-release DMF TID cumulatively for at least 4 years in DEFINE/CONFIRM and ENDORSE. Overall incidence of AEs in each group was as follows: BID/BID, 89%; TID/TID, 90%; PBO/BID, 93%; PBO/TID, 90%; GA/BID, 86%; and GA/TID, 84%. Incidence of serious AEs by group was: BID/BID, 18%; TID/TID, 19%; PBO/BID, 22%; PBO/TID, 15%; GA/BID, 13%; and GA/TID, 18%. The incidence of discontinuations due to AEs was 4%-6% and 14%-23% in patients continuing and new to delayed-release DMF, respectively. The incidence of serious infections was ≤3% in all treatment groups, with no confirmed opportunistic infections. There were no new findings in hematologic outcomes compared with DEFINE/CONFIRM. Hepatic AEs occurred in ≤3% of patients in any treatment group; there was no evidence of increased risk of renal or urinary events. There were 20 malignancies in 19 patients (11 continuing treatment and eight new to delayed-release DMF). There were four deaths, none of which were considered related to study drug. Updated safety data with longer-term follow-up will be presented.

Conclusions: Sustained treatment with delayed-release DMF continues to demonstrate an acceptable safety profile with no new or worsening safety signals in patients with RRMS.

P067

Effect of peginterferon beta-1a on MRI measures and freedom from measured disease activity: 2-year results from the phase 3 ADVANCE study

DL Arnold[1,2], PA Calabresi[3], BC Kieseier[4], SI Sheikh[5], A Deykin[5], S Liu[5], X You[5], B Sperling[5], S Hung[5]
[1]Montreal Neurological Institute, McGill University, Montreal, QC, Canada, [2]NeuroRx Research, Montreal, QC, Canada, [3]Johns Hopkins University, Department of Neurology, Baltimore, MD, United States, [4]Heinrich-Heine University, Department of Neurology, Düsseldorf, Germany, [5]Biogen Idec Inc., Cambridge, MA, United States

Background: Subcutaneous (SC) peginterferon beta-1a (PEG-IFN) provided improvements in clinical and magnetic resonance imaging (MRI) outcomes versus placebo at Year 1 of the Phase 3 ADVANCE study in relapsing-remitting multiple sclerosis (RRMS), with a safety profile reflecting that of established interferon beta-1a therapies.

Objectives: Here we report the effect of PEG-IFN on MRI lesions, and freedom from measured disease activity (FMDA: absence of clinical [relapses and 12-week sustained disability progression] and MRI [gadolinium-enhancing and new or newly-enlarging T2 hyperintense lesions] disease activity) over 2 years of treatment.

Methods: After completing Year 1 of ADVANCE, patients who received placebo during Year 1 were re-randomized to SC PEG-IFN 125 μg administered Q2W or Q4W. Patients randomized to PEG-IFN in Year 1 remained on the same dosing regimen in Year 2 (continuous PEG-IFN Q2W or Q4W).

Results: In Year 2, the mean number of new or newly-enlarging T2 lesions was numerically lower (Q2W 1.9; Q4W 5.6) than in Year 1 (Q2W 4.1; Q4W 9.4). Over 2 years, versus patients originally assigned to placebo, those on continuous PEG-IFN had significant reductions in new or newly-enlarging T2 hyperintense (Q2W 67%, p< 0.0001; Q4W 16%, p=0.097), T1 hypointense (Q2W 59%, p< 0.0001; Q4W 12%, p=0.11), and gadolinium-enhancing (Q2W 60%, p=0.0002) lesions; mean number of gadolinium-enhancing lesions was increased by 40% in patients on PEG-IFN Q4W over 2 years (p=0.22). Relative to those patients receiving continuous PEG-IFN Q4W, patients receiving continuous PEG-IFN Q2W had significant reductions in new or newly-enlarging T2 hyperintense (60%), T1 hypointense (53%) and gadolinium-enhancing (71%) lesions (all p< 0.0001). At Year 2 of ADVANCE, significantly higher proportions of patients receiving continuous PEG-IFN Q2W had FMDA (25.9%), compared with those receiving continuous PEG-IFN Q4W (13.5%; odds ratio [OR] of FMDA vs. Q2W: 0.447; p< 0.0001), and those patients switched to PEG-IFN from placebo (9.9%; OR of FMDA vs. Q2W: 3.192; p< 0.0001).

Conclusions: The efficacy of PEG-IFN on MRI endpoints is maintained beyond 1 year with greater effects observed with Q2W versus Q4W dosing. During Year 2 of the ADVANCE study, significantly more patients receiving continuous PEG-IFN Q2W had FMDA, versus those receiving continuous PEG-IFN Q4W or those switched to PEG-IFN from placebo.

P068

Ambulation benefit with laquinimod in patients with worsening MS (EDSS over 3) is consistent with reduction in confirmed disability progression

TL Vollmer[1], G Comi[2], G Cutter[3], G Giovannoni[4], JR Steinerman[5], N Sasson[6], T Gorfine[6], V Knappertz[5,7]
[1]University of Colorado, Aurora, CO, United States, [2]San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy, [3]University of Alabama at Birmingham, Birmingham, AL, United States, [4]Hospital Universitari de la Vall d'Hebron, Barcelona, Spain, [5]Teva Pharmaceutical Industries, Frazer, PA, United States, [6]Teva Pharmaceutical Industries, Netanya, Israel, [7]Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany

Background: In pooled data from the Phase III ALLEGRO and BRAVO studies of oral laquinimod (LAQ) 0.6mg once-daily (QD) vs. placebo (PBO) in RRMS, a 46% reduction in 6-month confirmed disability progression (CDP) (Vollmer, ECTRIMS 2011) was not accompanied by a significant treatment (Tx) effect on the Multiple Sclerosis Functional Composite (MSFC). However, for a subgroup of LAQ-treated patients (pts) with worsening MS (EDSS >3 at baseline [BL]), a 53% reduction in 6month CDP was accompanied by a significant MSFC effect vs. PBO.

Objectives: To investigate LAQ 0.6mg QD Tx effects on individual MSFC components in the pooled ALLEGRO and BRAVO pt subgroup with BL EDSS score >3, and to determine the association between MSFC component scores and improvements in CDP.

Methods: Pooled data from ALLEGRO and BRAVO (N=1990) were used for this *post hoc* analysis of LAQ vs. PBO Tx effects on change in MSFC subscores at 24 months for the Paced Auditory Serial Addition Test (PASAT), 9-Hole Peg Test (9HPT), and Timed 25-Foot Walk (T25FW), in pts with EDSS >3 at BL. Adjusted mean z-score differences and 95%CIs were evaluated by ANCOVA. CDP was defined as an increase of 1 point if BL EDSS was ≤5.0, or of ≥0.5 point if BL EDSS was 5.5.

Results: Overall, 655 pts (33%) had a BL EDSS score >3 (LAQ n=328, PBO n=327), with a mean (SD) BL EDSS score of 4.1 (0.7). At BL, pts in the EDSS >3 subgroup were older than pts with BL EDSS ≤3 (mean age 41 vs. 37 years, respectively), had longer disease duration (5.2 vs. 3.7 years), and less brain volume (1547 vs. 1601 cm³). Mean (SD) T25FW time at BL was 8.29 (6.8) seconds (5.40 [5.3] seconds in the EDSS ≤3 subgroup). A 59% LAQ Tx effect on mean [SE] T25FW time (-2.79 [0.96] seconds, 95%CI -4.66, -0.92; *p*=.0035) appeared to drive the overall MSFC benefit in the EDSS >3 subgroup. There was no significant difference between LAQ and PBO for change in PASAT or 9HPT z-scores, though change directions favored LAQ. Further, an interaction between LAQ Tx effect on T25FW and CDP was found: pts on PBO in the EDSS >3 subgroup who also showed CDP declined by 8.6 seconds more than equivalent LAQ-treated pts.

Conclusions: In pts with worsening MS and EDSS >3 at BL, LAQ was associated with a substantial benefit on ambulatory function as measured by the T25FW, consistent with LAQ CDP benefit in these pts.

P069
Laquinimod effect on confirmed disability progression: minimal mediation by relapse or T2 lesions reduction

MP Sormani[1], TL Vollmer[2], G Comi[3], Y Sidi[4], JR Steinerman[5], T Gorfine[4], V Knappertz[5,6]

[1]University of Genoa, Genoa, Italy, [2]University of Colorado, Aurora, CO, United States, [3]San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy, [4]Teva Pharmaceutical Industries, Netanya, Israel, [5]Teva Pharmaceutical Industries, Frazer, PA, United States, [6]Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany

Background: Patients (pts) with RRMS treated with oral laquinimod (LAQ) 0.6mg QD had large, consistent reductions in 3- and 6-month confirmed disability progression (CDP) vs. placebo (PBO) in the phase III ALLEGRO and BRAVO trials. LAQ had a more pronounced effect on indices of underlying neurodegeneration (CDP, brain tissue loss) than on markers of acute inflammation

(relapse, new T2 lesions). The extent to which the LAQ mechanism on CDP overlaps with the mechanism for reducing acute inflammatory events is unknown. In a recent *post hoc* analysis, fingolimod treatment (Tx) effect on CDP was substantially (60%) mediated by its effect on relapses in the first study year (Sormani, 2013).

Objectives: To determine the proportion of LAQ 0.6mg Tx effects on CDP mediated by its effect on relapse and new T2 lesions.

Methods: From pooled individual pt data in ALLEGRO and BRAVO, CDP (increase of ≥1 EDSS point from baseline [BL] if BL EDSS ≤5, or of ≥0.5 if BL EDSS >5, sustained 3 or 6 months) was assessed by adjusted logistic regression model with BL EDSS and log of the number of relapses in the 2 years before screening as covariates. Numbers of relapses and new T2 lesions in study year 1 were then independently added to the model. The proportion of Tx effect (PTE) on CDP explained by each potential surrogate was assessed using Freedman's formula (1992). Also assessed was intramuscular (IM) IFNβ-1a PTE on 3-month CDP mediated by its effect on relapses and new T2 lesions in BRAVO study year 1.

Results: Effect sizes of 3- and 6-month CDP reduction with LAQ vs. PBO changed minimally when year 1 relapses were included in the logistic model, indicating LAQ effects on 3- and 6-month CDP were only marginally mediated by its effect on relapse (PTE=19% and PTE=11%, respectively). CDP reductions with LAQ vs. PBO were similar after adjusting for new T2 lesions at year 1 (PTE=0%, both 3- and 6-month CDP). In BRAVO, compared with LAQ, IFNβ-1a effects were mediated by relapses and new T2 lesions to a greater extent: Relapse PTE was 18% with LAQ vs. 31% with IFNβ-1a, and T2 lesion PTE was 0% with LAQ and 36% for IFNβ-1a.

Conclusions: These mediation data suggest that most of the LAQ effect on disability reduction is explained by mechanisms other than suppression of acute inflammation. LAQ appears to have a different mechanism than those of all currently approved MS treatments.

P070
Laquinimod disability progression effects are maintained with increasingly rigorous confirmation time intervals

G Comi[1], TL Vollmer[2], L Kappos[3], X Montalban[4], N Sasson[5], T Gorfine[5], V Knappertz[6,7]

[1]San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy, [2]University of Colorado, Aurora, CO, United States, [3]Clinical Research and Biomedicine, University Hospital Basel, Basel, Switzerland, [4]Hospital Universitari de la Vall d'Hebron, Barcelona, Spain, [5]Teva Pharmaceutical Industries, Netanya, Israel, [6]Teva Pharmaceutical Industries, Frazer, PA, United States, [7]Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany

Background: Oral laquinimod 0.6mg once-daily (QD) demonstrated consistent reductions of 3-month confirmed disability progression (CDP) in the phase III ALLEGRO and BRAVO trials.

Objectives: To explore the durability of laquinimod effect on CDP, additional analyses were performed utilizing increasingly rigorous durations for disability confirmation.

Methods: Using pooled data from the ALLEGRO and BRAVO trials, laquinimod effects on 6-, 9-, and 12-month CDP were analyzed. CDP was defined as an increase in EDSS of ≥1 point from baseline for subjects with baseline EDSS ≤5.0, or an increase in EDSS of ≥0.5 point from baseline for subjects with baseline EDSS of 5.5. In order to have a confirmation of disease progression, the increased EDSS value compared to the reference value had to be increased at all the time points. Therefore, all initial progressions for patients with 12-month CDP events had to occur in the first study year.

Results: The treatment effect of laquinimod on CDP was maintained over all tested confirmation intervals. The hazard ratios of the treatment effect were 0.66, 0.54, 0.53, and 0.55 for 3, 6, 9, and 12-months CDP, respectively; p< .005, all comparisons. As expected, there was a reduction in the incidence of CDP over time demonstrated for the placebo group: proportions of placebo patients with CDP at 3, 6, 9, and 12 months were 15%, 12%, 9% and 7%, respectively. No baseline demographic, clinical, or MRI factors were predictive of CDP at the different time points.

Conclusions: Despite increasingly demanding criteria for confirmed disability progression, a profound effect of laquinimod for reducing disability progression was consistently demonstrated.

P071
Temporal pattern of laboratory changes with laquinimod treatment

TL Vollmer[1], G Comi[2], PS Sørensen[3], N Sasson[4], T Gorfine[4], V Knappertz[5,6]

[1]University of Colorado, Aurora, CO, United States, [2]San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy, [3]Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark, [4]Teva Pharmaceutical Industries, Netanya, Israel, [5]Teva Pharmaceutical Industries, Frazer, PA, United States, [6]Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany

Background: The precise mechanism of action of laquinimod and the onset of its activity in multiple sclerosis (MS) patients are currently unknown. When 0.6mg of laquinimod is administered, several laboratory parameters are altered in a time-dependent fashion.

Objectives: To characterize the magnitude and temporal pattern of laboratory changes in hepatic, hematological, and other laboratory parameters following laquinimod administration.

Methods: Laquinimod 0.6 mg/day was administered to a total of 983 MS patients for up to 2 years as part of the pivotal double-blind, placebo-controlled relapsing-remitting MS studies, ALLEGRO and BRAVO. Blood samples from these studies were analyzed by a central lab, including levels of aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transpeptidase [GGT], and a complete hematological blood count, as well as C-reactive protein and fibrinogen.

Results: Liver enzymes: Elevations generally occurred within 6 months after initiation of treatment and were mostly mild and asymptomatic. Fibrinogen: A small increase in the group mean level of fibrinogen (well below the normal upper limit value) was already demonstrated after the first month of treatment; returned to baseline at month 6 on drug, without further increase during 3 years of follow up. CRP: No differences were noted between placebo and laquinimod treated subjects at any time during study. White Blood Cells: A small increase in the group mean level (well below the normal upper limit value), consistent across subtypes, was seen after the first 2 months of treatment and remained stable thereafter for the 3 years of follow up. Hemoglobin: A mild, asymptomatic, nonprogressive decrease in Hgb level occurred early after initiation of treatment and was usually reversible without cessation of therapy or need for anti-anemic preparations. Platelets: A small decrease in platelets was noted that followed the same temporal pattern.

Conclusions: Laquinimod-induced laboratory changes followed a stereotypical temporal pattern, with mild changes occurring in the first months of treatment that then stabilized or reverted to baseline levels. This pattern suggests an initial induction followed by adaptive responses. These changes were nonprogressive and asymptomatic.

P072
Effect of high- dose erythropoietin on clinical disability and MRI in patients with progressive multiple sclerosis

KI Schreiber[1], M Magyari[1], FT Sellebjerg[1], P Iversen[2], L Börnsen[3], RL Ratzer[1], CG Madsen[2], JR Christensen[1], H Siebner[2], E Garde[4], PS Sorensen[1]

[1]Rigshospitalet, Danish MS Research Center, Copenhagen, Denmark, [2]University Hospital Hvidovre, Danish Centre for Magnetic Resonance, Copenhagen, Denmark, [3]Rigshospitalet, Danish Multple Sclerosis Research Center, Copenhagen, Denmark, [4]University Hospital Hvidovre, Danish Research Centre for Magnetic Resonance, Copenhagen, Denmark

Background: Erythropoietin, (EPO) a haematopoietic growth factor may be neuroprotective and therefore a possible therapy for progressive Multiple Sclerosis (MS).

Objectives: To evaluate the effect of recombinant human erythropoietin treatment on clinical outcome measures in patients with secondary or primary progressive MS (SPMS and PPMS).

Methods: Patients with PPMS or SPMS without relapses during the last year, aged 19 to 60 years, and a disease duration of at least 2 years were included if they had clinically progressed within the prior 2 years. EDSS was 4.0-6.5. Main exclusion criteria were steroid therapy, interferon-beta or glatiramer acetate therapy in the last month, or therapy with any other immunosuppressive drugs 6 months prior to enrolment. Patients with cardiac, haematological, renal or psychiatric disease were excluded. The study was a single-centre, double-blind, placebo-controlled, parallel group trial.It was investigator driven. EPO (48000 IU) or placebo was given intravenously 17 times during the first 24 weeks. All patients received Methylprednisolone 1 gr i.v. prior to the first and second dose of EPO / placebo. The primary outcome measure was the change from baseline to 24 weeks in a composite score of maximum gait distance, 9-hole peg test, and TRAIL making B.

Results: 56 patients were screened and 52 were randomized to either EPO (26) or placebo (26). At baseline the demographic characteristics were balanced. Bloodletting was done when the haematocrit increased to more than 0.50 for men and more than 0.48 for women. In the EPO group 16 had at least 1 bloodletting. When this need was reiterated and/or patients had side effects such as headache, flushing and increasing blood pressure, the dose of EPO was subsequently reduced to 30000 IU. In the EPO group

10 of the 26 had reduced doses. We found no difference in the primary outcome between the EPO and the placebo group in an intention-to-treat analysis (p=0.22) or in a per-protocol analysis (patients who received a minimum of 14 doses) (p=0.12). There were no significant differences in the changes measured for secondary outcomes, neither the clinical nor MRI measures.

Conclusions: This treatment trial of high dose EPO did not reveal any beneficial effect on clinical disability in SPMS or PPMS after 24 weeks of treatment and does not warrant a larger scaled trial.

P073

Quantifying the effect of natalizumab on the total disability burden of MS patients in AFFIRM using an exploratory area under the curve analysis

RA Rudick[1], S Shang[2], Q Dong[2], D Paes[2], D Mikol[2], S Belachew[2]
[1]Mellen Center, Cleveland Clinic Foundation, Cleveland, OH, United States, [2]Biogen Idec, Cambridge, MA, United States

Background: MS patients can have fluctuating and variable disease courses. Confirmed Expanded Disability Status Scale (EDSS) progression and improvement measures may not capture all the relevant changes in disability that occur in a clinical trial.

Objectives: To assess the treatment effect of natalizumab on disability changes over time using an exploratory analysis that captures patient EDSS worsening and improvement over the full time of the AFFIRM trial.

Methods: AFFIRM was a phase III, randomized, placebo-controlled, clinical trial for relapsing MS patients; EDSS assessments were performed every 3 months. EDSS scores were plotted over time for each patient (natalizumab, n=627; placebo, n=315). The area under the EDSS/time curve was calculated (using the trapezoidal rule[1]), then the product of the patient's baseline EDSS score and the trial duration was subtracted from it, the result was defined as the area under the curve (AUC) with units in EDSS years. A positive AUC indicates a net worsening in EDSS over time from baseline; a negative AUC indicates a net improvement. Least squares (LS) mean AUC, adjusted for baseline EDSS, was compared between treatment groups using ANCOVA on rank test. Patient proportions with AUC ≥ 1.0, ≥ 1.5, or ≥ 2.0 EDSS years were compared by Fisher's exact test.

Results: Natalizumab patients had a net improvement in disability over time (-0.15 EDSS years) while placebo had a net worsening (+0.33 EDSS years), as measured by LS mean AUC; the difference (0.48 EDSS years) was highly significant ($P < 0.0001$). Compared to placebo, natalizumab improved mean AUC by 0.53 EDSS years in patients with baseline EDSS ≥ 2.5 ($P < 0.01$) and by 0.44 EDSS years in patients with baseline EDSS < 2.5 ($P < 0.001$). Natalizumab decreased the risk of a net worsening in disability of ≥ 1.0, ≥ 1.5, and ≥ 2.0 EDSS years by 44% (natalizumab, 14%; placebo, 25%; $P < 0.001$), 53% (natalizumab, 8%; placebo, 17%; $P < 0.001$), and 55% (natalizumab, 5%; placebo, 11%; $P < 0.001$), respectively; similar natalizumab-associated risk reductions (between 46-58%) were observed in both baseline EDSS subgroups.

Conclusions: AUC measurements of EDSS are useful to compare the overall trial experience of MS patients with respect to disability changes over time. In AFFIRM, natalizumab-treated patients had less disability burden over time and were less likely to have a net worsening in disability of ≥ 1.0, ≥ 1.5, or ≥ 2.0 EDSS years, compared to placebo.

[1]Liu C and Blumhardt LD, JNNP 1999; 67:451-6

P074

Impact of peginterferon beta-1a treatment and disease factors on risk of physical deterioration in patients with multiple sclerosis: ADVANCE study

ET Kinter[1], S Guo[2], A Altincatal[2], I Proskorovsky[3], G Phillips[1], B Sperling[1]
[1]Biogen Idec Inc., Cambridge, MA, United States, [2]Evidera, Lexington, MA, United States, [3]Evidera, Montreal, QC, Canada

Background: ADVANCE, a Phase 3, randomized, double-blind study, showed superior efficacy of subcutaneous peginterferon-beta-1a (PEG-IFN) 125 µg administered every 2 (Q2W) and 4 (Q4W) weeks over placebo at 1 year in patients with relapsing-remitting multiple sclerosis (RRMS; n=1512).

Objectives: To explore the influence of treatment and disease factors on clinically-meaningful physical deterioration (CMPD) as assessed by the Multiple Sclerosis Impact Scale (MSIS-29) and 12-item Short Form Survey (SF-12).

Methods: The MSIS-29 and SF-12 were administered at baseline and 12, 24, and 48 weeks. CMPD was defined as worsening of at least 7.5-points and 6.0-points in the MSIS-29 physical scale (PS) and SF-12 physical component scale (PCS), respectively, based on their clinically-minimal importance change identified from literature. A repeated-measure logistic regression (GLMM approach) was used to assess the impact of treatment, baseline, and time-dependent predictors, and interaction terms of treatment and predictors on the risk of experiencing CMPD based on each measure. Factors with p>0.1 were excluded in the final model, unless they were clinically meaningful.

Results: Having a recent relapse (< 29 days since onset vs. ≥ 30 days prior to an assessment visit) was significantly associated with 4.1 (95% CI: 2.1-7.8) and 3.4 (95% CI: 1.8-6.7) times greater risk of CMPD based on the MSIS-29 PS and SF-12 PCS, respectively. Experiencing a sustained disability progression (yes vs. no) significantly increased the risk of CMPD among the placebo-treated patients (odds ratios: 4.2 [95% CI: 1.8-10.1] with MSIS-29 PS and 4.9 [95% CI: 2.1-11.8] with SF-12 PCS). However, such an impact was reduced and not statistically significant among the PEG-IFN-treated patients (odds ratios: 2.9 [95% CI: 1.0-9.0] and 2.3 [95% CI: 0.8-7.0] with MSIS-29 PS and 1.5 [95% CI: 0.5-4.7] and 1.1 [95% CI: 0.4-3.6] with SF-12 PCS for PEG-IFN Q2W and Q4W, respectively). The effects of PEG-IFN treatments and placebo on CMPD were not statistically significant.

Conclusions: Relapses and sustained disability progression are the key contributors to CMPD. PEG-IFN treatment may have a potential benefit in preventing CMPD by not only reducing the risk of these MS-related events, but also lowering the adverse impact of sustained disability progression on CMPD when it occurs.

P075

Alemtuzumab improves MRI outcomes regardless of subgroup versus interferon beta-1a in relapsing-remitting MS patients who relapsed on prior therapy

F Barkhof[1], E Fisher[2], J Palmer[3], DH Margolin[3], DL Arnold[4,5], on behalf of the CARE-MS II Investigators

[1]VU University Medical Center, Amsterdam, Netherlands, [2]Cleveland Clinic, Department of Biomedical Engineering, Cleveland, OH, United States, [3]Genzyme, a Sanofi Company, Cambridge, MA, United States, [4]NeuroRx Research, Montréal, QC, Canada, [5]Department of Neurology and Neurosurgery, Montréal Neurological Institute, McGill University, Montreal, QC, Canada

Background: In the phase 3 CARE-MS II trial (NCT00548405) in patients with active relapsing-remitting multiple sclerosis (RRMS) who relapsed on prior therapy, alemtuzumab was superior to subcutaneous interferon beta-1a (SC IFNB-1a) over 2 years in terms of clinical efficacy, and the reduction in magnetic resonance imaging (MRI) lesion activity and brain volume loss.

Objectives: Investigate MRI outcomes in CARE-MS II subgroups stratified by baseline patient demographics, disease characteristics, and prior SC IFNB-1a use.

Methods: Patients were randomized to receive alemtuzumab 12 mg/day intravenously on 5 days at baseline and on 3 days 12 months later, or SC IFNB-1a 44 μg 3 times weekly. Annual cranial MRI were analyzed blinded to treatment. Treatment effects on risk of gadolinium (Gd)-enhancing lesions, new/enlarging T_2-hyperintense lesions, new T_1-hypointense lesions, or brain volume loss (brain parenchymal fraction change [BPF]) over 2 years were analyzed for subgroups stratified by: gender, age, race, geographic region, baseline Gd-enhancing lesion activity, T_2 lesion volume, BPF and Expanded Disability Status Scale score, highly active disease ($\geq$2 relapses in year prior to randomization and $\geq$1 Gd-enhancing lesion at baseline), disease duration, relapses in prior 2 years, and prior SC IFNB-1a use. Odds ratios (ORs) were calculated by logistic regression (covariate adjustment for baseline Gd-enhancing, T_2 or T_1 lesion count). BPF was analyzed using a ranked ANCOVA model.

Results: In all examined subgroups, alemtuzumab (n=426) significantly reduced the risk of T_2 lesions (OR range: 0.11-0.37, p< 0.01) and T_1 lesions (0.07-0.33, p< 0.05) vs SC IFNB-1a (n=202) at Month 24. Risk of Gd-enhancing lesions was lower with alemtuzumab in all subgroups, with significant risk reductions (0.19-0.38, p< 0.05) in most. A lower risk of Gd-enhancing, T_2 and T_1 lesions was observed with alemtuzumab vs SC IFNB-1a irrespective of prior SC IFNB-1a use (OR range: 0.20-0.33; all p< 0.005). There was significantly less brain volume loss with alemtuzumab for subgroups of patients who at baseline had: median BPF $\geq$0.816, T_2 lesion volume < 5.7 cm^3, EDSS score $\geq$2.5, disease duration < 3.8 years, non-highly active disease, or no prior SC IFNB-1a use (all p< 0.05).

Conclusions: Alemtuzumab reduced MRI lesion activity and slowed brain volume loss better than SC IFNB-1a in most examined subgroups of RRMS patients who relapsed on prior therapy. These findings support the superior efficacy of alemtuzumab over SC IFNB-1a in RRMS.

P076

Double-blind, placebo- and active comparator-controlled study in healthy males to assess the safety, pharmacokinetics and -dynamics of 2B3-201

W Gladdines[1], K Kanhai[2], I Stavrakaki[1], RGJA Zuiker[2], PJ Gaillard[1], GJ Groeneveld[2], F Lönnqvist[1]
[1]to-BBB technologies BV, Leiden, Netherlands, [2]Centre for Human Drug Research, Leiden, Netherlands

Background: Intravenous high-dose methylprednisolone (MP, 500- 1000 mg daily for 3 to 5 consecutive days) has for long been the mainstay of relapse treatment in MS. However, it is inconvenient and its acute side effects, including insomnia, depression, agitation are undesirable. Both the dose and the dosing frequency can be reduced by incorporating MP in (PEGylated) liposomes, creating a slow-release formulation with reduced systemic toxicity but with similar peripheral efficacy. Moreover, by adding glutathione to the PEGylated liposomes (2B3-201) an enhanced delivery of MP into the brain is achieved, thereby potentially enhancing central activity. Preclinical studies in animal models of MS showed that 2B3-201 had fewer behavioral side effects and a superior efficacy compared to free MP.

Objectives: This first-in-human study was designed to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of 2B3-201, including its immune-suppressive effects, as compared to free MP and placebo.

Methods: In this double-blind, 3-way cross over study, 18 healthy male subjects were divided over 3 cohorts and received ascending doses of 2B3-201, active comparator (free MP) or placebo (5% dextrose). MP plasma concentrations, lymphocyte counts, ACTH and fasting glucose were determined, as well as other standard safety parameters at days 0 to 3 and day 7 following each dose. In addition, neurocognitive tests were performed at regular intervals. A safety and PK interim analysis was performed after the completion of cohort 1.

Results: 2B3-201 was shown to have a plasma half-life of 23 h, compared to a half-life of 3 h for free MP. 2B3-201, at doses of 150 mg, 300 mg and 450 mg, resulted in a similar reduction in the lymphocyte count as 1000 mg of free MP. This effect was sustained considerably longer after 450 mg 2B3-201 administration to >74 h. Similar patterns were observed for a decline in ACTH and a rise in fasting glucose (measured up to 48h). All pharmacodynamic outcome measures had returned to baseline at 7 days after dosing. Furthermore, no signs of CNS side effects or serious AEs were observed with 2B3-201. The AEs were generally mild and self-limiting.

Conclusions: 2B3-201 at doses up to 450 mg was considered safe. In addition, 2B3-201 shows a long plasma half-life (23h) and immunosuppressive effects that last for at least 3 days. This supports continued development of 2B3-201 as a safe single dose treatment of acute relapses in MS.

P077

Lymphocyte count reductions with delayed-release dimethyl fumarate: integrated analysis of the phase 2, phase 3, and extension studies

RJ Fox[1], A Chan[2], R Gold[2], JT Phillips[3], K Selmaj[4], R Zhang[5], H Yuan[5], M Novas[5], V Viglietta[5], NC Kurukulasuriya[5]
[1]Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic, Cleveland, OH, United States, [2]St. Josef Hospital, Ruhr University, Bochum, Germany, [3]Multiple Sclerosis Program, Baylor Institute for Immunology Research, Dallas, TX, United States, [4]Medical University of Lodz, Lodz, Poland, [5]Biogen Idec, Inc., Cambridge, MA, United States

Background: Delayed-release dimethyl fumarate (DMF) demonstrated efficacy and safety in relapsing-remitting multiple

sclerosis in placebo-controlled clinical trials, including a Phase 2b trial and the Phase 3 DEFINE and CONFIRM studies. The most common adverse events with delayed-release DMF were flushing and GI events, but delayed-release DMF was also associated with a reduction in lymphocyte counts.

Objectives: Describe the clinical relevance of lymphocyte count reductions with delayed-release DMF, based on integrated analyses of the placebo-controlled Phase 2b and 3 studies and the open-label ENDORSE extension study.

Methods: The population for the integrated analysis of the Phase 2b and 3 studies comprised 2,428 RRMS patients (aged 18-55 years; EDSS score 0-5.0) who received treatment with placebo (PBO; n=836) or delayed-release DMF 240 mg BID (n=769) or TID (n=823) for up to 96 weeks. CONFIRM included a glatiramer acetate reference comparator arm (n=351; results not shown). Hematological tests were performed at weeks 4, 8, and 12, and at 12-week intervals thereafter. ENDORSE is an ongoing, 5-year, dose-blind extension of the Phase 3 studies.

Results: In delayed-release DMF-treated patients, mean white blood cell and lymphocyte counts decreased by approximately 11% and 30%, respectively, through Week 48, then plateaued, but remained within normal limits throughout the observation period. Percentages of patients with worst post-baseline Common Terminology Criteria (CTC) Grades 1, 2, or 3, respectively, were higher in the BID (10%, 22%, 6%) and TID (8%, 18%, 3%) groups than in the PBO group (2%, 2%, < 1%). Percentages of patients with >1 Grade 3 or 4 lymphocyte count were 0% (PBO), 3% (BID), and 1% (TID), and with consecutive Grade 3 or 4 lymphocyte counts were 0% (PBO), 2% (BID), and 1% (TID). The incidence of Grade 3 or 4 lymphopenia increased through Week 48, then stabilized. There was no clear pattern of increased incidence of infections or serious infections with increasing post-baseline lymphocyte CTC grade. No patients discontinued study drug due to lymphopenia. Four weeks after stopping delayed-release DMF, mean lymphocyte counts increased but did not return to baseline. Data from the ENDORSE extension study of DEFINE/CONFIRM will be presented.

Conclusions: Treatment with delayed-release DMF was associated with decreased lymphocyte counts but with the currently available data, no overall increased risk of infection was observed.

P078
Teri-PRO: study design and US patients' baseline characteristics
PK Coyle[1], KR Edwards[2], BO Khatri[3], C LaGanke[4], S Brette[5], S Cavalier[6]
[1]Stony Brook University Medical Center, Stony Brook, NY, United States, [2]Multiple Sclerosis Center of Northeastern New York, Latham, NY, United States, [3]Regional MS Center, Center for Neurological Disorders, Milwaukee, WI, United States, [4]North Central Neurology Associates, Cullman, AL, United States, [5]Lincoln, Boulogne-Billancourt, France, [6]Genzyme, a Sanofi Company, Cambridge, MA, United States

Background: Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting multiple sclerosis (MS). Phase 3 studies of teriflunomide in patients with relapsing MS (RMS; TEMSO, NCT00134563; TOWER, NCT00751881) showed consistent efficacy across key clinical and magnetic resonance imaging (MRI) outcome measures (MRI assessed in TEMSO only), and a well-characterized safety profile. The phase 4 Teri-PRO study (NCT01895335) is examining the efficacy and tolerability of, and satisfaction with, teriflunomide in routine clinical practice using patient-reported outcomes (PROs) from patients with RMS.

Objectives: To describe baseline characteristics of patients enrolled in Teri-PRO in the United States.

Methods: Teri-PRO is a global, prospective, single-arm, multi-center, open-label study that will evaluate approximately 1000 patients with RMS receiving teriflunomide once daily for 48 weeks, with doses given according to local labeling at sites in Europe, North America, and Latin America. The primary outcome is global satisfaction, as measured by scores on the Treatment Satisfaction Questionnaire for Medication (TSQM; version 1.4) assessed at 48 weeks (or end of treatment). Secondary outcomes include PRO changes (assessed using the TSQM version 1.4, Multiple Sclerosis International Quality of Life questionnaire, Patient-Determined Disease Steps scale, and MS Performance Scale) over the study period; treated relapse and disability assessment; and safety (including adverse events and laboratory evaluation).

Results: As of December 31, 2013, 291 patients were screened, 261 (89.7%) included in the study, and 221 (84.7%) and 40 (15.3%) were treated with teriflunomide 14 mg and 7 mg, respectively. The mean (standard deviation; SD) age was 50.7 (10.4) years, 76.2% of the patients were female, and 91.5% were Caucasian. The mean (SD) time since first symptom was 13.9 (9.8) years, mean (SD) baseline Expanded Disability Status Scale score was 3.7 (1.9), and 64.8% of patients were on prior disease-modifying therapies in the last 2 years. Data on US patients enrolled by May 2014 (planned N=500) will be presented in the poster.

Conclusions: Teri-PRO will provide valuable information on the current use of teriflunomide in the clinical setting, including patient satisfaction, safety, and efficacy. This real-world experience, with an emphasis on PROs, will complement data from phase 2 and 3 trials.

P079
Long-term MRI outcomes from patients treated with teriflunomide: results from a phase 2 extension study
DBK Li[1], AL Traboulsee[1], P Truffinet[2], D Dukovic[3], PW O'Connor[4]
[1]University of British Columbia and MS/MRI Research Group, Vancouver, BC, Canada, [2]Genzyme, a Sanofi Company, Chilly-Mazarin, France, [3]Sanofi, Bridgewater, NJ, United States, [4]University of Toronto, Toronto, ON, Canada

Background: Teriflunomide is a once-daily oral immunomodulator for the treatment of relapsing-remitting multiple sclerosis (MS). In phase 2 and 3 studies, teriflunomide had consistent beneficial effects on disability progression, relapse rates, and magnetic resonance imaging (MRI) outcomes, and demonstrated a manageable safety and tolerability profile.

Objectives: To report MRI outcomes from patients treated long-term with teriflunomide.

Methods: In the core phase 2 study (NCT01487096), patients with relapsing forms of MS (aged 18-65 years; Expanded

Disability Status Scale score ≤6; ≥2 clinical relapses in the previous 3 years and 1 relapse in the preceding year) were randomized (1:1:1) to teriflunomide, 14 mg or 7 mg, or placebo. Patients (n=147) completing the 36-week treatment period entered the long-term open-label extension (NCT00228163). Patients either continued with teriflunomide therapy or, for those initially receiving placebo, were re-randomized (1:1) to teriflunomide, 14 mg or 7 mg. MRI scans were evaluated every 48 weeks up to Week 480.
Results: The cumulative duration of teriflunomide exposure, including both treatment groups, was >990 patient-years. Sixty-four patients had MRI assessments at Week 480. The mean (standard error; SE) number of gadolinium-enhancing T1 lesions at Week 0 (Week 36/end of core study) was 1.60 (0.512) and 0.80 (0.211), and at Week 480, 0.29 (0.113) and 0.33 (0.120), in the 14-mg and 7-mg groups, respectively. Mean (SE) number of newly active T2 lesions at Week 0 was 3.11 (0.654) and 3.47 (0.825), and at Week 480, 1.21 (0.419) and 1.61 (0.393), in the 14-mg and 7-mg groups, respectively. Patients in the teriflunomide 14-mg group had less of an increase from baseline in T2 lesion volume than patients in the 7-mg group (mean [SE] change: 2352.91 mL [706.379] vs 4076.71 mL [1110.026]) and less decline from baseline in cerebral volume (mean [SE] percent change: -3.276% [0.4312] vs -4.575% [0.6530], respectively) at Week 432.
Conclusions: Disease activity, as measured by MRI, continued to be low in patients treated with teriflunomide in the long-term extension. Together with the low rates of disability progression and relapses observed in this extension study, the favorable MRI outcomes support the long-term treatment benefit with teriflunomide in patients with MS.

P080

Convenience of glatiramer acetate 40mg/mL three times weekly: evidence from the GLACIER study

JS Wolinsky[1], TE Borresen[2], DW Dietrich[3], BF Gilder[4], Y Sidi[5], JR Steinerman[6], V Knappertz[6,7], S Kolodny[8], GLACIER Study Group

[1]University of Texas, Health Science Center at Houston, Houston, TX, United States, [2]Mecklenburg Neurological Associates, Charlotte, NC, United States, [3]Advanced Neurological Specialists, Great Falls, MT, United States, [4]Swedish Medical Center, Littleton, CO, United States, [5]Teva Pharmaceutical Industries, Netanya, Israel, [6]Teva Pharmaceutical Industries, Frazer, PA, United States, [7]Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany, [8]Teva Pharmaceutical Industries, Cleveland, OH, United States

Background: Improving convenience and patient (pt) experience could support adherence to safe and effective injectable RRMS treatments (Tx) such as glatiramer acetate (GA). Reducing GA injection frequency may enhance convenience for MS pts.
Objectives: To measure pt perceptions of the convenience of GA dosing regimens in the open-label phase IIIb **GL**atiramer **A**cetate low frequen**C**y safety and pat**I**ent **E**xpe**R**ience (**GLACIER**) study, which compares the safety and tolerability of once-daily (QD) GA 20mg/mL (GA20) with 3 times weekly (TIW) GA 40mg/mL (GA40) in pts with RRMS.
Methods: Pts age ≥18 years with confirmed RRMS (McDonald, 2010) and EDSS 0-5.5 treated with GA20 for ≥6 months before

screening were eligible. Pts were randomized 1:1 to continue GA20 or convert to GA40, for a 4-month Tx phase. The Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) convenience subscale was completed at baseline (BL) and months 1, 2, and 4. This subscale assessed difficulty of GA use, difficulty scheduling GA injections, and convenience/inconvenience of taking GA as instructed. Each item is scored from 1-7, and the final subscore is presented from 0-100; higher scores = greater convenience. Adjusted mean change from BL TSQM-9 scores, Tx effect, and 95%CIs were derived by mixed-model repeated measures analysis, adjusted for BL TSQM-9 score, Tx group, month, and Tx-by-month interaction. At BL, pts completed the following statement on a Teva-derived questionnaire: "*I expect GA 40mg/mL TIW will be* [more, equally, or less] *convenient than GA 20mg QD*."
Results: Most pts (GA40 n=108, GA20 n=101) were female (82%) and Caucasian (94%). Mean (±SD) age was 51 (10) years. At BL, 87% of pts expected that GA40 would be more convenient than GA20, 8% responded "equally," and 3% "less," convenient (2% of pts did not answer this question). Adjusted mean change (±SE) in TSQM-9 score from BL to month 4 was 1.75 (1.46) with GA20 and 8.75 (1.40) with GA40, showing a Tx effect of 7.01 (95%CI 3.02, 10.99) for GA40. Unadjusted TSMQ-9 scores from BL to month 1 increased >10 points (75.6 to 85.9) with GA40 and were sustained through month 4 (84.7), while GA20 scores changed little from BL (75.9) to month 4 (77.6).
Conclusions: Pt expectations that GA 40mg injections 3 times weekly would be more convenient than daily injections were confirmed in this head-to-head comparison in GLACIER. Perceptions of increased convenience were evident soon after converting to GA 40mg TIW from GA20mg QD and were sustained.

P081

Time to brain atrophy is prolonged in continuously fingolimod-treated MS patients vs placebo or interferon beta 1-a in phase 3 studies of fingolimod

D Häring[1], D Tomic[1], D Piani Meier[1], N Sfikas[1], P Chin[2], G Francis[2]

[1]Novartis Pharma AG, Basel, Switzerland, [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States

Background: Multiple sclerosis (MS) is associated with accelerated brain volume (BV) loss. The phase 3 fingolimod trials demonstrated a significant reduction in BV loss versus both placebo (pbo) in FREEDOMS and FREEDOMS II and intramuscular interferon beta-1a (IFN beta-1a IM) in TRANSFORMS. Patients completing the controlled phase of trials continued with fingolimod in the extension studies, allowing an investigation of the impact of long-term continuous fingolimod treatment in delaying BV loss.
Objectives: To quantify the relative time delay in MRI-measured BV loss caused by continuous fingolimod-treatment relative to placebo or INF beta-1a IM.
Methods: End of core study (EoS) values were used to establish percentage BV change (PBVC) for placebo (FREEDOMS; n=331 and FREEDOMS II; n=249) or IFN beta-1a IM (TRANSFORMS; n=359). PBVC was determined using the Structural Image Evaluation, using Normalization, of Atrophy (SIENA). PBVC was assessed annually in all extension studies. The day from first dose at which continuously fingolimod 0.5mg-treated patients

reached mean levels comparable to those of the control groups at EoS was calculated, and a p-value obtained, by bootstrapping under the assumption of a linear change in PBVC between two consecutively observed MRI scans.

Results: Number of scans available for fingolimod 0.5mg were n=290/115 at Month (M) 36/48 in FREEDOMS; n=83/6 at M 36/48 in FREEDOMS II; and n=314/218/33 at M24/36/48 in TRANSFORMS. Placebo-treated patients at EoS/M24, had a mean PBVC vs. baseline of -1.31% in FREEDOMS and -1.28% in FREEDOMS II as measured on average on days 719 and 725 relative to the first dose, respectively. Fingolimod treated patients took an additional 12 M (1158 and 1133 days, relative to first dose in FREEDOMS and FREEDOMS II respectively) to reach comparable levels of PBVC (both $p < 0.05$). IFN beta-1a IM -treated patients at EoS/M12 had a mean PBVC vs. baseline of -0.45%, measured on average on day 357 in TRANSFORMS. Fingolimod treated patients took more than an additional 5 M (521 days relative to first dose) to reach comparable levels of PBVC ($p < 0.0001$). Results were similar for median (instead of mean) time and PBVC, or in the subgroup of patients who remained in the study until M 36.

Conclusions: Patients on continuous fingolimod 0.5mg treatment took 56-61% longer vs. pbo, and 45% longer vs. IFN beta-1a IM to reach comparable levels of BV loss. Fingolimod significantly delays BV loss in patients with MS.

P082

A randomized, double-blind, placebo-controlled phase IIa study of alpha B-crystallin in multiple sclerosis

JM van Noort[1], M Bsibsi[1], PJ Nacken[1], R Verbeek[1], EH Venneker[1]
[1]Delta Crystallon, Leiden, Netherlands

Background: During multiple sclerosis (MS), widespread accumulation occurs of the small heat shock protein alpha B-crystallin (HspB5) in oligodendrocytes and myelin. HspB5 fulfills important neuroprotective functions in the central nervous system (CNS), and has a particularly prominent role in limiting oxidative injury. One mechanism through which HspB5 exerts its protective functions is Toll-like receptor 2-mediated activation of regulatory microglia and macrophages. Recent evidence indicates that this protective role of HspB5 can be subverted by HspB5-reactive human memory T cells that enter the CNS during MS, and secrete interferon-gamma (IFN-g) in response to their target. IFN-g subsequently changes the HspB5-induced protective microglial/macrophage response into a strongly pro-inflammatory, destructive response, the molecular signature of which is associated with inflammatory demyelination during MS. These data indicate that selective inhibition of the local IFN-g response by HspB5-reactive T-cells should inhibit such a destructive response. In a previous Phase I study, intravenous HspB5 was found to be safe and well tolerated in healthy subjects over a wide dose range. Additionally, we identified a dose of HspB5 that led to significant suppression of HspB5-specific memory T cell responses.

Objectives: In this study, we examined the safety, tolerability, and the immunological as well as clinical effects of intravenous HspB5, administered to relapsing-remitting MS patients in a tolerizing regimen.

Methods: Based on our Phase I findings, three dose levels of HspB5 were selected for evaluation in MS patients. Thirty two relapsing-remitting MS patients were randomized into four arms to receive either placebo or any one of the three HspB5 dose levels. Patients were monitored for 24 weeks by monthly neurological examination, MRI, assessment of vital signs, urinanalysis, clinical chemistry and blood sampling to evaluate immunological parameters, and followed up for another 24 weeks.

Results: Results obtained so far indicate that also in MS patients, intravenous HspB5 is safe and well tolerated at all doses tested.

Conclusions: The full set of clinical and immunological data illustrating its effects on MS will become available this summer, and will be presented and discussed at the meeting.

P083

Safety and tolerability of fingolimod in relapsing-remitting multiple sclerosis: results from a large open-label clinical trial

A Laroni[1], D Brogi[1], V Brescia Morra[2], L Guidi[3], C Pozzilli[4], G Comi[5], A Lugaresi[6], R Turrini[7], D Raimondi[7], A Uccelli[1], GL Mancardi[1], EAP Investigators
[1]University of Genova, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Genova, Italy, [2]University Federico II, Department of Neurological Sciences, Napoli, Italy, [3]S. Giuseppe Hospital, Neurology Unit, Empoli, Italy, [4]University La Sapienza, Department of Neurology, Roma, Italy, [5]Vita-Salute San Raffaele University, Scientific Institute San Raffaele, Department of Neurology, INSPE, Milano, Italy, [6]University 'G. D'Annunzio', Department of Neuroscience and Imaging, Chieti, Italy, [7]Novartis Farma, Origgio, Italy

Background: Fingolimod 0.5 mg was the first oral therapy approved for treatment of relapsing-remitting multiple sclerosis (RRMS). Between EMA approval and fingolimod availability on the Italian market, an open-label single arm study was initiated in Italy, in patients without alternative therapeutic options.

Objectives: Evaluating safety and tolerability data in this population.

Methods: Main inclusion criteria were: diagnosis of RRMS, Expanded Disability Status Scale score of 0-6.5, no other suitable treatments for MS. Key exclusion criteria were: history of chronic disease of the immune system other than MS, active systemic infections, history or presence of malignancy, uncontrolled diabetes or diabetic retinopathy, macular edema (ME), severe cardiovascular (CV) disease. Safety and tolerability of fingolimod were evaluated by recording adverse events (AEs) and serious AEs (SAEs), vital signs, laboratory (lab) tests and ophthalmology assessments.

Results: Of the 906 enrolled patients, 825 (91%) completed the study. 34/906 (3.7%) prematurely discontinued due to an AE and 3/906 (0.3%) due to pregnancy. Mean duration of treatment was 158.2 days (± 94.2). AEs were recorded in 35.4% of patients, the most frequent being headache (4.1%), influenza (2.1%), lymphopenia (1.8%), asthenia (1.8%) and pyrexia (1.8%). 18/906 (2.0%) patients had a self-limiting CV AE (including 2 cases of atrioventricular block - AVB- second degree Mobitz type I) with onset during the first dose monitoring period (6 hours). Most AEs (94%) were mild or moderate and did not lead to fingolimod

discontinuation. SAEs were noted in 2.9% of patients and included 3 cases of ME, 2 cases of troponin increase with normal electrocardiogram, 1 case of AVB second degree Mobitz type I, 1 case of pneumonia, 1 case of acute respiratory failure, 1 case of transaminase increase and 1 case of autoimmune thrombocytopenia. There were no systemic or disseminated opportunistic infections. Lab abnormalities were mainly recorded for transaminases: transaminase increase was reported as SAE in one case and caused study drug discontinuation in 6 cases. Of the 3 pregnancies occurred during the study, there were 2 healthy births and 1 elective abortion.

Conclusions: The results of this study are consistent with the previous clinical trials and confirm that fingolimod is safe and well tolerated in patients with RRMS.

P084

Dose-response and safety of high dose vitamin D supplementation: subgroup analysis of an exploratory randomized double blind placebo controlled trial

K O'Connell[1], K Mulready[2], J Brady[2], O Kenny[1], K Kinsella[1], S Jordan[1], C McKenna[3], C Muldowney[3], S Basdeo[4], J Fletcher[4], D Murphy[5], E Heffernan[5], R O'Laoide[5], L Cassidy[6], K O'Rourke[7], N Tubridy[1], C McGuigan[1], M Hutchinson[1]
[1]St Vincents University Hospital, Department of Neurology, Dublin, Ireland, [2]Mater University Hospital, Department of Biochemistry, Dublin, Ireland, [3]St Vincent's University Hospital, Pharmacy Department, Dublin, Ireland, [4]Trinity College Dublin, Department of Immunology, Dublin, Ireland, [5]St Vincents University Hospital, Department of Radiology, Dublin, Ireland, [6]Royal Victoria Eye and Ear Hospital, Dublin, Ireland, [7]Mater University Hospital, Department of Neurology, Dublin, Ireland

Background: Increasing evidence links vitamin D deficiency to both susceptibility to, and severity of, multiple sclerosis. We report the dose- response results in a sub-group analysis of a double blind randomized placebo-controlled clinical trial examining the immunological effects of two doses of vitamin D (5000 IU or 10,000 IU daily) compared to placebo over 24 weeks in both healthy control participants and patients presenting with CIS.

Objectives: To assess the dose response, safety and tolerability of high dose vitamin D in healthy control participants over 24 weeks.

Methods: Healthy control participants, aged 25 -40 years, with a 2:1 female to male ratio and no contraindications to high dose vitamin D supplementation were randomized to receive either, placebo, 5000 IU or 10000 IU of vitamin D for a 24 week period in a 1:1:1 fashion. All participants had renal function and serum calcium measured at 4 weekly intervals and vitamin D and PTH at baseline and weeks 4, 8,16, 24. Adverse events were recorded at each visit.

Results: 38 healthy control participants {mean age 30 years (SD:4.5), 26 (68%) women} were recruited from November 2012 to June 2013. Mean baseline serum 25(OH)D was 52 (SD: 24.6) nmol/L and PTH 4.7 (1.7) pmol/L. Using a cut-off of serum 25(OH)D < 50 nmol/L as deficient and 50-72.5 nmol/L as insufficient, 22 (58%) participants were classed as deficient, 7 (18%) insufficient and 9 (24%) had an acceptable serum 25(OH)D level of >72.5nmol/L. After seasonal adjustment of vitamin D levels, 76% participants remained deficient or insufficient at baseline.

The greatest mean changes in serum 25(OH)D levels were seen between baseline and 16 weeks of dosing: placebo group: -4.2 (SD: 22.5) nmol/L, 5000 IU group: +83.2 (27.2) nmol/L, 10,000 IU group +154.8 (66.2). Serum levels plateaued after 16 weeks. No increases in serum calcium, urea and creatinine levels were observed despite a maximum vitamin D level of 402 nmol/L achieved. No serious adverse events were reported in the course of this study.

Conclusions: This study adds to the growing evidence that: a) vitamin D deficiency remains highly prevalent in higher latitudes and b) high dose vitamin D supplementation is safe.

EU Clinical Trials Register: EudraCT: 2012-000635-68. ClinicalTrials.gov identifier: NCT01728922

P085

Safety and tolerability of peginterferon beta-1a in patients with relapsing-remitting multiple sclerosis: 2-year data from the ADVANCE study

BC Kieseier[1], PA Calabresi[2], Y Cui[3], Y Zhu[3], S Hung[3], A Deykin[3], A Seddighzadeh[3]
[1]Heinrich-Heine University, Department of Neurology, Düsseldorf, Germany, [2]Johns Hopkins University, Department of Neurology, Baltimore, MD, United States, [3]Biogen Idec Inc., Cambridge, MA, United States

Background: In ADVANCE, a randomized, double-blind, 2-year, Phase 3 study, subcutaneous (SC) peginterferon-beta-1a (PEG-IFN) 125 µg administered every 2 (Q2W) or 4 (Q4W) weeks showed superior efficacy over placebo at 1 year in patients with relapsing-remitting multiple sclerosis (RRMS; n=1512). 1332 (88%) participants completed Year 1 of the study.[1]

Objectives: To evaluate the safety and tolerability of PEG-IFN in patients with RRMS over 2 years of the ADVANCE study.

Methods: After completing Year 1 of ADVANCE, patients who received placebo during Year 1 were re-randomized to SC PEG-IFN 125 µg administered Q2W or Q4W (PBO-to-PEG-IFN). Patients randomized to PEG-IFN in Year 1 remained on the same dosing regimen in Year 2. Safety data were summarized for all patients who received ≥1 dose of active study treatment over 2 years.

Results: Completion rates at Year 2 were similar across the PEG-IFN groups and across the PBO-to-PEG-IFN groups. Among patients who received PEG-IFN at any time over 2 years (Q2W n=740; Q4W n=728) the incidence of adverse events (AEs) was 94% for each dosing group, and the majority of AEs were mild or moderate in severity. The incidence of severe AEs was 21% and 20% for Q2W and Q4W groups, respectively. The most common AEs across both dosing groups were injection site erythema (Q2W 64%; Q4W 59%), influenza-like illness (Q2W 51%; Q4W 50%), pyrexia (Q2W 43%; Q4W 41%), and headache (Q2W 42%; Q4W 41%). Discontinuations due to AEs were 6% for each PEG-IFN group. Over 2 years, the incidence of serious AEs was higher in the Q4W group (22%) than the Q2W group (16%), with MS relapse the most frequently reported event (Q4W 14%; Q2W 10%). There were a total of nine deaths over the 2-year period, of which four occurred in Year 1 and five occurred in Year 2 (PEG-IFN Q2W n=3; PBO-to-PEG-IFN Q4W n=2 [of which three were considered related to study treatment: PEG-IFN Q2W n=1; PBO-to-PEG-IFN Q4W n=2]). The majority of reductions in

hematological parameters and elevations in liver enzymes were not clinically significant and did not result in treatment discontinuation.

Conclusions: The nature, type, and frequency of AEs with PEG-IFN over 2 years are consistent with those observed during Year 1, and are consistent with the known profiles of interferon beta therapies in MS. The safety profile of PEG-IFN was also similar across the Q2W and Q4W dose regimens over 2 years.

[1]Calabresi PA, et al. *Lancet Neurol*, In Press.

P086

An interim analysis of the German START-study confirms the good cardiac safety profile of fingolimod

V Limmroth[1], S Hoyer[2], M Lang[3], S Schmidt[4], T Ziemssen[5]
[1]*Neurologische Klinik, Kliniken der Stadt Köln, Cologne, Germany, [2]Novartis Pharma GmbH, Nuremberg, Germany, [3]Neurologische Praxis, NTD Study Group, Ulm, Germany, [4]Neurologische Gemeinschaftspraxis, NTD Study Group, Bonn, Germany, [5]Neurologische Klinik, Universität Dresden, Dresden, Germany*

Background: Fingolimod, a sphingosine 1-phosphate receptor (S1PR) modulator, was the first oral therapy approved for the treatment of relapsing-remitting MS (RRMS). Following treatment initiation, fingolimod activates S1PR at the surface of cardiac myocytes, resulting in transient pulse rate reduction, and in rare cases in atrioventricular conduction blocks.

Objectives: The START-study (cFTY720DDE17) characterizes the cardiac safety profile of fingolimod in RRMS patients after treatment initiation.

Methods: The START study is a prospective, 1-week, multi-center, open-label study enrolling up to 7,000 RRMS patients in more than 250 centers in Germany, according to the EU label criteria of fingolimod. The study consists of a screening period, a baseline visit during which the first fingolimod dose is taken, and a final visit after one week. During screening and at the final visit, a 12-lead ECG is carried out. The procedure at baseline is as follows: prior to the first intake of fingolimod, a 12-lead ECG is recorded. After the first dose, a continuous 6h Holter ECG is recorded, while pulse and blood pressure are measured simultaneously, every hour. A final 12-lead ECG is performed afterwards. In 200 patients, diagnostics include a 24h ECG during screening and at baseline.

All ECG recordings are centrally evaluated by cardiologists.

The cardiac safety profile analyzed by the START study focuses in particular on cardiac events requiring extended monitoring according to the label: bradycardia, prolongation of QTcF (Fridericia)-interval as well as second- and third degree AV blocks.

Results: The previous START interim analysis was based on 1230 patients (March 2014). Only 0.7% of the patients developed bradycardia (< 45 bpm) at any time during the 6h observation period, and no patient required medication to treat bradycardia. There was no QTcF-interval prolongation beyond 500msec. Only 43 out of 2702 patients (1.6%) developed a 2nd degree AV-block Mobitz type I or higher. All cardiac events were transient. There was no evidence of either bradycardia, QTcF-prolongation or AV block II[0] or III[0] at the end of study, approximately seven days after the first exposure to fingolimod.

The results of the most recent analysis conducted in August 2014 will be presented.

Conclusions: This study confirms the good cardiac safety profile of fingolimod, which has already been documented in the previous pivotal multicenter trials.

P087

Vitamin D levels in multiple sclerosis in correlation to age, sex, EDSS and dosage of substitution. First results of a prospective study

WL Poellmann[1], M Starck[1], J Koehler[1]
[1]*Marianne Strauss Klinik, Berg, Germany*

Background: Vitamin D in multiple sclerosis (MS) is still controversial discussed regarding the impact of serum levels and possible therapeutic options.

Objectives: Therefore we initiated a non-interventional study in MS patients in our center to address these questions. We now present the design of the study and preliminary data of the included patients since October 2013.

Methods: Since October 2013 the 25-OH vitamin D3 levels (normal range between 20 and 70 µg/l), epidemiological data (sex, age) type of MS (rrMS, spMS, ppMS) EDSS as well as medication have been recorded. In every group of MS type at least 100 patients will be evaluated and observed over a period of two years. Patients with 25-OH vitamin D3 levels below 45 µg/l are allocated randomly to a substitution with either up to 10.000 IE or 20.000 IE weekly. Patients will be followed over at least one year with including 25-OH-vitamin D3 level control.

Results: We present the data of 161 consecutive MS patients, 65 men and 96 women, mean age 53 (20-77) years: The course of disease was relapsing-remitting in 43, secondary progressive in 98 and primary progressive in 17 patients, a CIS diagnosed in three. 113 patients (70 per cent) received disease modifying therapy. Mean EDSS was 5,7 (1,5 - 8). Mean 25-OH vitamin D3 level was low with 19,7 µg/l. Women tended to have higher mean vitamin D levels than men (20,11 vs. 18,7 µg/l). Lower 25-OH vitamin D3 levels were seen in younger patients (median 11,5 µg/l in the age group 30-39 years) than in patients 60-69 years (median 22,5 µg/l). Relatively small differences of mean vitamin D levels were seen in relation to EDSS groups: 17,3 µg/l in patients up to EDSS 3,5, 22,3 µg/l in EDSS 4.0 -5,5, 19,1 µg/l in EDSS 6.0-6,5 and 19,7 µg/l beyond EDSS 7.0. 40 patients substituted with vitamin D were seen again up to March 2014.

High dose substitution with 20.000 IE led to a higher increase of 25-OH vitamin D levels (mean 51,4 µg/l) than weekly doses below 10.000 IE (mean 27,5 µg/l).

Conclusions: 25-OH vitamin D3 levels were below normal (< 20 µg/l) in 103 of our 161 MS patients since yet. High dose substitution led to a higher increase of 25-OH-vitamin D levels than weekly doses below 10.000 IE. In the short run of up to 6 months therapy there were no effects detected on disability progression.

P088

Alemtuzumab reduces disease activity in treatment-naive patients with highly active relapsing-remitting multiple sclerosis

S Krieger[1], C Lubetzki[2], J Palmer[3], DH Margolin[3], on behalf of CARE-MS I Study Investigators

[1]*Mount Sinai Medical Center, New York, NY, United States,*
[2]*Hôpital de la Salpêtrière, Paris, France,* [3]*Genzyme, a Sanofi Company, Cambridge, MA, United States*

Background: In the phase 3 Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE-MS) I study in treatment-naive relapsing-remitting MS (RRMS) patients, intravenous (IV) alemtuzumab significantly improved annualized relapse rate (ARR), magnetic resonance imaging (MRI) outcomes, and proportion of patients disease activity-free compared with subcutaneous interferon beta-1a (SC IFNB-1a), with manageable safety.

Objectives: Compare efficacy and safety of alemtuzumab vs SC IFNB-1a in a subset of treatment-naive (CARE-MS I) patients with highly active disease.

Methods: CARE-MS I (NCT00530348) was a 2-year, randomized, rater-blinded study of IV alemtuzumab (12 mg for 5 days at baseline and 3 days 12 months later) vs SC IFNB-1a (44 mcg 3 times weekly). Patients with highly active RRMS had ≥2 relapses the year before randomization and ≥1 gadolinium (Gd)-enhancing lesion at baseline. Sustained accumulation of disability (SAD) was ≥1-pt increase in Expanded Disability Status Scale (EDSS) score (≥1.5 pt if baseline EDSS=0) for 6 months. MRI was performed annually. Clinical disease activity was ≥1 relapse or 6-month SAD, MRI activity was ≥1 new Gd-enhancing or new/enlarging T2-hyperintense lesion, and MS disease activity was clinical or MRI activity.

Results: Demographics were similar in alemtuzumab (n=105) and SC IFNB-1a (n=61) highly active patients. At Year 2, alemtuzumab reduced ARR (0.20 vs 0.41; P=0.0068) by 51% vs SC IFNB-1a. A higher proportion of alemtuzumab patients were relapse-free (76.2 vs 50.4%; hazard ratio 0.40; 95% confidence interval 0.24-0.68; P=0.0007). Alemtuzumab patients had fewer mean Gd-enhancing, new/enlarging T2, and new T1 hypointense lesions and black hole conversions and smaller reductions from baseline in brain parenchymal fraction (P< 0.05). As in the overall CARE-MS I population, mean change in EDSS scores did not differ between treatment groups. Alemtuzumab patients were more likely to be clinical, MRI, and MS disease activity-free (P≤0.0025). Treatment-emergent adverse events (AEs) occurred in 97.1 and 93.4% of alemtuzumab and SC IFNB-1a patients, including infections (65.7 vs 42.6%), thyroid events (13.3 vs 9.8%), and immune thrombocytopenia (ITP; 1.9 vs 0%). Two alemtuzumab patients had grade 4 serious AEs deemed related to treatment (one each with ITP and agranulocytosis).

Conclusions: Alemtuzumab reduced MS disease activity vs SC IFNB-1a in treatment-naive patients with highly active RRMS, with no new safety signals.

P089

Interferon beta-1b in treatment-naïve paediatric patients with relapsing-remitting MS: baseline data from the BETAPAEDIC study

J Gärtner[1], W Brück[1], A Weddige[1], K Reinhardt[1], JP Bugge[2], The BETAPAEDIC Study Group
[1]*University Medical Center, Göttingen, Germany,* [2]*Bayer Pharma AG, Berlin, Germany*

Background: The BETAPAEDIC study is the first prospective, international, multicentre, observational study assessing the safety and tolerability of interferon beta-1b (IFNB-1b) in juvenile patients with relapsing-remitting MS (RRMS).

Objectives: To describe baseline clinical characteristics from the BETAPAEDIC study.

Methods: Treatment-naïve adolescents (12-16 years) diagnosed with RRMS according to revised McDonald (2005) or Poser criteria and scheduled by the investigator to be treated with IFNB-1b were enrolled at 13 clinical centres. The observation period will last for 2 years with visits planned every 6 months. Clinical effectiveness will be evaluated by relapse rate, EDSS progression, and MRI. Adverse events (AEs) and serious AEs will be recorded and followed up. The development of neuropsychological function will be measured by IQ assessment (WISC-IV or SPM+), visual and motor integration (Beery VMI), attention and concentration (d2 Test). These outcomes will be assessed at baseline and after 24 months and will be compared with age-matched normative values. Fatigue will be assessed by the FSS. Enrollment is completed and baseline characteristics are reported.

Results: 65 patients were enrolled (mean age 14.2 years; mean BMI 23.5 kg/m^{2}). Mean time since disease onset was 0.91 (+/- 1.37) years and mean time since diagnosis was 0.44 (+/-1.27) years. 69.2% of patients met the criteria for diagnosis by both McDonald and Poser criteria while 30.8% were diagnosed by McDonald alone. Patients reported mean 2.2 (+/-2) clinical events within the 2 years prior to the study (based on clinical documentation in 89.2% of patients and/or patient reports in 83.1%). EDSS change of >=1 within the last 2 years was reported in 32.3% of patients. Mean EDSS score was 0.7 (+/-1.0). Most patients (93.8%) did not appear to have cognitive impairment, based on physician's impression. Brain MRIs were available for 96.9% of patients; mean number of lesions was 15.2 (+/-13.5). Contrast-enhancing lesions were observed in 53.8% of patients. Assessments of neuropsychological function and fatigue were available for >=80.0% and 84.6% of patients, respectively.

Conclusions: The BETAPAEDIC study will provide important information about the safety of INFB-1b in juvenile patients with RRMS. Clinical data including neuropsychological function and MRI analyses will be obtained to further understand the effectiveness of INFB-1b in this population.

P090

Efficacy and safety of alemtuzumab in treatment-naive patients with relapsing-remitting MS: four-year follow-up of the CARE-MS I study

AJ Coles[1], DL Arnold[2], JA Cohen[3], EJ Fox[4], H-P Hartung[5], E Havrdova[6], KW Selmaj[7], DH Margolin[8], J Palmer[8], P Oyuela[8], MA Panzara[8], DAS Compston[9], on behalf of the CARE-MS I Investigators
[1]*University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom,* [2]*Montréal Neurological Institute, McGill University, Department of Neurology and Neurosurgery, Montréal, QC, Canada,* [3]*Mellen Center and Department of Biomedical Engineering, Cleveland Clinic, Cleveland, OH, United States,* [4]*University of Texas Medical Branch, Round Rock, TX, United States,* [5]*Heinrich-Heine University, Department of Neurology and Center for Neuropsychiatry, Düsseldorf, Germany,* [6]*First School of Medicine, Charles University, Department of Neurology, Prague, Czech Republic,* [7]*Medical University of Łódź, Department of Neurology, Łódź, Poland,* [8]*Genzyme, a Sanofi Company, Cambridge, MA, United*

States, [9]University of Cambridge, Department of Clinical Neurosciences, Cambridge, United Kingdom

Background: Alemtuzumab is approved in over 30 countries for relapsing-remitting multiple sclerosis (RRMS). The phase 3 CARE-MS I study in treatment-naive patients with active RRMS showed alemtuzumab had a superior effect on relapse rate over subcutaneous interferon beta-1a (SC IFNB-1a) and manageable safety over 2 years; 3-year follow-up showed durable efficacy of alemtuzumab, with only 18% of patients receiving a third annual treatment course.

Objectives: To examine 4-year efficacy/safety in alemtuzumab patients and 2-year efficacy/safety in patients who switched from SC IFNB-1a to alemtuzumab.

Methods: In the 2-year CARE-MS I study (NCT00530348), treatment-naive RRMS patients received alemtuzumab (12 mg/day intravenously [IV] on 5 consecutive days and on 3 consecutive days 12 months later) or SC IFNB-1a (44 µg 3 times/week). In the extension study (NCT00930553), patients received as-needed alemtuzumab re-treatment (12 mg/day IV on 3 consecutive days) ≥ 1 year apart or permitted use of approved disease-modifying therapy (DMT), on evidence of relapse or magnetic resonance imaging activity. Former SC IFNB-1a patients received 2 alemtuzumab courses in extension.

Results: The extension enrolled 349 (95%) eligible patients from the core study alemtuzumab arm. Through 4 years, 73% of these patients received only 2 annual courses, while 21% and 5% received 1 or 2 additional courses, respectively, and < 5% of patients received another DMT during extension. Nine patients discontinued from the study, none of which resulted from adverse events (AEs). Among patients who received SC IFNB-1a in the core study, 144 (83%) entered the extension and 132 (92%) of these patients received 2 courses of alemtuzumab. There were 8 withdrawals in the crossover group during the 2-year extension period, none due to AEs. Efficacy and safety data will be reported for Year 2 of the extension for the alemtuzumab cohort (Years 3 and 4 of alemtuzumab exposure), and the former SC IFNB-1a crossover cohort (Years 1 and 2 of alemtuzumab exposure).

Conclusions: The majority of treatment-naive patients who received 2 courses of alemtuzumab during the core study did not require further treatment during the 2-year extension period, and few sought alternative therapies or withdrew from the study. Among former SC IFNB-1a patients who received alemtuzumab during the extension, few sought treatment with other therapies or withdrew from alemtuzumab; the majority received both treatment courses and remained in the study.

P091

Attitudes of people with multiple sclerosis towards clinical research

S Jordan[1], K O'Connell[1], M Duggan[1], N Tubridy[1], M Hutchinson[1], C McGuigan[1]
[1]St Vincent's University Hospital, Neurology, Dublin, Ireland

Background: Clinical research remains invaluable in understanding the natural history of Multiple Sclerosis (MS) and the benefits of therapeutic interventions. Treatment options have increased for people with MS. Early access to these potentially effective new therapies is usually through enrolment in clinical trials. In practice many people are reluctant to participate in research. An understanding of patients' attitudes towards clinical research is important to identify potential barriers to participation and see if these can be addressed.

Objectives: To ascertain patients' attitudes towards clinical research and identify issues that inhibit recruitment.

Methods: A questionnaire was distributed to patients attending an MS clinic at a tertiary referral centre with an academic/clinical research unit. Demographic and clinical data was collected and analysed using Sphinx software.

Results: Data collection is ongoing but an initial sample of n=33 has been analysed. The population was 23 female/10 male with 30% in the 31-40 year age range. 21/33 of the did not recall being asked to participate in clinical research previously. Of the 12 patients who had been approached to take part in research 9 had participated. 7 had completed a questionnaire-based research, 5 had been in a clinical drug trial. Of those who had previously participated: 5/9 thought it had been beneficial and 11 stated that they would participate again. 20/33 reported they would be interested in participating in clinical trials because of the perceived close clinical monitoring; 18/33 considered that access to a novel therapy would encourage participation. Factors inhibiting recruitment included: safety concerns of a trial medication 18/33 and time constraints 11/33. 23/33 believed that patients should participate in clinical research. 17/33 would participate in a study comparing active treatments, but not a placebo controlled study. 21/33 consider clinical research of benefit to all patients with MS, 20/33 believe it added to medical knowledge, 3/33 thought that it was of benefit to the research team and doctors only.

Conclusions: Initial results, reveals barriers to participating in clinical research in an MS population; include safety concerns and time constraints with regards attending study visits. This allows us to consider these issues when planning further studies to encourage maximum participation.

P092

GNbAC1, a monoclonal antibody against the MSRV envelope protein, pharmacodynamic responses in patients with multiple sclerosis

F Curtin[1]
[1]GeNeuro, Plan les Ouates, Switzerland

Background: Human endogenous retrovirus (HERV) genes represent 8% of the human genome. Among HERV genes, the Multiple Sclerosis associated Retrovirus (MSRV) DNA contains copies expressing a protein called Env, which can activate a pro-inflammatory and autoimmune cascade via Toll-Like receptor 4. MSRV-Env expressed in multiple sclerosis (MS) plaques has an inhibitory effect on oligodendrocyte precursor cell differentiation and affects remyelination. GNbAC1, a humanised monoclonal antibody, binds MSRV-Env. Blocking MSRV-Env by GNbAC1 is expected to have a neuroprotective effect in MS.

Objectives: To assess the safety, pharmacokinetics and pharmacodynamics over 1 year of GNbAC1, a monoclonal antibody agonist of the Multiple Sclerosis associated Retrovirus (MSRV) Env protein in multiple sclerosis (MS) patients.

Methods: We report the results of Phase II single ascending dose study followed by a 12-month open-label extension to evaluate the safety, pharmacokinetics and pharmacodynamics of GNbAC1

in 10 MS patients. First, in Cohort 1, 5 patients were randomized to receive a single intravenous infusion of 2 mg/kg of GNbAC1 or placebo; in Cohort 2, 5 patients were randomized to receive an intravenous infusion of 6 mg/kg of GNbAC1 or placebo. Then, all patients of Cohorts 1 and 2 pursued treatment with 11 GNbAC1 infusions at 2 mg/kg and 6 mg/kg dose respectively at 4-week intervals in an open label setting.

Results: GNbAC1 was well tolerated at both doses. Pharmacokinetic data confirm a dose linear pharmacokinetics with an elimination half-life of 25-36 days compatible with monthly infusions. Pharmacodynamic markers based on brain MRI and cytokines and MSRV biomarkers are presented. MSRV biomarkers decreased during treatment with GNbAC1 and brain MRI showed overall stability; no particular trends could be observed for cytokines over time.

Conclusions: The 12-month results confirm the positive long-term GNbAC1 safety profile in MS patients. The pharmacodynamic data suggest a favourable effect of GNbAC1 on MS. These results pave the way to a large Phase IIb study testing the efficacy and safety of the first monoclonal antibody targeting the MSRV-Env protein.

P093

First-in-human phase 1 study of invariant NKT cell ligand OCH

D Noto[1], M Araki[2], W Sato[1], T Okamoto[3], M Murata[3], S Miyake[1,4], T Yamamura[1,2]
[1]National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP), Department of Immunology, Kodaira, Japan, [2]National Center Hospital, NCNP, Multiple Sclerosis Center, Kodaira, Japan, [3]National Center Hospital, NCNP, Department of Neurology, Kodaira, Japan, [4]Juntendo University Graduate School of Medicine, Department of Immunology, Bunkyo-ku, Japan

Background: We have previously reported that OCH, a sphingosine-truncated analog of α-galactosylceramide (αGC), that selectively induces IL-4 production from invariant NKT (iNKT) cells, would suppress the development of autoimmune disease models, including experimental autoimmune encephalomyelitis (EAE) (Miyamoto et al. Nature 2001).

Objectives: Here we report on the results of the First-in-Human phase 1 study of OCH for healthy subjects, which we have recently conducted in the NCNP as an investigator initiated trial. The aim of the study was to evaluate safety and pharmacokinetics of a single oral administration of OCH, and investigate alterations in immunological parameters and gene expression profiles.

Methods: Fifteen healthy subjects were enrolled and allocated to 1 of 5 cohorts and given escalating doses of OCH. We investigated lymphocyte subsets in peripheral blood with flow cytometer, and analyzed gene expressions of whole blood with DNA microarray.

Results: Mild leukopenia occurred in two subjects, but recovered without any treatments. All other adverse events were grade 1. Plasma concentration of OCH was much higher than anticipated based on preclinical study, indicating the bioavailability of OCH may be higher than rodents and primates. Flow cytometer analysis of lymphocyte subsets revealed that GM-CSF producing fractions in CD4+ memory T cells and CD8+ T cells were reduced after administration of OCH in all cohorts. IFN-γ producing fraction in CD4+ memory and CD8+ T cells were also reduced in lower dose

cohorts. DNA microarray analysis revealed that expressions of some genes associated with autoimmune responses were decreased, and some immunoregulatory genes were increased.

Conclusions: The results were potentially interesting and allowed us to start an early phase 2 study for patients with multiple sclerosis (MS). At April 2012, we have finished administration of OCH to two MS patients and analysis of immunological parameters.

P094

Safety and tolerability of daclizumab HYP treatment in relapsing-remitting multiple sclerosis: results of the DECIDE study

K Selmaj[1], L Kappos[2], DL Arnold[3,4], E Havrdova[5], A Boyko[6], M Kaufman[7], H Wiendl[8], J Rose[9], S Greenberg[10], E Demirhan[11], K Riester[11], M Sweetser[11], J Elkins[11]
[1]Medical University of Lodz, Lodz, Poland, [2]University Hospital, Basel, Switzerland, [3]NeuroRx Research, Montreal, QC, Canada, [4]McGill University, Montreal, QC, Canada, [5]First School of Medicine, Charles University, Prague, Czech Republic, [6]Moscow Multiple Sclerosis Center, Moscow, Russian Federation, [7]Carolinas Medical Center, Charlotte, NC, United States, [8]University of Münster, Münster, Germany, [9]University of Utah Medical School, Salt Lake City, UT, United States, [10]Abbvie Biotherapeutics Inc, Redwood City, CA, United States, [11]Biogen Idec, Cambridge, MA, United States

Background: Daclizumab high-yield process (DAC HYP), a humanized monoclonal IgG1 antibody against CD25 subunit of interleukin-2 receptor. The placebo-controlled portion of prior trials in patients with relapsing-remitting multiple sclerosis (RRMS) was 1 year in duration.

Objectives: To evaluate the safety and tolerability data of DAC HYP in patients with RRMS over a 2-3 year treatment period.

Methods: We conducted a randomized, double-blind, double-dummy active controlled trial comparing subcutaneous (SC) DAC HYP 150 mg once every 4 weeks with intramuscular (IM) interferon beta-1a (IFN β-1a) 30 mcg once weekly for 96 to 144 weeks. Safety and tolerability were measured by adverse event (AE) monitoring, physical and neurological exams, vital signs, clinical lab evaluations (hematology, blood chemistry, thyroid function panel, and urinalysis), Beck Depression Inventory Second edition (BDI-II), and immunogenicity and injection site assessments. Safety endpoints will be summarized by treatment group.

Results: A total of 1841 randomized patients were treated with either DAC HYP or IFN β-1a. At baseline, mean (SD) age across both treatment groups was 36.3 (9.3) years and 68% of patients were female. Mean (SD) time to diagnosis was 4.2 (4.8) years. Approximately half of randomized patients (53%) had not received any prior treatment for MS. Final safety results will be presented.

Conclusions: The DECIDE study provides a robust assessment of the safety and tolerability of DAC HYP when administered over 2-3 years to RRMS patients.

P095

Efficacy of teriflunomide in patients with early stage MS: analysis of the TOPIC study using 2010 McDonald diagnostic criteria

JS Wolinsky[1], P Truffinet[2], D Bauer[3], AE Miller[4], for the Investigators of the TOPIC Study and the MRI-AC in Houston, TX

[1]*University of Texas Health Science Center at Houston, Houston, TX, United States, [2]Genzyme, a Sanofi Company, Chilly-Mazarin, France, [3]Sanofi, Bridgewater, NJ, United States, [4]Icahn School of Medicine at Mount Sinai, New York, NY, United States*

Background: TOPIC (NCT00622700) was a phase 3 study to evaluate the efficacy and safety of teriflunomide in patients with clinically isolated syndrome (CIS): patients who had experienced a first clinical episode suggestive of multiple sclerosis (MS). Teriflunomide 14 mg reduced the risk of relapse determining conversion to clinically definite MS (primary endpoint) by 42.6% vs placebo (P=0.0087), and of a new relapse or magnetic resonance imaging (MRI) lesion (key secondary endpoint) by 34.9% (P=0.0003). The 7-mg dose was also superior to placebo, with a smaller effect. The approach to diagnosis of MS changed during TOPIC (first patient randomized, February 2008; last patient, last visit, December 2012). The McDonald criteria were revised in 2010, potentially allowing earlier diagnosis of MS and at the first clinical episode in some patients.

Objectives: To apply 2010 McDonald diagnostic criteria to re-analyze TOPIC study outcomes.

Methods: A total of 614 patients with CIS received once-daily treatment with teriflunomide 14 mg, 7 mg, or placebo for up to 108 weeks. Key inclusion criteria were first clinical episode suggestive of MS within 90 days and an MRI scan showing ≥2 T2 lesions ≥3 mm in diameter. The 2010 McDonald criteria were applied retrospectively; patients were grouped according to their baseline disease characteristics as meeting new criteria, not meeting new criteria, or unclassifiable (insufficient information). Time to MS diagnosis based on 2010 McDonald criteria was analyzed for the group of patients not meeting these criteria at baseline. Using the three groups described above, subgroup analyses were performed for primary and key secondary endpoints.

Results: At entry, 245 patients did not meet 2010 McDonald criteria. Of the remaining patients, 78 met the criteria for MS, and 291 were unclassifiable. For patients not meeting 2010 McDonald criteria, the probability of conversion to MS based on 2010 McDonald criteria by 108 weeks was 54.1% (teriflunomide 14 mg), 63.0% (teriflunomide 7 mg), and 74.4% (placebo). In these patients, teriflunomide treatment reduced the probability of conversion to MS by 39.1% (14 mg, P=0.0222) or by 38.3% (7 mg, P=0.0265) vs placebo. There was no evidence of a differential treatment effect across the subgroups for the primary and key secondary efficacy endpoints.

Conclusions: This analysis confirms the efficacy of teriflunomide in the treatment of patients with early stage MS and shows the consistency of treatment effect using various endpoints and diagnostic criteria.

P096
Differential recovery from relapse between treatment groups in the CONFIRM study of delayed-release dimethyl fumarate

A Chan[1], JT Phillips[2], RJ Fox[3], A Zhang[4], M Okwuokenye[4], NC Kurukulasuriya[4]
[1]*St. Josef Hospital, Ruhr University, Bochum, Germany, [2]Baylor Institute for Immunology Research, Multiple Sclerosis Program, Dallas, TX, United States, [3]Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic, Cleveland, OH, United States, [4]Biogen Idec Inc., Cambridge, MA, United States*

Background: Delayed-release dimethyl fumarate (DMF) demonstrated efficacy on clinical and radiological measures and an acceptable safety profile in patients with relapsing-remitting multiple sclerosis (RRMS) in the Phase 3 DEFINE and CONFIRM studies.

Objectives: Evaluate the association between relapse and disability progression in a post hoc analysis of data from the CONFIRM study.

Methods: Eligible patients were 18−55 years of age with a diagnosis of RRMS (McDonald criteria) and an Expanded Disability Status Scale (EDSS) score of 0−5.0, inclusive. Patients were randomized to receive placebo, delayed-release DMF 240 mg twice (BID) or three times daily (TID), or subcutaneous glatiramer acetate (GA; reference comparator). The analysis examined incomplete recovery (disability progression linked to relapse within a specific interval): the proportion of patients who showed 12-week confirmed disability progression (defined as a ≥1.0 point increase from a baseline EDSS score of ≥1.0 confirmed for 12 weeks, or a ≥1.5 point increase from a baseline EDSS score of 0 confirmed for 12 weeks) 180 days from the start date of relapse to the start date of disability progression. The odds of relapse-led disability progression were assessed using logistic regression, adjusted for baseline covariates. Only results from patients treated with delayed-release DMF BID in CONFIRM are reported, as this represents the approved maintenance dose in the US and European Union.

Results: The intent-to-treat population comprised 363, 359, and 350 patients assigned to the placebo, delayed-release DMF BID, and GA groups, respectively. At 2 years, the proportion of patients with incomplete recovery was 8.0% in the placebo group, 3.9% in the delayed-release DMF BID group, and 6.6% in the GA group. Odds ratios (95% confidence intervals) for incomplete recovery were 0.470 (0.243, 0.907) for delayed-release DMF BID (p=0.0243) and 0.796 (0.450, 1.407) for GA (p=0.4321).

Conclusions: This post hoc analysis of CONFIRM suggests that patients treated with delayed-release DMF had reduced odds of relapse-led disability progression compared with patients receiving placebo.

P097
Pooled safety analyses from the teriflunomide clinical development program

TP Leist[1], MS Freedman[2], L Kappos[3], TP Olsson[4], AE Miller[5], JS Wolinsky[6], PW O'Connor[7], M Benamor[8], P Truffinet[8], D Dukovic[9], G Comi[10]
[1]*Comprehensive Multiple Sclerosis Center, Thomas Jefferson University Hospital, Philadelphia, PA, United States, [2]University of Ottawa and the Ottawa Hospital Research Institute, Ottawa, ON, Canada, [3]University Hospital Basel, Basel, Switzerland, [4]Karolinska Institute, Stockholm, Sweden, [5]Icahn School of Medicine at Mount Sinai, New York, NY, United States, [6]University of Texas Health Science Center at Houston, Houston, TX, United States, [7]University of Toronto, Toronto, ON, Canada, [8]Genzyme, a Sanofi Company, Chilly-Mazarin, France, [9]Sanofi, Bridgewater, NJ, United States, [10]University Vita-Salute San Raffaele, Milan, Italy*

Background: Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting multiple sclerosis. In phase 2 and 3 studies, teriflunomide has shown beneficial effects on clinical and magnetic resonance imaging parameters vs placebo, with the 14-mg dose consistently demonstrating greater efficacy than the 7-mg dose. In individual studies, teriflunomide was well tolerated, with a well-characterized safety profile.

Objectives: To report safety outcomes using pooled data from four, double-blind, placebo-controlled trials of teriflunomide.

Methods: Data were pooled from the phase 2 (NCT01487096) and phase 3 TEMSO (NCT00134563), TOWER (NCT00751881), and TOPIC (NCT00622700) studies. Patients were randomized to receive teriflunomide 14 mg, 7 mg, or placebo. Safety assessments included treatment-emergent adverse events (TEAEs), laboratory parameters, and physical examinations. Per protocol, confirmed alanine aminotransferase (ALT) >3× upper limit of normal (ULN) or neutrophil count < 1000 cells/μL, regardless of presence/absence of symptoms, mandated study discontinuation.

Results: A total of 3044 patients were included in analyses, representing >1500 patient-years of cumulative treatment exposure per group. Common TEAEs reported more frequently with teriflunomide were hair thinning, diarrhea, ALT elevation, headache, and nausea. Most TEAEs were transient and mild to moderate in intensity. Discontinuations due to TEAEs were more frequent in patients receiving teriflunomide (14 mg, 12.5%; 7 mg, 11.2%; placebo, 7.5%). ALT increases were the most common reason for treatment discontinuation in all groups (due to protocol requirements). ALT elevations ≤3× ULN occurred more frequently with teriflunomide; however, the incidence of ALT >3× ULN and serious hepatic TEAEs was similar across groups. Decreases in neutrophil or lymphocyte counts were not associated with an increased risk of infection. Serious infections occurred with similar frequency (≤2.7% of patients) in all groups. Malignancies occurred in ≤0.5% of patients in any group (14 mg, n=3; 7 mg, n=2; placebo, n=5). No hematological or lymphoproliferative malignancies were reported.

Conclusions: Pooled safety data from >3070 patient-years of teriflunomide exposure were consistent with those of individual studies and did not identify any unexpected safety signals with either dose. As teriflunomide 14 mg is more efficacious, with a similar safety profile to the 7-mg dose, it has a better benefit-to-risk profile.

P098

TRUST study design-a study to evaluate an integrated approach for optimized patient management in multiple sclerosis patients treated with natalizumab

H-P Hartung[1], T Ziemssen[2], A Bayas[3], B Tackenberg[4], J Würfel[5,6], V Limmroth[7], R Linker[8], M Mäurer[9], J Haas[10], M Stangel[11], O Harlin[12], C Winterstein[12], M Meergans[12], C Wernsdörfer[12], A Gass[13]

[1]University of Düsseldorf, Dept. of Neurology, Düsseldorf, Germany, [2]University of Dresden, Center of Clinical Neuroscience, Dresden, Germany, [3]Hospital of Augsburg, Dept. of Neurology, Augsburg, Germany, [4]Philipps University, Dept. of Neurology, Marburg, Germany, [5]University of Göttingen, Göttingen, Germany, [6]Charite, Berlin, Germany, [7]Cologne City Hospitals, University of Cologne, Dept. of Neurology, Cologne, Germany, [8]Friedrich-Alexander-Universität, Dept. of Neurology, Erlangen, Germany, [9]Caritas Hospital, Dept. of Neurology, Bad Mergentheim, Germany, [10]Jewish Hospital Berlin, Centre for Multiple Sclerosis, Berlin, Germany, [11]Hannover Medical School, Dept. of Neurology, Hannover, Germany, [12]Biogen Idec, Ismaning, Germany, [13]Universitätsmedizin Mannheim, University of Heidelberg, Dept. of Neurology, Mannheim, Germany

Background: Natalizumab is an intravenously applied humanized monoclonal antibody, indicated as escalation treatment for RRMS patients. Close monitoring of natalizumab patients is required to optimise benefit/risk considerations, however real-life patient management utilising biomarkers for risk stratification and MRI-monitoring is heterogeneous amongst neurologists.

Objectives: To investigate the impact of an integrated patient management approach including innovative patient monitoring systems incorporating biomarkers, MRI surveillance and an expert referral system on outcome of natalizumab (Tysabri®) treated relapsing-remitting multiple sclerosis (RRMS) patients, an open-label real-world study is being conducted in Germany (TRUST).

Methods: Biomarkers such as quantitative anti-JCV antibody-status and L-selectin, a new MRI algorithm with quarterly scans in anti-JCV antibody positive patients from month 18, and an expert advisory referral system will be evaluated by measuring disease activity in various risk strata, and safety events of interest such as PML. Long-term data on patient-reported outcomes, decisions to continue/discontinue therapy, practicability of patient monitoring, pharmaco-economic aspects and the overall safety profile of natalizumab will be collected from RRMS Patients in approx. 200 neurological clinics and practices all over Germany. The non-interventional prospective design allows the role of biomarkers in treatment decisions- and frequent MRI- for early detection of PML in a real-world setting. In addition to the web-based documentation of clinical parameters, TRUST may provide an infrastructure that facilitates patient management including individual benefit/risk considerations and decision making in clinical practice. The Multiple Sclerosis Documentation System (MSDS 3D) was therefore adapted for use in TRUST. Close data monitoring will be applied in order to ensure high quality of data.

Results: Outlook: TRUST starts in spring 2014.

Conclusions: Annual interim analyses are intended to deliver continuous information and transparency with regard to an optimized patient management and safety profile of natalizumab-treated patients.

P099

Physician and participant treatment guesses in the double-blind CombiRx study

SS Cofield[1], T Gustafson[2], GR Cutter[1], JS Wolinsky[3], FD Lublin[2], The CombiRx Investigators

[1]University of Alabama at Birmingham, Birmingham, AL, United States, [2]Icahn School of Medicine at Mount Sinai, New York, NY, United States, [3]University of Texas Health Science Center at Houston, Houston, TX, United States

Background: Double-blind trials are designed to reduce bias in evaluating trial endpoints. Yet some medications have noticeable

side effects that may reduce the effectiveness of the blind. CombiRx was a multi-center, double-blind, three-arm trial with 50% taking combination therapy of interferon (IFN) and glatiramer acetate (GA) versus 25% on each active with matching placebo.

Objectives: To assess the accuracy of both participant and physician naming their treatment at study termination.

Methods: Participants and physicians were asked to guess the treatment arm at early termination or the end of 3 years on trial: IFN+GA, IFN alone, GA alone, No Guess or Not Applicable (selected as participant response when lost to follow up).

Results: Of 1008 randomized, 986 (97.8%) had the physician or participant response, 944 (93.7%) had both: 54.8% physician (27.6% participant) responses indicated No Guess. Of the 445 Physician (714 Participant) that selected a treatment: 68.3% (72.4) were correct, with 10.6% (10.9) guessing IFN but taking IFN+GA, 6.5% (4.1) guessing GA but IFN+GA, 6.1% (6.7) guessing IFN+GA but IFN, 4.5% (5.7) guessing IFN+GA but GA, with 4.0% (2.4) guessing the wrong single agent arm [2.2% (1.3) guess IFN but GA, 1.8% (1.1) guess GA but IFN]. Treatments with No Guess were 48.2% (47.6) IFN+GA, 25.6% (24.7) IFN, 26.2% (27.7) GA.

Of the 404 with both a participant and physician treatment guess, 84.9% agreed and 76.1% were correct, with 9.3% guessing IFN but taking IFN+GA, 3.8% guessing GA but IFN+GA, 5.5% guessing IFN+GA but IFN, 3.8% guessing IFN+GA but GA, with 1.5% guessing the wrong single agent arm (0.9% guess IFN but GA, 0.6% guess GA but IFN).

Considering only those that guessed a treatment allocation, of the participants taking IFN (IFN or IFN+GA): 88.9% physicians (93.1% participants) guessed IFN or IFN+GA. Of the participants taking GA (GA or IFN+GA): 83.1% physicians (83.8% participants) guessed GA or IFN+GA.

Considering all 1008 treatment allocations, of the 749 participants taking IFN (IFN or IFN+GA): 39.4% physicians (66.2% participants) guessed IFN or IFN+GA. Of the 758 participants taking GA (GA or IFN+GA): 37.1% physicians (59.2% participants) guessed GA or IFN+GA.

Conclusions: A larger proportion of physicians declined a treatment guess but the proportions correct and direction of incorrect guesses was similar between physicians and participants. A low percentage of both physicians and participants that guessed were completely incorrect by guessing the wrong single agent treatment arm.

P100
Indirect comparison of glatiramer acetate 40mg/mL TIW and 20mg/mL QD dosing regimen effects on relapse rate: results of a predictive statistical model
G Cutter[1], JS Wolinsky[2], G Comi[3], D Ladkani[4], V Knappertz[5,6], A Vainstein[7], N Sasson[7], O Khan[8,9]
[1]University of Alabama at Birmingham, Birmingham, AL, United States, [2]University of Texas, Health Science Center at Houston, Houston, TX, United States, [3]San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy, [4]Teva Pharmaceutical Industries, Petach Tiqva, Israel, [5]Teva Pharmaceutical Industries, Frazer, PA, United States, [6]Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany, [7]Teva Pharmaceutical Industries, Netanya, Israel, [8]Multiple Sclerosis Center, Wayne State University School of Medicine, Detroit, MI, United States, [9]Sastry Foundation Advanced Imaging Laboratory, Wayne State University School of Medicine, Detroit, MI, United States

Background: The GALA trial in RRMS showed glatiramer acetate (GA) 40mg 3 times weekly (TIW) significantly reduces annualized relapse rate (ARR) vs. placebo. The lack of GA 20mg once-daily (QD) dosing in GALA precludes direct comparison with 40mg TIW. Daily GA 20mg and 40mg dosing was assessed in the FORTE study.

Objectives: To perform indirect comparisons of GA 20mg QD and GA 40mg TIW effects on ARR using statistical regression models to predict 1) ARR of typical patients (pts) who received GA 20mg QD in clinical trials if they had received 40mg TIW; and 2) ARR of typical GALA 40mg TIW pts if they had received GA 20mg QD.

Methods: The ARR of GA 40mg TIW in GALA was estimated using negative binomial regression as a function of pt baseline (BL) characteristics. Initially 8 BL covariates were used in the model as main effects; the final model included only 4 that were predictive ($p \leq .05$) of ARR: age, BL EDSS, presence of GdE lesions at BL ($0/\geq 1$) and number of relapses in the year before screening (1/2); and country/geographical region was forced into the model. Predicted ARR for GA 40mg TIW with GALA averaged BL covariates was compared with observed ARR to validate the tool. The model was then used to predict ARR for pts in studies of 20mg QD (REGARD, BEYOND, CONFIRM) had they instead received 40mg TIW, given their BL characteristics. The predictive model built from FORTE GA 20mg QD data used the same 4 covariates to predict ARR for GALA pts had they instead received GA 20mg QD, which was indirectly compared with the reported ARR in GALA.

Results: Supporting final model validity, predicted ARR for GALA pts receiving GA 40mg TIW (0.32, 95%CI 0.27-0.38) was similar to the actual ARR (0.33, 0.28-0.39). Predicted ARRs for typical REGARD (0.31, 0.26-0.36) and BEYOND (0.32, 0.27-0.38) pts, had they received GA 40mg TIW, were similar to reported ARRs for GA 20mg QD in REGARD (0.29, 0.25-0.34) and BEYOND (0.34, 0.28-0.42). Predicted ARR for a typical CONFIRM pt (0.32, 0.27-0.38) had he/she received GA 40mg TIW was slightly higher than observed ARR (0.29, 0.23-0.35). In the predictive model built from FORTE data, predicted ARR for a typical GALA pt had she/he received GA 20mg QD (0.29, 0.24-0.35) was similar to the reported ARR (0.33, 0.28-0.39).

Conclusions: Indirect comparison of the effects on ARR of GA 40mg TIW in GALA with effects of GA 20mg QD from large, prospective, well-controlled trials using predictive models demonstrates the similar efficacy of the two GA dosing regimens.

P101
Effect of fingolimod on evolution of baseline enhancing MRI lesions into persistent T1 hypointense lesions: post hoc analysis of the FREEDOMS study
EW Radue[1], T Sprenger[1,2], A de Vera[3], G Francis[4], E Rochotte[3], D Tomic[3], L Kappos[2]
[1]Medical Image Analysis Center (MIAC), University Hospital, Basel, Switzerland, [2]University Hospital, Department of Neurology, Basel, Switzerland, [3]Novartis Pharma AG, Basel, Switzerland, [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States

Background: In relapsing-remitting multiple sclerosis (RRMS), the presence of gadolinium-enhancing (Gd+) T1 lesions on brain MRI reflects active focal inflammation. Fingolimod significantly reduced the formation of Gd+ lesions in the 2-year, phase 3, double-blind, randomized, placebo (Pbo)-controlled, FREEDOMS study in RRMS. Some Gd+ lesions evolve into persistent T1 hypointense lesions, considered as indicators of severe tissue damage.

Objectives: To evaluate the effect of fingolimod therapy on the evolution of pre-existing Gd+ lesions to persistent T1 hypointense lesions in RRMS patients in the FREEDOMS study.

Methods: Gd+ lesions detected in baseline MRI scan (acquired during screening period) were followed at each post baseline scan to report persistent T1 hypointense lesions. Summary statistics were generated at both the patient and lesion level by treatment group (fingolimod 0.5mg, 1.25mg and Pbo). The percentage (%) of Gd+ lesions that evolved into T1 hypointense lesions and % of patients in whom this was observed was estimated at Months (M) 6, 12 and 24 by a logistic Generalized Estimating Equation (GEE) method and a logistic regression model adjusted for treatment and number of Gd+ lesions at screening.

Results: Of the 1270 patients with available scans at screening, 38% of the fingolimod 0.5 mg group and 36.8% of the Pbo group had ≥1 Gd+ lesion. Groups were balanced except for lower mean number (SD) of Gd+ lesions/patient at screening in the Pbo (3.4[4]) vs. the fingolimod groups (0.5 mg: 4.3[8.4]; 1.25 mg: 4.6[6.5]). The mean % Gd+ lesions at screening that evolved into T1 hypointense lesions was lower in the fingolimod 0.5 mg group vs. Pbo, at all-time points (M6, 39% vs 53% [odds ratio, OR] 0.61,p=0.006, M12: 30% vs.43% [OR 0.62,p=0.012] and M 24, 29% vs. 38% [OR:0.63,p=0.018]). The % patients who had any Gd+ lesion at screening that evolved to a T1 hypointense lesion was lower at M 6, 12 and 24 for fingolimod 0.5 mg vs. Pbo (M0-6: 63% vs 75%, p=0.014; M0-12: 65% vs.76%,p=0.031; M0-24: 66% vs.76%,p=0.042). Data for fingolimod 1.25 mg/day were comparable after correction for imbalances at screening.

Conclusions: Fingolimod 0.5 mg significantly reduced the proportion of Gd+ lesions, at screening, that evolved into persistent T1 hypointense lesions at M6, M12 and M24, versus placebo. These findings indicate that fingolimod reduces the permanent damage caused by acute inflammatory lesions already present before starting treatment.

P102

No evident disease activity at 24 weeks in patients with relapsing MS treated with interferon β-1a SC vs. interferon β-1a IM in the EVIDENCE study

PK Coyle[1], J Fang[2], A Hassan[2], C Cha[2], F Dangond[2], AT Reder[3]
[1]Stony Brook University, Department of Neurology, Stony Brook, NY, United States, [2]EMD Serono, Inc., Rockland, MA, United States, [3]University of Chicago, Chicago, MA, United States

Background: EVIDENCE (EVidence of Interferon Dose-response: European North American Comparative Efficacy) was an assessor-blinded, randomized, parallel-group study conducted over an average of 64 weeks. It was designed as a head-to-head study comparing efficacy and safety of two interferon beta (IFN β) therapies for treatment of relapsing MS (RMS).

Objectives: A *post hoc* analysis was conducted to examine the efficacy of IFN β-1a subcutaneously (SC) vs. IFN β-1a intramuscularly (IM) in achieving clinical activity free and no evident disease activity (NEDA) status in the EVIDENCE study.

Methods: Patients with RMS were randomized to receive IFN β-1a SC (N=339) or IFN β-1a IM (N=338). Percentages of patients with the following outcomes were analyzed by chi-squared test: clinical activity free, defined as no relapses or sustained disability (increase of ≥1.0 point in EDSS from baseline sustained for ≥12 weeks) at 24 and 48 weeks; and NEDA[1] (composite of clinical activity free, no new or enlarging T2 lesions, and no gadolinium [Gd]-enhancing lesions) at 24 weeks. As only T2 but not Gd-enhanced T1 scans were performed at 48 weeks, a less stringent definition of disease activity free (composite of clinical activity free and no new or enlarging T2 lesions) was assessed at 24 and 48 weeks.

Results: Significantly more patients receiving IFN β-1a SC were clinical activity free than patients receiving IFN β-1a IM at 24 weeks (72% vs. 58%; p< 0.001) and at 48 weeks (56% vs. 46%; p=0.01). In addition, significantly more patients receiving IFN β-1a SC than patients receiving IFN β-1a IM were disease activity free at 24 weeks (46% vs. 29%; p< 0.001) and at 48 weeks (34% vs. 19%; p< 0.001). At 24 weeks, NEDA was observed in significantly more patients receiving IFN β-1a SC than those receiving IFN β-1a IM (36% vs. 22%; p< 0.001).

Conclusions: Significantly greater responses in terms of clinical or disease activity free status, including NEDA at 24 weeks, were consistently achieved in patients with RMS randomized to treatment with IFN β-1a SC than with IFN β-1a IM.

1. Cleveland Clinic Center for Continuing Education. Multiple Sclerosis Virtual Grand Rounds Treating to Target in MS: Disease Free Status? http://www.clevelandclinicmeded. com/online/webcasts/ms-vgr/treating-to-target-in-MS/.

P103

Alemtuzumab improves MRI outcomes in relapsing-remitting multiple sclerosis patients who relapsed on prior therapy: three-year follow-up of CARE-MS II

E Fisher[1], F Barkhof[2], JA Cohen[3], EJ Fox[4], KW Selmaj[5], DH Margolin[6], J Palmer[6], DL Arnold[7,8], on behalf of the CARE-MS II Investigators
[1]Department of Biomedical Engineering, Cleveland Clinic, Cleveland, OH, United States, [2]VU University Medical Centre, Amsterdam, Netherlands, [3]Mellen Center and Department of Biomedical Engineering, Cleveland Clinic, Cleveland, OH, United States, [4]University of Texas Medical Branch, Round Rock, TX, United States, [5]Medical University of Łódź, Department of Neurology, Łódź, Poland, [6]Genzyme, a Sanofi Company, Cambridge, MA, United States, [7]NeuroRx Research, Montréal, QC, Canada, [8]Department of Neurology and Neurosurgery, Montréal Neurological, Montréal, QC, Canada

Background: Alemtuzumab is approved in over 30 countries for treatment of relapsing-remitting multiple sclerosis (RRMS). In the CARE-MS II trial in active RRMS patients who relapsed on prior therapy, alemtuzumab had superior efficacy vs subcutaneous interferon beta-1a, including reduction in magnetic resonance imaging (MRI) activity and brain volume loss over 2 years.

Durable effects on clinical efficacy were still observed at Year 3 in an extension study.

Objectives: To examine MRI outcomes over 3 years in alemtuzumab-treated patients who relapsed on prior therapy.

Methods: Patients who received alemtuzumab (12 mg/day intravenously on 5 consecutive days and on 3 consecutive days 12 months later) in CARE-MS II (NCT00548405) continued uninterrupted follow-up in the extension study (NCT00930553), during which they were eligible for alemtuzumab re-treatment on evidence of disease activity. MRI scans were acquired at baseline, and at 1, 2, and 3 years. MRI measurements included proportions of patients with gadolinium (Gd)-enhancing, new or enlarging T_2-hyperintense, and new T_1-hypointense lesions; proportion of patients MRI activity-free (absence of both Gd-enhancing and T_2 lesions); T_2 and T_1 lesion volumes; and brain volume loss (brain parenchymal fraction change).

Results: Of 435 alemtuzumab-treated patients in the core study, 393 entered the extension and 80 (20%) received alemtuzumab re-treatment in Year 3. The proportions of patients with new or active lesions were low and did not differ significantly between Years 2 and 3 for Gd-enhancing lesions (8.7% [95% CI: 6.0, 11.5] vs 13.5% [10.0, 17.0]), T_2 lesions (23.7% [19.6, 27.8] vs 31.0% [26.3, 35.8]), or T_1 lesions (7.2% [4.6, 9.7] vs 12.5% [9.1, 15.9]). A majority of patients were free of MRI activity at Year 3 (68%). At Year 3, there were no significant changes from baseline in either median T_2 lesion volume (-1.6% [IQR: -13.8, 9.5]) or T_1 lesion volume (1.9% [IQR: -33.7, 42.3]). The median rate of brain volume loss decreased over time (Year 0–1: -0.48% [95% CI: -0.57, -0.38], Years 1-2: -0.22% [-0.29, -0.16], Years 2–3, -0.10% [-0.22, -0.03]).

Conclusions: Most patients who relapsed on prior therapy were free of new lesions and MRI activity in the third year after initiating treatment with alemtuzumab. A continued slowing of brain volume loss was observed in Year 3. Given that most patients did not receive additional alemtuzumab or other disease-modifying therapy in their third year, the results support the durable efficacy of alemtuzumab in RRMS.

P104
No evident disease activity in relapsing MS patients treated with interferon β-1a SC vs. interferon β-1a IM: subgroup analyses of the EVIDENCE study

PK Coyle[1], J Fang[2], A Hassan[2], C Cha[2], F Dangond[2], AT Reder[3]
[1]Stony Brook University, Department of Neurology, Stony Brook, NY, United States, [2]EMD Serono, Inc., Rockland, MA, United States, [3]University of Chicago, Chicago, IL, United States

Background: Previously, the EVIDENCE (EVidence of Interferon Dose-response: European North American Comparative Efficacy) study showed that more patients with relapsing MS (RMS) remained relapse-free at 24 weeks with interferon beta-1a (IFN β-1a) subcutaneously (SC) than with IFN β-1a intramuscularly (IM) (75% vs. 63%, p< 0.001).

Objectives: *Post hoc* analyses were conducted to investigate the efficacy of IFN β-1a SC vs. IFN β-1a IM in achieving clinical activity free (CAF) and no evident disease activity (NEDA) status in subgroups from EVIDENCE defined by baseline (BL) disability or disease activity.

Methods: Patients with RMS were randomized to receive IFN β-1a SC 44 µg 3 times weekly (N=339) or IFN β-1a IM 30 µg once weekly (N=338). Subgroups were defined by the following BL characteristics: EDSS score ≤ and >3.5; EDSS score ≤ and > median value of 2.0; and presence/absence of highly active disease (≥2 relapses in previous year and ≥1 gadolinium-enhancing [Gd+] lesion at study entry). In each subgroup, the percentages of patients with the following outcomes were analyzed by chi-squared test: CAF, defined as no relapses or disease progression (increase of ≥1.0 point in EDSS from BL sustained for ≥12 weeks) at 24 and 48 weeks; and NEDA (composite of CAF, no new or enlarging T2 lesions, and no Gd+ lesions) at 24 weeks. As only T2 but not Gd-enhanced T1 scans were performed at 48 weeks, a less stringent definition of disease activity free (DAF; composite of CAF and no new or enlarging T2 lesions) was also assessed at 24 and 48 weeks.

Results: In the EDSS ≤3.5 subgroup, significantly more patients receiving IFN β-1a SC than IFN β-1a IM were CAF at 24 weeks (74% [211/287] vs. 59% [167/285]; p< 0.001) and 48 weeks (58% [164/284] vs. 48% [137/284]; p=0.023); were DAF at 24 weeks (47% [131/277] vs. 28% [78/275]; p< 0.001) and 48 weeks (35% [95/274] vs. 19% [53/275]; p< 0.001); and had NEDA at 24 weeks (38% [106/278] vs. 22% [60/277]; p< 0.001). In the EDSS >3.5 subgroup, patient numbers were small (n=44-47, IFN β-1a SC; n=43-45, IFN β-1a IM), and no meaningful statistics could be obtained. In all other subgroups analyzed, numerically larger percentages of patients receiving IFN β-1a SC than IFN β-1a IM had CAF, DAF or NEDA status, but the difference between treatment groups did not always reach statistical significance.

Conclusions: In patients with RMS and BL EDSS ≤3.5, IFN β-1a SC was significantly superior to IFN β-1a IM on multiple measures of clinical/disease activity free status, including NEDA at 24 weeks.

P105
A double-blind, randomized, versus-placebo study of palmitoylethanolamide in relapsing-remitting multiple sclerosis

N Orefice[1], M Calabrese[2], A Carotenuto[3], I Cerillo[3], S Montella[3], G Cerullo[3], A Marsili[3], R Lanzillo[3], F Saccà[3], V Brescia Morra[3], A Calignano[1], G Orefice[3]
[1]Federico II University, Department of Pharmacology, Naples, Italy, [2]University of Verona, Neurology Unit, Department of Neurological and Movement Sciences, Verona, Italy, [3]Federico II University-School of Medicine, Department of Neurosciences, Reproductive and Odontostomatological Sciences, Naples, Italy

Background: Palmitoylethanolamide (PEA), the naturally occurring amide of ethanolamine and palmitic acid, is an endogenous lipid that promotes inflammation and pain resolution. Many preclinical and clinical studies have shown that the exogenously administration of PEA exerts antiinflammatory, pain-relieving and neuroprotective effects. PEA has been reported to reduce inflammatory markers in animal models of multiple sclerosis (MS).

Objectives: To evaluate the potential antiinflammatory effects of oral administration ultra-micronized PEA (PEA-um®) by evaluation: I) plasmatic levels of the endocannabinoid system such as Anandamide (AEA) and its congeners, Oleoylethanolamide

(OEA) and PEA; II) plasmatic levels of pro-inflammatory cytokines as Interferon-y (INF-y) and Tumor Necrosis Factor-α (TNF-α), III) correlation the antiinflammatory effect with progression of disability.

Methods: Twenty-nine RR-MS patients (17 Male, 12 Female; mean age 27±8 years), in therapy with interferon beta-1a 44 mcg (three times weekly) for at least 6 months, have been randomized in two group: interferon + PEA 600mg/day (group A), or interferon + placebo (600mg/day) (group B) for 12 months. All patients underwent peripheral blood withdrawal to evaluate the plasma levels of PEA, AEA, OEA, INF-γ and TNF-a, and clinical assessment with the Expanded Disability Status Scale (EDSS) at baseline and every three months. Statistical analysis has been performed, using repeated measures ANOVA under unequal variances.

Results: Our data show that PEA-um® administration significant increases AEA (p< 0.0001) and PEA (p< 0.0169) endogenous plasma levels compared *vs* placebo. No statistical differences in OEA plasma levels have been observed. We found a significant decrease of INF-y (p< 0.0001) and TNF-α (p< 0.0001) plasma levels in PEA-um® treated patients compared *vs* placebo patients while no difference in EDSS score was observed.

Conclusions: A number of disease-modifying therapies have been recently approved for the treatment of MS. These molecules which prevent relapses and new lesions are more efficient than the "old" first line therapies and/or more convenient, especially with oral agents. In this study, we indicate that PEA-um® could be considered as an appropriate add-on therapy for the treatment of RR-MS patients.

Despite, other studies are necessary to confirm the best responder profile and the full potential of PEA-um® in MS-related disease and inflammatory progression.

P106

Integrated analysis of daclizumab HYP pharmacokinetics from three phase 1 studies

AA Othman[1], JQ Tran[2], MT Tang[3,4], S Dutta[1]
[1]AbbVie, Clinical Pharmacology and Pharmacometrics, North Chicago, IL, United States, [2]Biogen Idec, Clinical Pharmacology and Pharmacometrics, Cambridge, MA, United States, [3]AbbVie Biotherapeutics, Redwood City, CA, United States, [4]Current address: Genentech, Clinical Pharmacology, San Francisco, CA, United States

Background: Daclizumab is an IgG1 monoclonal antibody that inhibits interleukin-2 (IL-2)-mediated signaling through the high-affinity IL-2 receptor. Daclizumab High Yield Process (HYP) demonstrated benefits in treatment of relapsing-remitting multiple sclerosis (RRMS) in a large Phase 2b trial (SELECT).

Objectives: The present analysis summarizes and integrates available pharmacokinetic data from daclizumab HYP Phase 1 studies in healthy volunteers.

Methods: A non-linear mixed-effects model of daclizumab HYP pharmacokinetics was developed using 938 measureable serum concentrations from 70 subjects who received active treatment in three daclizumab HYP Phase 1 studies. The three studies were double-blind, randomized, placebo-controlled evaluations of daclizumab HYP pharmacokinetics, safety and tolerability in healthy volunteers following single subcutaneous administration

(50, 150 or 300 mg), multiple subcutaneous administrations (100 or 200 mg biweekly with a 200 mg loading dose), or single intravenous administration (200 or 400 mg).

Results: Daclizumab HYP pharmacokinetics was described with a two-compartment model with a first-order absorption and linear elimination at doses ≥100 mg. A typical 70 kg individual is estimated to have serum daclizumab HYP clearance of 10 mL/hr and a steady-state volume of distribution of 6.4 L. Daclizumab HYP subcutaneous bioavailability (100 to 300 mg doses) was > 80% and the mean absorption time was 4.6 days. Bodyweight explained only 20% of daclizumab HYP pharmacokinetic variability. Sex, age, race or presence of antibodies was not found to correlate with daclizumab HYP clearance. Effective half-life with monthly administration was estimated to be 21 to 25 days.

Conclusions: Daclizumab HYP is characterized by slow clearance, linear pharmacokinetics (doses ≥100 mg), high subcutaneous bioavailability and half-life suitable for monthly administration. With monthly subcutaneous administration, daclizumab HYP C_{max} to C_{trough} ratio is predicted to be approximately 2.5 and steady-state accumulation ratio is predicted to be approximately 1.9.

P107

24 month PANGAEA: a 5-year non-interventional study of safety, efficacy and pharmacoeconomic data for fingolimod patients in daily clinical practice

T Ziemssen[1], A Fuchs[2], H-J Schwarz[3], T van Lokven[2], C Cornelissen[2]
[1]Karl Gustav Carus University Hospital, Center of Clinical Neuroscience, Dresden, Germany, [2]Novartis Pharma GmbH, Nuremberg, Germany, [3]Kantar Health, Munich, Germany

Background: Once daily oral fingolimod, a sphingosine 1-phosphate receptor (S1PR) modulator, is approved for the treatment of relapsing remitting multiple sclerosis (RRMS) and more than 91,500 patients have been treated with fingolimod in both the clinical trial and post-marketing settings; as of Feb 28, 2014 total patient exposure exceeded 135,800 patient years.

Objectives: PANGAEA (Post-Authorization Non-interventional German sAfety of GilEnyA in RRMS patients) is a non-interventional study (NIS), conducted in Germany, to investigate long-term safety, tolerability and efficacy in daily clinical practice, as well as pharmacoeconomic factors.

Methods: In a sub-study pharmacoeconomic aspects of fingolimod were also investigated. Recruitment into the study finished in December 2013. 4222 patients from 505 active centers were enrolled into PANGAEA, and will be observed over 5 years. This interim analysis includes data from 3641 patients.

Results: The proportion of female patients was 71.6 % and the average age was 39.4 ± 10.0 years.
The annual relapse rate of all PANGAEA patients improved from 1.5 ± 0.13 (baseline) to 0.42 ± 0.08 in the first year of PANGAEA and to 0.49 ± 0.12 in the second year of PANGAEA. Of all PANGAEA patients 63.2% in the first and 64.1% in the 2nd year of PANGAEA were relapse free. The average EDSS of all PANGAEA patients was stable over 24 months at 3.0 (±0.06 Baseline; ±0.14 month 24). The proportion of patients with at least 6 months stable EDSS improved from 85.0% (month 3) to 94.0% (month 24). 12.7% of all patients discontinued the fingolimod therapy, 4.7%

because of adverse events. After 24 months, more than 98.0% of patients and physicians rated fingolimod tolerability as good or very good.

6815 adverse events were documented in PANGAEA. 168 (3.9%) adverse events were rated as serious. 45.4% of the patients experienced no adverse events so far.

Conclusions: The results of the 3rd yearly interim analysis of PANGAEA support the positive safety and efficacy profile demonstrated in phase III clinical trials. PANGAEA is a valuable source of fingolimod data in daily clinical routine.

P108

Efficacy of delayed-release dimethyl fumarate in multiple sclerosis patients with moderate disability: an integrated analysis of the phase 3 studies

M Hutchinson[1], A Zhang[2], M Yang[2], M Okwuokenye[2], NC Kurukulasuriya[2], RJ Fox[3], R Gold[4]

[1]St. Vincent's University Hospital, Dublin, Ireland, [2]Biogen Idec Inc., Cambridge, MA, United States, [3]Cleveland Clinic, Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland, OH, United States, [4]St. Josef Hospital, Ruhr University, Bochum, Germany

Background: Delayed-release dimethyl fumarate (DMF) demonstrated efficacy on clinical and radiologic measures and an acceptable safety profile in patients with relapsing-remitting multiple sclerosis (RRMS) in the Phase 3 DEFINE and CONFIRM studies.

Objectives: To evaluate the clinical efficacy of delayed-release DMF (measured in terms of annualized relapse rate [ARR], proportion of patients relapsed, and risk of 12-week sustained disability progression) according to Expanded Disability Status Scale (EDSS) score at baseline, in a post hoc integrated analysis of DEFINE and CONFIRM.

Methods: Eligible patients were 18−55 years of age and had a diagnosis of RRMS per McDonald criteria and an EDSS score of 0−5.0, inclusive. Patients were randomized to receive placebo, delayed-release DMF 240 mg twice (BID) or three times daily (TID), or subcutaneous GA (reference comparator; CONFIRM only). The analysis included patients receiving placebo or delayed-release DMF 240 mg BID (currently the approved dosing regimen in all regions) with an EDSS score ≥3.5 at baseline.

Results: The integrated intent-to-treat population included 771 and 769 patients in the placebo and delayed-release DMF BID groups, respectively; among them, 228 and 223 had a baseline EDSS score ≥3.5. In those patients with an EDSS score ≥3.5, adjusted ARR (95% confidence interval; CI) was 0.418 (0.323, 0.542) in the placebo group and 0.269 (0.201, 0.361) in the delayed-release DMF BID group, representing a relative reduction of 36% (HR [95%CI]=0.64 [0.47, 0.88], p=0.0059). The proportion of patients relapsed over 2 years (based on the Kaplan-Meier method) was 47.2% in the placebo group and 35.3% in the delayed-release DMF BID group, representing a relative reduction of 34% (HR [95%CI]=0.66 [0.49, 0.90], p=0.0093). The estimated proportion of patients with 12-week sustained disability progression was directionally lower in the delayed-release DMF BID group versus placebo (15.5% vs 21.8%), although not statistically significant (p=0.1106). Clinical efficacy outcomes in subgroups defined by additional baseline EDSS score cutoffs (ranging from ≥2 to ≥4) will be presented.

Conclusions: Delayed-release DMF BID demonstrated efficacy on clinical measures (ARR and proportion of patients relapsed) in patients with moderate disability at baseline.

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Modeling concentration-efficacy relationship for MRI lesion counts under siponimod treatment and its dependence on the effect on lymphocyte reduction

M Savelieva[1], E Wallström[1]

[1]Novartis Pharma AG, Basel, Switzerland

Background: Siponimod (BAF312), a novel sphingosine 1-phosphate receptor (S1P)-1,5 modulator, reduces the peripheral lymphocyte counts in blood and also readily enters the CNS where it is believed to have a direct effect on the CNS-based pathology in multiple sclerosis by acting on S1P1 and/or S1P5 receptor expressing cells such as astrocytes and oligodendrocytes. To understand this dual mechanism of action, an analysis of the relationship between siponimod plasma concentration (as a proxy to CNS concentration) and the brain MRI lesions dynamics is necessary, together with the correlation between brain MRI lesions and lymphocyte counts.

Objectives: To characterize the correlation between (1) the siponimod concentration and monthly number of combined unique active lesions (CUAL), and (2) the correlation between the extent of lymphocyte reduction with siponimod and lesion count reduction.

Methods: Data from 296 relapsing remitting multiple sclerosis patients from the placebo-controlled phase II study was analyzed. A PK/PD sequential modeling approach was used to evaluate the number of lesions at a population level, including the inter-patient variability. Negative binomial regression, with an Emax function characterizing drug effect, was used to characterize the lesion count dynamics. Individual number of CUALs at every month up to month six was related to time, individual predicted steady-state concentrations and off-set placebo effect. Inter-patient variability was accounted via placebo random effect. Covariate analysis investigated the effect of disease severity (baseline Gd-T1 lesion load), demographic covariates (sex, age and weight) and individual post hoc estimates of the lymphocyte count reduction on the underlying placebo and the drug effect on lesion count.

Results: Covariate analysis revealed effects of age and baseline Gd-T1 lesion load on the placebo MRI effect. Sex had an effect on Emax, the maximal effect of lesion count reduction. Weight had no effects on any of the parameters. Individual lymphocyte reduction effect showed a possible positive correlation with the drug effect on MRI reduction, but statistically sound assessment of this effect would require more data on lymphocyte counts to be analyzed.

Conclusions: The full PK/PD modeling approach allowed for a robust assessment of the parameters of interest. Negative binomial random-effect concentration-response model characterized the data well and confirms previous MRI dose-response relationship findings for siponimod.

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Five-year follow-up of delayed-release dimethyl fumarate in RRMS: integrated clinical efficacy data from the DEFINE, CONFIRM, and ENDORSE studies

NC Kurukulasuriya[6], R Gold[1], JT Phillips[2], A Bar-Or[3], M Hutchinson[4], L Kappos[5], R Zhang[6], M Yang[6], V Viglietta[6], RJ Fox[7]

[1]St. Josef Hospital, Ruhr University, Bochum, Germany, [2]Baylor Institute for Immunology Research, Multiple Sclerosis Program, Dallas, TX, United States, [3]McGill University, Montreal Neurological Institute, Montreal, QC, Canada, [4]St. Vincent's University Hospital, Dublin, Ireland, [5]University Hospital, Basel Neurology, Basel, Switzerland, [6]Biogen Idec Inc., Cambridge, MA, United States, [7]Cleveland Clinic, Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland, OH, United States

Background: Oral delayed-release dimethyl fumarate (DMF) demonstrated efficacy and safety in patients with relapsing-remitting multiple sclerosis (RRMS) in the 2-year, Phase 3 DEFINE and CONFIRM studies. ENDORSE is an ongoing, 5-year, dose-blind extension study evaluating long-term safety and efficacy.

Objectives: To report long-term (5-year follow-up) clinical efficacy outcomes with delayed-release DMF from DEFINE, CONFIRM, and ENDORSE.

Methods: In ENDORSE, patients randomized in DEFINE/CONFIRM to delayed-release DMF 240 mg twice (BID) or three times daily (TID) continued the same dosage. Patients randomized to placebo (PBO) or glatiramer acetate (GA) were re-randomized 1:1 to delayed-release DMF 240 mg BID or TID. Interim efficacy data were analyzed (June 12, 2013 cutoff) according to treatment arm in the parent/extension study: BID/BID, TID/TID, PBO/BID, PBO/TID, GA/BID, GA/TID. Results from patients treated with delayed-release DMF 240 mg BID in ENDORSE are reported, as this represents the approved dose in the United States and the European Union.

Results: Of 2,079 patients completing DEFINE/CONFIRM, 1,736 were dosed in ENDORSE (n=501 [BID/BID], 502 [TID/TID], 249 [PBO/BID], 248 [PBO/TID], 118 [GA/BID], and 118 [GA/TID]). BID/BID patients showed consistent efficacy over 4 years (2 years in parent studies, 2 years in ENDORSE). Adjusted annualized relapse rates (ARRs) (95% confidence interval [CI]) for BID/BID during Years 1 and 2 (2 years in parent studies) and Years 3 and 4 (2 years in ENDORSE) were as follows: 0.202 (0.162-0.252), 0.163 (0.128-0.208), 0.138 (0.104-0.183), and 0.142 (0.108-0.187), respectively. For patients switching treatment from PBO or GA, the ARRs (95% CI) during Years 3 and 4 (Years 1 and 2 of ENDORSE) were 0.177 (0.122-0.256) and 0.126 (0.083-0.194) for the PBO/BID and 0.184 (0.111-0.305) and 0.128 (0.070-0.233) for the GA/BID patient groups, respectively. Estimated probability of disability progression remained low among patients who continued treatment with delayed-release DMF. Updated data (5-year follow-up) will be presented.

Conclusions: Treatment with delayed-release DMF was associated with low relapse rates and estimated disability progression over 4 years; with neuroradiologic efficacy and an acceptable safety profile, these results support its potential as a long-term treatment option for RRMS.

P111
Innate immune modulator MIS416 enhances systemic levels of negative regulators of inflammation in phase 2a clinical trial plasma samples

G Webster[1], V Pearson[1], R Girvan[1]
[1]Innate Immunotherapeutics Ltd, Auckland, New Zealand

Background: Innate immune modulator, MIS416, is in clinical development for the treatment of secondary progressive multiple sclerosis (SPMS). MIS416 is a microparticulate formulation of bacterial ligands for NOD-2 and TLR9 cytosolic receptors. Following systemic administration, MIS416 targets liver associated phagocytic cells and initiates complex innate immune signalling pathways that have the potential to counter-regulate inflammatory pathways associated with SPMS based on studies in mouse EAE [1] and human compassionate use experience.

Objectives: Analysis of phase 2a clinical trial plasma samples for MIS416 pharmacodynamic activity and anti-inflammatory mediators.

Methods: Patients (n-15) with SPMS were treated weekly with 0.5 mg MIS416 intravenously for 12 weeks (trial ref. no. NCT01191996). Peripheral blood serum was collected at baseline, pre and 24 hour post administration of MIS416 at weeks 1, 2, 3 and 4 and pre dose at weeks 7 and 10. Flow cytometry bead arrays were used to quantify multiple immune related proteins.

Results: Longitudinal analysis of serum demonstrated that in accordance with the composition of MIS416 and targeted proximal signalling pathways, innate IFNγ and interferon-inducible chemokines such as MIG and IP-10 were transiently elevated following each dose. Importantly, pro-inflammatory mediators such as IL-12p70, TNFα and IL-1β remained undetectable and magnetic resonance imaging confirmed MIS416 treatment did not activate existing or new lesions. Of particular clinical significance was the induction of negative regulators of inflammation such as IL-10 and IL-12p40, which also both showed transient elevation associated with each weekly dose of MIS416. Furthermore, the magnitude of the IL-10 and IL-12p40 response showed a positive correlation with the magnitude of the IFNγ response.

Conclusions: These data support the hypothesis that innate IFNγ induced *de novo*, can negatively regulate inflammation by induction of anti-inflammatory feedback pathways. As well as influencing peripheral inflammation, the observation that anti-inflammatory proteins can be measured in the serum of SPMS patients raises the potential for these to directly access the CNS and act locally to counter regulate innate inflammatory pathways that underpin disease pathogenesis in SPMS patients.

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P112
Impact of fingolimod on achieving no evidence of disease activity in pre-treated patients with high disease activity in FREEDOMS and FREEDOMS II

N Bergvall[1], D Tomic[1], N Sfikas[1], L Kappos[2]
[1]Novartis Pharma AG, Basel, Switzerland, [2]University Hospital, Basel, Switzerland

Background: The efficacy of fingolimod vs placebo on magnetic resonance imaging (MRI) and clinical outcomes in patients with multiple sclerosis (MS) has been demonstrated in two large phase 3, placebo-controlled trials, FREEDOMS[1] and FREEDOMS II.[2]

Objectives: To estimate differences between fingolimod 0.5 mg and placebo for achieving no evidence of disease activity (NEDA), defined by clinical and MRI outcomes, in patients with MS who

show evidence of high disease activity despite prior use of disease-modifying therapy (DMT).

Methods: *Post hoc* pooled analyses of FREEDOMS and FREEDOMS II were performed in subgroups of patients who had high disease activity despite DMT use in the past year. Patients in subgroup 1 had >=1 relapse in the previous year and either >=1 gadolinium (Gd)-enhancing T1 lesion or >=9 T2 lesions at baseline; those in subgroup 2 had equal or more relapses in the year before baseline than in the previous year. NEDA was defined as the proportion of patients free from relapses and 3-month CDP (clinical composite), free from Gd-enhancing T1 lesions and new or newly enlarged T2 lesions (MRI composite), or free from all disease measures (overall composite). Differences between the fingolimod and placebo cohorts were assessed using a logistic model adjusted for demographic and disease characteristics at baseline.

Results: For the overall composite, fingolimod-treated patients were significantly more likely to show NEDA vs placebo-treated patients (subgroup 1: 21% vs 6%; odds ratio [OR], 5.17; 95% confidence interval [CI], 2.53-10.55; subgroup 2: 26% vs 9%; OR, 4.04; 95% CI, 2.22-7.34). Patients receiving fingolimod were significantly more likely not to show clinical disease activity at month 24 than patients receiving placebo in both subgroups (subgroup 1: OR, 2.27; 95% CI, 1.46-3.53; subgroup 2: OR, 2.55; 95% CI, 1.65-3.96). A significant difference was also observed for NEDA on the MRI composite in favour of fingolimod (subgroup 1: OR, 5.44; 95% CI, 3.10-9.54; subgroup 2: OR, 4.35; 95% CI, 2.61-7.24).

Conclusions: Among patients who had high disease activity despite DMT use within the year before the study, those treated with fingolimod were significantly more likely than those treated with placebo not to show evidence of disease activity on all composite measures used.

References:

1. Kappos L *et al*. *N Engl J Med* 2010;362:387-401.
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P113

Natalizumab decreases progression of disability in RRMS patients as measured by the composite EDSS-Plus in AFFIRM

Q Dong[1], RA Rudick[2], D Paes[1], D Mikol[1], S Belachew[1]
[1]Biogen Idec, Cambridge, MA, United States, [2]Mellen Center, Cleveland Clinic Foundation, Cleveland, OH, United States

Background: The Expanded Disability Status Scale (EDSS)-Plus was developed to assess worsening in ambulatory and upper limb function or EDSS in patients with progressive MS and is the primary endpoint in ASCEND (A Multicenter Randomized, Double-Blind, Placebo-Controlled, Study of the Efficacy of Natalizumab on Reducing Disability Progression in Subjects with Secondary Progressive MS).

Objectives: To determine the effects of natalizumab on EDSS-Plus progression in relapsing-remitting MS (RRMS) patients in AFFIRM.

Methods: Here EDSS-Plus progression is defined as 6-month confirmed progression of disability in ≥1 of 3 measures: 1) EDSS progression of ≥1 point for baseline EDSS ≤5.5 or ≥0.5 for baseline EDSS ≥6.0; 2) ≥20% increase from baseline in Timed 25-Foot Walk time; or 3) ≥20% increase from baseline in 9-Hole Peg Test time. Sensitivity analyses include progression in ≥2 of the 3 measures and/or with 3-month confirmation. Patient The proportion of patients with progression were compared between treatment groups in the overall population (natalizumab, n=627; placebo, n=315) and in the subgroup with EDSS ≥2.5 (natalizumab, n=288; placebo n=143) using logistic regression.

Results: Natalizumab reduced the risk of EDSS-Plus progression by 36% in the overall population (natalizumab, 21%; placebo, 33%; *P*=0.0001) and by 33% in patients with EDSS ≥2.5 (natalizumab, 24%; placebo, 36%; *P*=0.01), compared to placebo. When confirmed progression in ≥2 measures was utilized, natalizumab reduced the risk by 58% in the overall population (natalizumab, 4%; placebo, 10%; *P*=0.001) and by 45% in patients with EDSS ≥2.5 (natalizumab, 8%; placebo, 14%; *P*=0.08). Treatment effects with 3-month confirmation were similar to those with 6-month confirmation in each instance; the relative reduction in risk of progression with natalizumab treatment ranged from 24%-53% (*P*< 0.0001-*P*=0.02).

Conclusions: The possible utility of EDSS-Plus in RRMS is unclear**.** In post hoc analyses of AFFIRM the EDSS-Plus composite identified significant treatment effects of natalizumab on preventing progression of disability in RRMS patients. This was apparent in the overall population and in the subgroup with baseline EDSS ≥2.5, the latter of whom exhibited higher rates of progression. The magnitude of treatment effect was greater when progression was assessed on ≥2 components of the composite. Treatment effects on each component of EDSS-Plus will be presented.

Cognitive function

P114

Independent component analysis of cognitive performance in primary-progressive multiple sclerosis

M Petracca[1,2], H Bender[2], C Farrell[2], R Teodorescu[2], J Howard[3], C Riley[4], V Stein[2], F Arias[2], M Fabian[5], F Lublin[2], M Inglese[2,5,6]
[1]Federico II University, Neuroscience, Naples, Italy, [2]Mount Sinai School of Medicine, Neurology, New York, NY, United States, [3]New York University, Neurology, New York, NY, United States, [4]Columbia University, Neurology, New York, NY, United States, [5]Mount Sinai School of Medicine, Neuroscience, New York, NY, United States, [6]Mount Sinai School of Medicine, Radiology, New York, NY, United States

Background: Primary-Progressive Multiple Sclerosis (PP-MS) is characterized by steady clinical deterioration without remission from disease onset[1]. Cognitive impairment occurs in about 47.4% of PP-MS patients. We hypothesize that an inefficient cortical reorganization might play a role in the development of cognitive deficits[2,3].

Objectives:

1) to explore resting state (RS) functional connectivity (FC) abnormalities in patients with PP-MS through an independent component analysis (ICA) approach;
2) to investigate whether such abnormalities correlate with cognitive performance.

Methods: We studied 26 patients with PP-MS (M/F=12/14, mean age 51±10 yrs, median EDSS 4; range 1.5-6, disease duration

8±4.5yrs) and 20 healthy controls (CTRLs) (M/F=9/11, mean age 51±10yrs). All subjects underwent MRI on a 3T scanner. The MRI protocol included:

    a) T2 Dual turbo spin echo;
    b) T1 weighted 3D turbo field echo;
    c) echo planar imaging for RS fMRI.

On the same day, PP-MS patients underwent neurological examination and neuropsychological testing (MACFIMS battery). RS fMRI sequences were pre-processed using DPARSF pipeline from SPM8. 50 independent RS networks (RSN) were detected and extracted with MELODIC toolbox from FSL[4]; and the following networks involved in cognitive functions were identified: working memory network-WMN; salience network-SN; executive control network-ECN; default mode network-DMN; anterior hippocampal network-AHN; posterior hippocampal network-PHN. For each RSN, intrinsic FC of each cluster was computed and compared between CTRLs and patients. Between-group differences were assessed using SPM8. Correlation of clinical parameters with FC data was assessed with Spearman's correlation coefficient.

Results: Compared to CTRLs, patients with PP-MS experienced a decreased RS FC in regions of the:

    1) WMN
    2) SN
    3) ECN
    4) DMN
    5) AHN
    6) PHN

In PP-MS patients, decreased RS FC in WMN was significantly correlated with total coding (TC) scores (p< 0.01); decreased RS FC in DMN was correlated with TC (p< 0.05) and FAS scores (p< 0.01); decreased RS FC in SN was correlated with TC scores (p< 0.05). Correlation trends were detected between RS FC in DMN and DKEFS scores (p=0.07), and RS FC in ECN and DKEFS scores (p=0.08).

Conclusions: These results suggest that in PP-MS patients is present a widespread dysfunction of cortical organization; the disruption of connectivity in DMN, WMN and ECN seems to be clinically relevant in such patients, affecting in particular processing speed, executive functions and verbal fluency.

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Thalamic functional connectivity and cognitive impairment: comparison between relapsing remitting and secondary progressive multiple sclerosis

F Tona[1], E Sbardella[1,2], N Petsas[1,2], MC Piattella[1], L Prosperini[1], C Pozzilli[1], P Pantano[1]
[1]University Sapienza, Neurology and Psychiatry, Rome, Italy, [2]Santa Lucia Fundation, Rome, Italy

Background: In Multiple Sclerosis (MS) the severity of cognitive impairment increases with disease progression, but the underlying pathophysiological mechanisms are still unclear. Abnormalities in thalamo-cortical functional connectivity (FC) correlated with Paced Auditory Serial Addition Test (PASAT) scores in relapsing-remitting (RR) MS (Tona et al, 2014).

Objectives: The aim of this work was to evaluate thalamo-cortical FC changes in patients with secondary progressive (SP) MS, as compared to both RR and healthy subjects (HS), and to investigate correlations with cognitive impairment.

Methods: We recruited 40 patients with diagnosed MS (20 RR and 20 SP) and 20 HS. All subjects underwent multimodal MR imaging, including fMRI at rest; they were also scored with PASAT. Data were analysed with tools from FMRIB Software Library; the seed-based method was used to identify the thalamic RS network (RSN) (cluster level, P < .05, corrected for family wise error [FWE]).

Results: Thalamic RSN was altered in both SP and RR with respect to HS; greatest FC abnormalities were observed in SP. In particular, thalamo-cortical FC was lower in RR than in HS in left temporo-occipital, frontal and parietal cortices, bilaterally and in the cerebellum; SP showed decreased FC in the same brain areas, which were even more extensively affected, and, in addition, in the medial thalami.

Thalamo-cortical FC was higher in RR than in HS in the right frontal and in the mesial occipital and cingulate cortices, bilaterally; SP showed increased FC also in the right temporo-occipital cortex, hippocampi and posterior thalami, in addition to the aforementioned brain areas. PASAT scores were significantly lower in patients than HS and in SP than in RR. In RR, PASAT scores significantly correlated with thalamo-cortical FC in the frontal cortex bilaterally, thalami and left anterior insula, indicating that worse the performance greater the FC. In SP widespread hyperconnectivity, including the cerebellum, thalami, posterior cingulate, anterior insula and multiple foci in the whole cerebral cortex, inversely correlated with PASAT scores.

Conclusions: Our data indicate that thalamic RSN is progressively altered in the two MS subtypes: SP showed more extensive patterns of both significantly decreased and increased FC than RR. Moreover, the significant correlation between cognitive impairment and increased thalamo-cortical FC suggests that the recruitment of additional areas within the thalamic RSN is unable to prevent the cognitive decline.

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Emotional modifications in multiple sclerosis: a neuropsychological and fMRI study

L Pfaff[1], D Gounot[1], J-B Chanson[2], J-P Armspach[1], J De Seze[2], F Blanc[1]
[1]University of Strasbourg, CNRS, ICUBE-IPB, UMR 7357, Strasbourg, France, [2]Hôpitaux Universitaires de Strasbourg, Neurologie, Strasbourg, France

Background: Affective disorders are frequent in multiple sclerosis (MS), but their specificity remains controversial and the underlying neurobiological mechanism poorly documented. Previous studies suggested that decreased brain activity in prefrontal and amygdala network associated with lack of functional connectivity between these areas was correlated with negative emotion recognition.

Objectives: The aim of this study is to specify the nature of this emotional dysfunction in MS and compare this data with fMRI measures using for the first time "real life "emotional scene, regarding negative and positive valence.

Methods: 16 right-handed women with relapsing-remitting MS and 16 right-handed healthy controls matched for age, sex and education were evaluated by a comprehensive

neuropsychological battery, a facial emotional recognition test (The Florida Affect Battery, FAB), and other emotional scales (EHD, Hamilton, TAS 20).

During fMRI scanning period, participants had to visualize emotional scene stemming from the IAPS, differing in valence (positive, negative, neutral), and arousal (ranging from calm to excited). After MRI occurs a debriefing, participants estimated their experience by seeing again every image and scoring the valence and the arousal sensation.

Results: MS patient (EDSS scores: $1,41 \pm 1,40$) do not differ with control in the depression-scale and psychical anxiety dimension but only for somatic anxiety dimension (p=0.03). MS patient are also more alexithymics than controls (p=0.02), and this for dimension "difficulty to identify feelings" (p=0.013) and "poverty of introspection" (p=0.042), but not for "verbalization of feelings" (p=0.5). Furthermore, MS-group showed significantly less correct answers in the FAB (p=0.004), and emotional experience was more scattered for them during the debriefing (p< 0.005).

In fMRI, all subjects show significant brain activation in amygdala, frontal and visual areas, with a strong modulation for arousal. A different pattern of activation exists between patient and control for positive stimulation with less amygdala activation (p< 0.001, unc.).

Conclusions: Patients with MS present difficulty to identify emotion and scattered emotional experience. fMRI data suggested that these difficulties are associated with differences in brain activation, including amygdala.

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Brain intrinsic resting-state functional connectivity modulation induced by mental effort in multiple sclerosis patients with fatigue

C Zecca[1], E Pravatà[1,2,3], MA Rocca[3], GC Riccitelli[1,3], A Cianfoni[2], M Filippi[3], C Gobbi[1]
[1]Multiple Sclerosis Center, Neurocenter of Southern Switzerland, Ospedale Regionale di Lugano, Neurology, Lugano, Switzerland, [2]Neuroradiology Department, Neurocenter of Southern Switzerland, Ospedale Regionale di Lugano, Lugano, Switzerland, [3]Neuroimaging Research Unit, Institute of Experimental Neurology, Vita-Salute San Raffaele University, Milan, Italy

Background: Fatigue is a common and debilitating symptom related to multiple sclerosis (MS). Fatigue may follow physical or mental efforts, resulting in physical (PF) and cognitive (CF) fatigue respectively. The physiopathological substrates of F are still not clarified. FC-MRI is a functional MRI technique able to study the functional correlation of integrated brain networks at res, without being influenced by task performance.

Objectives: To investigate modifications of the resting-state functional connectivity (RS-FC) induced by the execution of a cognitively effortful task in patients with relapsing-remitting MS (RRMS) with CF.

Methods: Twenty-two clinically stable RRMS patients, 11 with CF (F) and 11 without CF (nF) according to the Fatigue Scale for Motor and Cognitive Functions (FSMC) and 12 age- and gender-matched healthy control subjects (HS) were enrolled. RS-FC scans were acquired on a 3T MR scanner immediately before (t0), immediately after (t1) and 20 minutes after (t2) execution of the Paced Auditory Serial Addition Test (PASAT). Differences of RS-FC between F, nF and HS were investigated at each time point using a data-driven intrinsic connectivity contrast technique. Correlations between RS-FC at t2 and its variations between t0 and t2 and neuropsychological measures were also investigated. Dual-echo, 3D T1 weighted and diffusion-tensor MRI scans were acquired to evaluate T2 lesion load, atrophy and white matter microstructural damage.

Results: T2 lesion load and brain atrophy did not differ between F and nF patients. Self-reported CF after PASAT (PASAT-F) was significantly higher in F than nF patients and HS (p=0.016, Mann-Whitney U test). Compared to nF and HS, F patients had higher RS-FC at t2 between the left dorsolateral prefrontal cortex (L-DLPFC) and pre-motor, secondary visual, left frontal and temporal areas (p=0.01, FDR-corrected). Significant correlations were found between increased RS-FC at t2 and FSMC (r=0.65-0.73, p=0.001) and PASAT-F (rho=0.4-0.59, p=0.044-0.02). Tractographic reconstruction of cortico-thalamic fibers, using the L-DLPFC as a seed region, showed reduced fractional anisotropy in F compared to nF patients at this level (0.39 vs. 0.43, p=0.047).

Conclusions: In RRMS patients, CF is related to hyperconnectivity within fronto-temporo-occipital networks despite relax after mental effort, and to disconnection of thalamo-cortical projections.

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Brief computerized cognitive testing in pediatric-onset multiple sclerosis (MS)

LE Charvet[1,2], MW Porter[1,2], B Harel[3], N Amadiume[1,2], AL Belman[1,2], LB Krupp[1,2]
[1]Stony Brook University, Department of Neurology, Stony Brook, NY, United States, [2]Lourie Center for Pediatric MS, Stony Brook, NY, United States, [3]CogState Inc., & Child Study Center, Yale University School of Medicine, New Haven, CT, United States

Background: Pediatric-onset MS has an incidence of 0.2 to 0.6 per 100,000 children and requires multi-center collaboration to study. For these youngest patients, it is critical to identify cognitive impairment at its earliest point. The CogState computerized brief battery has demonstrated sensitivity in adults and children with other neurologic disorders and is utilized as a cognitive outcome for clinical trials. It has the advantages of a large normative database, ease of administration, and culture-free stimuli with data managed through a central server.

Objectives: To pilot the utility of the CogState brief battery for cognitive assessment in pediatric-onset MS.

Methods: Thirty-five (35) consecutively-recruited participants during routine outpatient visits at the Lourie Center for Pediatric MS. In addition to neurologic examination and the Symbol Digit Modalities Test (SDMT), patients completed the CogState brief battery which includes tasks measuring information processing (Detection and Identification), working memory (One-Back), and visual memory (One-Card Learning).

Results: Diagnoses were MS (n=32) or clinically-isolated (n=1) or radiologically-isolated (n=2) syndromes. Ages ranged from 10 to 24 years (mean 18.27±3.12) with EDSS scores from 0.0 to 4.0 with a median of 1.0 and average disease duration was 3.63 ± 3.23 years. Mean SDMT z score was -0.44 ±1.18 (range of -1.76 to 3.39), with thirty-one percent (31%) scoring in the impaired range

(one standard deviation or more below the mean). All participants' CogState data met criteria demonstrating acceptable completion and integrity. Mean z-scores were below average for Detection, Identification and One-Back tasks (speed; -1.19 ± 1.63, -1.13 ± 1.40, -1.03 ± 1.03 respectively) but not for One Card Learning (accuracy; -0.18 ± 1.03) with impairment rates of 51%, 54%, 54% and 23%. EDSS was significantly correlated with CogState Detection, Identification and One-Back scores (r=-0.34, p=.049, r=-0.47, p=0.005, r=-0.44, p=0.009) but not One Card Learning (r=-0.29, p=0.09) or the SDMT (-0.29, p=0.10). SDMT z-scores were more strongly related to the CogState One Back task, r=0.34, p=0.05. All participants impaired on the SDMT were also impaired on at least one of the four CogState indices (100% agreement).

Conclusions: The CogState brief battery is a practical computerized battery that is sensitive to detecting cognitive involvement in pediatric-onset MS and may be a useful measure of cognition for collaborative studies.

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A new computerized tool detects subtle differences in information processing speed in children with MS

S Bigi[1], RA Marrie[2], C Till[3], A Yeh[1], N Akbar[1], A Feinstein[4], B Banwell[1,5]
[1]The Hospital for Sick Children, Division of Neurology, Toronto, ON, Canada, [2]University of Manitoba, Departments of Internal Medicine and Community Health Sciences, Winnipeg, MB, Canada, [3]York University, Department of Psychology, Toronto, ON, Canada, [4]University of Toronto, Department of Psychiatry, Toronto, ON, Canada, [5]The Children's Hospital of Philadelphia, Division of Neurology, Philadelphia, PA, United States

Background: Information processing speed (IPS) increases with myelination. Decreased IPS is often the first sign of neurocognitive impairment in children and teens with multiple sclerosis (MS). Prompt identification of pediatric MS patients with impaired IPS requires a sensitive testing metric that can be administered in a clinical setting. The computerized version of the Symbol Digit Modalities Test (c-SDMT) measures IPS over 8 consecutive trials/session. Faster performance (=increase in IPS) across successive trials is expected.

Objectives: 1) To establish normative c-SDMT data in healthy children (HC); 2) To examine test-retest reliability of the c-SDMT in HC; 3) To compare the overall c-SDMT-performance and increase in IPS over 8 consecutive trials between HC and MS patients.

Methods: Cross-sectional study including 478 HC (237 female, 49.5%) and 27 MS patients (22 female, 81.5%), divided into five age-epochs (of 2 years each, range from 8-18 years). IPS was assessed using the mean time on 8 consecutive trials on the c-SDMT. Test-retest reliability was evaluated using an intraclass correlation coefficient (ICC). Multiple linear regression models on rank transformed data were used for predictive analyses in HC. The performance of each MS patient was compared to 4 sex and age matched HC.

Results: Across all ages, HC showed a median (IQR) c-SDMT score of 14.2 seconds (12.5-17.4). In the linear regression analysis, age and academic giftedness were significantly associated with faster IPS in HC (p< 0.001). Furthermore, older HC between 12-18 years were also able to show a faster performance (=increase

in IPS) across 8 consecutive trials (12-13 years: p=0.004; 14-18 years: p < 0.001), whereas the IPS in HC below 12 years of age did not increase over 8 consecutive trials. Test-retest reliability was high (ICC= 0.91) in HC across all age groups. In the sex and age matched comparison between HC and MS patients, the median (IQR) c-SDMT score was 12.8 seconds (11.7-15.9) in MS patients and 12.1 seconds (11.8-12.8) in HC (p=0.23). However, MS patients were significantly less likely to show a faster performance across successive trials compared to matched HC (p< 0.001).

Conclusions: The c-SDMT reliably measures IPS in healthy children and adolescents. Although the median c-SDMT score did not differ between MS patients and healthy controls, the failure to perform the test more quickly over the trials suggests that MS patients may be less able to access neural networks sub serving practice efficiency.

P120

How does neurological reserve compare between MS patients and healthy controls?

CE Schwartz[1,2,3], A Ayandeh[1], B Weinstock-Guttman[4], RH Benedict[4], R Zivadinov[4], M Ramanthan[5]
[1]DeltaQuest Foundation, Concord, MA, United States, [2]Tufts University Medical School, Medicine and Orthopaedic Surgery, Boston, MA, United States, [3]Oslo and Akershus University College of Applied Sciences, Nursing, Oslo, Norway, [4]University of Buffalo, Department of Neurology, Buffalo, MA, United States, [5]University of Buffalo, Pharmaceutical Sciences, Buffalo, NY, United States

Background: Neurological reserve has been implicated as a possible protective factor in MS, perhaps buffering the individual from disease progression. There is burgeoning research on neurological reserve in MS and other diseases causing dementia, but passive (i.e., past) and active (i.e.,current) reserve pursuits are yet to be compared to healthy controls.

Objectives: To investigate differences in passive and active neurological reserve between disease-course groupings of MS patients healthy controls.

Methods: This cross-sectional cohort study (mean age=46; 63% female) included 349 healthy controls, and subjects with clinically isolated syndrome (CIS; n=67), relapsing-remitting MS (RRMS; n=358) and progressive MS (PMS; n=179). Passive reserve was operationalized as occupational attainment and education. Active reserve comprised 6 strenuous (high-impact exercise, low-impact exercise, fighting sports, organized sports, job-related exercise, TV/computer-related exercise) and 6 non-strenuous (reading, internet usage, job-related, games, spiritual, TV) activities. Multivariate Analysis of Variance models tested the hypothesis of a group difference in passive and active reserve, after adjusting for age and gender. Post-hoc estimation investigated group differences.

Results: There were group differences in passive reserve (p< 0.04); post-hoc tests suggested that PMS patients had lower passive reserve than healthy controls (p< 0.004). There were group differences in strenuous (p< 0.0001) and non-strenuous (p< 0.0001) active reserve pursuits. Compared to healthy controls, all forms of MS engaged in fewer high-impact exercise (all p< 0.0001), low-impact exercise (all p< 0.0001), organized sports

(all p< 0.0001), and job-related strenuous active pursuits (all p< 0.001). RRMS and PMS engaged in less computer- or TV-based exercise (p< 0.02 & 0.05, respectively), and PMS did less fighting sports (p< 0.03). RRMS (p< 0.04) and PMS (p< 0.03) read less than healthy controls. CIS engaged in more and PMS engaged in fewer job-related non-strenuous activities (p< 0.05 & 0.0001, respectively). RRMS (p< 0.005) and PMS (p< 0.0001) watched more TV than healthy controls, but were similar in regard to games, internet usage, and spiritual pursuits.

Conclusions: PMS had lower passive reserve, and all MS patients engaged in fewer strenuous active reserve pursuits and less reading compared to healthy controls. They watched more TV. Lifestyle-modifying interventions should prioritize replacing TV-watching with more stimulating activities.

P121

Cortical lesions and cognitive impairment in multiple sclerosis: cortex or juxta-cortex?

C Louapre[1,2], ST Govindarajan[1], C Giannì[1,2], N Madigan[3], AS Nielsen[4], J Cohen-Adad[5], RP Kinkel[3], C Mainero[1,2]
[1]AA Martinos Center For Biomedical Imaging, Charlestown, MA, United States, [2]Harvard University, Boston, MA, United States, [3]Beth Israel Deaconess Medical Center, Boston, MA, United States, [4]Virginia Mason Medical Center, Seattle, WA, United States, [5]Ecole Polytechnique de Montréal, Montreal, QC, Canada

Background: Cortical lesions are a major determinant of impaired neuropsychological performance (NP) in multiple sclerosis (MS). Previous data suggested that focal juxta- and leuko-cortical lesions better predict NP in MS than purely intracortical lesions, suggesting that the location of pathology within the cortical width might impact differently NP in MS.

Objectives: To determine the relation between NP and tissue damage at different depths through the cortical width up to the juxta-cortical white matter (WM), across the whole brain, using a quantitative, surface-based analysis of T2* relaxation rates from ultra high resolution 7 Tesla MRI.

Methods: Thirty-one patients (5 Early MS, 16 RRMS, 10 SPMS) underwent a modified version of the MACFIMS battery; 7T multi-echo T2* imaging ($0.33{\times}0.33{\times}1$ mm^3) for T2* maps; 3T MRI for acquisition of T1-weighted images optimized for cortical surface reconstruction using FreeSurfer. T2* maps were registered to cortical surfaces, and sampled along the cortex at 25%, 50%, and 75% depth from the pial surface, and at 1 mm below the cortex. The relation between T2* at each depth, individual NP scores and a global cognitive index (CI), calculated from a principal component analysis on the whole battery, was tested by a General Linear Model including age, gender, education as nuisance regressors (p< 0.05 corrected for multiple comparisons).

Results: Cortical T2* increase (underlying decrease of myelin and iron content) correlated with global CI decrease in cortical and juxtacortical areas mainly including the bilateral precuneus, isthmus cingulate, superior and caudal middle frontal gyri. The total surface area of significant correlation between CI and T2* was greater at 75% (167 cm^2) than at 50% (138 cm^2) and 25% (78 cm^2) depth, and at 1 mm below the cortex (24 cm^2). The total area of significant negative correlation between T2* and individual attention, visuo-spatial, and processing speed tests scores was also maximal at 75% depth. On the contrary, for the Wisconsin Card

Sorting Test, the total error and perseveration scores correlated mainly with intracortical T2* at 25% and 50% respectively.

Conclusions: In MS, impairment of cognitive domains assessing cortical-subcortical functions is associated with pathology in deepest cortical layers, next to WM, and in juxta-cortex. Reduced performance in executive functions, which mainly relies on cortical integrity, is better predicted by intracortical pathology closer to the pial surface.

P122

A longitudinal evaluation of cognitive fatigue in MS using the PASAT

JA Berard[1], L Rees[2], MS Freedman[3], LAS Walker[2]
[1]Ottawa Hospital Research Institute, Psychology, Ottawa, ON, Canada, [2]The Ottawa Hospital, Psychology, Ottawa, ON, Canada, [3]The Ottawa Hospital, Medicine, Ottawa, ON, Canada

Background: Cognitive fatigue (CF) can be defined as an inability to maintain task performance throughout the duration of an attention-demanding cognitive task. Past research by our team has shown that individuals with MS are more susceptible to CF when compared to healthy controls (HCs); however, this has not yet been examined longitudinally.

Objectives: The primary goal was to evaluate CF in a sample of early-phase relapsing-remitting MS (RRMS) and to examine how an individual's susceptibility to CF changes over a 3-year period.

Methods: Twenty-five individuals with a confirmed diagnosis of RRMS were compared to 20 HCs. Individuals completed the 3" Paced Auditory Serial Addition Test (PASAT) at baseline and 3-year follow-up as part of a larger neuropsychological battery. The PASAT was scored using three different methods: total correct, total correct dyads, and percent dyad scores. CF was analyzed by comparing performance on the 1st of the task vs. the 2nd half of the task across the three scoring methods. Results are preliminary given that some follow-up assessments are pending.

Results: Performance on the PASAT improved over time in both groups regardless of scoring method utilized; however, healthy controls consistently performed better than the MS group at both times. CF was evident in both groups at baseline across the three scoring methods; however, neither group appeared more susceptible to CF than the other. At follow-up, CF was noted for both groups (using total correct and total dyad scores); with the MS group showing more cognitive fatigue than HCs when using the total correct score. While CF was still evident at follow-up, neither group showed a greater *vulnerability* to CF at follow-up when compared to their vulnerability at baseline. In fact, the degree of CF was less striking at follow-up.

Conclusions: The ability of the PASAT to differentiate between groups remains stable over time, with the MS group consistently performing worse than HCs. However, performance in both groups improved over time (i.e. benefited from practice). As previously reported by our team, the MS group showed greater vulnerability to CF, but only at follow-up, and only with traditional scoring methods. Although CF was present at both time points for both groups, all were less severely cognitively fatigued at follow-up. Contrary to expectations, in this group of individuals with early-phase RRMS, there was no evidence of cognitive worsening over time. Neither performance, nor CF, was worse at the three-year follow-up.

P123

Application of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) to pediatric-onset MS

LB Krupp[1,2], LE Charvet[1,2], MW Porter[1,2], N Amadiume[1,2], AL Belman[1,2]

[1]*Stony Brook University, Department of Neurology, Stony Brook, NY, United States,* [2]*Lourie Center for Pediatric MS, Stony Brook, NY, United States*

Background: The possibility of cognitive impairment is a major concern in MS, including the youngest affected with pediatric-onset. There is a need for brief, practical and universal assessment approaches. The BICAMS battery was developed by an international committee and validated for use in adults. It includes the Symbol Digit Modalities Test (SDMT) supplemented with the learning trials from the California Verbal Learning Test (CVLT) and Brief Visuomotor Retention Test-Revised (BVMT-R).

Objectives: To extend the application of the BICAMS approach to all MS subgroups we evaluated its utility in patients with pediatric onset.

Methods: Thirty-nine consecutively-recruited outpatients diagnosed with pediatric-onset MS (n=35), CIS (n=1) or RIS (n=3) completed a modified version of the BICAMS assessment during routine clinic visits. The adult BICAMS battery was modified by replacing the CVLT-II with the Rey Auditory Verbal Learning Test (RAVLT). While both are verbal list learning tasks, the same RAVLT form can be used in patients as young as 8 years and through adult and also has more available alternate forms. Performances were compared to published norms.

Results: Participants ages ranged from 10 to 24 years (mean 18.4±3.2) with EDSS scores from 0.0 to 4.0 with a median of 1.0. Mean SDMT z score was -0.55 ±1.20, with a range of -2.76 to 1.20. Mean RAVLT learning z-score was -0.44 ± 1.39, with a range of -3.71 to 2.19. Mean BVMT-R learning z score was -0.17 ± 1.42 with a range of -3.99 to 2.24. Percent of sample impaired (falling one standard deviation or more below normative mean) was 31% for the SDMT, 28% for the RAVLT, and 27% for the BVMT-R. These rates of impairment are consistent with what has been reported in larger pediatric MS samples with more extensive batteries.

Conclusions: The BICAMS battery is suitable for a pediatric-onset sample. A verbal learning task able to be uniformly administered across the full age span may have advantages.

P124

Rasch analysis of performance based cognitive measures in two distinct medical diseases, MS and HIV

S Hum[1], Y Lapierre[2], NE Mayo[3], LE Finch[3], A Tsuchida[4], LK Fellows[5]

[1]*McGill University, MS Clinic, Montreal, QC, Canada,* [2]*Montreal Neurological Institute, MS Clinic, Montreal, QC, Canada,* [3]*McGill University Health Centre Research Institute, Montreal, QC, Canada,* [4]*McGill University, Montreal, QC, Canada,* [5]*McGill University, Neurology and Neurosurgery, Montreal, QC, Canada*

Background: Recent findings from modeling cognitive impairment in people who are HIV+ showed it to be compatible with diffuse dysfunction rather than focal damage: Domain-specific neurocognitive tests fit a unidimensional construct and could be aligned hierarchically to produce a measure with valid units. We tested whether cognitive impairment in MS would have similar characteristics.

Objectives: The objective was to estimate the extent to which the tests of cognitive ability behave in the same manner in MS and HIV.

Methods: A sample of 75 HIV+ people and 79 people with relapsing-remitting MS who tested in the none or mild cognitive impairment range on screening were recruited from MUHC sites and completed a battery of computerized and bedside cognitive tests. Rasch analysis was used to test fit of the items to the underlying hierarchy and identify items that were redundant. First the items were fit on the HIV+ sample, then on the MS sample, and then on the combined sample.

Results: The HIV+ group, 93% men, was 47 years old (SD 8.5) and diagnosed with HIV for 14 years (SD 6.6). The MS group, 77% women, was 38.5 years old (SD 8.2) and had disease onset 6.4 years (SD 2.8) prior. In all samples, all items fit a unidimensional hierarchy, with the exception of items from the MMSE, which were all passed. Out of the remaining 57 items, 28 uniquely fit the HIV+ sample, 23 uniquely fit the MS sample, and 32 fit for both combined. For the final model, all 32 items were calibrated in the combined HIV+/MS groups. The items that fit the Rasch model were well distributed along a standardized continuum (mean 0; SD 1) with a location of 0 (logits) and an SD of 1.7. The mean location of people, however, was higher than expected with a mean location of 1.79 logits and SD, 0.9. Reliability of the person estimates of cognitive ability was 0.64 which is low owing to the mistargeting of the items to the ability of the persons tested. There was no differential item functioning across conditions.

Conclusions: The tests fit with a model for a unidimensional cognitive ability construct in both HIV+ and MS, suggesting that cognitive impairment can be understood in terms of diffuse dysfunction in both conditions. The findings provide a path to accurately measure this construct, important for testing interventions.

P125

The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS): an Irish validation study

K O'Connell[1], DW Langdon[2], M Hutchinson[1], N Tubridy[1], C McGuigan[1]

[1]*St Vincents University Hospital, Dublin, Ireland,* [2]*Royal Holloway, University of London, Department of Clinical Psychology, Surrey, United Kingdom*

Background: Cognitive impairment is common in MS irrespective of disease stage or subtype. It is typically under-reported; formal neuropsychological testing detects subtle evidence of cognitive impairment. The Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS) has the primary objective of identifying a brief cognitive assessment tool that could be administered by healthcare professionals without formal neuropsychological training to identify early or subtle cognitive impairment among MS patients.

Objectives: To validate BICAMS amongst an Irish population.

Methods: Consecutive patients attending the MS outpatient department from January - April 2014 were recruited. Age, gender, education, handedness, MS subtype, expanded disability

status scale (EDSS) and disease duration were recorded. They were administered BICAMS composed of Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT2) and Brief Visuospatial Memory Test (BVMTR). Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS). The control population consisted of unaffected relatives or friends and were matched for age, gender and education. Impairment on individual tests was defined as -1.5 SD below reference group means.

Results: Sixty-eight patients (73% female; age: 43.9 years (12.1); education: 13.6 years (2.7)) and 61 controls (66% female; age 43.3 years (12.7); education: 14.1 years (3.2)) were recruited. The patient group were 70% RRMS, 28% SPMS and 2% PPMS with mean EDSS 2.9 (2.1) and disease duration 13.3 (10.2) years. Mean scores and standard deviations for patients and controls respectively were 46 (12.9) and 55.9 (10.9), $p < 0.001$, $d=0.83$ for SDMT; 45.3 (10.2) and 52.8 (8.8), $p < 0.001$, $d=0.79$ for CVLTII and 17.9 (7.1) and 20.7 (6.6), $p=0.02$, $d=0.41$ for BVMTR.

Using regression based norms derived from the control sample only 28 (42%) of patients compared to 48 (79%) of control's results were within the normal range on all 3 tests.

Eleven (16%) and 13 (19%) of patients fulfilled criteria for depression and anxiety respectively based on their HADS score but no statistically significant association with individual test scores or cognitive outcome was seen.

Conclusions: This study demonstrates that BICAMS is a valid and easy to administer assessment of cognitive function in an outpatient clinic without access to specialized neuropsychology services.

P126

Spatial memory test (SMT): a self-administered iPad®-based tool for assessing nonverbal episodic memory dysfunction in MS

S Rao[1], R Rudick[1], J Alberts[1], D Schindler[1], M Buss[1], C Reece[1], L Mourany[1], G Losinski[1], B Mamone[1]
[1]Cleveland Clinic, Cleveland, OH, United States

Background: The 10/36 Spatial Memory Test (10/36) is widely used to measure nonverbal episodic memory impairment in MS as part of the Brief Repeatable Battery of Neuropsychological Tests (Rao, 1991). We developed a self-administered iPad-based version of the 10/36 called the Spatial Memory Test (SMT). The SMT varies from the 10/36 by using a 7 x 5 grid; the rectangular grid format conforms better to the iPad dimensions than the square (6 x 6) 10/36 format.

Objectives: To report

(1) effects of age, education and gender on SMT performance,
(2) SMT test-retest reliability and practice effects, and
(3) convergent validity of the SMT and 10/36.

Methods: Cognitively intact adults (N=80; 33 females; mean age=34.1 yrs., SD=12.8; mean education=15.8 yrs., SD=2.4) were administered the SMT. Participants with a history of major medical, neurologic or psychiatric illnesses, active substance abuse, current psychoactive medication usage (chronic sedatives/ hypnotics and narcotic analgesics), MMSE < 28, and Beck Depression Inventory > 9 were excluded. Effects of age and education were correlated with SMT performance. A subset

of participants (N=33) were administered the SMT twice to examine test-retest reliability (concordance correlation coefficient). Another subset (N=25) were administered both the SMT and 10/36 to examine convergent validity (Pearson correlation). For both SMT and 10/36, learning effects were examined by presenting the same design (10 interspersed filled circles) for 5 trials (SMT and 10/36 used different designs; maximum number of correctly recalled items=50).

Results: As expected for an episodic memory test, SMT performance correlated negatively with age (r=-.49, p< 0.001), but did not correlate with education (r=-.02, p=0.83). Females performed slightly better (3.0 items) better than males (p=0.08). SMT test-retest reliability (CCC)=0.53. A non-significant (p=0.34) increase in total recalled items (mean=1.2) was observed from the 1st to 2nd administration. Convergent validity between the SMT and 10/36 was significant (r=0.46, p=0.02).

Conclusions: The SMT is a self-administered nonverbal episodic memory test based on the 10/36, demonstrates adequate test-retest reliability and minimal practice effects, and is influenced by age, minimally by sex, and, most importantly, not by education. A larger scale validation test is underway to determine the SMT sensitivity to episodic memory deficits in MS.

P127

A comparison of the Brief International Cognitive Assessment for Multiple Sclerosis and the brief repeatable battery in multiple sclerosis patients

E Portaccio[1], B Goretti[1], C Niccolai[1], B Hakiki[1], M Giannini[1], L Pastò[1], C Pecori[1], L Razzolini[1], M Falautano[2], E Minacapelli[2], V Martinelli[2], C Incerti[3], U Nocentini[3], M Murgia[4], G Fenu[4], E Cocco[4], MG Marrosu[4], E Garofalo[5], FI Ambra[5], M Maddestra[6], M Consalvo[6], RG Viterbo[7], M Trojano[7], NA Losignore[8], GB Zimatore[8], E Pietrolongo[9], A Lugaresi[9], L Pippolo[10], M Roscio[10], A Ghezzi[10], D Castellano[11], S Stecchi[11], MP Amato[1]
[1]University of Florence, Department of Neurofarba, Florence, Italy, [2]IRCCS San Raffaele, Milan, Italy, [3]Santa Lucia Foundation, Rome, Italy, [4]University of Cagliari, Cagliari, Italy, [5]Ospedale dei Colli Monaldi Cotugno CTO, Napoli, Italy, [6]Hospital of Lanciano, Lanciano, Italy, [7]University of Bari, Bari, Italy, [8]Hospital of Barletta, Barletta, Italy, [9]University of Chieti, Chieti, Italy, [10]Hospital of Gallarate, Gallarate, Italy, [11]Villa Mazzacorati, Bologna, Italy

Background: The BICAMS (Brief International Cognitive Assessment for Multiple Sclerosis) has been recently developed as a brief, practical and universal screening for cognitive impairment (CI) in MS subjects. However, little is known on its performance in comparison to the other neuropsychological batteries.

Objectives: To assess the performance of BICAMS as screening for CI as detected by the Rao´s Brief Repeatable Battery (BRB).

Methods: In a group of relapsing-remitting (RR) MS patients, CI was defined as the failure of at least two tests on the BRB, based on the Italian normative data. Failure on the BICAMS was defined as the failure of at least 1 test of the battery. We assessed sensitivity, specificity, positive and negative predicting values (PPV, NPV) of the BICAMS in predicting CI as defined using both the whole BRB and the BRB without the Symbol Digit Modalities Test (SDMT; "uncontaminated" condition).

Results: Eighty RRMS patients (62 women, age 40.2 ± 9.5 years, education 12.5 ± 3.9 years, Expanded Disability Status Scale 2.4 ± 0.9) were recruited. CI on the BRB was detected in 23 (28.8%). The failure on the BICAMS detected CI with a sensitivity of 90%, specificity of 100%, PPV of 100%, NPV of 96.2% and accuracy of 97.2%. When SDMT was excluded from the BRB, sensitivity was 25.0%, specificity 80%, PPV 26.7%, NPV 78.6% and accuracy 67.6%.

Conclusions: The performance of the BICAMS was comparable to that of the BRB. However, it is largely dependent on the SDMT. These findings highlight the validity of the BICAMS and confirm the key role of the SDMT for screening CI in MS subjects.

P128

Demonstration of altered neural substrates of information processing speed in pediatric-onset MS using an fMRI version of the SDMT

N Akbar[1,2], C Till[3], J Sled[1], SM Doesburg[1], M Binns[4], AR McIntosh[4], M Lysenko[3], B Banwell[1,5]
[1]The Hospital for Sick Children, Toronto, ON, Canada, [2]University of Toronto, Institute of Medical Science, Toronto, ON, Canada, [3]York University, Psychology, Toronto, ON, Canada, [4]Rotman Research Institute, Baycrest, Toronto, ON, Canada, [5]Children's Hospital of Philadelphia, Philadelphia, PA, United States

Background: The Symbol Digit Modalities Test (SDMT) is a sensitive tool for measuring information processing speed, which is commonly affected in pediatric MS. The functional MRI (fMRI) version of the SDMT (fMRI-SDMT) can be used to understand the neural underpinnings of reduced processing speed in this population.

Objectives: To determine which regions underlie processing speed in pediatric-onset MS individuals compared to healthy controls using the fMRI-SDMT. In addition, to investigate the relationship between fMRI-SDMT blood-oxygenation level dependent (BOLD) activation patterns and behavioural performance on this task.

Methods: Data were collected from 23 right-handed individuals aged 13-24 with pediatric-onset relapsing-remitting MS (mean age=18, 16 female, mean disease duration=62 months, median EDSS=1.5) and 16 healthy controls matched by age, sex and socio-economic status. All participants underwent a 3.0 Tesla MRI scan which included structural acquisitions (T_1, T_2, PD, FLAIR) and the fMRI-SDMT. Briefly, this paradigm requires participants to indicate with a button press whether a single pairing of a symbol to a number matches any of those shown in a key above displaying 9 such pairings. Response time and accuracy were recorded. fMRI data were analyzed using mixed-effects general linear models with FSL's FEAT software.

Results: Groups did not differ on the fMRI-SDMT with respect to response time (t=-.236, p=.815) or percent accuracy (Mann-Whitney U=145, p=.495). The pediatric MS group demonstrated higher overall activation compared to the healthy controls in the following regions: (i) right precuneus (z=3.43, p< .001), (ii) right superior lateral occipital (z=3.12, p=.002), (iii) right lingual gyrus (z=3.12, p=.002) and (iv) left superior parietal (z=3.06, p=.002). Within the pediatric MS group, faster response time was associated with greater activation of the left cerebellum (z=3.96,

p< .001), bilateral precentral gyrus (z=3.07, p=.002), thalamus (z=3.57, p=.008), and left supramarginal gyrus (z=3.97, p=.0241).

Conclusions: Information processing speed performance is reliant on the recruitment of a greater number of parietal and occipital regions in pediatric MS. This may help offset deficits in processing speed given that performance was overall not impaired in this group. In the pediatric MS group, greater activation was associated with better/ faster cognitive performance suggesting that fMRI could potentially be used as a marker for adaptive functional reorganization.

P129

Longitudinal MRI and neuropsychological assessment of patients with clinically isolated syndrome

T Uher[1,2], J Blahova-Dusankova[1], D Horakova[1], N Bergsland[2,3], M Tyblova[1], RHB Benedict[2], T Kalincik[4,5], DP Ramasamy[2], Z Seidl[6], J Hagemeier[2], M Vaneckova[6], J Krasensky[6], E Havrdova[1], R Zivadinov[2,7]
[1]Charles University in Prague, First Faculty of Medicine and General University Hospital, Department of Neurology and Center of Clinical Neuroscience, Prague, Czech Republic, [2]School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo Neuroimaging Analysis Center, Department of Neurology, Buffalo, NY, United States, [3]IRCCS "S.Maria Nascente", Don Gnocchi Foundation, Milan, Italy, [4]Melbourne Brain Centre, University of Melbourne, Department of Medicine, Melbourne, Australia, [5]Royal Melbourne Hospital, Department of Neurology, Melbourne, Australia, [6]Charles University in Prague, First Faculty of Medicine and General University Hospital, Department of Radiology, Prague, Czech Republic, [7]School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, MR Imaging Clinical Translational Research Center, Buffalo, NY, United States

Background: Cognitive impairment (CI) may occur in clinically isolated syndrome (CIS) patients. While the relationship between CI and magnetic resonance imaging (MRI) has been investigated extensively in multiple sclerosis (MS), MRI correlates of CI in CIS patients are unknown.

Objectives: To investigate the evolution of CI and to determine brain MRI structural correlates associated with CI in CIS patients on disease-modifying treatment (DMT).

Methods: This prospective 24-month observational study examined 81 CIS patients treated with 30 μg of intramuscular interferon beta-1a once a week. MRI acquisition and neuropsychological (NP) assessment was performed at baseline, 6, 12 and 24 months. Participants were tested with Czech validated version of Minimal Assessment of Cognitive Function in MS battery (MACFIMS) and MRI measures of lesion activity and burden, and global, tissue specific and regional brain atrophy were performed.

Results: Over 24 months, 36 CIS patients developed clinically definite MS (CDMS). CI was observed in 10 (12.3%) CIS patients at baseline and at the 24 months follow-up. Eight CIS patients changed their CI status over the follow-up (4 improved and 4 worsened). Significant differences in absolute change of T2-lesion volume (p = .0003) and percent change of whole brain (p = .002), gray matter (p = .009), cortex (p = .009) and lateral ventricle volumes (p = .0001) were detected between clinically definite MS

and stable CIS group over 24 months. No significant difference in development of CI was detected between stable CIS patients and those who developed CDMS. In multivariate regression and mixed-effect model analyses, no significant relationship was found between NP and MRI parameters.

Conclusions: The present study showed lack of cognitive deterioration in the majority of the CIS subjects treated with disease modifying drugs over the 2-years follow-up. In contrast, the CIS patients who converted to CDMS developed global and regional brain atrophy. The findings from this study show that structural MRI outcomes are not strongly associated with cognitive status, a phenomenon formerly described as cognitive-pathological dissociation. The lack of significant relationship between MRI metrics and cognition in this group of CIS patients could be attributed to several factors including the cognitive reserve, brain plasticity, effect of disease-modifyng therapy and relatively short follow-up period.

P130

Perservation of GM volume is related to increased learning effect on PASAT in patients with CIS

T Uher[1,2], RH Benedict[2], D Horakova[1], N Bergsland[2,3], J Blahova-Dusankova[1], M Tyblova[1], DP Ramasamy[2], Z Seidl[4], M Vaneckova[4], J Krasensky[4], E Havrdova[1], R Zivadinov[2,5]
[1]Charles University in Prague, First Faculty of Medicine and General University Hospital, Department of Neurology and Center of Clinical Neuroscience, Prague, Czech Republic, [2]School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo Neuroimaging Analysis Center, Department of Neurology, Buffalo, NY, United States, [3]IRCCS "S.Maria Nascente", Don Gnocchi Foundation, Milan, Italy, [4]Charles University in Prague, First Faculty of Medicine and General University Hospital, Department of Radiology, Prague, Czech Republic, [5]School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, MR Imaging Clinical Translational Research Center, Buffalo, NY, United States

Background: Repeated administration of Paced Auditory Serial Addition Test-3 (PASAT) results in considerable learning effect in short- or long-term follow-up studies. However, the relationship between learning effect of PASAT and magnetic resonance imaging (MRI) outcomes was not investigated in serial studies.

Objectives: To investigate the evolution of PASAT performance and to determine brain MRI structural correlates associated with cognitive functioning in clinically isolated syndrome (CIS) patients on disease-modifying treatment (DMT).

Methods: This prospective 48-month observational study examined 128 CIS patients treated with 30 μg of intramuscular interferon beta-1a once a week. Participants were tested with PASAT at disease onset and then every 6 months. In addition, MRI measures of lesion activity and burden, and global, tissue specific and regional brain atrophy were performed at baseline, at 6 months and then annually over the 48-month follow-up. Linear mixed model analysis adjusted for age, gender, education and DMT, was used to calculate temporal association between MRI measures and PASAT performance.

Results: CIS patients showed in average 2.5% GM volume loss over 4 years. Patients with significantly lower loss of gray matter

(GM) volume had the most increased PASAT score absolute change over 48 months (p = .008). There was also a trend for the association between higher corpus callosum (CC) area at baseline and increased PASAT score absolute change over 48 months (p = .046).

Conclusions: The present study showed the relationship between increased learning effect on PASAT and lower GM volume loss in CIS patients on DMT. These findings suggest that treatment strategies oriented toward GM volume preservation may play an important role in prevention of cognitive deterioration in CIS patients.

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Effectively assessing executive function impairment in MS: comparisons of the Delis-Kaplan executive function system and Wisconsin card sorting tests

L Glukhovsky[1], ES Gromisch[1], G Hoffnung[1], S Flood[1], FW Foley[1,2]
[1]Yeshiva University, Ferkauf Graduate School of Psychology, Bronx, NY, United States, [2]Holy Name Medical Center Multiple Sclerosis Center, Teaneck, NJ, United States

Background: Cognitive impairment has been estimated to affect 45-65% of patients with multiple sclerosis (MS), with deficits in executive function among the most common cognitive features. Affected patients may experience difficulties in problem solving, decision-making, judgment, task-shifting, strategic planning, and organizational abilities. Such critical skills require sensitive and specific neuropsychological assessments to identify impairment; however, few studies have compared these assessments for their efficacy in detecting executive functioning deficits.

Objectives: This study aimed to compare the sensitivity and specificity of two commonly used assessments for executive function impairment in MS: the Delis-Kaplan Executive Function System Sorting Test (DST) and Wisconsin Card Sorting Test (WCST).

Methods: The DST and WCST were administered to 121 participants at a large outpatient medical center in Teaneck, NJ. All participants signed research consents and had been diagnosed previously with MS. A receiver-operating characteristic (ROC) analysis was conducted to compare T scores from both tests (DST Confirmed Correct Sorts, CCS; WCST Percent Errors, PE) against a composite T score based on the Minimal Assessment of Cognitive Function in MS (MACFIMS). Frequencies were also calculated to compare the number of participants the DST and WCST identified as impaired.

Results: ROC analysis revealed similar levels of sensitivity and specificity in the DST and WCST for identifying impaired executive function. At 1.5 standard deviations (SD) down from the mean, the DST CCS measure yielded a classification accuracy of 82%, and the WCST PE yielded a classification accuracy of 79%. At 2.0 SD down from the mean, the DST CCS measure yielded a classification accuracy of 88%, and the WCST PE measure yielded a classification accuracy of 91%. Frequency calculations revealed that at the -1.5 SD criterion, 9% of participants showed impairment on the DST CCS and 21% showed impairment on the WCST PE. At the -2.0 SD criterion, 2% of participants showed impairment on the DST CCS and 13% showed impairment on the WCST PE.

Conclusions: The DST and WCST were found to be similarly effective in classifying executive function impairment among patients with MS. However, the DST holds an advantage over the WCST because it has several forms to accommodate longitudinal patient retesting. This research provides valuable information about prevalence rates and effective assessment of executive function impairment in MS.

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Brief International Cognitive Assessment for MS (BICAMS): preliminary findings from the Canadian validation study

LAS Walker[1], L Osman[2], JA Berard[2], LM Rees[1], D Cousineau[3], H MacLean[4], MS Freedman[4]
[1]The Ottawa Hospital, Psychology, Ottawa, ON, Canada,
[2]Ottawa Hospital Research Institute, Ottawa, ON, Canada,
[3]University of Ottawa, Psychology, Ottawa, ON, Canada, [4]The Ottawa Hospital, Neurology, Ottawa, ON, Canada

Background: The Brief International Cognitive Assessment for MS (BICAMS) was developed by a panel of experts as a brief, cognitive assessment for MS that can be used in centers with staff members who may not have neuropsychological training. The BICAMS tests were chosen on the basis of their sensitivity to deficits in MS, psychometric properties (reliability, validity), international application, ease and speed of administration, feasibility in the specified context, and acceptability to patients. There is a global initiative to validate BICAMS across cultures in order to establish it as a useful cognitive outcome measure that will foster international collaboration.

Objectives: The primary goal was to validate BICAMS in an English-speaking Canadian sample by establishing its ability to differentiate between individuals with MS and healthy controls. In addition, test-retest reliability was examined.

Methods: Thirty-three individuals (8 males, 25 females) with a confirmed diagnosis of MS (25 relapsing-remitting, 5 secondary progressive, 3 primary progressive) were compared to 22 healthy controls (HC) (4 males, 18 females) on BICAMS performance. Results are preliminary given that recruitment efforts are ongoing. BICAMS includes three subtests: Symbol Digit Modalities Test (SDMT), California Verbal Learning Test - II (CVLT-II; learning trails), and Brief Visuospatial Memory Test - Revised (BVMT-R; learning trials). Participants were evaluated at baseline and after a two-week follow-up interval.

Results: One-way ANOVA analyses revealed that the MS group performed significantly worse than HC on all BICAMS subtests (SDMT: $F(1,54) = 13.06$, $p = .001$; CVLT-II: $F(1,54) = 6.61$, $p = .013$; BVMT-R: $F(1,54) = 11.49$, $p = .001$). In the MS sample, test-retest reliability was very strong for the SDMT (r = .90, p < .0001) and the CVLT-II (r = .79, p < .0001), and strong for the BVMT-R (r = .57, p < .0001).

Conclusions: The current findings provide support for the use of BICAMS as a tool for identifying cognitive deficits in individuals with MS. In this Canadian sample, results were consistent with studies in other countries. BICAMS effectively differentiates between groups and also demonstrates strong to very strong test-retest reliability over a two-week interval. In summary, BICAMS continues to demonstrate robust psychometric properties in this Canadian sample.

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Physical disability and cognitive impairment evolution in benign multiple sclerosis: a five years prospective study

A Gajofatto[1], MR Bianchi[1], M Turatti[2], S Forlivesi[1], F Gobbin[1], S Monaco[1], MD Benedetti[3]
[1]University of Verona, Dpt of Neurological and Movement Sciences, Verona, Italy, [2]Casa di Cura Pederzoli, Neurology Unit, Peschiera del Garda, Italy, [3]Azienda Ospedaliera Universitaria Integrata, Neurology Unit, Verona, Italy

Background: Benign multiple sclerosis (BMS) definition is generally based on a minimum disease duration (DD) during which a maximum expanded disability status scale (EDSS) score is reached. However, EDSS does not account sufficiently for cognitive deficits, which may be as disabling as motor impairment

Objectives: To study prospectively the evolution of physical disability and cognitive performance of BMS patients

Methods: Among 300 patients seen at Verona MS Center between January and June 2008, 36 patients with relapsing-remitting (RR) course, DD ≥10 years, and EDSS score ≤2.0 were defined BMS cases. Of these, 24 gave consent for inclusion in the study along with 13 sex- and age-matched non-benign MS (n-BMS) patients with RR course, DD≥10 years and EDSS score from 2.5 to 4.5. The two groups were followed for 5 years with neurological examination at least every year and neuropsychological assessment at baseline and at study conclusion. Conventional MRI analysis was done for patients who had a brain scan with the same protocol in 2008 and 2013

Results: At inclusion BMS subjects were 41±8 years old (mean±standard deviation) with median DD of 15 years (range 11-29) and median EDSS score 1.5 (range 0-2), while n-BMS patients were 46±8 years old, had median DD of 16 years (range 10-27) and median EDSS score 3.0 (range 2.5-4.5). At baseline 16% of patients in both groups failed two or more neuropsychological tests. After 5 years, 23 BMS and 12 n-BMS patients had completed the study. The EDSS score worsened in 8% and 46% of cases, respectively (p=0.008), while the proportion of patients with ≥2 failed neuropsychological tests at 5 years increased at 25% in both groups. BMS and n-BMS patients who failed ≥2 tests had a significantly worse work and financial status both at baseline and at 5 years follow-up even after excluding subjects with EDSS score >3.5. Brain MRI T2 lesion location and number increase over time were not significantly associated with neurological and cognitive outcomes

Conclusions: Patients classified as having BMS according to widely used criteria had better physical disability outcome at 5 years compared to n-BMS cases. However, rates of initial cognitive impairment and neuropsychological decline over time did not differ between the two groups, including the possible impact on work and social functioning. Neuropsychological testing is essential even in MS patients with minimal or no physical disability given the distinct trajectories followed by disease progression in cognitive and motor domains

P134

SDMT performance predicts real-world functioning in adults with multiple sclerosis (MS)

LE Charvet[1,2], M Kasschau[1,2], W Scherl[1,2], M Amella[1,2], P Melville[1], L Krupp[1,2]

[1]*Stony Brook University, Department of Neurology, Stony Brook, NY, United States, [2]Lourie Center for Pediatric MS, Stony Brook, NY, United States*

Background: Information processing speed is a common area of cognitive impairment for individuals living with MS but the link to real-world functioning is unclear.

Objectives: To compare performance on the Symbol Digit Modalities Test (SDMT) as a measure of speeded information processing to a real-world measure of day-to-day functioning, Timed Instrumental Activities of Daily Living (TIADLs).

Methods: As part of a larger study of cognitive impairment in MS, adults with MS were administered the SDMT and a TIADLs assessment. The TIADLs assessment was an expanded version of a system developed for use in dementia populations and previously validated for use in an MS sample. Tasks include simulated daily activities such as making change, reading a prescription bottle, looking up information in a phone book, selecting food items, and following a shopping list. The tasks are structured to require only minimal motor use.

Results: Participants were 55 adults with MS (83% RRMS, 36% SPMS, 1% PPMS), ages 19 to 66 (mean age 48.9 ± 11.7 years) and 71% female. Median EDSS was 3.5 with a range of 0.0 to 7.5. Mean years of education were 15.0 ± 2.6 years. SDMT raw scores ranged from 21 to 73 (mean 47.2 ± 11.2) corresponding to a mean z score of -1.14 ± 1.15. Total time for completion of the five initial TIADLs tasks significantly correlated with SDMT score, r=-0.59 p< 0.001, and the relationship strengthened with the expanded TIADLs version, r=-0.75, p< 0.001. TIADLs scores were not significantly related to EDSS.

Conclusions: TIADLs provide a sensitive measure of real-world functioning in adults with MS. SDMT performance significantly predicts TIADLs performance and indicates the consequences of cognitive impairment in day-to-day life.

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Predictive validity of the BRB-N in the assessment of cognitive impairment in RRMS according to EDSS disability degree

M López-Góngora[1], A Escartin[1], G Izquierdo[2], M Borges[2]
[1]*Hospital Santa Creu i Sant Pau, Neurology Department, Barcelona, Spain, [2]Hospital Universitario Virgen Macarena, Neurology Department, Sevilla, Spain*

Background: The Brief Repeatable Battery of Neuropsychological tests (BRB-N) is a widely used neuropsychological battery for the assessment of cognitive impairment in MS. This battery evaluates verbal memory acquisition and delayed recall, visual memory acquisition and delayed recall, attention, concentration, visual precision search, information processing speed, working memory and verbal fluency. A Spanish version of the BRB-N with two parallel forms of the test, as well as normative data for Spanish population is available.

Objectives: The aim of the present study was to study the psychometric properties of the Spanish version A of the BRB-N as well as to find out predictive values for Relapsing-Remitting Multiple Sclerosis (RRMS) patients according to their EDSS disability degree.

Methods: Observational, cross-sectional and multicenter study. Enrollment period started in July 2012 and finished in October 2013. The stability of the scores was analyzed with the Intraclass Correlation Coefficient (ICC) between the results of the first visit and those from the retest visit (n=56 patients). The study also analyzed the Spearman correlation coefficients between BRB-N battery, EQ-5D questionnaire and the Beck Depression Inventory-II (BDI-II) scores. Finally, the predictive validity of the battery was evaluated by sensitivity and specificity values using the disability groups (1=mild disability; 0=moderate disability) as Gold Standard.

Results: 291 RRMS patients from 21 Neurology Departments in Spain were included. The mild disability group (EDSS 0-3) included 152 (52.20%) patients and the moderate disability group (EDSS 3.5-5.5) included 139 patients (47.80%). There was a high correlation between test scores and retest (ICC=0.96). All correlations between CI, Health Related Quality of Life (HRQoL) and depression were low-moderate and statistically significant (p< 0.01; p< 0.05). Sensitivity and specificity values of the battery were 69.70% and 64.00% respectively.

Conclusions: BRB-N has adequate psychometrical properties. The results of the test-retest reliability analysis suggested that the BRB-N battery is a stable instrument for assessing RRMS patients. The results of the analysis on the predictive validity of the BRB-N showed an acceptable level of predictive validity, although future research should optimize the sensitivity of the battery in order to enable the early detection of physical disability of patients.

P136

Cognitive disturbances and psychoaffective deficits in children and juveniles with multiple sclerosis: the MUSIC*ADO* - multicentric validation study

P Calabrese[1], K Storm van`s Gravesande[2], E Kalbe[3], J Kessler[4], U Fulda[5], V Mall[2]
[1]*University of Basel, Dept. of Cognitive Neuroscience, Basel, Switzerland, [2]University of Munich, Dept. of Neuropediatrics, Munich, Germany, [3]University of Vechta, Dept. of Psychology, Vechta, Germany, [4]University of Cologne, Psychology, Cologne, Germany, [5]Merck-Serono, Darmstadt, Germany*

Background: Cognitive and psychoaffective disturbances may present already in children affected by multiple sclerosis (MS). The most vulnerable areas include attention, visual-perceptual abilities, executive functions, and - in contrast to adults - impaired verbal skills. Nonetheless, these deficits are mostly underrecognized since there is a lack of adequate screening instruments which might be used by clinicians during clinical visits for children and adolescents.

Objectives: The aim of the MUSIC*ADO*-study is to validate an already existing and child and adolescent-adapted screening tool (MUSIC = **MU**ltiple **S**clerosis **I**nventory of **C**ognition for **ADO**lescents). Additional clinicometric methods are used in order to validate this measure and a questionnaire for depression and fatigue is added.

Methods: This multicentric study has been initiated in May 2012 and, up to now, a total number of n=104 patients and 125 age-matched controls, aged between 9 and 18 years have been enrolled.

The adopted psychometric tool MUSIC and additional methods to assess IQ, attention, visual-perceptual abilities, executive functions, verbal skills, quality of life, depression, and fatigue are performed at one visit by a psychologist. The duration of the tests is about 2 to 2,5 hours. Currently, 2 study sites in Austria and 22 study sites in Germany are registered.

Results: A first analysis of the clinicometric data based on a large adolescent cohort of patients and controls qualifies the selected dimensions as relevant components of a screening tool to detect cognitive deficits and related comorbidities at an early stage of the disease.

Conclusions: Although preliminary, our data underline the ned for an age-appropriate psychometric test to identify cognitive and non-cognitive disturbances in early, adolescent MS. Such a tool may help to apply interventions timely.

P137
Does the presence of brain lesions predict cognitive functioning after acute demyelination in children?

AE Sye[1], LH Verhey[1], JK Mah[2], BL Brooks[3,4,5], EA Yeh[1,6], B Banwell[1,6,7], C Till[1,8]
[1]Hospital for Sick Children, Neurosciences and Mental Health, Toronto, ON, Canada, [2]Alberta Children's Hospital, Neurology, Calgary, AB, Canada, [3]Alberta Children's Hospital, Neurosciences Program, Calgary, AB, Canada, [4]University of Calgary, Pediatrics and Clinical Neurosciences, Calgary, AB, Canada, [5]Alberta Children's Hospital, Research Institute, Calgary, AB, Canada, [6]Hospital for Sick Children, Neurology, Toronto, ON, Canada, [7]Children's Hospital of Philadelphia, Neurology, Philadelphia, PA, United States, [8]York University, Psychology, Toronto, ON, Canada

Background: Acute CNS demyelination occurs in 0.9 per 100,000 Canadian children and adolescents. Childhood demyelination may manifest as a monophasic illness or, in 25% of patients, may represent the first attack of multiple sclerosis (MS). Although cognitive impairment (CI) has been well described in pediatric MS, previous studies have suggested that a subset of children with monophasic demyelination may also suffer from CI in the areas of fine-motor and visual-motor skills, attention, memory, and processing speed.

Objectives: This study examined the association between neurocognitive outcomes and the presence of T2 lesions of the brain six months after an incident demyelinating event.

Methods: 34 consecutive children were recruited from two tertiary Canadian children´s hospitals, aged 7-13 (mean=12.3 ± 2.6). Patients underwent standardized clinical and MRI examinations and cognitive testing six-months after onset. MRI scans of the brain were assessed for the presence of T2-weighted lesions using a binary classification. A valid MRI was not available for 9 of the patients. Patients with ≥1 brain lesion (n=11) versus no lesions (n=14) on MRI were compared on measures assessing: attention and speed of processing; working memory; vocabulary; visual-motor integration; verbal learning and memory.

Results: Mean scores across all neuropsychological tests fell within the average range with only 4 (12%) or fewer patients performing 1.5 SDs below normative values on any one test. None of the patients were identified as having CI as based on overall performance on the battery. Patients with visible brain lesions did not differ from those without on any of the cognitive outcomes. Of the 34 patients, 11 now have a diagnosis of MS.

Conclusions: Neurocognitive impairment was not seen in this cohort of children with a single demyelinating episode evaluated 6 months after symptom onset. It is of note that all children, whether or not they eventually received the diagnosis of MS or had brain lesions, scored in the normal range- suggesting that cognitive impairment is not a feature of monophasic demyelination nor is it detected extremely early in MS. Further work will determine whether more sensitive cognitive metrics reveal subtle deficits. Serial evaluation is required to determine the time course of cognitive impairment in MS. Finally, premorbid cognitive abilities, or cognitive reserve, may influence the ability to detect impairment in children tested close in time to incident ADS.

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Attention network efficiency and performance variability is associated with white matter microstructure in persons with multiple sclerosis

MA Wojtowicz[1], EL Mazerolle[2], A Omisade[1], JD Fisk[3]
[1]Dalhousie University, Psychology and Neuroscience, Halifax, NS, Canada, [2]University of Calgary, Department of Radiology, Calgary, AB, Canada, [3]Dalhousie University, Psychology and Neuroscience, Psychiatry, Halifax, NS, Canada

Background: Impairments in attention and information processing speed are common in persons with multiple sclerosis (MS) and may contribute to impairments of other cognitive abilities. However, their associations with measures of structural change on brain magnetic resonance imaging (MRI) remain unclear.

Objectives: We examined the associations between diffusion tensor imaging (DTI) measures of white matter microstructure and the efficiency of alerting, orienting and executive attention networks as well as information processing speed and performance variability using the Attention Network Test-Interactions (ANT-I).

Methods: Nineteen female relapsing-remitting MS patients and 19 matched healthy controls completed the ANT-I and DTI MRI scans. Parameters: 1.5T GE MRI, SE-EPI sequence with TR=12s, TE=71ms, 55 directions, b-value=850s/mm2, FOV=260mm2, 128x128 matrix, 45 3mm slices. Relations between ANT-I performance and DTI measures were examined by analyzing fractional anisotropy (FA) maps using tract-based spatial statistics.

Results: MS patients were slower and more variable in their performance of the ANT-I compared to controls (p< .05) but the groups did not differ in their attention network efficiency scores. No significant associations between FA and mean response speed were observed for either group. Control participants had no significant associations of FA values with performance variability or attention network efficiency. Amongst the MS patients, less variable performance was associated with higher FA values in the posterior thalamic radiation and the splenium of the corpus callosum. In addition, more efficient alerting network performance was associated with higher FA in the left external capsule and more efficient orienting network performance was associated with higher FA in multiple white matter regions, including: body/genu of corpus callosum, bilateral superior corona radiata, left anterior

frontal regions, anterior corona radiata, and left external capsule. No significant association with executive network efficiency and FA were observed for MS patients.

Conclusions: DTI measures of white matter microstructure appear sensitive to performance variability on timed tests of attention and information processing speed in persons with MS. Moreover, DTI may also allow for improved understanding of specific associations between cognitive processes such as alerting and orienting network efficiencies and white matter microstructure in persons with MS.

P139

The role of the cerebellum in cognitive test performance in children and adolescents with multiple sclerosis

K Weier[1], C Till[2,3], V Fonov[1], EA Yeh[3,4], DL Arnold[1], B Banwell[5], DL Collins[1]

[1]McGill University, Montreal Neurological Institute, Montreal, QC, Canada, [2]York University, Department of Psychology, Toronto, ON, Canada, [3]The Hospital for Sick Children, Neurosciences and Mental Health Program, Toronto, ON, Canada, [4]University of Toronto, Department of Pediatrics (Neurology), Toronto, ON, Canada, [5]University of Pennsylvania, Children's Hospital of Philadelphia, Philadelphia, PA, United States

Background: Pediatric-onset multiple sclerosis (MS) is often accompanied by cognitive impairment. Severity of cognitive dysfunction has been associated with neuroimaging features, including reduced thalamic and whole brain volume. The cerebellum is also affected in both pediatric- and adult-onset MS patients, though the functional impact of cerebellar pathology on cognition is not well understood.

Objectives: To investigate the relationship between cerebellar volumes and cognitive function in children and adolescents with pediatric-onset MS.

Methods: High resolution T1w RF-spoiled GRE scans (1.5T) of 29 consecutively recruited pediatric-onset relapsing remitting MS patients (22 girls; mean age 16.2y; mean disease duration 4.6y; median EDSS=1) were analysed cross-sectionally and compared to 35 age- and sex-matched healthy controls (HC). Global and regional cerebellar volumes were generated automatically using RASCAL. Total cerebral volume was generated using BeAST. Cognitive function was assessed using Full scale IQ and Vocabulary subtest of the WASI (Wechsler Abbreviated Scale of Intelligence), SDMT (Symbol Digit Modalities Test), VMI (Beery Visual Motor Integration), TMT-B (Trail Making Test - Part B), and the Grooved Pegboard test was used for motor function. Independent sample t-tests and hierarchical stepwise multiple linear regression (MLR) were used to examine associations between cognitive outcomes and cerebellar volumes after accounting for cerebral volume.

Results: Performance on all cognitive and motor tests differed significantly between groups (MS worse than HC). Cerebellar volumes did not differ between groups [e.g. total cerebellar volume [mean (standard deviation) MS = 130cc (12.7), HC = 134cc (14.8); p=0.27], nor were they associated with duration of disease. However, in the MS group, lower cerebellar posterior lobe volume was associated with poorer SDMT performance, controlling for sex and cerebral volume (R^2=0.54). The full model for the

prediction of Vocabulary test scores (R^2=0.67) included sex, cerebral volume and infratentorial lesion volume (LV). In the MLR analysis of all remaining variables, cerebellar measures were not included as significant predictors in the full model after accounting for cerebral volume.

Conclusions: Cerebellar posterior lobe volume, a known region for cognitive processing, and infratentorial LV accounts for partial variance on measures of information processing and vocabulary in pediatric-onset MS patients.

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Subjective and objective measures of cognition in MS: a preliminary analysis of correlations and test-retest reliability

L Osman[1], JA Berard[1,2], LM Rees[1,2,3], D Cousineau[2], MS Freedman[1,2,3], H MacLean[1,2,3], LAS Walker[1,2,3]

[1]Ottawa Hospital Research Institute, Ottawa, ON, Canada, [2]University of Ottawa, Ottawa, ON, Canada, [3]The Ottawa Hospital, Ottawa, ON, Canada

Background: The Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) is a screening tool for cognitive impairment in MS. The relationship between MSNQ (self- and informant- report) and both cognition and depression were examined. Significant correlations were expected between MSNQ-informant and objective cognition, and between MSNQ-self and self-report ratings of depression. Moderate test-retest reliability was expected for the MSNQ.

Objectives: The relationship between subjective cognition and mood, and objective cognition was measured over time. Test-retest reliability was examined.

Methods: 27 individuals with MS (21 RRMS, 4 SPMS, 2 PPMS) recruited from the Ottawa Hospital MS Clinic completed the Brief International Cognitive Assessment for MS (BICAMS) at baseline and two weeks follow-up. The BICAMS includes the Symbol Digit Modalities Test [SDMT], the California Verbal Learning Test - Second Edition learning trials [CVLT-II] and the Brief Visuospatial Memory Test - Revised learning trials [BVMT-R]. Other measures include: Auditory Consonant Trigrams (9" & 18"; ACT), Paced Auditory Serial Addition Test (PASAT), Controlled Oral Word Association Test (FAS & Animals), Daily Fatigue Impact Scale (D-FIS). Participants completed self-report measures of depression: Beck Depression Inventory Fast Screen for Medical Patients (BDI-FS); Patient Health Questionnaire - 9 (PHQ-9); and Center for Epidemiological Studies in Depression Questionnaire (CES-D). Participants and an informant completed the MSNQ.

Results: At time 1 the only significant correlation was between MSNQ-I and BDI-FS (r = 0.42, p< .05). At time 2 MSNQ-S correlated with PHQ-9 (r = 0.39, p< .05) and MSNQ-I correlated with SDMT (r = -.43, p< .05), ACT-9 (r = -0.44, p< .05) and ACT-18 (r = -0.43, p< .05). Both MSNQ-S (r = 0.83, p< .001) and MSNQ-I (r = 0.81, p< .001) showed high test-retest reliability.

Conclusions: Expected relationships between self-report cognition and mood; and informant-report cognition and objective cognition, were observed at time 2. The lack of similar relationships at time 1 is unexpected. Post-hoc regression analyses were conducted to determine if D-FIS (i.e. fatigue on the day of testing) impacted target relationships. Although not statistically significant, D-FIS

approached significance (p = 0.066) as a potential moderator when examining informant ratings of cognition and mood (Adjusted R^2 = 0.094). Informants' ability to estimate cognition may have been confounded by MS participants' level of fatigue on the day of testing.

P141

Self-reported cognitive fatigue is a function of time on task in multiple sclerosis

J Sandry[1,2], H Genova[1,2], J DeLuca[1,2,3], G Wylie[1,2,4]
[1]Kessler Foundation, West Orange, NJ, United States, [2]Rutgers New Jersey Medical School, Physical Medicine and Rehabilitation, Newark, NJ, United States, [3]Rutgers New Jersey Medical School, Neurology & Neurosciences, Newark, NJ, United States, [4]War Related Illness & Injury Study Center, Department of Veterans Affairs, East Orange, NJ, United States

Background: Fatigue is perhaps the most common complaint associated with Multiple Sclerosis (MS) with prevalence estimates ranging between 70-90 percent. Fatigue can be experienced both centrally (cognitive) and peripherally (physical) and cognitive fatigue may manifest as both subjective sensations and/or objective changes in performance.

Objectives: The aim of the current investigation was to identify the task parameters associated with feelings of subjective cognitive fatigue in MS. A number of different predictions were tested against each other. The hypotheses were: 1) cognitive fatigue is a result of cognitive load, 2) cognitive fatigue is a result of cognitive domain or 3) cognitive fatigue is a function of time on task. An interactive cognitive fatigue hypothesis was also possible, whereby cognitive fatigue may result from an interaction between the different factors.

Methods: Thirty-three individuals with MS and 23 Healthy Controls participated. Experimental manipulation included Cognitive Domain (Processing Speed vs Working Memory), Cognitive Load (High vs Low), and Time (Block/Run 1, 2, 3, 4). Domain and Load were counterbalanced and manipulated within participants. Subjective cognitive fatigue was measured using a Visual Analogue Scale (VAS) for fatigue at baseline and after each Run.

Results: Data analysis was completed using a 2 Group (MS vs Healthy Controls) x 2 Cognitive Domain x 2 Cognitive Load x 4 Run Mixed ANOVA. Subjective reports of cognitive fatigue on the VAS were higher for the Processing Speed task (p < .001), increased across Runs (p < .001), and were higher in the MS group (p = .01). The significant Run by Group interaction (p = .02) revealed that the MS group reported higher subjective cognitive fatigue across time. Subjective cognitive fatigue was not correlated with objective cognitive fatigue (behavior; all p's = n.s).

Conclusions: Subjective cognitive fatigue was higher for both the MS and healthy control group in the processing speed task. Irrespective of cognitive load, subjective cognitive fatigue increased as a function of time on task and this effect was magnified for the MS group. Subjective cognitive fatigue was independent of objective cognitive fatigue. These findings support the hypothesis that subjective cognitive fatigue occurs in MS as a function of time on task.

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Response inhibition on a Go/No-go task in pediatric-onset multiple sclerosis patients: an fMRI study

M Lysenko[1], N Akbar[2], EA Yeh[3], B Banwell[3,4], C Till[1,3]
[1]York University, Toronto, ON, Canada, [2]University of Toronto, Toronto, ON, Canada, [3]The Hospital for Sick Children, Toronto, ON, Canada, [4]Children's Hospital of Philadelphia, Philadelphia, PA, United States

Background: Inhibitory control, defined as the ability to withhold a response, is typically preserved in patients with multiple sclerosis (MS), despite impairment in other executive functions. The role of functional reorganization in the preservation of inhibitory control has been documented in adults with MS, but has received little attention in children and adolescents with MS.

Objectives: This study examined the concept of functional reorganization concerning inhibitory control using a simple Go/No-go (GNG) functional MRI paradigm in pediatric-onset MS.

Methods: Twenty pediatric-onset relapsing remitting MS patients (13 female; mean age = 19.4 ± 3.0 years; mean disease duration = 5.1 ± 3.1 years) and 17 age-and sex-matched healthy controls (14 female; mean age = 19.3 ± 2.6 years) underwent a neuropsychological test battery and structural and functional imaging on a 3 T MRI scanner. Brain activation associated with response inhibition on an 8-minute GNG task was compared between the MS and control groups.

Results: Patients and controls did not differ on any of the neuropsychological outcomes in the test battery, nor with respect to reaction time ($p = 0.13$) or accuracy ($p = 0.87$) on the GNG task. Patients who were younger at disease onset (r = 0.38, $p = 0.054$) and had a higher T1-weighted lesion volume (r = -0.32, $p < 0.10$) had lower accuracy on the GNG task, trending towards significance. Regarding brain activation, the control group demonstrated greater functional activation as compared with the patient group in several regions, including the cerebellum, brainstem, lateral occipital cortex, parahippocampal gyrus, precuneus, superior parietal lobe, precentral gyrus and superior frontal gyrus. Relative to the controls, the patient group did not show greater activation in any brain region.

Conclusions: Findings demonstrate that cognitively intact pediatric-onset MS patients show less brain activation than controls when inhibiting a simple motor response despite no differences in behavioural performance. Functional differences were observed in the posterior and anterior regions of the response inhibition network in the MS group that may suggest a less developed attention network. Further characterization of cerebellar-neocortical connectivity is required to understand the potential for functional plasticity in response to injury in pediatric-onset MS.

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Age of onset and cognitive reserve as moderators of cognitive decline in pediatric-onset multiple sclerosis patients

C Till[1,2], B Hosseini[1], D Flora[1], BL Banwell[3]
[1]York University, Psychology, Toronto, ON, Canada, [2]The Hospital for Sick Children, Neurosciences and Mental Health, Research Institute, Toronto, ON, Canada, [3]Children's Hospital of Philadelphia, Dept. of Neurology, Philadelphia, PA, United States

Background: Cognitive impairment is reported to occur in 30 to 50 per cent of pediatric-onset MS patients with difficulties in working memory and information processing commonly observed. Little is known about the long-term impact of the disease on cognitive development and how certain predictors may moderate cognitive outcomes.

Objectives: To determine how age of disease onset and cognitive reserve impact the maturation of working memory and processing speed in pediatric-onset MS patients.

Methods: This study collected serial cognitive data from 35 individuals with pediatric-onset MS with a focus on working memory and processing speed. Of the 35 participants, 7 completed only one assessment, 5 completed two assessments, 13 completed three assessments, 10 completed four or more assessments. Working memory was assessed by the Trails Making Test-Part B (TMT-B) and processing speed was assessed by the Symbol Digit Modalities (SDMT) - oral version. Growth curve modeling was used to assess cognitive trajectories over time and to examine how age at disease onset, baseline Full Scale IQ, and socioeconomic status may moderate rate of change.

Results: Results showed that growth curves varied considerably across individuals. Younger age at disease onset was associated with a greater likelihood of cognitive decline on both the TMT-B (estimate = 0.06, *SE* = 0.02, *p* = 0.001) and SDMT (estimate = 0.48, *SE* = 0.16, *p* = 0.005). Proxies of cognitive reserve, including baseline IQ and parental socioeconomic status, did not predict cognitive outcome trajectories.

Conclusions: Findings suggest that younger age at disease-onset increases the vulnerability for disrupted development of working memory and processing speed. Proxies of cognitive reserve did not protect against the progression of decline on these specific cognitive measures. Young patients with MS should be advised to seek follow-up cognitive evaluation to assess cognitive maturation and to screen for the potential late emergence of cognitive deficits.

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Transfer of information across the corpus callosum is slowed in patients with multiple sclerosis compared to healthy controls

J Bacon[1,2], T Bacon[2], I Kister[2], J Herbert[2]
[1]Yeshiva University, Pscyhology, New York, NY, United States,
[2]New York University School of Medicine, Neurology, New York, NY, United States

Background: The corpus callosum, a heavily myelinated tract connecting the right and left hemispheres, is a frequent and early locus of disease activity in multiple sclerosis (MS) . We predicted that, relative to controls, MS subjects would have exaggerated delays in reaction times on a task that involved transcallosal transfer of visual information to the left hemisphere (LH) language area compared to a task with no callosal transfer.

Objectives: To compare differences in reaction time between patients with MS and healthy controls on a task that involves transfer of information from one hemisphere to the other and a task that does not involve transcallosal transfer.

Methods: MS patients were divided into three disability strata: No Disability (ND), EDSS=0-1, n=19; Mild Disability (MilD), EDSS=1.5-3.5, n=39; and Moderate Disability (MoD), EDSS=4-6.5,

n=10. 22 healthy volunteers served as controls. A trial consisted of a three-letter word presented for 150 milliseconds to either the right visual field (RVF) or left visual field (LVF). Subjects were required to speak the word as quickly as possible and reaction time of articulation (RTA) was recorded. Since a word presented to the RVF projects to the LH, ipsilateral to Broca's area, RTAs should be faster than for a word presented to the LVF, which projects to the right hemisphere, contralateral to the LH language area. We predicted RVF/LVF differences would be exaggerated in MS subjects compared to controls. Data were analyzed using distribution-free non-parametric statistics. A difference score (DS) was computed for each subject by taking the difference between the median RTA for LVF and RVF word presentations.

Results: In accordance with Dunn´s procedure, we first showed a significant overall effect between groups using the Kruskal-Wallis test (p< 0.001). We then compared the control group to each of the MS groups using the Mann Whitney U. DS for controls (Mdn=18.8) was not significantly different from the ND group (Mdn= 12.8), U = 159.0, p = 0.19, but was significantly different from the MilD group (Mdn=36.3), U = 286.0, p = .032, r =0.28, and the MOD group (Mdn=52.5), U = 21.0, p < 001, r = 0.64.

Conclusions: Compared to controls, MS subjects exhibited longer time to articulation when a stimulus was presented to the hemisphere contralateral to the language area. Our test demonstrates sensitivity to delays in cross-hemisphere processing and greater slowing with increased disability.

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Correlates of cognitive performances with fractional anisotropy decrease in clinically isolated syndromes

D Hamel[1], M Deloire[2], F Munsch[3], N Moscufo[4], D Meier[4], A Saubusse[2], J Charre-Morin[2], C Guttmann[4], B Brochet[5]
[1]Université de Bordeaux, U INSERM 862, Bordeaux, France,
[2]CHU de Bordeaux, Neurology, Bordeaux, France, [3]Université de Bordeaux, TRAIL, Bordeaux, France, [4]Brigham & Women's Hospital, Neurological Imaging, Boston, MA, United States,
[5]Université de Bordeaux & CHU de Bordeaux, Bordeaux, France

Background: Clinically isolated syndromes (CIS) could be associated with cognitive impairment (CI), which increases in frequency in the first years of the disease. This stage could be particularly relevant to study the early mechanisms of CI in multiple sclerosis (MS). Diffusion tensor imaging (DTI) allows to study white matter tracts integrity and to examine the association between cognition and diffuse tissue pathology.

Objectives: To study anatomical connectivity abnormalities associated with CI in CIS patients by using DTI with Tract-Based Spatial Statistics (TBSS) analysis.

Methods: Twenty-four CIS patients and 71 healthy controls (HC) matched for age, gender and educational level, were assessed by neuropsychological testing of information processing speed (IPS), attention, executive functions (EF)working memory (WM) and episodic memory (EM). All patients and 31 HC underwent 3 T MRI including DTI. A global cognitive (GC) composite z-score and a z-score for each cognitive domain were calculated. Fractional anisotropy (FA) and mean diffusivity mapping were derived from DTI data by using FSL software. The "skeleton" of

intracerebral connexion bundles was established using the TBSS method. Maps of the FA voxel-based correlations with cognitive z scores will be determined by TBSS. Prior to the voxel-wise analysis, group comparison was made between the whole-brain TBSS skeleton mean FA for CIS patients and HC. MRI and neuropsychological parameters between HC and patients were compared. Correlations between the DTI measures and the cognitive performances were studied in CIS patients.

Results: CI was detected in 47.6 % of CIS patients (>=3 tests of the battery failed). A small significant difference in the whole-brain TBSS skeleton mean FA was demonstrated between CIS patients (0.32 ±0.17) and HC (0.33 ±0.18) (p< 0.05). GC z-score and mean FA correlated significantly (p< 0.05) in CIS patients with a significant FA reduction particularly in superior longitudinal fasciculus, corpus callosum, internal capsule, posterior thalamic radiation and brainstem. IPS z score correlated significantly with FA reduction (p< 0.05) in the same tracts on CIS patients.

Conclusions: Cognitive impairment correlate with white matter integrity at the very early stages of MS.

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CTIP performance in early relapsing-remitting MS: group differences and potential confounds

LAS Walker[1,2], JA Berard[2], LI Berrigan[3], LM Rees[1,2], MS Freedman[4,5]
[1]The Ottawa Hospital, Psychology, Ottawa, ON, Canada, [2]University of Ottawa, Psychology, Ottawa, ON, Canada, [3]Dalhousie University, Psychology, Halifax, NS, Canada, [4]The Ottawa Hospital, MS Clinic, Ottawa, ON, Canada, [5]University of Ottawa, Neurology, Ottawa, ON, Canada

Background: The Computerized Test of Information Processing (CTIP) is a sensitive measure of information processing speed deficits in multiple sclerosis (MS) and has been demonstrated to be more palatable to those with MS than other available measures.

Objectives: The current goal was to determine if performance differences are detectable early in the disease. The impact of language, subjective fatigue, depression, and motor speed on performance was also examined.

Methods: Seventy individuals with early-phase relapsing-remitting MS (RRMS) were compared to 72 matched healthy controls on CTIP performance. The CTIP includes three subtests: simple reaction time (SRT), choice reaction time (CRT) and semantic search reaction time (SSRT).

Results: With the exception of slower performance by the MS group on SRT, no group differences were detected. With regard to potential confounds, CTIP performance was not affected by depression. Language performance (i.e. semantic retrieval) correlated with SSRT in both groups and CRT in controls. Fatigue impacted all subtests in both groups with the exception of SRT in controls. Motor speed also impacted performance on all subtests in both groups, although this effect can be largely removed by scores which subtract out SRT (i.e. motor speed).

Conclusions: In contrast to findings with a general MS sample, group differences in processing speed were not detected in these mildly affected individuals. The differences detected between groups on processing speed measures in past research may be due to the influence of other cognitive processes (i.e. working memory), as well as the fact that our sample was earlier in the disease process. Current findings demonstrated that performance on the CTIP is influenced not only by processing speed, but also some aspects of language given that CRT and SSRT correlated with semantic retrieval. Increased subjective fatigue is associated with poorer CTIP performance. Lastly, individuals with slower motor speed are vulnerable to poorer CTIP performance. Nonetheless, scoring options allow for some control of this. Thus, when interpreting CTIP performance, clinicians must consider the potential influence of other factors aside from processing speed alone.

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Does cognitive impairment, fatigue, depression or physical disability influence computer assisted tests for driving performance in MS patients?

S Gierer[1], E Kannamüller[1], S Gierer[1]
[1]Neurologische Gemeinschaftspraxis Dillingen, Dillingen an der Donau, Germany

Background: MS patients suffering from physical disability, fatigue, cognitive impairment or depression may be affected in their ability to drive. This is an important issue for the individual MS patient as it is for the society which has not yet been noted and studied adequately.

Objectives: The aim of the study was to assess the amount of MS patients who might have restrictions in their ability to drive and to determine whether cognitive impairment, fatigue, depression or physical disability influence computer assisted tests for driving performance in MS patients.

Methods: We studied 92 MS patients using cognitive tests (MUSIC), a fatigue scale (FSMC) and a computer based battery for driving fitness ("Wiener Testsystem"), which consists of 5 separate tests measuring visual perception, reactivity, stress tolerance and concentration. The EDSS and the time since disease onset was determined for each patient. Patients who received steroids in the previous 4 weeks and patients suffering from impairment of motor function leading to decrease of reaction capabilities were excluded.

Results: 41% of patients showed an impaired performance in 2 or more of the 5 tests of driving fitness, which was specified as "impaired driving performance" (IDP). High EDSS (r= -0,41, p< 0,01), cognitive impairment (r=0,34, p< 0,01), duration of the disease (r=-0,29, p< 0,01) and fatigue (r=-0,25, p< 0,05) were predictors of IDP whereas depression was not. In a logistic regression model with IDP as the outcome and age, depression, fatigue syndrome, EDSS, duration of disease and cognitive impairment as independent variables in the model, the only significant predictors were EDSS (p< 0,01) and impaired cognition (p< 0,05).

Conclusions: The amount of MS patients missing criteria for ability to drive in computer based tests is high. Since some of the tests depend on reaction time it is evident that a higher EDSS results in insufficient test performance. However, cognitive deficits are an independent predictor for IDP, so that physical disability is only one part of the story. In the individual patient, deficits have to be explored in detail. Testing of driving skills by a driving instructor or by using a driving simulator may help to determine the ability to drive in the individual patient.

Inhibitory control in early multiple sclerosis
L Crivelli[1], MF Farez[1], RF Allegri[1], MP Fiol[1], MC Ysrraelit[1], J Correale[1]
[1]*Institute for Neurological Research Dr. Raúl Carrea (FLENI), Buenos Aires, Argentina*

Background: Cognitive impairment can be present early on in the course of MS. Executive functions are among the most frequently affected cognitive domains. However, executive functioning has not been studied thoroughly during initial stages of MS. Inhibitory control, a key component of executive function, is defined as the capacity to suppress inappropriate or unnecessary behavior, promoting flexible responses to changing environments. Given the fact that MS patients may present frontal lesions with white matter involvement affecting frontal lobe tracts during early stages of the disease, we hypothesize that inhibitory control is impaired in MS patients.

Objectives: The purpose of this study is to characterize inhibitory function in patients with early MS.

Methods: Patients were recruited from the outpatient MS clinic at the Raul Carrea Institute for Neurological Research (FLENI) by attending neurologists. Twenty-nine relapsing-remitting MS patients, fulfilling 2005 McDonald criteria, with less than 2 years disease duration and scores ≤ 2 on EDSS, were included. Twenty-nine subjects matched for age, gender, and educational level, recruited from a local volunteer group, served as controls. Both groups underwent complete neuropsychological evaluation. Inhibitory control was assessed using a computerized test (STOP-IT). The local ethics committee approved the protocol and all subjects signed an informed consent form.

Results: In line with previous reports, patients and controls differed significantly in scores obtained for the following tests: attention (Digit Symbol Test p=0.003); verbal memory (Selective Memory Test p=0.004); language (Verbal Fluency p=0.001); and executive function (PASAT3 sec. p=0.004, WAIS III Digits backwards p=0.03). Furthermore, when tested with STOP-IT, patients presented a 33.37 msec delay in inhibition of response, compared to controls (p=0.032). Although patients took longer to inhibit response, no differences were observed in likelihood of achieving response inhibition, between patients and controls (p=0.4).

Conclusions: Patients with recent MS diagnosis present specific inhibitory control deficits. Inhibitory control is an important component of executive functions and when altered, can have significant impact on patients´ quality of life. Careful dissection of executive function into its basic components, combined with analysis of impaired domains can help individualize the design of cognitive rehabilitation strategies.

Accuracy of clinical screening for cognitive impairment in multiple sclerosis: an empirical study
G Hoffnung[1], L Glukhovsky[1], S Flood[1], J Botvinick[1], J Sloan[1], FW Foley[1,2]
[1]*Yeshiva University, Bronx, NY, United States, [2]Holy Name Medical Center, Teaneck, NJ, United States*

Background: Cognitive dysfunction is a frequently occurring symptom of multiple sclerosis (MS) and it has become an increasingly important focus of MS medical care in recent decades. While empirical studies have found that approximately 50% of MS patients are at risk for cognitive impairment, it is difficult under normal clinical conditions to identify those who are at risk for cognitive impairment and should be referred for neuropsychological testing.

Objectives: There is sparse literature on validated methods for physician screening of cognitive symptoms in MS and little has been published regarding the accuracy of current physician screening. The present study seeks to examine the accuracy of physician referral for neuropsychological testing for cognitive impairments. We hypothesize that current screening and referral practices will prove only marginally accurate. If confirmed, this study seeks to point further toward the need for the development of quick and accurate screening tools in the clinical setting.

Methods: The study considered a group of MS patients (n= 187) from a large outpatient medical center who were referred by physicians for further neuropsychological testing in response to physician examination/screening. Referred patients' cognitive functioning was assessed using the MACFIMS (minimal assessment of cognitive function in multiple sclerosis) battery (Benedict, et al., 2002) and the presence of objective cognitive impairment was determined based on the criteria of Benedict and colleagues (2006).

Results: Of the 187 patients referred by physicians for testing, only 100 (53.5%) displayed objective cognitive impairment while 87 (46.5%) did not display cognitive impairments, numbers that are statistically equivalent with what would be predicted from a random sampling.

Conclusions: The findings of the study are preliminary, but suggest low accuracy in physician referral for the detection of objective cognitive impairments in MS. This study highlights the need for the development of reliable and valid screening tools that can be quickly administered in the busy clinic setting. One recent study found that an abbreviated California Verbal Learning Test-II (CVLT-II) that takes approximately 3 minutes to administer can accurately detect verbal memory problems in MS (Gromisch et al, 2013). Future research needs to develop screening tests that are accurate for other cognitive problems in MS.

Cognitive impairment as measured by Audio Recorded Cognitive Screen in an MS clinic population with up to 6 years follow up
K Ribbons[1], P Schofield[2,3], RA Lea[1], P Caruana[3], S Agland[3], J Lechner-Scott[1,3]
[1]*Hunter Medical Research Institute, University of Newcastle, Newcastle, Australia, [2]University of Newcastle, Newcastle, Australia, [3]John Hunter Hospital, Neurology, Newcastle, Australia*

Background: Cognitive impairment is common in MS and occurs across all disease stages. Currently used screening tools for evaluating cognitive ability do not assess the range of cognitive domains or adjust for demographic variables that impact on an individual's performance, making it difficult to evaluate MS-specific impairment. In the current study we have utilized the Audio Recorded Cognitive Screen (ARCS) to evaluate cognitive impairment in a cohort of 322 MS clinic patients.

Objectives: To assess the rate of decline in cognition in our clinic cohort and to analyse the factors influencing it.

Methods: In addition to providing an overall assessment of cognitive performance, the ARCS evaluates domains known to be impacted on by MS including memory, fluency, attention, visuospatial functioning and language. Scaled scores adjust data for the patient's age, gender and education. Impairment was defined as a score of 1.5 SD below the normal population mean score for the total ARCS or on any scaled domain score. Impaired patients were compared to non-impaired patients and correlations analysed using Kendall´s Tau B statistic tests and multifactorial linear regression.

Results: Annual ARCS has been undertaken on patients attending the MS clinic at the John Hunter Hospital, Newcastle, Australia. The cohort was 81% female with an average disease duration of 8+0.4 years, mean age at diagnosis of 38.1+0.6 years and 71% had education to the senior secondary or tertiary education levels. 138 of RRMS were followed up over a mean time of 31 months (min 9m, max 72m). 87 RRMS patients were rated impaired at baseline. 71% of these deteriorated during follow up: 37% of patients experienced decline in memory, 41% in fluency, 8% in visual, 36% in attention, 12% in language and 26% in total ARCs. Of the group receiving treatment during follow up, only 37% had a decline in fluency compared to 64.3% in the non-treatment group (P=0.028). After adjusting for the effects of age, gender, education and time between visits the effect of treatment on the fluency domain remained significant (P=0.05). Scores in the fluency domain were associated with disease duration, education and EDSS.

Conclusions: The ARCS detected changes in the main domains affected by MS. In this non-controlled patient group an effect of treatment was observed in the fluency domain. Larger studies over a prolonged period are required to determine whether disease modifying treatment attenuate cognitive decline.

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Self-reported episodic memory and future thinking and their relation to cerebral structure in early multiple sclerosis patients

GO Nygaard[1,2], KB Walhovd[3], AM Fjell[3], NI Landrø[3], J-L Chepkoech[3], EG Celius[1], HF Harbo[1,2]
[1]*Oslo University Hospital, Department of Neurlogy, Oslo, Norway,* [2]*University of Oslo, Faculty of Medicine, Oslo, Norway,* [3]*University of Oslo, Institute of Psychology, Oslo, Norway*

Background: Self-reported episodic memory may be affected in relapsing remitting multiple sclerosis (RRMS), but it is not clear whether it is related to cerebral structure after controlling for depression and fatigue. Self-reported memory, the quality of episodic memories and future thinking may be related.

Objectives: To examine episodic memory and future thinking in early RRMS patients and to investigate whether cortical and subcortical structures relate to these functions.

Methods: RRMS patients diagnosed within the last three years (n=60) and matched healthy controls (n=60) underwent MRI and neuropsychological testing, including Past Time Travel (PTT) and Future Time Travel (FTT), (experimental tests of the quality of episodic memory and future thinking, scored on a likert scale from least to most vivid imaginations 0-5), filled in the Everyday Memory Questionnnaire (EMQ, scored on a likert-like scale from most seldom to most common memory problems 1-9), fatigue severity scale (FSS) and Beck Depression Inventory (BDI). Cortical parcellation and subcortical segmentation were performed using the software Freesurfer based on a 3 dimensional T1 MRI sequence. General linear models were constructed to investigate the relation between test results and cortical structure.

Results: Patients and controls scored similarly on EMQ (patients 2.5, SD 0.9, controls 2.4, SD 0.7, t=0.79, p=0.43). Within the patient group PTT was related to FTT (r=0.45, p=0.001) and PTT correlated negatively with EMQ (PTT: r=-0.31, p=0.029, FTT: r=-0.21, p=0.14). Both EMQ and FTT correlated with FSS and BDI, thus these factors were added as covariates in the analyses. The patients had smaller cortical volumes and smaller volumes of thalamus, putamen, caudate nuclei and pallidum bilaterally, but similar hippocampal and intracranial volumes, compared to the controls. Preliminary results show that higher EMQ and FTT were associated with a larger surface area of a region of the left lateral occipital and inferior parietal lobe, and a larger cortical volume in the same region for FTT. Subcortical structures were not associated with EMQ, FTT or PTT.

Conclusions: In this early RRMS patient sample EMQ was similar to healthy controls and was related to PTT. Preliminar results indicate that higher EMQ and FTT were associated with a larger surface area of the same cortical region. Self-reported episodic memory in early RRMS patients may have a structural brain correlate after controlling for fatigue and depression.

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Including ecological assessment in cognitive screening: a new approach to detect cognitive impairment in MS patients

D Hamel[1], MSA Deloire[2], A Saubusse[2], B Brochet[1,2]
[1]*Université de Bordeaux, INSERM U 862, Bordeaux, France,* [2]*CHU de Bordeaux, Neurology, Bordeaux, France*

Background: Assessment of cognitive impairment (CI) in persons with multiple sclerosis (PwMS) requires large neuropsychological (NP) batteries covering different domains: information processing speed (IPS), episodic memory (EM), working memory (WM), attention and executive functions (EF). The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), which includes a test of IPS, the Symbol Digit Modalities test (SDMT), and 2 tests of EM, is easy to use but does not detect all patients with CI. Quick and patients-friendly ecological tasks in a virtual environment (VE) are promising.

Objectives: To compare a short battery including two tests of the BICAMS and a VE task to a large comprehensive NP battery.

Methods: A sample of 28 PwMS with cognitive complaints and at least two three cognitive tests impaired at a large NP battery were matched to 19 healthy controls (HC).

The large battery (A) included 13 paper-pencil NP tests of IPS, EM, WM, EF and attention and several computerized tasks from the Test of Attentional Performance (TAP). The short battery (B) included the SDMT, the immediate recall score of the California Verbal Learning Test and an in-house developed task assessing divided attention in a VE: the Urban Daily Cog©. The percentages of cognitively impaired patients at the B battery (at least 1 test < 1.5 standard deviation (SD) of HC) and at the A battery (at

least 3 tests < 1.5 SD of HC) were calculated. Predictives values of the short B battery were calculated to predict cognitive status assessed by the large battery.

Results: On the basis of cognitive performances, 92.8% and 89.3% of PwMS were classified as cognitively impaired using A and B battery respectively. Accuracy of the B battery to predict impairment at the A battery was 82.1%, with a sensitivity of 88.5%.

Conclusions: A short battery including two tests of the BICAMS and a virtual ecological attention task has good accuracy to predict CI at a large cognitive battery.

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Incipient cognitive dysfunction revealed by dual-task posturography in patients with multiple sclerosis

L Prosperini[1], L De Giglio[1], L Castelli[2], G Sellitto[2], MR Marchetti[2], C Pozzilli[1]

[1]Sapienza University, Neurology and Psychiatry, Rome, Italy, [2]S. Andrea Hospital, Physical Therapy Unit, Rome, Italy

Background: Deficits in attention and executive function processes have been independently associated with postural instability and falls in patients with multiple sclerosis (MS). However, whether a dual-task paradigm may even reveal an incipient cognitive dysfunction (CD) has not investigated yet.

Objectives: To explore the role of dual-task posturography paradigm in discriminating patients with and without CD.

Methods: After excluding those having clinically relevant depression or dementia, eligible patients were tested by means of single-task and dual-task posturography, Symbol Digit Modalities Test (SDMT), and Modified Fatigue Impact Scale (MFIS). Patients were categorized as presenting an overt or incipient CD if they scored >2 standard deviation (SD), or >1 SD but < /=2 SD below the Italian normative mean of SDMT, respectively. Postural sway was estimated using a force platform (ProKin PK254P, Tecnobody) by asking patients to maintain their balance for 30s as steady as possible under eyes opened (single-task) and while performing the Stroop word-colour task (dual-task). Dual-task cost (DTC) was calculated as percentage change from single- to dual-task condition. The association between CD and DTC was investigated by an ANCOVA model.

Results: Eighty-five patients (55 F, 30 M), with a mean (SD) age of 39.2 (10.2) years, mean (SD) MS duration of 12.4 (8.6) years and median [range] Expanded Disability Status of 3.0 [1.0-6.0] were tested. Of them, 28 (32.9%) and 21 (24.7%) presented an overt and incipient CD, respectively. Patients with either overt and incipient CD were older and more disabled than cognitively intact (CI) ones (p< 0.05). Patients with overt CD had also longer MS duration (p< 0.001) and slower walking speed (p=0.021) than CI ones. There were no differences between patients with overt and incipient CD. There was a significant effect of CD on DTC after controlling for gender, age, education, MS duration, EDSS score, single-task postural sway, fatigue and walking speed (F=6.856, p=0.002). Contrast analysis revealed that either overt and incipient CD were associated with greater DTC (p=0.024 and p< 0.001, respectively), while there was no difference between overt and incipient CD.

Conclusions: Our findings support the hypothesis that two simultaneously performed tasks may compete for common brain network resources in patients with MS. Therefore, dual-task posturography may be considered a promising tool to detect an incipient cognitive impairment.

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Incidental recall performance on a processing speed test is associated with verbal memory abilities in multiple sclerosis

C Mavis[1,2], B Roberg[1], S O'Bryan[1], L Wilson[1], B Williams[1], C Ray[1], S Lynch[3], J Bruce[1]

[1]University of Missouri-Kansas City, Psychology, Kansas City, MO, United States, [2]Avila University, Psychology, Independence, MO, United States, [3]University of Kansas Medical Center, Kansas City, KS, United States

Background: Information processing speed and auditory verbal memory are frequently impaired in people with multiple sclerosis (MS). Whereas information processing speed can be quickly assessed, assessment of auditory verbal memory abilities can be time consuming in clinical settings.

Objectives: The current study examined the association between performance on the incidental recall trial of frequently used information processing speed measure and performance on a verbal memory task in a sample of MS patients.

Methods: MS patients ($n = 56$) and controls ($n=25$) were recruited through an advertisement in the regional MS Society newsletter, by word-of-mouth, and through a neurology clinic as part of a larger study examining social cognition in MS. Information processing speed was assessed using the Symbol Digit Modalities Test (SDMT) followed by an incidental recall trial. Verbal memory was assessed via the Auditory Verbal Learning Test (AVLT) followed by short and long-delay recall trials.

Results: ANOVA revealed significant differences between MS and control participants in incidental recall of the SDMT ($p< .05$). Within the MS group, better incidental recall performance on the SDMT was associated with better performance on the AVLT learning ($r = .37$, $p< .05$), AVLT short-delay ($r = .42$, $p< .05$), and AVLT long-delay trials ($r = .50$, $p< .05$). Linear regression showed that SDMT incidental recall performance accounted for unique variance in delayed memory after controlling for speed of information processing ($\Delta R^2 = .20$, $\Delta F = 14.70$, $p< .05$).

Conclusions: Performance on an incidental recall trial of the SDMT was significantly associated with auditory verbal memory. Incidental recall provided a particularly strong estimate of performance on a delayed trial of the AVLT. SDMT incidental recall may provide unique information about memory deficits when time constraints prevent formal memory assessment.

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Changes in subjective cognitive difficulties, mental health and information processing speed at one year follow up in MS patients

M Hebert[1], LI Berrigan[1], RA Marrie[2], V Bhan[1], S Patten[3], K McKay[4], JD Fisk[1,5], CIHR Team in the Epidemiology and Impact of Comorbidity on Multiple Sclerosis

[1]Dalhousie University, Halifax, NS, Canada, [2]University of Manitoba, Winnipeg, MB, Canada, [3]University of Calgary, Calgary, AB, Canada, [4]University of British Columbia, Vancouver, BC, Canada, [5]Capital District Health Authority, Halifax, NS, Canada

Background: Cognitive impairments are common among persons with multiple sclerosis (MS) as are subjective cognitive complaints. The association between subjective and objective cognitive problems is unclear and can be affected by depression and anxiety.

Objectives: We investigated changes in subjective cognitive difficulties over one year to determine if these were associated with objective changes in cognitive performance, depression or anxiety.

Methods: Study participants were recruited consecutively from adults with definite MS attending a regional specialized clinic for MS care. 349 had complete data at baseline and one year follow up. Subjective cognitive difficulties were assessed via the cognition subscale of the Health Utilities Index-3 (HUI-3) and a difference >0.05 on this single attribute utility was used to classify participants as reporting worsened, stable, or improved cognition between assessments. These three groups were then compared on the basis of changes in their ratings of anxiety and depression on the Hospital Anxiety and Depression Scale (HADS) and changes in objective cognitive performance as measured by the oral Symbol Digit Modalities Test (SDMT).

Results: At baseline, 188/349 (53.9%) participants reported at least some cognitive difficulties in thinking and solving day-to-day problems; 191/349 (54.7%) reported cognitive difficulties at one-year follow-up. When changes in HUI-3 cognition ratings were examined, 200 (57.3%) participants reported stable cognition, 71 (20.3%) reported worsening and 78 (22.3%) reported improvement. A one-way ANOVA revealed no difference between groups on changes in SDMT performance ($F(2,346)=0.337$, $p>0.05$) but differences were found between the stable, worsened and improved groups on HADS ratings of anxiety ($F(2,346)=6.206$, $p<0.003$) and depression ($F(2,346)=4.435$, $p<0.014$). Tukey's post-hoc tests revealed that relative to those who reported stable cognition, those who reported worsened cognition had increased ratings of anxiety and those who reported improved cognition had lessened anxiety. Those who reported worsened cognition also had increased ratings of depression relative to those who reported improved cognition.

Conclusions: Subjective cognitive difficulties are common among clinic-attending MS patients. Changes in subjective ratings of cognition between annual clinic visits may be associated with changes in mental health symptoms and may not be reflected in changes in performance on commonly used screening tests of information processing speed.

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Cognitive impairment, oxidative stress and neurodegeneration in multiple sclerosis

AJ Hughes[1], I-Y Choi[2], P Lee[3], P Adany[4], DR Denney[1], SG Lynch[2]

[1]*University of Kansas, Psychology, Lawrence, KS, United States,* [2]*University of Kansas Medical Center, Neurology, Kansas City, KS, United States,* [3]*University of Kansas Medical Center, Molecular and Integrative Physiology, Kansas City, KS, United States,* [4]*University of Kansas Medical Center, Hoglund Brain Imaging Center, Kansas City, KS, United States*

Background: Accumulating evidence points to neurodegeneration as the primary force driving cognitive impairment in multiple

sclerosis (MS). In addition to examining traditional structural markers of neurodegeneration (e.g., atrophy), recent work in our laboratory has assessed cerebral glutathione (GSH), a neuroprotective antioxidant that is diminished in MS patients. The present study examined associations between cognitive performance in MS and both structural and GSH measures obtained through magnetic resonance imaging.

Objectives: To assess group differences for MS patients and healthy controls (HC) on neuropsychological measures; and to examine correlations between test performance and lesion volume (LV), brain parenchymal fraction (BPF), grey matter fraction (GMF), white matter fraction (WMF), and GSH.

Methods: 52 MS patients and 21 HC were administered the Rey Auditory Verbal Learning Test (RAVLT), Tower of London (TOL), Stroop, Symbol Digit Modalities Test (SDMT), and Brief Visuospatial Memory Test (BVMT). Testing was followed by a series of neuroimaging and spectroscopy scans.

Results: Patients performed worse than HC on all measures of processing speed (all $ps<.05$). Patients also performed worse on initial learning trials of the RAVLT ($p=.02$) and BVMT ($p=.02$), and had poorer scores on immediate recall and delayed recognition ($ps=.04$). No differences were observed in executive function. BPF and particularly GMF were most strongly aligned with test performance, with robust correlations observed on nearly all measures and Pearson's r ranging between .33 and .65 for GMF. LV and WMF were less strongly related to test performance. Correlations with GSH measures were smaller than those involving GMF and BPF; however, modest correlations were observed for GSH levels on the RAVLT, SDMT, and BVMT.

Conclusions: Cognitive impairment in processing speed and learning efficiency is highly correlated with BPF and particularly GMF, and modestly correlated with GSH. Results provide further evidence for neurodegeneration as the most likely process underlying cognitive impairment in MS. Relations between cognitive measures and GSH may be limited by the dynamic nature of this imaging measure. Further investigation is warranted to determine molecular mechanisms underlying neurodegeneration.

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The efficacy of Wechsler Memory Scale-fourth edition (WMS-IV) in memory evaluation in multiple sclerosis patients

CT Spedo[1,2], MP Foss[1], DA Pereira[2], RM Conde[1], TR Brozinga[1], VD Marques[1], AA Barreira[1]

[1]*Ribeirão Preto Medical School, Neuroscience and Behavior Sciences, Ribeirão Preto, Brazil,* [2]*Brazilian Institute of Neuroscience (IBNeuro), Brasília, Brazil*

Background: The WMS-IV is gold standard in memory assessment. The looking for more accurately tools to investigate and to describe the cognitive impairments of MS patients is a necessary challenge.

Objectives: To investigate the memory functioning and its processes in relapsing-remitting multiple sclerosis patients (MS-RR) and to compare it with healthy controls through the WMS-IV.

Methods: Twenty MS-RR (mean age: 39.5; EDSS=3,5 schooling=13), and 20 controls (mean age: 41.1, schooling=11) answered the WMS-IV flexible approach Logical memory/ Visual Reproduction (LMVR). The scale allows us to obtain raw, index

and contrast scaled scores. Bayesian posterior inference of parameters of the data were analyzed using Markov-chain Monte Carlo method (Open BUGS software, v. 3.2.3). Significance level as parameter for Bayesian inferences were obtained (MPlus software, v.7.11).

Results: All raw scores of LM and some of VR presented higher effect size and significance level in differentiation of the groups. The contrast scaled scores VRrec/VR-II delayed had higher effect size (effSz=1.0) between groups. All index of WMS-IV had higher effect size but the Immediate Memory Index vs. Delayed Memory Index contrast scaled scores had the best higher effect size (effSz=2.6) and higher area under the curve (AUC=0.95, sensitivity=0.96, specificity=0.87, cutoff=70.1) between MS and control groups. The MS-RR patients had more impaired ability to recall orally presented information and ability to recall and manipulate the visual information than controls. Nevertheless, their visual memory index is worse than their auditory index. The patients with MS had memory problems associated with delayed memory performance when compared with healthy people with similar immediate memory performance, noticing that patients present impaired capacity of consolidation. The free recall of non-verbal informations indicates that MS-RR had lower capacity to free recall non-verbal informations learned, suggesting that MS-RR benefits himself with tip. By otherwise, they are able to recall the previous auditory information learned regardless of his ability to free access, needing less of tip for auditory stimuli than visual stimuli.

Conclusions: The WMS-IV is a very useful tool to differentiate and characterize the memory process in MS-RR.

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Cognitive impairment and corpus callosum atrophy in multiple sclerosis

MY Pérez Martín[1], M González Platas[1], A Jiménez Sosa[2], L Miceli Sopo[1], S López Gallardo[1]
[1]Hospital Universitario de Canarias, Service of Neurology, La Laguna, Spain, [2]Hospital Universitario de Canarias, Research Unit, La Laguna, Spain

Background: Cognitive impairment affects 43-75% of the patients with multiple sclerosis patients (MS). Several studies have shown that neuropsychological impairment correlates with brain atrophy.

Objectives: To estimate the relationship between total and regional corpus callosum (CC) atrophy and cognitive performance in MS patients.

Methods: We included 96 Remitting-Relapsing MS (RRMS) patients; mean age 39±9 years, 71 women, schooling 12±3 years, mean disease duration 25±9 years and Expanded Disability Status Scale (EDSS) score 2.1±1.1. All participants underwent brain magnetic resonance and comprehensive cognitive testing. Total and regional CC atrophy was measured with the corpus callosum index (CCI).

Results: Multiple linear regression analysis showed that CCI predicts Selective Reminding Test (SRT_Total) (β =30.1; p= 0.004), Symbol Digit Modalities Test (SDMT) (β =45.5; p=0.004) and Paced Auditory Serial Addition Test (PASAT) (β =56.2; p=0.013). Corrected multiple R^2=0.45, 0.51 and .033 respectively), controlling for age, schooling and disease duration. Anterior CC segment

was significantly associated with SRT_Total (β = 0.86; p= 0.009) and SDMT (β =1.43; p=0.004). Atrophy of posterior CC segment (splenium) was associated to poor outcome in SDMT (β = 1.47; p= 0.002), PASAT (β = 1.43; p= 0.026) and semantic fluency (SF) (β = 0.67; p=0.005). Visual memory and visuospatial functions measures not correlated with total or regional CC atrophy.

Conclusions: Atrophy of the CC is related with cognitive dysfunction in MS. Atrophy of posterior portion is associated with verbal memory and processing speed and atrophy of splenium with working memory and verbal fluency.

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Do disease modifying treatments affect cognitive performance in early multiple sclerosis?

MC Graves[1], K Ribbons[2], R Lea[3], S Vucic[4], CP Shaw[5], S Broadley[6], P Schofield[7], J Lechner-Scott[2]
[1]Hunter Medical Research Institute, Molecular Genetics, New Lambton, Australia, [2]John Hunter Hospital, Neurology, Newcastle, Australia, [3]Hunter Medical Research Institute, New Lambton, Australia, [4]University of Sydney, Director of Neurophysiology, Westmead Hospital, Sydney, Australia, [5]Barwon Health, Neuroscience, Geelong, Australia, [6]Griffith University, School of Medicine, Gold Coast, Australia, [7]University of Newcastle, Newcastle, Australia

Background: Cognition is impaired in multiple sclerosis (MS) even in early disease.

Objectives: The aim of this study was to determine the level of cognitive impairment in early RRMS and the impact of disease modifying therapies on the rate of change in performance over 24 months

Methods: RRMS patients aged 18-65, with an EDSS ≤ 3, receiving disease modifying treatments (DMT) for at least 3 months and within 6 years of diagnosis were recruited to the study (n=103). DMT included interferons, glatiramer acetate and natalizumab. Age and gender matched healthy controls (HC) (n=32) were recruited from the Hunter Medical Research Institute community database. Each participant underwent cognition testing (Audio Recorded Cognition Screen - ARCS and Paced Auditory Serial Addition Test-PASAT) with the self- reported fatigue (Modified Fatigue Impact Score- MFIS) and mood (Depression, Anxiety and Stress Score- DASS21) questionnaires at baseline, 12 months and 24 months. HC were evaluated at baseline and 24 months.

Results: 103 MS participants completed all questionnaires (baseline), 83(81%) at 12 months and 50(48%) at 24 months. Dropout rate was contributed to by pregnancy and change to oral treatment. The level of disability accumulation and duration of disease was significantly greater in patients receiving natalizumab. MS participants were significantly different in all outcome measures (PASAT, ARCS, DASS and MFIS) compared to HC. The mean PASAT scores slightly increased over 12 and 24 months in the MS cohort, suggestive of a learning effect. The major cognitive domain affected, as measured by the ARCS, was the memory domain (85.46 +/- 20.13 vs 95.63 +/- 11.60, p= 0.008). ARCS scores showed a trend to decline over time especially the memory domain (p=0.06) however no difference between the DMT groups was found.

Conclusions: Cognitive function, especially short term memory, is impaired in MS. However, over the 24 month observation

period in this study, the level of impairment was not seen to significantly worsen over time. In this cohort of early diagnosed MS participants, the level of disability and disease duration was higher in natalizumab treated patients, however their level of cognitive impairment and change over time did not differ significantly from those MS participants on other DMT. This study underlines the importance of using sensitive tests over a prolonged period (> 2 years) to assess impact on change in cognition.

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Prevalence of cognitive impairment in newly diagnosed MS patients

SA Morrow[1], H Rosehart[2], K Pantazopoulos[3], M Blair[3]
[1]University of Western Ontario, Clinical Neurological Sciences, London, ON, Canada, [2]London Health Sciences Centre, London, ON, Canada, [3]St. Joseph's Health Care, London, ON, Canada

Background: Cognitive impairment (CI) is known to be a common and debilitating consequence of multiple sclerosis (MS), affecting approximately 43-60% of MS with a significant impact on quality of life. Studies have shown that CI can manifest early in the disease process, as early as the 1st demyelinating event (clinically isolated syndrome, CIS). The frequency of CI in newly diagnosed patients has not been systematically studied to date.
Objectives: To determine the prevalence and pattern of CI in newly diagnosed MS patients.
Methods: Starting in 2012, newly diagnosed MS patients of any type were offered cognitive testing to serve as baseline for future assessments, regardless of subjective cognitive complaints. A retrospective chart review of MS patients assessed in the Cognitive MS clinic, a part of the London (ON) MS clinic, identified 96 MS patients assessed with the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) battery within one year of a confirmed MS diagnosis, as well as the Fatigue Severity Scale (FSS), Hospital Anxiety and Depression Scale (HADS), Beck Depression Index Fast Screen (BDIFS).
Results: The average age of this cohort was 36.9 (±11.2) years, 70 (72.9%) were female and 75 (78.1%) identified themselves as Caucasian. The mean years of education was 14 (±2.3). Most of the cohort (81, 84.4%) was diagnosed with relapsing remitting (RR) MS and the median EDSS at the time of diagnosis was 2.0 (range 0-5.0). Only 30 (31.3%) of the cohort were normal on all cognitive tests. Impairment ranged from 1 test (19, 19.8%) to 9 or all (2, 2.1%) tests, representing impairment in 1 domain alone (27, 28.1%) to 6 or all domains (2, 2.1%) included in the MACFIMS battery. The Symbol Digit Modalities Test (SDMT), a measure of processing speed, showed the most impairment (34, 37.5%) while the Controlled Oral Word Association Test (COWAT), a measure of verbal fluency, was least frequently impaired (15, 15.7%). The mean FSS score was 3.9 (±1.8). The mean BDIFS score was 3.7 (±3.5); based on standard classification, 25 (26%) were mild, 14 (14.6%) were moderate and 2 (2.1%) demonstrated severe depression. The mean HADS scores for depression and anxiety were 4.4 (±4.0) and 7.7 (±4.2), respectively. When grouped according to affected and non-affected based on HADS scores, 52 (54.2%) were positive for depression and 23 (24.0%) demonstrated anxiety.
Conclusions: CI and depression are both common findings in newly diagnosed MS patients.

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Executive functions evaluation in MS Patients without cognitive impairment: a task switching experimental paradigm

S Migliore[1], G Curcio[2], A Couyoumdjian[3], A Ghazaryan[4], D Landi[5], F Moffa[4], MG Palmieri[5], MM Filippi[4], F Vernieri[1]
[1]Università 'Campus Bio-Medico', Rome, Italy, [2]Università di L'Aquila, L'Aquila, Italy, [3]Università 'La Sapienza', Rome, Italy, [4]Ospedale Fatebenefratelli, Isola Tiberina, Rome, Italy, [5]Università 'Tor Vergata', Rome, Italy

Background: Impaired executive functioning can be present since early stages of Multiple Sclerosis (MS); this pattern was correlated with changes in fronto-subcortical fiber tracts (Roca et al., 2008). A specific method for assessing executive functions is the task-switching paradigm, that examines the processes to shift between one task to another; the subjects complete a set of task, engaging interleaving operations that must be performed in an alternating or repeating sequence (Monsell, 2003). Task-switches are usually slower than task repetitions, giving way to the 'switch cost'. Such a task is very challenging and allows to assess both speed and accuracy of performance, providing a complete scenario of executive abilities.
Objectives: Given the small number studies available concerning the primary impairment of executive functions in the early stages of MS, the aim of this study is to explore the executive functions in MS patients without cognitive impairment compared to healthy controls (HC) by means of a task-switching paradigm.
Methods: Twenty-four patients with diagnosis of MS (Polman et al., 2005) [20 Relapsing-Remitting (RR); 2 Clinically Isolated Syndrome (CIS) and 2 Primary Progressive (PP)] and 25 HC (paired for age, sex and education) were enrolled. Participants were asked to complete two different tasks in rapid and random succession, so that the task may change from one trial to the subsequent (switch trial), or may be repeated (repetition trial). A full neuropsychological battery, including working memory, information processing speed, verbal memory and learning, visuo-spatial memory and executive functions, was administered to exclude subjects with cognitive impairment.
Results: A significant difference between MS patients and HC was found: analyses on switch and repetition trials showed that the MS patients performed significantly worse just in switch trials (p=0,04). Moreover, a significant increase in Reaction Times (RT) in MS groups to shift between one task to the other was observed. No differences were observed in RT related to the disengagement from the previously executed task.
Conclusions: This study suggests a primary engagement of executive functions in MS patients without cognitive impairment, mainly depending by the functional integrity of the prefrontal cortex. Detecting early executive dysfunctions with specific cognitive testing could be useful for a prompt enrolment of MS patients into adequate rehabilitation protocols.

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Cognitive impairment in patients with neuromyelitis optica spectrum disorder: a preliminary report

S-H Kim[1], J-W Hyun[1], I-H Jeong[1], A Joung[1], H-J Jo[1], E-S Yu[2], W Kim[3], HJ Kim[1]
[1]Research Institute and Hospital of National Cancer Center, Neurology, Go-Yang, Korea, Republic of, [2]Research Institute

and Hospital of National Cancer Center, Mental Health Clinic, Go-Yang, Korea, Republic of, [3]The Catholic University of Korea, Neurology, Seoul, Korea, Republic of

Background: A few studies have recently reported that about half of patients with neuromyelitis optica spectrum disorder (NMOSD) have cognitive impairment. However, the patterns of cognitive impairment differ among studies. There is relatively limited research on cognitive impairment in patients with NMOSD.

Objectives: To investigate the prevalence and pattern of cognitive impairment in patients with NMOSD.

Methods: At least 100 patients with NMOSD and 50 healthy controls (HCs) are planned to be enrolled in this study. So far, 33 patients with NMOSD and 26 HCs have been tested. In all subjects, cognitive function was measured using the following tests from the Brief Repeatable Battery of Neuropsychological Tests: the Auditory Verbal Learning Test (AVLT), Rey Complex Figure Test (RCFT), Controlled Oral Word Association Test (COWAT), and Paced Auditory Addition Test (PASAT). The Symbol Digit Modalities Test (SDMT), digit span test, Stroop test, and Patient Health Questionaire-9 (PHQ-9), a tool for specific to depression were also performed. In each cognitive domain, a score below the fifth percentile of the normative value was considered abnormal, and patients with impaired performance on at least three of 13 tests were considered cognitively impaired. Logistic regression analysis was used to evaluate the association between patient variables and cognitive impairment.

Results: The mean disease duration of NMOSD was 9.2 years, and the median Expanded Disability Status Scale (EDSS) score was 3.0. There were no significant differences in age, sex ratio, or education level between the NMOSD and HC groups. Seven (23%) patients with NMOSD were impaired in three domains, and five (16%) patients were impaired in at least four domains. Impairment in patients with NMOSD was most commonly observed in the SDMT (33%), followed by RCFT-delayed recall (36%) and AVLT-immediate recall (24%). No association was found between cognitive impairment and physical disability, illness duration, or the presence of typical brain lesions of NMOSD. The NMOSD group had higher PHQ-9 scores than did the HC group, but depression was not correlated with performance on any cognitive test.

Conclusions: Our preliminary analysis showed that about 40% of patients with NMOSD had cognitive impairment. Visuospatial memory, verbal memory, and speed of information processing were commonly impaired, whereas verbal fluency, attention, and executive function were relatively spared.

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Utilization of the Brief International Cognitive Assessment for Multiple Sclerosis during treatment of relapses in patients with multiple sclerosis

O Oztürk[1], B Piri Cinar[2], S Ozakbas[3]
[1]Dokuz Eylul University, Izmir, Turkey, [2]Giresun State Hospital, Giresun, Turkey, [3]Dokuz Eylul University, Dept. of Neurology, Izmir, Turkey

Background: As would be expected a substantial number of multiple sclerosis (MS) patients are compromised neuropsychologically. The Expanded Disability Status Scale (EDSS) has been the most widely used clinical outcome measure in therapeutic trials of MS, but it has some limitations including poor assessment of cognition.

Objectives: In the present study, we examined the changes in measurement of cognitive functions during pulse methylprednisolon (MP) treatment of MS exacerbations using the Brief International Cognitive Assessment for MS (BICAMS). We aimed to determine the availability and usefulness of BICAMS in the attack period.

Methods: Forthy-nine (30 female) MS patients in an attack period were included in this study. Mean age was 36,41 ±8,36. All patients received 1000-mg intravenous MP for 5 days, followed by tappering dose of oral prednisolone for 20 days. BICAMS battery, which includes Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT2) and the revised Brief Visuospatial Memory Test (BVMTR), EDSS, MUSIQoL, Multiple Sclerosis Neuropsychology Questionnaire patents form (MSNQ-P) and Fatigue Impact Scale (FIS) were administered. Assessment other than MUSIQoL was performed before pulse MP therapy, on day 6, and on day 30. MUSIQOL was not performed on day 6.

Results: Mean CVLT2 score was significantly improved on day 6 (p=0.000) and on day 30 (p=0.000). There was no difference between day 6 and day 30 (p=0.517). Mean SDMT score was also improved both on day 6 (p=0.003) and day 30 (p=0.000). M BVMTR score was improved on day 6 (p=0.000) and on day 30 (p=0.000). There was a strong correlation between CVLT2 and SDMT (r=0.551). Correlations between CVLT2 and BVMTR (r=0,624), and BVMTR and SDMT (r=0,494) were also found strong. On day 30 strong correlations were continuing. Mean MSNQ-P score was 20,32±10,88 before treatment. İt was improved to 18,28±12,95 (p=0.000) on day 6, and 17,28±12,49 (p=0.000) on day 30. Mean Beck Depression score (14,65±8,2) was also improved on day 6 (13,06±9,28) (p=0.000) and day 30 (12,28±8,58) (p=0.000). FIS scores were improved from 44,57±28,53 on day 0, to 41,44±29,82 on day 6 (p=0.002) and 40,83±27,80 on day 30 (p=0.000).

Conclusions: The present study is the first one regarding utilization of BICAMS battery in attack period. Our results indicated that BICAMS battery is well accepted by MS patients and may be used for rapid evaluation of cognition in an attack period. However, these preliminary findings need to be corroborated in larger cohorts.

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Are both storage and executive control components of working memory equally affected in pediatric-onset multiple sclerosis patients?

C Till[1,2], M Sadeghi[1], M Lysenko[1], N Akbar[3], BL Banwell[4]
[1]York University, Psychology, Toronto, ON, Canada, [2]The Hospital for Sick Children, Neurosciences and Mental Health, Research Institute, Toronto, ON, Canada, [3]University of Toronto, Institute of Medical Science, Toronto, ON, Canada, [4]Children's Hospital of Philadelphia, Dept. of Neurology, Philadelphia, PA, United States

Background: Working memory (WM) dysfunction is common amongst patients with pediatric-onset multiple sclerosis (MS). WM consists of two key cognitive functions, storage and

executive demand, which can be manipulated in the measurement of WM capacity.

Objectives: Using a computerized WM task, we examined whether both storage and executive demand components of WM are equally affected in individuals diagnosed with MS prior to age 18.

Methods: Twenty-two patients with relapsing remitting MS (M=18.99 years; ages 13-24) and eighteen age-matched controls (M=19.17 years; ages 14-24) completed a cognitive screening battery. While in a 3T MRI scanner, the alpha-span task was administered. This task is a letter span task that systematically manipulates span-size (3 or 5 letter array) with the added component of simultaneously presenting a secondary processing task whereby the participant has to verify the serial or alphabetized order of the target array (e.g. "G-3?" interpreted as: "Was G the third letter in the array?"). Executive control was operationalized as the difference between alphabetize and serial conditions. Reaction time and percent accuracy were measured.

Results: Patients and controls did not differ in terms of age, sex, or performance on standardized cognitive measures. On the alpha-span task, results revealed main effects of span-size [$F(1,81)$=12.67, p=0.001] and executive demand [$F(1,81)$=5.83, p=0.018), with slower reaction times with increased span-size and executive demand (alphabetize condition). There was no significant interaction between group x span-size or group x executive demand, indicating that the effects of condition were equal across both the control and patient groups. Post hoc analyses revealed that patients and controls did not differ in terms of reaction time or accuracy, with the exception of the 'Serial 3' span in which controls were faster than patients [$F(1, 39)$=4.69, p=0.037].

Conclusions: Both patients and controls show slower reaction times when the executive demands of a WM task are increased. Findings suggest that storage and executive control components of WM are not differentially vulnerable to impairment in pediatric-onset MS.

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Sustained attention, reaction time and traffic perception tests characterize different aspects of cognition and fatigue in MS patients

E Kannamüller[1], S Gierer[1], S Gierer[1]
[1]Neurologische Gemeinschaftspraxis Dillingen, Dillingen an der Donau, Germany

Background: Although there is a reasonable intersection of fatigue and cognitive impairment in MS patients, both symptoms are not the same. Fatigue is characterized by a decrease of performance by time whereas cognitive impairment is usually not.

Objectives: The aim of the study was to test whether impaired ability to keep sustained attention over a longer period is a distinctive aspect of fatigue whereas a test for visual perception is an aspect of cognitive function which should not be influenced by fatigue.

Methods: We studied 92 MS patients using cognitive tests (MUSIC), a fatigue scale (FSMC), a test for visual observational abilities and skills in obtaining an overview in traffic situations (ATAVT Adaptive Tachistoscopic Traffic Perception Test) and a test for sustained attention in the form of sustained attention in a low-stimulus observation situation (VIGIL). VIGIL and ATAVT

are computer assisted tests. We also performed a simple PC based reaction task (RT).

Results: Of the 92 patients, 60% had fatigue (FSMC ≥ 53), 35% had cognitive deficits (MUSIC < 19) and 29% had both. According to European regulations, the ATAVT, RT and VIGIL are passed when the individual is above the 16th percentile related to a norm sample. 26% of the patients failed the RT, 22% failed the ATAVT and 34% failed the VIGIL. The Student's t-test reveals that patients with Fatigue performed worse in the RT ($t(90)$ = 3,29, p < .01) and VIGIL ($t(86)$ = 2,61, p < .05) compared to patients without Fatigue. In the ATAVT there is no significant difference between the two groups ($t(90)$= 1,79, n.s.) . Patients, who suffer from cognitive impairment performed worse in the ATAVT ($t(90)$ = 2,82, p < .01) and the RT ($t(90)$ = 2,49, p < .05), but not in the VIGIL ($t(86)$ = 1,17, n.s.).

Conclusions: Sustained attention is indeed a distinctive aspect of fatigue in MS patients, whereas observational abilities in a traffic perception test are reduced according to cognitive dysfunction but not to fatigue. The two tests are simple to conduct and helpful to differentiate fatigue from cognitive deficits.

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Regression-based norms for the Symbol Digit Modalities Test: demographic effects on identification of impairment in Dutch multiple sclerosis patients

J Burggraaff[1], D Knol[2], B Uitdehaag[1]
[1]VU University Medical Center, Neurology, Amsterdam, Netherlands, [2]VU University Medical Center, Epidemiology and Biostatistics, Amsterdam, Netherlands

Background: The Symbol Digit Modalities Test (SDMT) has been recommended as a brief screening and follow-up tool to detect cognitive deficits in Multiple Sclerosis (MS). One of the weaknesses in implementing the SDMT in clinical settings is the reliance on published normative data, varying in size and quality, and poor generalizability. Recently an alternative approach has been proposed using regression-based norms, that enables controlling for the effect of demographic variables on test performance. Using that approach higher rates of impairment for SDMT could be identified in previous studies. We endeavoured to investigate the applicability of regression-based SDMT norms in a Dutch MS sample.

Objectives: To establish regression-based norms that account for demographic effects on test performance for SDMT in Dutch MS patients, and to compare impairment identification rates with original normative data.

Methods: We calculated regression-based norms for the SDMT by using the performance of 95 healthy volunteers (HV), controlling for multiple demographic variables (age, age[2], gender and education). The regression-based normative equations were applied to the performance of 157 MS patients and used to compute predicted SDMT scores, and in turn to generate Z- and T scores based on the raw performance. Original and regression-based normative data for the SDMT were compared in terms of impairment classification rates, using Z-scores derived from each norming method.

Results: MS patients were younger than controls, however demographically matched on all other variables. A final regression model included only age as predictor variable, since regression

analyses revealed that this was the only demographic characteristic significantly influencing SDMT performance. Regression-based norms for SDMT, more readily detected impairment on the domain of information processing speed in MS patients than existing normative based norms (28 versus 15; p < 0.001). This resulted in two more patients (18 versus 16) being ascribed as cognitively impaired on the extended neuropsychological test battery.

Conclusions: These results indicate that using regression-based norms for the SDMT, identifies higher rates of impairment on information processing speed in Dutch MS patients. For easier application in clinical settings we propose a simplification of earlier presented methods.

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Relative corpus callosum volume is related to decreased information processing speed in relapse-remitting multiple sclerosis patients

T Uher[1], J Blahova-Dusankova[1], M Tyblova[1], Z Seidl[2], M Vaneckova[2], J Krasensky[2], E Havrdova[1], D Horakova[1]
[1]Charles University in Prague, First Faculty of Medicine and General University Hospital, Department of Neurology and Center of Clinical Neuroscience, Prague, Czech Republic, [2]Charles University in Prague, First Faculty of Medicine and General University Hospital, Department of Radiology, Prague, Czech Republic

Background: Atrophy of corpus callosum is an important predictor of relapse activity and sustained disability progression in multiple sclerosis (MS) patients. However, there are only few large studies investigating relationship between cognitive functioning and corpus callosum pathology in patients with relapse-remitting (RR) MS on disease-modifying treatment (DMT).

Objectives: To investigate brain magnetic resonance imaging (MRI) structural correlates associated with cognitive functioning in RR MS patients on DMT.

Methods: All 396 patients of this cross-sectional study were tested with Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT-II), Brief Visuospatial Memory Test (BVMT-R) and Paced Auditory Serial Addition Test-3 (PASAT). In addition, MRI measures of T2 and T1 lesion volume (LV), brain parenchymal fraction (BPF), and relative corpus callosum volume (r-CC) (estimated as a ratio of corpus callosum volume to the whole brain volume) were performed. Uni- and multi-variate linear regression models adjusted for age at onset, gender, education, depression, disease duration and potential practice effect were used to calculate association between MRI measures and cognitive performance.

Results: The mean age of patients was 37.6 (±9.1) years, mean and median of disease duration were 10.2 and 7.1 years respectively and 262 (71%) of patients were women. Abnormal SDMT score was observed in 65 (18%) of patients. In univariate models, an association between cognitive performance and lower BPF (p= < 0.001), lower r-CC (p= < 0.001 - 0.019), higher T1 LV (p= < 0.001) and higher T2 LV, (p= < 0.001) was found. In a multivariate model, patients with lower r-CC (p = 0.033), lower BPF (p = 0.011) and higher T1 (p = 0.005) but not T2 lesion volume (p = 0.731) showed an independent association with SDMT score. There was also an independent relationship between higher T1 LV

(p = 0.015), lower BPF (p = 0.020) and decreased PASAT score. No significant relationships between MRI outcomes and memory deficit estimated by CVLT-II and BVMT-R measures were found in the multivariate models.

Conclusions: The present study showed an independent relationship between relative corpus callosum volume and cognitive functioning in patients with RR MS. This finding emphasizes the important role of corpus callosum pathology in information processing speed rather than memory deficit, supporting the findings of previous research.

P168

Are there differences on the measures in the minimal assessment of cognitive function in MS by race/ethnicity?

ES Gromisch[1], G Mascialino[2], V Zemon[1], AE Hirky[1,2], MA Picone[3], S Kim[3,4], FW Foley[1,3]
[1]Yeshiva University, Ferkauf Graduate School of Psychology, Bronx, NY, United States, [2]NYU School of Medicine, Department of Psychiatry, New York, NY, United States, [3]Holy Name Medical Center, Teaneck, NJ, United States, [4]NYU School of Medicine, Department of Rehabilitation Medicine, New York, NY, United States

Background: MS is an autoimmune disorder that is more common among Whites, but can occur in several racial/ethnic groups, including African-Americans and Hispanics/Latinos. Studies investigating the differences among racial/ethnic groups in MS have found greater risk of disability in African-Americans and more normal functioning in Hispanics/Latinos. In pediatric MS, African-Americans had worse performance in language and complex attention measures when compared to Whites.

Objectives: To investigate whether there were differences on the measures in the Minimal Assessment of Cognitive Function in MS (MACFIMS) by racial/ethnic groups.

Methods: All participants were MS patients at Holy Name Medical Center who signed research consent forms and underwent neuropsychological assessments using the MACFIMS (California Verbal Learning Test-II (CVLT-II), Brief Visuospatial Memory Test-Revised (BVMT-R), Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Additions Test 3-seconds (PASAT 3-s), Controlled Oral Word Association Test (COWAT), Judgment of Line Orientation (JOLO), and Delis-Kaplan Executive Functions System Sorting Test (D-KEFS Sorting). The majority were White (N = 83), with 11 African-American participants and 8 Hispanic/Latino participants. Education did not differ between the groups, and hierarchical loglinear analysis showed gender and MS diagnosis could be removed from the model. Multivariate analysis of covariance (MANCOVA) was run with the raw scores from the MACFIMS as criterion variables, race/ethnicity as a fixed factor, and age and Incapacity Status Scale (ISS) Total Score (disease severity) as covariates.

Results: African-Americans performed significantly lower on the PASAT-3-s (p < .05), JOLO (p < .01), and D-KEFS Sorting (p < .05). There were significant differences on the SDMT (p < .05) and PASAT 3-s (p < .05) between Hispanics/Latinos and Whites, but when disability was removed from the model, they were no longer significant (SDMT: p = .328, PASAT: p = .158).

Conclusions: There were significant differences in performance on the PASAT 3-s, JOLO, and the D-KEFS Sorting among racial/ethnic groups, particularly between Whites and African-Americans. While our study is limited by a low *N*, the results raise questions about cognitive differences and warrant further study.

P169
MS-Cortex study: the contribution of cortical lesions to cognitive impairment in patients with multiple sclerosis

O Geisseler[1], T Pflugshaupt[1,2], L Bezzola[3], K Reuter[1], B Schuknecht[4], P Brugger[1], M Linnebank[1]
[1]University Hospital Zurich, Department of Neurology, Zurich, Switzerland, [2]Luzerner Kantonsspital, Department of Internal Medicine, Centre of Neurology and Neurorehabilitation, Luzern, Switzerland, [3]University of Zurich, Institute of Psychology, Division of Neuropsychology, Zurich, Switzerland, [4]Medizinisch Radiologisches Institut, Zurich, Switzerland

Background: By now, cortical involvement in Multiple Sclerosis (MS) is well established. Studies showed that grey matter lesions occur frequently and early in all multiple sclerosis phenotypes. However, the impact on cognitive and clinical impairment is still ambiguous.

Objectives: The purpose of this study is to investigate differences in cognitive functioning between patients with and without cortical lesions.

Methods: An extended neuropsychological examination and structural MRI, including a double inversion recovery sequence were conducted in 48 relapsing-remitting MS patients and 48 healthy age-, education- and sex-matched controls (HC). In addition, all patients underwent a neurological examination. Lesion burden was analysed with *MRIcron*, cortical thickness with *Freesurfer*.

Results: Thirty-eight patients (79%) showed at least one cortical lesion, building the CL group. Thus, the non-cortical lesion group (nCL) consisted of 10 MS patients (21%). Highest cortical lesion occurrence was seen bilateral in the parahippocampal gyrus. The CL group scored significantly lower than the nCL group in tests assessing memory functions, but not in other cognitive domains. Furthermore, the CL group showed a significant thinner cortex than the nCL as well as the HC group. No significant differences were observed between the two patient groups with regard to EDSS score, disease duration or age at disease onset.

Conclusions: Here we suggest that cortical lesions play a crucial role in the memory performance of RRMS patients. In contrast, the presence or absence of cortical lesions seems unrelated to basic clinical variables such as disease duration or EDSS score.

P170
Cognitive performance at early stages of MS in a Portuguese sample: influence of depressive symptoms, cognitive fatigue and disease characteristics

MR Neves[1], C Sousa[2], AM Passos[1], A Ferreira[1], MJ Sá[2]
[1]Instituto Universitário de Lisboa (ISCTE-IUL), Lisboa, Portugal, [2]Hospital S. João, Neurology Department, Porto, Portugal

Background: Cognitive impairment (CI) is known to be high prevalent among Multiple Sclerosis (MS) patients - 40 to 60% - and it has a negative impact on their quality of life.

The CI profile in MS usually involves memory, complex attention, information processing speed and executive functions. Depression and fatigue are common symptoms in MS and primary determinants to impaired quality of life of these patients. No association has been found between reports of fatigue and CI but depressive symptoms are thought to interfere largely with cognitive activities.

Objectives: (1) To compare the cognitive performance (CP) of MS patients and healthy subjects; (2) To analyze the influence of clinical factors as fatigue, depressive symptomatology, age of diagnosis and EDSS on the CP of MS patients.

Methods: A total of 109 healthy subjects and 63 MS patients were examined with *Brief Repeatable Battery of Neuropsychological Tests* (BRBN-T), *Beck Depression Inventory*, *Brief Symptom Inventory* and the subscale of Fatigue/Thinking of *Hamburg Quality of Life Questionnaire in Multiple Sclerosis*. The MS group (19 male and 44 female) was mainly diagnosed with RRMS (88,1%) according to McDonald's criteria and had levels of impairment in EDSS between 0 and 7.

Results: A standardized measure for CP was constructed and significant differences were found between MS patients and healthy subjects (t= 3,04; p=0.003). The tests that compose BRBN-T also revealed significant differences between MS patients and control group, except for *Selective Reminding Test*.

A multiple regression analysis was performed to analyze whether clinical factors can predict CP. The resulting predictors included depressive symptomatology (β= -2,77; p=0,009), age of diagnosis (β= -0,18; p=0,006) and EDSS score (β= -0,83; p=0,063). This final model revealed that 22,2% of CP is explained by those variables ($F_{(3,57)}$= 6,42; p= 0,001).

Conclusions: The results indicate that decline on CP is present at the early stages of MS and there are significant differences in most of the tested cognitive domains. The processing speed seems to be the most commonly affected cognitive domain, being the slowness in the speed of information processing one of the main characteristics of the CI in MS.

A link between depressive symptoms and cognitive functioning was found, especially in aspects of cognitive functioning including processing speed and executive functioning. No association was found between cognitive fatigue and the performance on cognitive tests.

P171
Reaction time distributions in early-phase relapsing-remitting multiple sclerosis differ from controls

GT Howell[1], J-A LeFevre[1,2], LM Rees[1,3,4], LI Berrigan[5], LAS Walker[3,4,6]
[1]Carleton University, Department of Psychology, Ottawa, ON, Canada, [2]Carleton University, Institute of Cognitive Science, Ottawa, ON, Canada, [3]University of Ottawa, School of Psychology, Ottawa, ON, Canada, [4]Ottawa Hospital Research Institute, Ottawa, ON, Canada, [5]Dalhousie University, Department of Psychiatry, Halifax, NS, Canada, [6]University of Ottawa, Division of Neurology, Faculty of Medicine, Ottawa, ON, Canada

Background: The Computerized Test of Information Processing (CTIP) consists of three reaction time (RT) tasks that have been used to measure processing speed (simple RT, choice RT, and

semantic search RT). Contrary to previous studies, Berrigan, LeFevre, Rees, Berard, Freedman, and Walker (2013) did not find the typical pattern of mean RT differences on the CTIP between patients with multiple sclerosis (MS) and matched controls, potentially due to the MS group's early-phase relapsing-remitting diagnosis.

Objectives: In the present study, we explored whether Berrigan et al.'s (2013) MS sample would show subtle differences in the distribution of RTs on the CTIP tasks, despite the lack of mean RT differences. Indeed, previous research has shown that individuals with MS respond more variably in RT tasks than controls. Using a methodology novel to the field, we reanalyzed the RT data using an ex-Gaussian approach that decomposed the RT distribution into estimates of the location of the leading edge (mu), variability in the leading edge (sigma), and the size of the distribution's tail (tau). We hypothesized that the MS group would have a larger value for the two parameters related to variance (sigma and tau) than matched controls.

Methods: 70 early-phase relapsing-remitting MS patients and 70 healthy matched controls completed the CTIP twice as part of a test battery. The ex-Gaussian was fit to each participant's RTs separately for the three CTIP tasks.

Results: The MS and control groups did not differ in mu. In contrast, the difference in tau approached significance ($p = .08$, $\eta_p^2 = .02$). For the semantic search RT task, the difference in sigma approached significance ($p = .08$, $\eta_p^2 = .02$) and there was significantly more variability in the overall RT distribution ($p = .05$, $\eta_p^2 = .03$).

Conclusions: The ex-Gaussian analysis showed that patients with early-phase relapsing-remitting MS differed from controls in subtle aspects of RT distribution on the CTIP tasks, despite the lack of mean RT differences. The MS group tended to have a greater build-up of slower responses in the RT distribution's tail on all CTIP tasks. The MS group also tended to have more variability in the leading edge and in the overall RT distribution for the semantic search RT task. Using this methodology, future research should examine RT distribution differences for subtypes of MS that are more cognitively affected to develop an understanding of exactly what aspects of RT distribution vary across a wide range of groups.

P172

Predictivity of executive functions deficit on episodic memory disorder in multiple sclerosis

R Barthelemy[1,2], B Lenne[1,3], D Leuse[1], H Mecheri[3], A Kwiatkowski[1,4], P Hautecoeur[1,4]
[1]Hôpital Saint Vincent de Paul, Neurology, Lille, France, [2]Centre d'Études et de Recherche sur la SEP, Lille, France, [3]Universite Catholique de Lille, Faculté de Lettres et de Sciences Humaines, Lille, France, [4]Universite Catholique de Lille, Faculté de Medecine, Lille, France

Background: Cognitive impairment in Multiple Sclerosis (MS) is one of the main factors of disability and poor quality of life. Several cognitive functions could be damaged, such as information processing speed (IPS), attention or executive functioning (EF); but alteration of memory is the most observed and reported by patients. However, a memory deficit could reflect the presence of another cognitive deficit and vice versa.

Objectives: To determinate the influence of the other cognitive functions on episodic memory disorder in MS.

Methods: 411 patients (244 RRMS; 126 SPMS; 41 PPMS) were assessed by an extensive neuropsychological battery (BCcogSEP, Dujardin et al., 2004, a French adaptation of the BRB-N, Rao et al. 1991) including 8 tests assessing 7 cognitive functions. A step wise multivariate regression analysis has been applied to determinate which cognitive functions were the most predictive of the episodic memory deficit, according to the phenotype.

Results: 62% patients were identified as cognitively impaired by the multidimensional neuropsychological battery (getting 4 or more pathological scores). Considering all phenotypes, the episodic memory performance (mean retrieval and learning index) was predicted by working memory (WM) and IPS (PASAT; $p< 0.0001$, Symbol Digit Modalities Test; $p< 0.0001$), inhibition ability (Go/No Go Task; $p< 0.0001$) and verbal initiation (verbal fluency; $p< 0.0001$). Episodic memory seems more influenced by IPS in RRMS patients, IPS and EF in SPMS and WM in PPMS.

Conclusions: Processes involved in an episodic memory task (encoding, stocking, retrieval) require an implication of executive functions, as well as a timed test requires an IPS. In our study, IPS and EF appeared to be the ones predicting the most the episodic memory performance, whatever were the processes. This study emphasizes the differential implication of IPS and WM on learning abilities according to disease courses, which directs further cognitive rehabilitation procedures aiming an improvement of learning abilities

P173

The relationship between SDMT and everyday life performance: actual reality

Y Goverover[1], CD Nancy[2], J DeLuca[2]
[1]New York University, New York, NY, United States, [2]Kessler Foundation, West Orange, NJ, United States

Background: To date, most studies of the Symbol Digit Modalities Test (SDMT) examine its utility as a brief screening test that may identify patients with Multiple Sclerosis (MS) who would benefit from a more thorough cognitive assessment or treatment. However, few of these studies assess whether performance on the SDMT is associated with everyday life activities.

Objectives: The aim of the current study was to examine whether performance on the SDMT is associated with performance of everyday life activities, specifically purchasing cookies and purchasing flight tickets online using the Actual Reality (AR) assessment.

Methods: Participants consisted of 20 adults diagnosed with MS. Participants performed the SDMT and the AR tasks. For the AR task, participants were asked to use a computer to purchase airline tickets or cookies via the internet. Task performance was scored based on whether participants accurately performed the steps to complete the task, the type of cues needed to complete each step of the task and time to task completion. Lower scores indicated greater independence in task performance.

Results: SDMT scores were significantly associated with AR performance. Thus, slowed information processing speed (SDMT) was significantly associated with worse performance on the AR.

Conclusions: The everyday functional independence of individuals with MS is dependent on the ability to efficiently use everyday

resources to perform everyday tasks. Everyday functioning is associated with SDMT performance. Thus, the SDMT can provide a meaningful data related to functional status of an individual with MS.

Comorbidities and risk behaviors

P174
Does smoking influence MRI disease activity in multiple sclerosis?

SAS Kvistad[1], K-M Myhr[1], T Holmøy[2], S Bakke[3], A Beiske[4], K Bjerve[5], H Hovdal[6], KI Løken-Amsrud[7], F Lilleås[8], R Midgard[9], T Pedersen[10], J Šaltytė Benth[11], S Wergeland[12], Ø Torkildsen[12]
[1]Haukeland University Hospital, Neurology, Bergen, Norway, [2]Akershus University Hospital, Neurology, Oslo, Norway, [3]Oslo University Hospital, Department of Neuroradiology, Oslo, Norway, [4]Multiple Sclerosis Centre, Hakadal, Norway, [5]St. Olavs Hospital, Department of Medical Biochemistry, Trondheim, Norway, [6]St.Olav University Hospital, Neurology, Trondheim, Norway, [7]Innlandet Hospital Trust, Department of Neurology, Lillehammer, Norway, [8]Curato, Oslo, Norway, [9]Department of Neurology, Molde, Norway, [10]Unilabs, Drammen, Norway, [11]University of Oslo, Institute of Clinical Medicine, Oslo, Norway, [12]Haukeland University Hospital, Department of Neurology, Bergen, Norway

Background: Smoking is a risk factor for MS and previous studies have reported that smoking affect disease progression. So far, no study has explored the association between smoking and MRI disease activity.
Objectives: To study if smoking is associated with MRI-activity and relapse-rate in MS patients and examine if there is a dose-response correlation between smoking and MRI activity.
Methods: Cohort study of 87 patients based on a multicenter, double-blind, randomized, placebo-controlled trial of patients with RRMS according to the McDonald criteria, followed for 2 years (The OFAMS study). Serum levels of cotinine, a nicotine metabolite that is widely used as a biomarker for recent tobacco use, were analyzed using an immunoassay. Patients were divided into three groups according to mean cotinine level, -levels < 10 for non-smokers, 10-300 for active smokers and levels >300 for heavy smokers. We analyzed serum samples from patients at baseline and month 6, 12, 18 and 24. MRI assessments were made at baseline, months 6, 12 and 24 and included the count of T1 gadolinium enhancing (T1Gd+) lesions, T2 lesions and combined unique activity (CUA; the sum of T1Gd+ lesions and new or enlarging T2 lesions). Associations between cotinine level and MRI activity were assessed by a logistic regression model.
Results: 29 patients had cotinine levels < 10, 9 patients had cotinine levels between 10- 300 and 42 patients had cotinine levels >300. There was no significant association between cotinine levels and MRI activity. For patients with cotinine levels >300 the odds ratio for new T1Gd + lesions were 0.81 (95% CI 0.43-1.55; p=0.526), for new T2 lesions 0.86 (95% CI 0.42-1.75; p=0.672) and for CUA 0.92 (95% CI 0.46-1.84; p=0.816) compared to the non-smokers. Cotinine levels were not associated with clinical disease activity assessed by relapse-rate or EDSS score. The

results were not influenced by interferon-beta treatment. Adjustments for gender, age, HLA-DRB1*15 status, body mass index, vitamin D-levels, vitamin A-levels or ENBA-1 IgG titers did not affect the results.
Conclusions: We did not find any association between smoking and MRI- or clinical disease activity. To our knowledge no other study has addressed this issue. Our results indicate that smoking does not directly influence MRI activity or relapse-rate and thus probably increases the risk for disease development and progression through other mechanisms.

P175
Smoking and HLA genes impact on disease activity and severity before and during treatment with interferon-beta

ER Petersen[1], HB Soendergaard[1], JH Lauersen[1], N Koch-Henriksen[2,3], M Magyari[1,3], PS Sørensen[1], F Sellebjerg[1], AB Oturai[1]
[1]Copenhagen University Hospital, Rigshospitalet, Department of Neurology, Danish Multiple Sclerosis Center, Copenhagen, Denmark, [2]University of Aarhus, Department of Neuroepidemiology, Aarhus, Denmark, [3]Copenhagen University Hospital, Rigshospitalet, The Danish Multiple Sclerosis Registry, The Danish MS Research Center, Copenhagen, Denmark

Background: Smoking increases the risk of MS and disease progression. HLA genes also influence MS risk, and an interaction with smoking has previously been reported. However, the effect and interaction of smoking and HLA type on treatment response have not yet been investigated.
Objectives: To investigate if smoking status and HLA type are associated with disease activity and disease severity in interferon-beta (IFN-beta) treated relapsing-remitting MS (RRMS) patients.
Methods: Patients with IFN-beta as their first immune therapy were selected for the study. Clinical data from two years before start of IFN-beta therapy to either treatment stop or to the last follow-up examination was obtained from the Danish MS Treatment Register. Multiple sclerosis severity scale (MSSS) scores and the annualized relapse rate (ARR) were used to describe disease activity and severity. Smoking status was acquired through a questionnaire survey and *HLA-DRB1*15:01* and *HLA-A*02:01* were determined by tag SNPs measured by PCR analysis.
Results: 1404 RRMS patients were included in the study; 394 males and 1010 females. 653 had smoked in the two year period before treatment start and 472 smoked during IFN-beta treatment. 834 were *HLA-DRB1*15:01* positive and 550 were *HLA-A*02:01 positive*.

Multivariate analysis showed that the ARR in the two year period before treatment start was higher in women (p=0.008) and in younger patients (p< 0.001). At treatment start the MSSS was higher in patients with later age at disease onset (p< 0.001), in patients who started treatment at an early age (p< 0.001) and in patients who smoked in the two year period before treatment start; the more package years the higher MSSS (p=0.005). During IFN-beta treatment ARR was higher in patients who started treatment in an early age (p< 0.001) and there was interaction between *HLA-DRB1*15:01 and* smoking for higher ARR on treatment (p=0.005). The annualized MSSS increase during treatment was

highest among patients with a late age at onset (p=0.045) and there was an interaction between *HLA-DRB1*15:01 and smoking* for higher annualized MSSS increase on treatment (p=0.003).

Conclusions: This study demonstrates for the first time a higher disease activity and severity in MS patients who smoked before and during treatment with IFN-beta, and the effect seems to be modulated by HLA-DRB1*15:01. The previously reported interaction between HLA genes, smoking and MS susceptibility may thus extend to an effect on the disease course.

P176

Obesity interacts with infectious mononucleosis in risk of multiple sclerosis

L Alfredsson[1], AK Hedström[1], IL Bomfim[2], J Hillert[2], T Olsson[2]
[1]*Karolinska Institutet, Institute of Environmental Medicine, Stockholm, Sweden,* [2]*Karolinska Institutet, Department of Clinical Neuroscience, Stockholm, Sweden*

Background: Environmental risk factors influencing MS risk include a history of infectious mononucleosis (IM) and adolescent obesity. Obesity results in a state of immunodeficiency which may alter the way a pathogen induces an immune response.

Objectives: We aimed to investigate the possible interaction between adolescent obesity and past IM with regard to MS risk.

Methods: Our report was based on two population-based, case-control studies, one with incident cases (1780 cases, 3885 controls) and one with prevalent cases (4502 cases, 4039 controls). Subjects were categorized based on adolescent body mass index (BMI) and past IM and compared with regard to occurrence of MS, by calculating odds ratios (ORs) with 95% confidence intervals (CIs) employing logistic regression. A potential interaction between adolescent BMI and past IM was evaluated by calculating the attributable proportion due to interaction.

Results: Regardless of HLA status, a substantial interaction was observed between adolescent obesity and past IM with regard to MS risk. The interaction was most evident when IM after the age of 10 was considered (AP 0.8, 95% CI 0.6-1.0 in the incident study, and AP 0.7, 95% CI 0.5-1.0 in the prevalent study). In the incident study, the OR of MS was 14.7 (95% CI 5.9-36.6) among subjects with adolescent obesity and past IM after the age of 10, compared to subjects with none of these exposures. The corresponding OR in the prevalent study was 13.2 (95% CI 5.2-33.6).

Conclusions: An obese state both impacts the cellular immune response to infections and induces a state of chronic immune-mediated inflammation which may contribute to explain our finding of an interaction between adolescent BMI and past IM. Measures taken against adolescent obesity may thus be a preventive strategy against MS.

P177

Central nervous system demyelinating disease in patients with inflammatory bowel disease

M Novotna[1,2], KM De Felice[3], FT Enders[4], WA Faubion[3], LE Raffals[3], OH Kantarci[1]
[1]*Mayo Clinic, Neurology, Rochester, MN, United States,* [2]*International Clinical Research Center, St. Anne's University Hospital Brno, Brno, Czech Republic,* [3]*Mayo Clinic,*

Gastroenterology and Hepatology, Rochester, MN, United States, [4]*Mayo Clinic, Division of Biomedical Statistics and Informatics, Rochester, MN, United States*

Background: Anti-TNFα therapy can induce remission in inflammatory bowel disease (IBD) but presumably can induce or unmask multiple sclerosis (MS) and MS-like idiopathic inflammatory-demyelinating disease of the central nervous system (IIDD), or increase activity in existing MS. This poses a clinical challenge in patients with both MS and IBD especially with failure of other IBD directed treatments.

Objectives: To study whether anti-TNFα therapy increases the risk of MS in patients with IBD.

Methods: We retrospectively identified 10712 adult patients referred for IBD evaluation to the Mayo Clinic, Rochester, MN from a five state capture area (Minnesota, Wisconsin, North Dakota, South Dakota, and Iowa) between 1996 and 2010. In two randomly sampled subsets (n=200), average non-diagnosis frequency for IBD was 14.3% with a predicted confirmed diagnosis of IBD in 9181 patients (n=3750 with anti-TNFα, n=5431 without anti-TNFα). In patients with additional IIDD diagnoses, this was confirmed by clinical, laboratory and imaging reviews. Risk of IIDD in patients with and without anti-TNFα exposure was estimated for IBD, Crohn's disease (CD) and ulcerative colitis (UC) groups separately (Wilcoxon rank sum and Fischer exact tests as appropriate).

Results: The frequency of IIDDs in patients with and without anti-TNFα was; IBD: 0.15% and 0.18% (RR=0.83, 95%CI:0.28-2.42; p=0.729); CD: 0.19% and 0.22% (RR=0.89, 95%CI:0.24-3.31; p=0.863); UC: 0.07% and 0.15% (RR=0.49, 95%CI:0.06-4.22; p=0.510). Following IBD diagnosis (median follow-up: 10.5 years; IQR:17.4) and anti-TNFα initiation (median follow-up: 0.8 years; IQR:6.1), the number needed to treat to harm one patient was 3333 (4202 for CD; 1335 for UC patients). IIDDs were confirmed in 34 patients (19 before and 15 after IBD onset). Except for 2 patients with nonspecific demyelinating disease, 32/34 had definite MS (9/32 PPMS). Of the 15 patients with IIDD (14 MS) onset after IBD (5 with anti-TNFα, 10 without anti-TNFα), median age at diagnosis of IBD was 30.4 (IQR:17.1) years. Median age at first neurological symptom was 35.0 (IQR:18.3) years. Anti-TNFα exposure always happened before MS onset.

Conclusions: Anti-TNFα agents do not seem to impact the risk of developing clinical MS in patients with IBD. In the absence of anti-TNFα therapy, risk of coexistence of MS and IBD (0.3%) is comparable to the population-based prevalence of MS from the same region in 2000 (0.2%).

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Prescription drug use among patients with multiple sclerosis

LW Svenson[1,2,3], DP Schopflocher[1,3,4], SA Warren[5]
[1]*University of Alberta, School of Public Health, Edmonton, AB, Canada,* [2]*Alberta Ministry of Health, Surveillance and Assessment, Edmonton, AB, Canada,* [3]*University of Calgary, Community Health Sciences, Calgary, AB, Canada,* [4]*University of Alberta, Faculty of Nursing, Edmonton, AB, Canada,* [5]*University of Alberta, Faculty of Rehabiliation Medicine, Edmonton, AB, Canada*

Background: While much is known about the use of disease modifying therapies for MS, there is little information on the general use of prescription medication.

Objectives: The objective of this study was to quantify the use of prescription drugs among people with MS through the linkage of population-based administrative health data.

Methods: The province of Alberta maintains a publicly funded, universally available health care system. As part of this system, a population registry is maintained containing key demographics and a unique lifetime identifier. Data on physician visits, hospitalizations and emergency department visits are maintained by the Ministry of Health. All individuals receiving one or more services for MS (ICD-9 340 or ICD-10 G35) were extracted from these databases for the period 1985 to 2013. To reduce the risk of false positive cases, a case was defined as having three or more physician visits or a single hospitalization or a single emergency department visit with MS coded. Prevalent cases in 2012 were then linked to the Alberta Pharmacy Information Network which contains records for all prescription drugs dispensed by community pharmacies. Drugs dispensed in 2013 were classified into 12 categories based on the Anatomical Therapeutic Chemical (ATC) Classification System. logistic regression was to compare those with and without MS to assess odds of receiving a given drug class.

Results: As of 2012, there were 9,354 cases of MS identified among those aged 20 and older. Females were more likely to have filled at least one prescription during 2013 (OR = 2.2, 95% CI: 2.1, 2.3). Among the 12 categories used, MS patients were more likely to fill prescriptions for alimentary tract (OR = 1.1, 95% CI: 1.1, 1.2), genitourinary (OR = 1.7, 95% CI: 1.6, 1.8), hormonal (OR = 1.1, 95% CI: 1.1, 1.2), anti-infective (OR = 1.1, 95% CI: 1.0, 1.1), musculoskeletal (OR = 1.4, 95% CI: 1.4, 1.5), and nervous system (OR = 2.8, 95% CI: 2.7, 2.9). MS patients were less likely to receive drugs for cardiovascular disease (OR = 0.8, 95% CI: 0.76, 0.84), anti-parasitic (OR = 0.8, 95% CI: 0.7, 0.9), respiratory (OR = 0.9, 95% CI: 0.8, 0.9), and sensory system (OR = 0.9, 95% CI: 0.86, 0.99).

Conclusions: MS patients were more likely to fill a prescription for 6 of the 12 drug groupings used and less likely to fill a prescription for four of the groupings. Based on the therapeutic groupings, the prescription drugs used appear to be consistent with the treatment of common MS co-morbidities.

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Comorbidities in patients with multiple sclerosis compared with the general population: retrospective analysis of the US MarketScan Database

G Capkun[1], R Lahoz[1], W Chen[2], A Moore[1], D Bischof[1], Y Geissbuehler[1], F Dahlke[1]

[1]*Novartis Pharma AG, Basel, Switzerland,* [2]*Novartis Pharma Co. Ltd, Shanghai, China*

Background: Limited data are available regarding comorbidities in patients with multiple sclerosis (MS). Results from a retrospective study using the US Department of Defense (DOD) database suggest that patients with MS are at greater risk of certain comorbidities vs the general population.

Objectives: To compare event rates (ERs) for selected comorbidities in real-world MS and matched non-MS cohorts from another US database and to validate the results of the DOD database.

Methods: The MarketScan Research administrative claims database, including data for >130 million people, was used to identify an MS cohort between 1 Jul 06 and 31 Mar 12. Treated and untreated patients aged 18-64 years with >=2 ICD-9 MS codes separated by >=30 days (second claim was the index date); and >=1 year of pre-index continuous health plan enrolment were included. A non-MS cohort comprised of individuals matched (10:1) for age and sex, enrolled in the calendar year of the corresponding MS patient's index date with 1 year of pre-index enrolment. ERs per 1000 patient-years for each cohort and crude ER ratios (ERRs) to compare ERs were calculated for comorbidities of interest (identified using ICD-9 codes in the follow-up period).

Results: The study included 49,231 and 492,310 individuals in the MS and non-MS cohorts, respectively. Mean ages were 47 years and 76.2% were women. Mean follow-up time in the MS and non-MS cohort was 999 and 1319 days, respectively. Cardiovascular events (ERR, 95% confidence interval; ischaemic stroke: 3.5, 3.2-3.7; hypertension: 1.2, 1.2-1.3; myocardial infarction: 1.7, 1.6-1.8), some infections and autoimmune disorders (any opportunistic infections: 3.3, 3.2-3.4; herpes virus infections: 1.4, 1.3-1.4; systemic lupus erythematosus: 2.3, 2.1-2.5) and certain malignancies (lymphomas: 1.6, 1.4-1.8; skin neoplasms: 1.2, 1.1-1.2; thyroid cancer: 1.4, 1.2-1.6) were significantly more common in the MS vs non-MS cohort. ERs for breast cancer were similar in both cohorts (1.1, 1.0-1.2). These ERRs are consistent with those from the DOD database, although ERs for each cohort tended to be lower in the MarketScan vs DOD database.

Conclusions: ERs of comorbidities, such as ischaemic stroke and opportunistic infections, were higher in patients with MS vs those without MS, which is of clinical relevance. These results are in line with those from the DOD database (presented previously) suggesting differences in the health profiles of patients with MS relative to the general population.

P180

Low prevalence of sleep disorders in demyelinating disease

M González-Platas[1], J González-Platas[2], M Bermúdez-Hernández[3], MY Pérez-Martín[1], C Croissier-Elías[1], P Pérez-Lorensu[4]

[1]*Hospital Universitario de Canarias, Servicio de Neurología, La Laguna, Spain,* [2]*Universidad de La Laguna, Facultad de Física, La Laguna, Spain,* [3]*Universidad de La Laguna, Facultad de Psicología, La Laguna, Spain,* [4]*Hospital Universitario de Canarias, Servicio de Neurofisiología, La Laguna, Spain*

Background: Sleep disorders are seen in patients with demyelinating disease (DD) more often than in the general population. Combination of physical and psychological factors such as pain, spasms, nocturia, depression, anxiety or medication effects could contribute to sleep disruption. The more common sleep disorders include insomnia, sleepness, sleep apnea, restless legs syndrome (RLS) or narcolepsy. Frequently, these disturbances have a major impact on health and quality of life (QoL) of patients to be associated with increased risk of mortality, obesity, cardiac disease or increased fatigue and depression.

Objectives: Estimate the prevalence of sleep disorders in patients seen in the DD consultation and the relationship of sleep disorder and QoL and fatigue.

Methods: 240 patients were included; mean age 43±11 years, 187 women. 163 patients with multiple sclerosis (MS): 144 relapsing-remitting (RR), 14 secondary progressive (SP) and 5 primary progressive (PP). 36 clinically isolated syndrome (CIS), 26 Radiological isolated syndrome (RIS) and 15 patients with others DD. All participants completed next questionnaires: Pittsburgh, Epworth and Standford scales, indirect symptoms of RLS and Obstructive Sleep Apnea (OSA), Fatigue Severity Scale (FSS) and Multiple Sclerosis Quality of Life-54 (MSQoL-54).

Results: Moderate/severe insomnia 12.5%, OSA 5.8%, RLS 9.6% (confirmed three cases), narcolepsy 0, fatigue (>4) 24.6%. Physical QoL 66.6±19.6, Mental QoL 66.1±21.9. Patients with an established diagnosis showed higher scores on insomnia compared to the group of CIS and RIS (F=3.85; p=0.023) but no differences were found in the other parameters. Fatigue showed high correlation with insomnia (r=0.443; p< 0.001), RLS (r=0.513; p< 0.001) and sleepiness $(r$=0.211; p=0.001). None of the variables included in the regression model were shown to be predictors of Physical and Mental QoL.

Conclusions: A high percentage of our sample sleeps well. Emphasize the low prevalence of sleep disorders (insomnia, fatigue, RLS,etc). We detected an overestimation in the RLS questionnaire and the low QoL recorded. As limitation, the inclusion of high number of early forms of DD with associated possible signs of anxiety pre-diagnostic uncertainty.

P181

Higher weight in adolescence and young adulthood is associated with an earlier age at MS onset

KS Kavak[1,2], BE Teter[1,2,3], J Hagemeier[4], K Zakalik[1,2], B Weinstock-Guttman[1,2,3]

[1]Jacobs Comprehensive MS Treatment and Research Center, Buffalo, NY, United States, [2]New York State MS Consortium, Buffalo, NY, United States, [3]State University of New York at Buffalo, Department of Neurology, Buffalo, NY, United States, [4]Buffalo Neuroimaging Analysis Center, Department of Neurology, Buffalo, NY, United States

Background: Although there seems to be growing evidence of an association between adolescent obesity and increased risk of multiple sclerosis (MS), it has yet to be determined if weight also influences the age at MS onset.

Objectives: In this study, we set out to retrospectively investigate whether higher weight or body mass index (BMI) in adolescence and young adulthood is associated with age at MS symptom onset in a sample of women with a clinical diagnosis of MS.

Methods: Our sample is comprised of a sub-group of 184 women registered with the New York State MS Consortium (NYSMSC) who completed an extensive questionnaire about reproductive events and are treated at our MS care center. Subjects were asked to recall their weight (in lbs) at the time of first menstruation and at age 25. BMI was calculated accordingly for age 25 but not extended to time of first menstruation, since height measures in adolescence could not reliably be deduced. Regression analyses were carried out to investigate the association between weight or BMI as a continuous measure, and age at MS onset. Additionally, overweight and non-overweight people at age 25 were compared based on a division of BMI ≥ 25 vs. < 25.

Results: Weight of subjects at their first menstruation was significantly related to younger age at symptom onset (β=-.073, p=.001). These results were also found at age 25 for weight (β= -.080, p< .001) and BMI (β=-.448, p=.001). Significantly earlier disease onset (26.9 years SD=9.9) was observed in subjects being overweight at 25 compared to those who were not overweight (32.1 years SD=9.2, p=.006).

Conclusions: Women who reported having a higher weight in adolescence and BMI in early adulthood were younger at MS symptom onset. Future research is warranted to investigate whether there is a direct causal link between body weight and MS in order to potentially influence lifestyle and dietary habits.

P182

Alcohol-use disorders and multiple sclerosis risk: a national record-linkage study

J Pakpoor[1], R Goldacre[2], G Disanto[3], G Giovannoni[3], M Goldacre[2]

[1]University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom, [2]University of Oxford, Unit of Health-Care Epidemiology, Nuffield Department of Population Health, Oxford, United Kingdom, [3]Queen Mary University of London, Barts and the London School of Medicine and Dentistry, Blizard Institute, London, United Kingdom

Background: Few studies have investigated the relationship between alcohol and MS risk, and these have often been limited by small sample sizes and inconsistent results. It has recently been reported that alcohol consumption exhibits a dose-dependent inverse association with MS risk.

Objectives: We aimed to determine if individuals with alcohol-use disorders, who may be presumed to consume large quantities of alcohol, have an altered MS risk compared to the general population.

Methods: A record-linkage study was conducted using linked datasets of English Hospital Episode Statistics (HES) (records of every episode of hospital admission and day case care in all English National Health Service hospitals) and death registrations for England from January 1999 to December 2011. Three cohorts of people with a record for alcohol use (10156 people), alcohol abuse (255827 people) and alcohol dependence (281305 people) were constructed by identifying the first recorded episode in which either condition was a diagnosis. A reference cohort was constructed of people admitted for various other minor medical and surgical conditions (6.7 million people). We then searched for any subsequent hospital care for, or death from, MS in these cohorts. The rate ratio was then calculated.

Results: There was a significantly increased risk of MS following alcohol use (p=0.003), alcohol abuse (p< 0.0001) and alcohol dependence (p=0.001). Considering the possibility of reverse causality we found an elevated risk of MS within one year of first admission for alcohol abuse only (p< 0.0001), but not for alcohol use or dependence (p=0.81 and p=0.25 respectively). Further, there was a significantly elevated risk of MS following alcohol use, abuse and dependence (p< 0.0001, p=0.003 and p=0.003 respectively) with a time interval of more than one year from first admission with the alcohol-use disorder. The association between alcohol-use disorders and risk of MS was more evident in males than females.

Conclusions: This study supports the presence of a significant positive association between alcohol-use disorders and MS risk, particularly in men. The strengths of this study are the prospective design and the enormous size of the HES database. The likely much higher levels of toxicity and alcohol dependency in our study may be associated with MS. Clinical advise with regard to alcohol consumption and MS remains largely speculative, and long-term follow-up studies are required to ascertain the relationship.

P183

The metabolic syndrome in disabled multiple sclerosis patients: prevalence and characteristics

M Livne[1,2], O Pinhas-Hamiel[2,3], G Harari[4], A Achiron[1,2]
[1]*Sheba Medical Center, Multiple Sclerosis Center, Ramat Gan, Israel,* [2]*Sackler School of Medicine, Tel-Aviv, Israel,* [3]*Sheba Medical Center, Pediatric Endocrinology, Ramat Gan, Israel,* [4]*Medistat, Tel-Aviv, Israel*

Background: Scarce information is available about the association of metabolic commodities and disability in patients with multiple sclerosis (MS).
Objectives: To examine the prevalence of the metabolic syndrome (MetS) and characterize its components in MS patients with significant disability.
Methods: The study enrolled MS patients suffering from significant disability with Extended Disability Status Scale (EDSS) score between 3.0 and 7.5. Medical history was obtained by an interview and data included demographic and clinical variables, weight, height, waist circumference (WC), blood pressure, fasting glucose, triglycerides, and HDL-C levels. BMI was calculated as weight (kg) divided by square of height (m²), and WC was measured with a soft tape on standing patients midway between the lowest rib and the iliac crest. MetS was defined according to the US National Cholesterol Education Program: Adult Treatment Panel III (NCEP/ATP III) criteria as the presence of any three of the following five components 1) central obesity as measured by WC (males >102 cm, females >88 cm), 2) triglycerides (TG) ≥150 mg/dl, 3) HDL-C < 40 mg/dl for males and < 50 mg/dl for females, or treated dyslipidemia 4) blood pressure >135/85 or treated hypertension, and 5) fasting glucose ≥100 mg/dl or known type 2 diabetes. Statistical analysis was performed by the SAS software.
Results: The study cohort comprised 130 MS patients, 72% females, mean±SD age 55.8±6.0 years, range 45-65 years, disease duration 18.2±10.1 years, EDSS 5.5±1.0. The prevalence of MetS was 36.9% with no gender difference. 55.9% had central obesity by WC, 28 % had treated hypertension, and 45.8% had elevated blood pressure, 11% had type 2 diabetes mellitus and 36.4% had hyperglycemia, 31.4% had treated dyslipidemia and 28.8% had elevated TG level, 31.4 had low HDL-C. MS patients with the MetS were significantly older (59.0±5.5 vs 53.8±5.5, years p< 0.0001), heavier BMI 29.0±6.9 vs 25.1±4.7 p=0.0009). There were no differences between groups in relation to neurological disability by the EDSS (5.7±1.0 vs. 5.4±1.0), disease duration (18.4±9.9 vs18.2±10.2 years) and number of steroid courses (6.6±9.5 vs. 6.3±8.4).
Conclusions: Significant number or MS patients have increased risk for cardiovascular morbidity as reflected by the prevalence of

MetS. This increased risk is associated with older age but not with gender, disease duration or degree of disability, suggesting a non-disease related effect.

P184

Burden of comorbidities in patients with incident multiple sclerosis prior to and following diagnosis: a nationwide population study

I-J Chou[1,2,3], C-F Kuo[4,5], WP Whitehouse[2], R Tanasescu[1], CS Constantinescu[1]
[1]*Division of Clinical Neuroscience, School of Medicine, University of Nottingham, Nottingham, United Kingdom,* [2]*Division of Child Health, Obstetrics and Gynaecology, School of Medicine, University of Nottingham, Nottingham, United Kingdom,* [3]*Division of Paediatric Neurology and Paediatric General Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan, Republic of China,* [4]*Division of Rheumatology, Orthopaedics and Dermatology, School of Medicine, University of Nottingham, Nottingham, United Kingdom,* [5]*Division of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital, Taoyuan, Taiwan, Republic of China*

Background: Comorbidities in individuals with multiple sclerosis (MS) may delay diagnosis and the accumulation of comorbidities over time add complexity of management. A better understanding of comorbid illness in MS may improve patient outcomes.
Objectives: To determine (1) the burden of comorbidities in incident patients with MS at diagnosis and (2) risk of developing new comorbidities after diagnosis.
Methods: We identified 2637 incident MS patients and 10207 matched controls from 1997 to 2005 using the Clinical Practice Research Data-link. Odds ratios (ORs) for Charlson comorbidity index and pre-specified comorbidities before MS diagnosis and hazard ratios (HRs) for development of incident comorbidities and all-cause mortality following diagnosis of MS were estimated.
Results: The association between MS and Charlson comorbidity index prior to diagnosis was dose-dependent with adjusted ORs (95% confidence intervals [CIs]) of 1.22 (1.09–1.36) and 1.86 (1.39–2.48) for the score categories of 1-2 and ≥3 (p_{trend} < 0.001), respectively. Most patients (87.26%) had diagnosis of neurological diseases other than MS prior to diagnosis. MS was associated with ORs (95% CI) of 17.19 (9.77-30.23) for hemiplegia and 2.24 (1.61-3.12) for cerebrovascular diseases. Cardiac arrhythmias, peripheral vascular disease, depression and anaemia were also more common in people with incident MS in the adjusted model. Cumulative probabilities of having a Charlson comorbidity index ≥ 1 at diagnosis and 5 year after diagnosis were 21.99% and 30.30% for MS patients and 17.32% and 25.21% for controls. MS was also associated with an adjusted HR (95% CI) of 1.08 (1.01–1.16) for having a Charlson comorbidity index ≥ 1. After adjusting for age, sex, index year, BMI class, smoking status, alcohol consumption and Charlson comorbidity index at diagnosis, MS was associated with a hazard ratio (95% CI) for all-cause mortality of 1.73 (1.50-2.00).
Conclusions: The majority of MS patients already have neurological diagnosis prior to the initial diagnosis. MS was associated

with greater comorbidity burden at diagnosis and the risk of incident comorbidity continues to rise following diagnosis.

P185
Smoking, systemic inflammation and T-cell reactivity in patients with multiple sclerosis and healthy controls

C Ammitzboell[1], LS Börnsen[1], HB Soendergaard[1], R Ratzer[1], MR Von Essen[1], PS Sorensen[1], JR Christensen[1], FT Sellebjerg[1]
[1]Copenhagen University Hospital, Rigshospitalet, Danish Multiple Sclerosis Centre, Department of Neurology, Copenhagen, Denmark

Background: Recent studies found evidence that systemic inflammation and peripheral activated T cells correlates with neuroinflammation, axonal damage and disease progression in patients with progressive multiple sclerosis (MS). Smoking is one of the environmental factors associated with the development and progression of MS. Furthermore smoking affects the immune system. How smoking affects the innate immune system and T cell autoreactivity needs further investigation.

Objectives: To study whether smoking is associated with systemic immune activation and T cell autoreactivity in MS patients and healthy controls (HC).

Methods: Initially, gene expression in peripheral blood mononuclear cells (PBMC) from 33 smoking and non-smoking MS patients was analyzed using Affymetrix microarrays. Furthermore, we collected blood samples from 100 smoking and non-smoking HC. CRP and cytokines were measured in serum, and freshly isolated PBMCs were CFSE stained and cultured with myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), EBV cell lysate, uninfected cell lysate or without antigen. Flow cytometric analysis was performed at day 7, after staining the PBMCs with flourochrome conjugated antibodies. Surface markers CXCR3, CCR6, CXCR5, and the cytokines interferon-gamma, IL17A, IL-21 and GM-CSF were determined in antigen-reactive CD4 T cells.

Results: We found 32 genes differentially expressed between smoking and non-smoking MS patients. Signaling pathway analysis revealed a network dominated by proinflammatory molecules in smoking MS patients. Concentrations of CRP (p=0.002) and interleukin-6 (p=0.003) were increased in serum in smoking versus non-smoking HCs. We found no difference in MBP, MOG and EBV-induced CD4+ T cell reactivity between smoking and non-smoking HC.

Conclusions: Smoking increases the expression of genes involved in proinflammatory pathways in MS patients and is associated with increased CRP and IL-6 concentrations in HCs. Smoking does not induce CD4+ T cell antigen specific immune responses in peripheral blood from HCs.

P186
Tobacco influence in the clinical progression of multiple sclerosis

S Batista[1], Z Argyropoulou[2], I Correia[1], C Nunes[1], C Macário[1], L Sousa[1]
[1]Centro Hospitalar e Universitário de Coimbra, Neurology, Coimbra, Portugal, [2]Faculty of Medicine, University of Coimbra, Portugal, Neurology, Coimbra, Portugal

Background: Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). Tobacco smoking has already been linked to an increased risk of MS but the association between smoking and progression of MS has not been fully clarified.

Objectives: The aim of this study was to investigate the effects of smoking on MS-related disability and quality of life.

Methods: A total of 120 MS patients were recruited consecutively from the follow-up consultations during a three-month period. All participants underwent a structured interview to assess smoking history: current smoking status, age of starting and quitting, and average number of cigarettes smoked per day. Patients were classified according to their current smoking status as non-smokers, current-smokers, past-smokers and second hand-smokers. Regarding the smoking status at disease onset they were classified as regular and non-smokers. Clinical and demographic data of all participants was obtained and MusiQol questionnaire was used to assess quality of life.

Results: The sample consisted of 73,3% female patients, with a mean age 44,05 (±12,56) years, mean disease duration 12.27 (± 10.35) years, 87,5% with a Relapsing-Remitting MS (RRMS) and 12,5% a Secondary-Progressive MS (SPMS). Considering the current smoking status, 18,3% patients were current-smokers, 47,5% non-smokers, 22,5% past-smokers and 11,7% second hand-smokers. Regarding the smoking status at MS onset, 26,7% were regular-smokers. Age of MS onset was lower in regular-smokers compared to non-smokers (29,53 ±10,04 vs 34,19 ±10,10; *p*=0,031). When analysing the impact of the current smoking status on EDSS accordingly the clinical subtype, we did not find any significant association in RRMS group. However, in SPMS the median EDSS was significantly higher in ever-smokers (7.0) and second hand-smokers (6.8) compared to non-smokers (5.5) (*p*=0,012). There was a significant correlation of EDSS with pack-year after disease onset (r=0,214; p=0.028) and smoking duration after disease onset (r=0,387; p=0,026). Current and second hand-smokers presented worse scores in some dimensions of MusiQoL compared to past and non-smokers: Relationship With Family (*p*=0,019) and Sentimental-Sexual Life (*p*=0,03).

Conclusions: This study suggests that smoking is associated with an earlier MS onset and worse long term prognosis, accumulating more disability and presenting inferior quality of life. In addition, smoking cessation is associated with a beneficial effect in the disease evolution.

P187
Prevalence and predictors of substance abuse in multiple sclerosis

N Brennecke[1], AL Boster[2,3], AM Wehr[4], JA Nicholas[2,3]
[1]Ohio State University College of Medicine, Columbus, OH, United States, [2]Ohio State University, Department of Neurology, Columbus, OH, United States, [3]Ohio State University Multiple Sclerosis Center, Columbus, OH, United States, [4]Ohio State University, Department of Biostatistics, Columbus, OH, United States

Background: Patients with multiple sclerosis (MS) have been shown to be more likely to engage in adverse health behaviors and suffer from depression relative to the general population, creating

interest in the prevalence and risk factors for substance abuse among this patient population.

Objectives: To assess the prevalence of substance abuse among MS patients in a large, academic MS clinic and to identify predictors associated with substance abuse.

Methods: MS patients presenting for routine clinic visits at The OSU MS Center were invited to voluntarily and anonymously participate by completing the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) and a demographic questionnaire to obtain data on age, sex, race, education, employment status, marital status and disability. Substance abuse was defined as any patient who stated that use of a substance (alcohol, tobacco, cannabis, cocaine, amphetamine, inhalants, sedative, hallucinogens, opiods or other) led to social, legal or financial problems in the past 3 months and/or failed to do what was expected of them because of substance use. A multivariate logistic regression model using backward selection was performed to identify predictors of substance abuse.

Results: A total of 255 MS patients were included in the study. Baseline demographics: 83% Relapsing Remitting MS, 82% Caucasian, 10% African American, 65% married, 77% female and 31% were between the ages of 36-45. A total of 29 patients (12%) were identified to have current substance abuse, 208 (88%) did not currently abuse substances and 18 were excluded due to missing data. Additionally, 87% utilized some substance in their lifetime of which 48% used a substance other than tobacco or alcohol. Employment status was found to be a significant predictor of current substance abuse. For unemployed patients with MS, the odds of current substance abuse was 4.67 times that of an employed patient with MS (95% CI: 1.99-10.97; p=0.002).

Conclusions: Substance abuse is present in the MS patient population. Unemployment significantly increased the risk of current substance abuse. Race, age, sex, MS disease course, disability and marital status were not significant predictors of substance abuse. Larger studies are needed to confirm the results obtained from this study. Since substance abuse may adversely affect MS patient health and ability to remain adherent to MS disease modifying therapy, screening for substance abuse should be considered by MS specialists, especially among patients who are unemployed.

P188

Elevated adiponectin levels induce pro-inflammatory responses in both myeloid cells and T-cells: linking adiposity and predisposition to pediatric MS

M Nyirenda[1], L Poliquin-Lasnier[1], H Hanwell[2], A Saveriano[1], A Rozenberg[1], R Li[1], CS Moore[1], C Belabani[3], T Johnson[3], J O'Mahony[2], RA Marrie[4], S Dunn[5], B Banwell[6], A Bar-Or[1,3]
[1]Neuroimmunology Unit, Montreal Neurological Institute, McGill University, Montreal, QC, Canada, [2]Neurosciences and Mental Health, Hospital for Sick Children Research Institute, Toronto, ON, Canada, [3]Experimental Therapeutics Program, Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada, [4]Departments of Internal Medicine and Community Health Sciences, University of Manitoba, Winnipeg, MB, Canada, [5]University Health Network, Toronto, ON, Canada, [6]Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, United States

Background: Overweight and obesity in childhood and early adolescence has been associated with an increased risk of MS in both adult and pediatric populations. However, the underlying pathobiology behind this association remains unknown.

Objectives: To examine whether altered secretion of adipose tissue hormones (adipokines) explain the association between adiposity and MS in a pediatric cohort, wherein we have previously identified an association between higher body mass index (BMI) percentiles and increased likelihood of MS outcome.

Methods: Levels of leptin, resistin, visfatin, and ghrelin (luminex) as well as adiponectin (total, and isoforms; ELISA) were blindly quantified in batch, in serum samples obtained from children (< 16 years old) presenting with incident acquired demyelinating syndromes (ADS), as part of the prospective Canadian Pediatric Demyelinating Disease Study. Results from children subsequently diagnosed with MS (ADS-MS; n=40) were compared to results from children remaining with monophasic ADS (ADS-Mono; n=119) or healthy controls (HC; n=29). The impact of adiponectin-containing pediatric MS sera was assessed on activated CD14+ myeloid cells (expression of CD80, CD83, CD86, TNFα and IL-6) and on CD4+ and CD8+ T cells (expression of IFNγ and IL-17), using flow cytometry and ELISA.

Results: Children with ADS-MS exhibited significantly higher levels of serum adiponectin compared to children with ADS-Mono (p = 0.0001) and HC children (p = 0.0002), independent of sex or age at ADS presentation. Elevated levels of low molecular weight (LMW) and medium molecular weight (MMW) adiponectin isoforms accounted for the increased levels of total adiponectin in the children with MS compared to the children with ADS-Mono (LMW; p = 0.0002; MMW: p = 0.0001) and the HC children (LMW; p = 0.0025; MMW: p = 0.0013). Pediatric MS serum induced adiponectin-dependent enhanced expression of CD80, CD83, CD86, IL-6 and TNFα by CD14+ monocytes, and increased expression of IFNγ by both CD4+ and CD8+ T cells. The enhanced T cell pro-inflammatory responses mediated by adiponectin in pediatric MS serum appeared to represent the combination of a direct effect on T cells, and an indirect effect mediated through myeloid cells.

Conclusions: Our findings suggest that elevated levels of adiponectin may contribute to an enhanced inflammatory state of both innate and adaptive immune responses involved in early disease mechanisms of childhood-onset MS.

P189

Investigating healthy lifestyle behaviors in multiple sclerosis: the role of neurological reserve and implicit processes of understanding

CE Schwartz[1,2], A Ayandeh[1,2], JD Rodgers[3], P Duberstein[4,5], B Weinstock-Guttman[3], RH Benedict[3]
[1]DeltaQuest Foundation, Concord, MA, United States, [2]Tufts University Medical School, Medicine and Orthopaedic Surgery, Boston, MA, United States, [3]University of Buffalo, Department of Neurology, Buffalo, MA, United States, [4]University of Rochester Medical Center, Psychiatry, Rochester, NY, United States, [5]University of Rochester Medical Center, Rochester Health Care Decision Making Group, Rochester, NY, United States

Background: Neurological reserve may slow disease progression in multiple sclerosis (MS), and is associated with not engaging in

destructive health behaviors. Lifestyle behaviors are important in MS, but research on lifestyle has been hampered by an inadequate conceptual frame. To address this problem, we propose viewing lifestyle behaviors from the perspective of neurological reserve theory. We introduce a new concept, implicit processes of understanding, comprised of social understanding, physical disability insight, and somatic awareness.

Objectives: We investigated the relationship between active (current) and passive (premorbid) neurological reserve, implicit processes of understanding, and healthy lifestyle behaviors.

Methods: This cohort study includes MS clinic patients and their caregiver-informants (n=118 pairs). Measures included a neurologist-administered EDSS; patient- and informant-completed self-report measures, and a heartbeat-perception test (interoception). Patient-Other congruence assessed implicit processes of understanding: Social Understanding (neurocognitive and personality); Physical Disability Insight; and Somatic Awareness (interoception).

Results: Active Reserve and Social Understanding were independent predictors of Healthy Lifestyle Behaviors ($R^2_{Adjusted}$=0.18; small effect sizes). Passive reserve, Physical Disability Insight, and Somatic Awareness had small effect-size associations with Healthy Lifestyle Behaviors.

Conclusions: Active Reserve and implicit processes of understanding are relevant to healthy lifestyle behaviors. Implications for lifestyle-changing interventions are discussed.

P190
Concomitant diseases and MRI outcomes in multiple sclerosis

R Zivadinov[1,2], B Raj[1], M Ramanathan[2], B Teter[2], J Durfee[1], M Dwyer[1], N Bergsland[1], D Hojnacki[2], B Weinstock-Guttman[2]
[1]State University of New York, Buffalo Neuroimaging Analysis Center, Buffalo, NY, United States, [2]State University of New York at Buffalo, Neurology, Buffalo, NY, United States

Background: While concomitant diseases occur in association with multiple sclerosis (MS), no studies utilized sensitive magnetic resonance imaging (MRI) measures to investigate their effect on central nervous system (CNS) disease outcomes.

Objectives: To investigate MRI characteristics of MS patients with or without concomitant diseases.

Methods: Conventional and non-conventional 1.5T MRI was obtained in a large cohort of 857 MS patients registered with the New York State MS Consortium. Presence of 15 concomitant diseases and 5 aggregate disease categories (presence of one concomitant, multiple concomitant, Th1-mediated, Th2-mediated, and non-Th mediated diseases) were tested against the general non-concomitant disease MS population with respect to MRI characteristics. Analyses were performed on each disease and category. The Th1 mediated disease included: systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease, diabetes mellitus type 1, manic depressive illness, psoriasis, allergies, thyroiditis and myasthenia gravis. The Th2 mediated diseases included asthma and ulcerative colitis, while non-Th-mediated disease included cancer, diabetes mellitus type 2, epilepsy, irritable bowel syndrome migraine and chronic obstructive pulmonary disease. The MRI outcomes included lesion, atrophy magnetization

transfer ratio (MTR) and diffusion-tensor imaging (DTI) measures. The analyses were corrected for multiple comparisons.

Results: Of the 857 MS patients included in the study, 43.5% had one and 10.5% had multiple concomitant diseases. Of those, 17.2% were Th1 mediated, 5.6% were Th2 mediated and 28.4% were non-Th mediated. The presence of one or more concomitant diseases had a significant effect on CNS repair mechanisms as measured by the decreased whole brain MTR (p< 0.05). Th1-deviation was associated with decreased whole brain MTR (p=0036) and increased DTI damage (p< 0.05), while Th2-deviation was associated with decreased DTI damage (p< 0.05). No association was found with MRI lesion and atrophy outcomes.

Conclusions: The presence of concomitant diseases in MS has an effect on the repair mechanisms which occur within the CNS. This effect may not be visualized with conventional MRI measures. The effect varies based on the immune deviation of the disease between Th1 and Th2 effects.

P191
Multiple sclerosis in patients with common variable immunodeficiency disease: co-incidence or consequence?

K Pandey[1,2], I Kister[1,2], J Herbert[1,2]
[1]Barnabas Multiple Sclerosis Comprehensive Care Center, Livingston, NJ, United States, [2]NYU Medical Center, New York, NY, United States

Background: CVID is the most common primary immunodeficiency diagnosed in adult populations. CVID is characterized by a history of recurrent sinopulmonary infections, marked reduction in at least two immunoglobulin isotypes and impaired responses to vaccination. However, despite deficiency in functional antibodies, autoimmune diseases such as cytopenias, autoimmune hepatitis or inflmmatory bowel disease, affect about 20% of CVID patients and are commonly the first clinical manifestation of immune deficiency . To our knowledge, multiple sclerosis (MS) has not been reported as an autoimmune condition associated with CVID.

Objectives: To describe a case series of patients with clinically definite Multiple Sclerosis (MS) and Common Variable Immunodeficiency Disease (CVID).

Methods: Case series.

Results: The Barnabas MS Comprehensive Care Center (Livingston, NJ), follows approximately 1,100 MS patients. 3 women between the ages of 34-56, with clinically definite relapsing-remitting MS, developed increased frequency of infections coincident with initiation of an immunomodulatory treatment for MS - in 2 cases Natalizumab, and the other Glatiramer Acetate. All 3 patients reported lifelong history of recurrent sinopulmonary infections. All patients underwent immunological evaluation; based on the clinical history, immunoglobulin profile and response to a panel of vaccines, all patients were diagnosed with CVID. Monthly **i**ntravenous immunoglobulin therapy, the treatment of choice for CVID, was initiated in all patients. All patients were able to continue with prescribed immunotherapy for MS.

Conclusions: The incidence of CVID in the general population is estimated to be 1:25,000-1:50,000. Our finding of 3 CVID cases in our 1,100-patient cohort raises the question of an association between the two conditions. A link between CVID and MS is biologically plausible in view of the known predilection of CVID patients to autoimmune diseases, but will require confirmation in a

rigorous epidemiologic study. Our case series serves to raise awareness among neurologists that MS patients with unusual or frequent infections, which may be unmasked upon initiation of an immunotherapy, warrant a thorough immunologic evaluation. Increased awareness will likely result in more reports of patients with MS and immunodeficiency and enhance our understanding of the interrelationship between immunodeficiency and autoimmunity.

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Body mass index in patients with multiple sclerosis: does disability matter?

O Pinhas-Hamiel[1,2], M Livne[2,3], G Harari[4], A Achiron[2,3]
[1]Sheba Medical Center, Pediatric Endocrinology, Ramat Gan, Israel, [2]Sackler School of Medicine, Tel-Aviv, Israel, [3]Sheba Medical Center, Multiple Sclerosis Center, Ramat Gan, Israel, [4]Medistat, Tel-Aviv, Israel

Background: We hypothesized that multiple sclerosis (MS) patients with significant disability will be heavier than the general population secondary to decreased motor function and immobility, recurrent steroid treatments and sedentary life style behavior.
Objectives: To examine potential interactions between body mass index (BMI) and significant disability in patients with MS.
Methods: The study enrolled 130 patients with MS with Extended Disability Status Scale (EDSS) score between 3.0 and 7.5. Medical history was obtained by an interview and data included demographic and clinical variables, weight, and height. BMI was calculated as weight (kg) divided by square of height (m^2). Overweight was defined as 25kg/m^2< BMI< 30kg/m^2 and obesity was defined as BMI≥30kg/m^2. Comparison was performed with data obtained from the Israeli National Health and Nutrition Survey in the general population. Statistical analysis was performed using the SAS software.
Results: The study cohort comprised 130 MS patients, 72% females, mean±SD age 55.8±6.0, range 45-65 years, disease duration 18.2±10.1 years, EDSS 5.5±1.0. Overall, 46.9% were with normal weight with no gender differences, compared to 27% in age matched normal population; 34.6% of the disabled MS patients were overweight (30% in females and 46% in males) compared with 45% in the general population (40% in females and 50% in males). Obesity was present in18.5% of MS patients (22.6% in females and 8.1% in males) compared with 28.3% in the general population (33.1% in females and 23.5% in males). No correlations were found between BMI and disease duration, prior steroid treatments or EDSS. Analysis of patients with EDSS ≤6.0 and patients with score >6.0 did not show any group differences in BMI. 58.5% of patients were engaged in physical activity, and adequate activity of more than 2.5h/week was positively associated with lower BMI.
Conclusions: MS patients with significant disability are 1.7 folds less overweight and obese compared to the general population. Physical activity may be a beneficial factor. No interactions between degree of disability and BMI were found.

P193
The burden of comorbid psychiatric disorders in worsening the quality of life in multiple sclerosis patients

L Lorefice[1], G Trincas[2], MF Moro[2], G Fenu[1], G Coghe[1], J Frau[1], A Picardi[3], G Busonera[4], MG Carta[2], E Cocco[1], MG Marrosu[1]
[1]University of Cagliari, Multiple Sclerosis Center, Department of Public Health, Clinical and Molecular Medicine, Cagliari, Italy, [2]University of Cagliari, Consultation Liaison Psychiatric Unit, Department of Public Health, Clinical and Molecular Medicine, Cagliari, Italy, [3]Italian National Institute of Health, Mental Health Unit, Centre of Epidemiology, Surveillance and Health Promotion, Roma, Italy, [4]CRS4, Technology Park, Distributed Computing Group, Pula, Italy

Background: People with Multiple Sclerosis (MS) report lower levels of general health and more impairment than those with other disabling conditions. (Patten et al., 2012; Lorefice et al., 2013). Reduced quality of life (QoL) in people with MS has been associated with severe neurologic disability and psychological distress (Wolling et al., 2013).
Objectives: The purpose of this study is to measure in a sample of patients with MS and in a sample of healthy controls, the possible impairment of QoL due to MS and the possible role of psychiatric disorders in amplifying the deterioration of the QoL. A secondary objective is to compare the effect of MS clinical features on QoL (course, disease duration, age at onset, EDSS score, disease modifying drugs) in psychiatric and no psychiatric MS patients.
Methods: Cases: 201 consecutive-MS-patients. Controls: 804 sex-and-age-matched subjects without MS, randomly selected from an epidemiological database study. (Carta et al., 2010). Psychiatric diagnoses according to DSM-IV were determined by psychiatrists using a semi-structured clinical interview (ANTAS-SCID) derived in part from the non-patient version (SCID-I/NP) for DSM-IV (First et al., 2002). QoL was evaluated with the Short Form Health Survey (SF-12) (Ware et al., 1996). The SF-12 includes the following dimensions: physical activity, physical health limitations on roles or activities, emotional state, physical pain, self-evaluation of general state of health, vitality, social activity and mental health. The period of QoL measurement was the month prior of SF-12 evaluation. Higher scores on the SF-12 correspond to better conditions and quality of life.
Results: MS was the strongest determinant in worsening the QoL in the overall sample (p< 0.001). In the total sample as in cases of MS the presence of mood disorders play a role in reducing QoL (p< 0.01). In particular, both depressive and bipolar spectrum disorders were significantly associated with a poorer QoL in MS sample (p< 0.01). Furthermore, in MS group the higher neurologic disability was a strong determinant in reducing QoL, in particular in MS patients without mood disorder (p< 0.0001). No association was found for other clinical MS features.
Conclusions: The study highlights the role of comorbidity of mood disorders in the reduction of QoL in MS. The results suggest that the clinician should pay attention not only to physical symptoms, but also to affective disorders in the management of MS.

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Subclinical coronary artery disease in multiple sclerosis patients

E Andreadou[1], S Gerakoulis[1], V Haina[1], S Katsavos[1], M-E Evangelopoulos[1], G Koutsis[1], M Anagnostouli[1], E Stamboulis[1], C Kilidireas[1], E Gialafos[1]
[1]Athens National and Kapodistrian University, Department of Neurology, 'Aeginition' Hospital, Athens, Greece

Background: The incidence and prevalence of ischemic heart disease in the MS population has been reported to be higher than expected in persons aged <60 years. Lower levels of physical activity in MS have been associated with subclinical atherosclerosis. Moreover, myocardial ischemia and arrhythmias with normal coronary arteries have been associated with upper thoracic spinal cord lesions, possibly attributed to coronary vasoconstriction due to intense activation of cardiac sympathetic nerves.

Objectives: Aim of this study was the detection of asymptomatic coronary artery disease (CAD) through perfusion test in patients with MS.

Methods: We enrolled 50 consecutive patients aged < 60 years withoout clinical history of CAD that fulfilled the 2005 revised McDonald criteria for definite MS. Patients with history of CAD, use of beta bocker or implanted pacemaker or defibrillator were excluded. Age at disease onset, disease duration, initial symptomatology, disease subtype, medication and EDSS score were recorded. MRI and CSF data were collected. After electrocardiogram, 24-ambulatory ECG recording (Holter) echocardiography and clinical examination as primary screening, pharmacologic stress thallium 201 scintigraphy and/or coronary angiography were performed.

Results: Mean age of the patients was 45.3±7 years mean disease duration was 6±13 years and mean EDSS score was 3.4 ± 1.8. Relapsing-remitting MS had 60%, secondary progressive 32% and primary progressive MS 8% of the patients. Thirteen patients ((26%, 9 males) had abnormal scintigraphy test although clinical profile was not suggestive of CAD. Holter didn't reveal arrhythmias and two patients had a critical ejection fraction (around 50%) in this group. All positive patients that underwent coronary angiogram (n=7) had normal coronary arteries implying vasoconstriction as a potential mechanism for the stress positive result. A common finding of all positive patients was the presence of demyelinating lesions in lower cervical (C5-7) and upper thoracic (Th1-4) spinal cord. No differences were observed in disease duration, EDSS and treatment approaches between the two groups.

Conclusions: Our study shows a high incidence of coronary artery disease of non-atheroscletic type. This finding might be due to the presence of lesions in upper thoracic spinal cord possibly interfering with ANS function. Our findings might have implications for treatment strategies and help to distinguish patients at higher risk.

CSF studies

P195

Genetic risk factors are associated with cerebrospinal fluid measures in multiple sclerosis

A Goris[1], I Pauwels[1], MW Gustavsen[2,3], B Van Son[4], K Hilven[1], SD Bos[2,3], EG Celius[2], P Berg-Hansen[2], J Aarseth[5], K-M Myhr[5,6], S D'Alfonso[7,8], N Barizzone[7], MA Leone[8,9], F Martinelli Boneschi[10,11], M Sorosina[11], G Liberatore[10,11], I Kockum[12], T Olsson[12], J Hillert[12], L Alfredsson[13], SK Bedri[12], B Hemmer[14], D Buck[14], A Berthele[14], B Knier[14], V Biberacher[14], V van Pesch[15], C Sindic[15], AB Oturai[16], HB Søndergaard[16], F Sellebjerg[16], PE Jensen[16], M Comabella[17], X Montalban[17], J Pérez-Boza[17], S Malhotra[17], J Lechner-Scott[18], S Broadley[19], M Slee[20], B Taylor[21], A Kermode[22], P-A Gourraud[23], S Sawcer[24], BK Andreassen[25], B Dubois[1,4], HF Harbo[2,3], the International Multiple Sclerosis Genetics Consortium

[1]KU Leuven, Department of Neurosciences, Leuven, Belgium, [2]Oslo University Hospital, Department of Neurology, Oslo, Norway, [3]University of Oslo, Institute of Clinical Medicine, Oslo, Norway, [4]University Hospitals Leuven, Department of Neurology, Leuven, Belgium, [5]Haukeland University Hospital, Department of Neurology, Bergen, Norway, [6]University of Bergen, Department of Clinical Medicine, Bergen, Norway, [7]University of Eastern Piedmont, Department of Health Sciences, Novara, Italy, [8]University of Eastern Piedmont, Interdisciplinary Research Center of Autoimmune Diseases (IRCAD), Novara, Italy, [9]AOU "Maggiore della Carità", Novara, Italy, [10]San Raffaele Scientific Institute, Department of Neuro-rehabilitation, Milan, Italy, [11]San Raffaele Scientific Institute, Division of Neuroscience, Milan, Italy, [12]Karolinska Institutet, Department of Clinical Neuroscience, Stockholm, Sweden, [13]Karolinska Institutet, Institute of Environmental Medicine, Stockholm, Sweden, [14]Technische Universität München, Department of Neurology, Munich, Germany, [15]Université Catholique de Louvain-la-Neuve, Neurochemistry Unit, Louvain-la-Neuve, Belgium, [16]Copenhagen University Hospital, Department of Neurology, Copenhagen, Denmark, [17]Hospital Universitari Vall d'Hebron, Institut de Receca Vall d'Hebron, Barcelona, Spain, [18]University of Newcastle, Hunter Medical Research Institute, Newcastle, Australia, [19]Griffith University, School of Medicine, Queensland, Australia, [20]Flinders University of South Australia, School of Medicine, Adelaide, Australia, [21]University of Tasmania, Hobart, Australia, [22]University of Western Australia, Centre for Neuromuscular and Neurological Disorders, Crawley, Australia, [23]University of California San Francisco, School of Medicine, San Francisco, CA, United States, [24]University of Cambridge, Department of Clinical Neurosciences, Cambridge, United Kingdom, [25]University of Oslo, Department of Molecular Biology, Oslo, Norway

Background: Immunological hallmarks of multiple sclerosis (MS) are production of antibodies expressed as oligoclonal bands (OCB) and/or an increased level of immunoglobulin G compared to serum (IgG index) in the cerebrospinal fluid (CSF) of MS patients. However, the underlying differences between OCB positive and negative MS patients and reasons for variability in IgG index are not known.

Objectives: Our aim was to identify genetic factors influencing the variation in the antibody production in the CSF in MS.

Methods: We performed a genome-wide association screen in MS patients collected from eight countries for two traits: presence or absence of OCBs (N=3,026) and IgG index levels (N=938). This screening phase was followed by a replication in 3,917 additional MS patients from eight countries.

Results: The Major Histocompatibility Complex (MHC) region is the main determinant of presence of OCBs, with up to two-fold differences in the odds of being OCB positive depending on genotype combinations. We furthermore identify a region near the *ELAC1/SMAD4* genes associated with OCB status. The previously reported Immunoglobulin Heavy Chain (IGHC) region and newly identified signals in the MHC region together explain 10% of the variation in IgG index. Both traits (OCB and IgG index) are

associated with clinical features of disease such as female gender, lower age at onset and increased severity.

Conclusions: This is the largest study so far investigating the genetic influence on antibody production in the CSF in MS, including 6,976 MS patients from nine countries. We confirm that genetic factors underlie antibody production in the CSF in MS and identify both the MHC and IGHC region as major determinants.

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CSF isoelectric focusing differentiates multiple sclerosis from other CNS autoimmune disorders

E Bernitsas[1], F Bao[1], S Sriwastava[1], C Caon[1], A Tselis[1], S Millis[1], O Khan[1]
[1]*Wayne State University, Detroit, MI, United States*

Background: *CSF oligoclonal bands (OCB) are one of immunopathologic features of CSF in patients with MS and other CNS autoimmune disorders (CAID). Isoelectric focusing (IEF) with IgG immunoblotting has been to shown to have greater sensitivity in detecting CSF oligoclonal bands than agarose gel electrophoresis. Widely used in the U.S. since 2004, few studies have examined the utility of CSF IEF in distinguishing multiple sclerosis from other CAID.*

Objectives: To examine the presence of CSF OCB detected by IEF in patients with MS and other CNS autoimmune disorders.

Methods: This was a retrospective study of patients with MS and other CAID, who underwent CSF analysis between 2004 and 2013. All patients met the established diagnostic criteria for each disease state, supported by tissue biopsy when indicated.

Results: 56 patients with MS and 53 patients with other CAID were included in the study. Other CAID included vasculitis (n=6), Sjogren's (n=7), sarcoidosis (n=30), lupus (n=6), and anti-phospholipid antibody syndrome (n=4), all with definite CNS involvement. Mean age in MS group was 36.9 years and other CAID was 38.6 years. Mean number of CSF OCB was 8.5 and 1.7, in the MS and other CAID groups, respectively (p< 0.0001). Mean number of isolated CSF OCB (ISO-OCB) was 7.8 and 1.2 in the MS and other CAID groups respectively (p< 0.0001). In simple logistic regression model, both total number of CSF OCB and ISO-OCB differentiated MS from other CAID, with an odds ratio of 4.1 (p< 0.0001) and 7.8 (p=0.0006), respectively. Receiving Operating Characteristic curve analysis was performed to evaluate the diagnostic efficiency of ISO-OCB in predicting MS. Diagnostic discrimination was excellent (AUC = .985). Model calibration was also excellent (Hosmer-Lemshow chi-square = .67, p = .99). ISO-OCB greater than or equal to 4.50 had a sensitivity of .839 and a specificity of .981. In other words, of the patients with a diagnosis of MS, 83.9% were correctly classified in this sample when using a cutoff score of greater or equal to 4.50. Of the non-MS patients, 98.1% were correctly classified.

Conclusions: CSF IEF demonstrates significantly higher number of total and isolated CSF OCB and differentiates MS from other CNS autoimmune disorders that also present with CSF OCB. At a cut off 4.5 ISO CSF OCB, MS can be differentiated from other CAID with a sensitivity of 84% and specificity of 98%. This may be a useful tool in clinical practice. Larger studies are warranted.

P197

Importance of CSF analysis in the era of McDonald 2010 criteria: a retrospective multicenter study in patients with a clinically isolated syndrome

H Tumani[1], C Trebst[2], A Spreer[3], N Borisow[4], A Harrer[5], I Brecht[6], M Buttmann[6], B Balint[7], O Stich[8], S Schlegel[9], A Winkelmann[10], R Roesler[9], F Lauda[1], A Huss[1], Ö Yildiz[2], E Voß[2], R Muche[9], S Rauer[8], F Then Bergh[11], F Paul[4], B Wildemann[7], J Kraus[5], K Ruprecht[4], M Stangel[2], M Otto[9], UK Zettl[10]
[1]*University Hospital Ulm, Neurology, Ulm, Germany,* [2]*Hannover Medical School, Hannover, Germany,* [3]*University of Göttingen, Göttingen, Germany,* [4]*Charité - Universitätsmedizin Berlin, Berlin, Germany,* [5]*Paracelsus Medizinische Privatuniversität, Salzburg, Austria,* [6]*University of Würzburg, Würzburg, Germany,* [7]*University of Heidelberg, Heidelberg, Germany,* [8]*University of Freiburg, Freiburg, Germany,* [9]*University of Ulm, Ulm, Germany,* [10]*University of Rostock, Rostock, Germany,* [11]*University of Leipzig, Leipzig, Germany*

Background: The majority of patients presenting with a clinically isolated syndrome (CIS) suggestive of multiple sclerosis (MS) do not fulfil the MRI criteria for dissemination in space and time according to McDonald 2010 criteria for diagnosis of MS. Therefore, reliable predictors for conversion to MS are still required in patients with CIS.

Objectives: To re-evaluate the utility of cerebrospinal fluid (CSF) in the context of the revised McDonald criteria, we conducted a retrospective multicenter study aiming to determine the prevalence and predictive value of oligoclonal IgG bands (OCBs) in patients with CIS.

Methods: Patients were recruited from 10 specialized MS centers in Germany and Austria. Inclusion criteria were

1) discharge diagnosis of CIS,
2) availability of baseline CSF data, and
3) availability of baseline and follow-up MRI data sufficient to be classified according to the Swanton and Montalban criteria.

Results: We collected data from 410 patients 282 (69 %) of whom were female. The mean age at clinical onset was 34 ± 16 years. At disease onset 44/410 (11%) CIS patients fulfilled the McDonald 2010 criteria for MS, 138/410 (33%) the Swanton MRI criteria (dissemination in space), 84/410 (21%) the Montalban MRI criteria (dissemination in time), and 44/410 (11%) had no brain MRI lesions. Intrathecal IgG OCBs were detected in 351/406 (86 %).

290/410 (71%) converted to MS either clinically or on MRI according to the McDonald 2010 criteria during the follow-up period of up to 154 months (median 32 months).

While the conversion rate in CIS patients not fulfilling the McDonald 2010 criteria at onset (366/410) but showing intrathecal OCBs (310/366) was 74% (229/310), it was 44% (23/52) in those CIS patients with negative OCBs.

The median conversion time for CIS patients with positive OCBs was 25 months (95%CI=21-34) compared to 47 months (95%CI=36-85) in those patients without OCBs. CIS patients with intrathecal OCBs were twice as likely to convert to CDMS compared to OCB-negative individuals (hazard ratio=2.1, *p*=0.0014).

Conclusions: Our data confirm that the presence of OCBs in patients with CIS increases the risk of disease progression substantially and independently of MRI criteria for dissemination in space and time. Absence of OCBs at disease onset is associated with decreased risk of and longer interval to progression. CSF examination continues to be an important diagnostic and prognostic tool in patients with CIS also in the era of the McDonald 2010 criteria.

P198

Comprehensive Immunophenotyping of CSF cells in relapsing-remitting multiple sclerosis patients with daclizumb therapy

Y-C Lin[1], P Winokur[1], A Blake[1], T Wu[1], E Romm[1], B Bielekova[1]
[1]*National Institutes of Health, National Institute of Neurological Disorders and Stroke, Bethesda, MD, United States*

Background: We have previously reported that daclizumab (DAC), a humanized monoclonal antibody (Ab) against alpha chain of IL-2 receptor (IL-2Ra; CD25) stabilizes clinical symptoms of multiple sclerosis (MS), the debilitating neuro-inflammatory disorder. By using 12 color flow cytometry combined with enhanced counting of immune cells in 50 times concentrated cerebrospinal fluid (CSF), we were also able to define extensive abnormalities of the intrathecal immunity in untreated relapsing-remitting MS (RR-MS) patients.
Objectives: The purpose of this study was to use the same methodology for assessing intrathecal effects of long-term (>2 years) DAC therapy.
Methods: All samples (N=65) were assigned an alpha-numeric code and personnel performing the studies were blinded to the diagnosis of the subjects. Specimen collection and processing was performed according to written standard operating procedures. CSF samples were spun within 20 minutes. The 12 color immunophenotyping panel was designed to distinguish 14 major subpopulations of immune cells and their activation status.
Results: The long-term DAC therapy "corrected" all intrathecal abnormalities that differentiate untreated RR-MS patients from healthy donors (HD). Specifically, the strong CSF enrichment of cells belonging to adaptive immunity (CD4, activated HLA-DR-expressing CD4 T cells, and plasmablasts) was completely normalized by long-term DAC therapy. Similarly, the MS-characteristic deviations of intrathecal innate immunity was likewise normalized by DAC therapy: specifically, the dramatic decrease of monocytes and increase in innate lymphoid cells (ILCs) was reverted to HD levels. Thus, difference between untreated RR-MS patients and HD or DAC-treated patients was highly statistically significant for all of these biomarkers, whereas no significant differences were identified between HD and DAC cohorts. DAC therapy also leads to profound increase in immunoregulatory CD56^{bright} NK cells, both in the blood and CSF. This change was described before and distinguishes both untreated RR-MS and HD cohorts from patients on long-term DAC therapy.
Conclusions: Our study provides strong evidence that all MS-related abnormalities of intrathecal immune responses have been normalized in patients on long-term DAC therapy, consistent with our observations that clinical and imaging markers of MS disease activity have been eliminated by this therapeutic modality in patients who tolerate this treatment long-term.

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Intrathecal B-cell response in multiple sclerosis brain recognizes auto-antigens

DL Walker[1], CE Estrem[1], SW Anderson[1], B Miller[1], MP Burgoon[1]
[1]*University of Colorado School of Medicine, Neurology, Aurora, CO, United States*

Background: Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) with demyelination and neuronal damage. MS is the most common cause of neurological disability in young adults. One hallmark of the inflammatory response in MS is the intrathecal synthesis of IgG and the presence of oligoclonal bands (OCBs) in the CNS. The specificity of the B cell response and the observed OCBs is unknown.
Objectives: We examined the repertoires of IgG expressed in lesions of patients with relapsing remitting (RRMS) or secondary progressive (SPMS) MS. Recombinant antibodies (rAb) were produced from identified IgG clones and characterized for specificity by immunostaining.
Methods: We performed laser capture microdissection to isolate individual CD38+ plasma cells from post-mortem brains of two RRMS and three SPMS patients. From sequence analysis of the expressed IgG repertoire in each brain, representative clones were synthesized as monoclonal rAbs to examine antigen specificity. Immunostaining was performed on human cell lines, and on mouse and human tissues.
Results: Repertoires of IgGs expressed in 2 RRMS brains demonstrated extensive somatic hypermutation and significant clonal expansion. All of the repertoires from 3 SPMS brains also demonstrated somatic hypermutation, but only one indicated significant clonal expansion while two SPMS repertories were more diverse. rAbs were constructed from 15 clones in the repertoires as monoclonal human IgG1, for functional analyses. Eight rAbs variously stained human cell lines of CNS or peripheral origin, including oligodendroglial, astroglial, neuronal, fibroblastic and epithelial cells. Seven rAbs also variously stained human or mouse tissue, including human astrocytes, the Bowman's capsule in kidney, vascular endothelium, and specific eye structures (retinal ganglion cells, specific layers in the iris or cornea). Seven rAbs did not stain.
Conclusions: This study identifies clonally expanded and hypermutated IgGs which are intrathecally expressed in either relapsing remitting or secondary progressive MS brains, at the sites of demyelination. rAbs from IgG clones variously stain human or mouse tissues, in the CNS and in the periphery. These data suggest that the intrathecal B cell response in MS reacts against autoimmune antigens, while the initiating factors for this response are unknown. This B cell response may act as antigen-presenting cells that mediate demyelination or neurodegeneration in MS.

P200

Increased intrathecal inflammation in progressive multiple sclerosis

M Komori[1], A Blake[1], Y-C Lin[1], D Ghazali[1], P Kosa[1], P Winokur[1], M Natrajan[1], E Romm[1], T Wu[1], B Bielekova[1]
[1]*NIH, NINDS, Bethesda, MD, United States*

Background: Lack of therapeutic efficacy of immunomodulatory therapies in progressive multiple sclerosis (MS) has been

interpreted as evidence that neurodegeneration rather than immunopathology drives central nervous system (CNS) tissue destruction in progressive MS.

Objectives: To assess presence of intrathecal inflammation in patients with different MS subtypes *in vivo* by combining immunophenotyping of cerebrospinal fluid (CSF) cells with measurements of immune-cell specific soluble biomarkers.

Methods: CSF of 418 subjects, including relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), primary-progressive MS (PPMS), non-inflammatory neurological disorders (NIND), other inflammatory neurological disorders (OIND), and healthy donors (HD) were collected and processed in a blinded fashion using standardized protocol. Electroluminescent assay system was optimized to quantify soluble biomarkers in the CSF supernatant, including soluble CD14 (sCD14), sCD163, sCD21, sCD23, and sCD27. Cellular origin of all measured biomarkers was assessed from purified immune cell subtypes isolated from three HD and stimulated in-vitro. Absolute numbers of CSF immune cells were quantified by flow cytometry in 50-fold concentrated CSF, and were compared with cell-specific soluble biomarkers.

Results: In contrast to enrichment of CSF T cells and B cells in RRMS only, all MS groups had elevated CSF levels of B cell-specific (sCD21) and T cell-specific (sCD27) biomarkers as compare to NIND and HD (p< 0.05 for all). Monocyte/microglial biomarker CSF sCD14 level was elevated in SPMS and PPMS compared to RRMS and NIND (p< 0.05). RRMS and SPMS showed higher level of sCD23, which originates both from B cells and monocytes/macrophages. OIND showed the highest mean levels of all inflammatory soluble biomarkers which corresponded to highest numbers of CSF immune cells.

Conclusions: While elevated levels of soluble cell-specific biomarkers in OIND and RRMS groups corresponded to high absolute numbers of CSF immune cells, we observed significant elevation of soluble immune biomarkers in progressive MS groups, despite the fact that their numbers of CSF immune cells are comparable to those of NIND and HD. Our results indicate that the sources of soluble immune biomarkers in progressive MS are non-mobile cells residing in CNS tissue. Our methodology has potential to guide development of new immunomodulatory therapies with high CNS penetrance that will be necessary for inhibiting intrathecal inflammation in patients with progressive MS.

P201

Diagnostic and prognostic significance of intrathecal synthesis of immunoglobulin free light chains in MS

V Nazarov[1], S Lapin[1], E Surkova[1], E Kairbekova[2], G Makshakov[2], E Evdoshenko[2]
[1]First Pavlov State Medical University, Saint-Petersburg, Russian Federation, [2]Saint-Petersburg City Clinical Hospital #31, Saint-Petersburg Center MS and Autoimmune Diseases, Saint-Petersburg, Russian Federation

Background: Increased intrathecal synthesis of immunoglobulins and oligoclonal synthesis (OCB) are among the major immunological findings in MS. Free light chains (FLC) are fragments of immunoglobulin molecules that are produced in parallel to OCB and their production reflects total immunoglobulin synthesis within CNS. Elevated concentration of the free light chains kappa (K-FLC) and lambda (L-FLC) can be found in CSF but its diagnostic and prognostic significance has to be determined.

Objectives: We evaluated parameters of intrathecal K-FLC and L-FLC production as an additional diagnostic and prognostic biomarker in MS.

Methods: Concentrations of albumin was measured with turbidimetric method, K-FLC and L-FLC were detected with novel ELISA based on a pair of monoclonal antibodies, and OCB with isoelectric focusing were studied in pared CSF and serum samples of 151 patients, including 92 patients with MS, 33 CIS patients followed until CDMS diagnosis and 26 patients with other inflammatory neurologic diseases of CNS. Several quotients and indices (Qalb, FLC quotient (Q) and indices (I) and kappa/lambda ratio (K/L ratio)) were calculated to deduce better diagnostic tool.

Results: Concentration of K-FLC, Q-kappa(Q-K), Index Kappa(I-K) were significantly elevated (p< 0.0001) in MS and CIS-MS group as compared with control group. K/L ratio was significantly elevated only in MS group. Concentration of K-FLC and related indices (Q-K, I-K) were significantly higher in OCB-positive samples than in OCB-negative (p< 0,01). ROC analysis has shown that among all diagnostic biomarkers Q-K is the best for MS diagnosis. The usefulness of Q-K can also be confirmed by positive Q-K in OCB-negative group in 42% of MS cases. Also L-FLC negatively correlated with time of CIS conversion to MS (r=-0.5763, p=0.0026).

Conclusions: Immunoglobulin FLC were found to be promising diagnostic and prognostic marker in MS.

P202

Intrathecal IgG from patients with multiple sclerosis target patient-specific phage peptides

T Pointon[1], S Manton[1], M Davis[1], G Braiotta[1], L Schambers[1], T Edwards[1], B Polonsky[1], M Graner[2], M Burgoon[1], X Yu[1]
[1]University of Colorado Anschutz Medical Campus, Neurology, Aurora, CO, United States, [2]University of Colorado Anschutz Medical Campus, Neurosurgery, Aurora, CO, United States

Background: Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) with demyelination and neuronal damage, and is the most common cause of neurological disability in young adults. A characteristic feature of the CNS inflammatory response in MS is the intrathecal synthesis of IgG and the presence of oligoclonal bands (OCBs). The specificity of the OCBs is unknown.

Objectives: To investigate the specificity of the intrathecal IgG and OCBs by panning phage-displayed random peptide libraries.

Methods: We applied CSF IgG obtained from 10 MS patients to screen phage-displayed random peptide libraries (7-mer and 12-mer). We characterized the binding specificity of phage peptides with highly sensitive phage-mediated immuno-PCR, and immunoblotting of MS CSF separated on isoelectric focusing (IEF) gels.

Results: We identified multiple high-affinity phage peptides for the CSF IgG from each patient. Phage-mediated immuno-PCR demonstrated that the phage peptides exhibited greater binding to intrathecal IgG of MS CSF compared to the serum from the same patient. IEF immunoblots showed that these peptides were recognized by OCBs in MS CSF. Furthermore, when representative phage peptides from each of the 10 patients were used to screen binding specificity with CSF from 32 MS patients and 13 inflammatory controls with phage-mediated immuno-PCR, only 2 phage peptides were found to share antigen reactivity with 2 additional

MS patients. Sequence alignment analysis of the peptides from the 10 MS patients revealed that they represent epitopes which share homology with proteins involved in cell stress, apoptosis, and inflammatory processes.

Conclusions: We identified distinct sets of high-affinity epitopes reacting to the intrathecal IgG in CSF from each of the 10 MS patient studied. These data suggest that the intrathecal IgG may target patient-specific antigens.

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Lipid-specific IgM oligoclonal bands in clinically isolated syndrome: 5-years follow-up

B Molla[1], I Boscá[1], F Pérez-Miralles[1], C Alcalá[1], M Simó-Castelló[2], E Beltrán[2], F Gascón[3], A Navarré[3], F Coret[3], B Casanova[1]
[1]Hospital Universitari i Politècnic La Fe, MS Unit - Neurology Department, Valencia, Spain, [2]Hospital Universitari i Politècnic La Fe, Laboratory of Immunology, Valencia, Spain, [3]Hospital Clínico Universitario, Unit of Neuroimmunology - Neurology Department, Valencia, Spain

Background: The presence of lipid-specific IgM oligoclonal bands in CSF (LS-OCMB) has been related to a poorer prognosis after a first symptom suggestive of demyelinating disease (CIS).

Objectives: To confirm the relation between the presence of LS-OCMB and the time to a second relapse after a CIS, and to study the influence of the presence of LS-OCMB and disability at 5 years and the need of first or second line treatments in these patients.

Methods: This is a prospective cohort study of patients presenting with a CIS between 2003 and 2009 (minimum 5 years of follow up) at the MS Units of La Fe University and Polytechnic Hospital and Clinic University Hospital from Valencia. Only patients who had LS-OCMB determined and who did not start any disease modifying therapy before second relapse were selected. Time to a second relapse, 5 year EDSS and the use of first line (interferon beta, glatiramer acetate) and second line therapy (natalizumab or fingolimod) or immunosuppressive therapy (cyclophosphamide, mitoxantrone, bone marrow transplantation) were recorded.

Results: Ninety-one patients presenting with a CIS were recruited; 74.7% females and mean age at onset 31.2±7.7 years. The most frequent presenting syndrome was optic neuritis (31.9%) followed by transverse myelitis (28.6%). LS-OCMB were present in 17.6% patients, and all but one (93.8%) had a second relapse within 5 years, compared to 57.3% in the LS-OCMB- group (p=0.006). Time to a second relapse was significantly lower for LS-OCMB+ patients (0.9 years vs 4.4 years in LS-OCMB-patients, p< 0.0001). EDSS 5 years after CIS did not differ significantly between groups (1.6 in LS-OCMB+ patients and 1.3 in LS-OCMB- patients, p>0.05), but first line and second line or immunosuppressive therapy was substantially more frequent in LS-OCMB+ patients (12.5% of LS-OCMB+ patients did not receive any treatment, 31.2% only first line therapies and 56.2% needed second line or immunosuppressive therapy, while 52.1% of LS-OCMB- patients did not receive any treatment, 30.1% received only first line therapy and 17.8% received second line or immunosuppressive therapy, p=0.002).

Conclusions: LS-OCMB were related to a higher risk of second relapse, a lower time to second relapse and to a higher frequency of treatment. Escalating therapy to second line or immunosuppressive drugs seems to be effective to prevent disability increase 5 years after CIS onset. LS-OCMB can help us select more active patients for early therapies.

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Subclinical intrathecal inflammation is risk for disease reactivation in early multiple sclerosis

S Rossi[1,2], V Studer[1,2], C Motta[1,2], G Macchiarulo[1,2], G Germani[1,2], D Centonze[1,2]
[1]Tor Vergata University, Clinica Neurologica, Dipartimento di Medicina dei Sistemi, Rome, Italy, [2]Fondazione Santa Lucia/ Centro Europeo per la Ricerca sul Cervello (CERC), Rome, Italy

Background: Pathogenic events leading to brain structural damage in multiple sclerosis (MS) start early, independently of clinical signs. An earlier diagnosis and a more accurate evaluation of disease activity are crucial in preventing long-term disability, but are hindered by the lack of reliable biomarkers of subtle intrathecal inflammation, undetectable by conventional imaging. Cerebrospinal fluid (CSF) biomarkers are promising sources of prognostic information.

Objectives: to clarify whether CSF interleukin-8 (IL-8) represent a valid biomarker of subclinical intrathecal inflammation and a sensitive predictor of disease activity in early MS; to determine if intrathecal inflammation, detected by CSF IL-8 high contents is associated with clinical progression in subjects with radiologically isolated syndrome (RIS) and to the risk of conversion to MS after clinically isolated syndrome (CIS).

Methods: IL-8 CSF levels were detected in RIS (n=18), CIS (n=39), relapsing-remitting (RR) (n=108), and primary progressive (PP) (n=28) MS and 76 controls. Disability progression and disease activity were evaluated by mean of clinical and magnetic resonance imaging (MRI) paramethers in a two years follow up. Subjects were also stratified according to CSF IL-8 contents into a high IL-8 and a low IL-8 group, using a cut-off of 1000 pg/ml.

Results: IL 8 CSF levels were higher in RRMS respect to controls (1434.1±1092.1 versus 774.2±758.5 pg/ml, p< 0.001) and PPMS (787.4±970.3 pg/ml, p< 0.05) patients, especially among subjects with active MRI scan at baseline (1666.5±1208.3 versus 1137.1±877.6 pg/ml, p=0.01). High IL-8 compared to low IL8 subjects showed higher proportion of clinical relapses and/or reactivation of MRI (68% versus 21%, p< 0.0001), and shorter first inter-attack interval (p< 0.01). High IL-8 levels were associated with clinical progression (89% versus 22%, p=0.01) in RIS patients, and to higher risk of conversion to MS (79% versus 40%, p=0.02) in CIS. Also a lower time to conversion was observed for both RIS (10.2±5.3 versus 19.5±0.7 months; p< 0.05) and CIS (8.1±3.7 versus 15.1±4.5 months; p< 0.01) in high IL-8 group. Multivariate logistic analyses indicated that the presence of asymptomatic intrathecal inflammation place subjects at substantial risk for MS conversion, regardless lesion load (p=0.02).

Conclusions: IL-8 might provide utility in determining the presence of active intrathecal inflammation in diagnostically undefined cases and in therapeutic management.

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What does an isolated cerebrospinal fluid monoclonal band mean: a tertiary centre experience

T Poyraz[1], D Kaya[2], E Idiman[2], S Cevik[3], N Karabay[4], D Arslan[2], Y Karakaptan[2]

[1]Medifema Private Hospital, Izmir, Turkey, [2]Dokuz Eylul University, Neurology, Izmir, Turkey, [3]Dokuz Eylul University, Biology, Izmir, Turkey, [4]Dokuz Eylul University, Radiology, Izmir, Turkey

Background: The presence of oligoclonal bands (OCBs) in cerebrospinal fluid (CSF) of multiple sclerosis (MS) is now well established to support the clinical diagnosis. On the other hand, a monoclonal response can represent the initial stage of an oligoclonal response, before the other antibody clones become visible.

Objectives: To evaluate the presence of an isolated CSF monoclonal immunoglobulin (Ig) band and to analyse the clinical and radiological diagnosis of those samples with a single Ig band.

Methods: 3524 CSF samples using agarose gel isoelectric focusing (IEF) were re-examined and those with an isolated CSF monoclonal Ig band were detected.

Results: In 1.4% a monoclonal band in CSF was detected. 27.5% of them were diagnosed clinically isolated syndrome (CIS), 49% relapsing remitting multiple sclerosis (RRMS) according to Poser criteria, 11.8% secondary progressive MS (SPMS), and 2% radiologically isolated syndrome (RIS). There was no primary progressive MS (PPMS) patient. The mean disease duration and the mean EDSS score of MS patients including CIS and RIS patients were 59.8±71.4 months and 2.6±1.8 respectively. 69% of them met all the Barhoff criteria. The remaining was diagnosed other inflammatory neurological diseases (OIND) (9.8%) (1pt with chronic inflammatory demyelinating polyneuropathy, 1pt with neuromyelitis optica, 1pt with paraneoplastic syndrome, 2pts with acute disseminated encephalomyelitis).

Conclusions: The presence of an isolated CSF monoclonal Ig band is rare. Although most of the samples were diagnosed as MS according to both clinical and paraclinical (MRI) criteria, they had only a single Ig band in CSF. Not only OCBs, but also an isolated CSF monoclonal band may be a cornerstone for the diagnosis of MS at least for some patients. On the other hand, single CSF band is an indication for repeating a CSF analysis, unless other criteria clearly point to a diagnosis of MS, and to consider an alternative diagnosis. Patients with an isolated CSF monoclonal band need careful consideration.

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Lipid-specific oligoclonal IgM bands: is there any influence on the response to treatment with fingolimod?

L Pérez-Romero[1], C Alcalá[2], F Pérez-Miralles[2], F Gascón[3], A Navarré[3], I Boscá[2], M Simó-Castelló[4], L Landete[1], F Coret[3], B Casanova[2]

[1]Hospital Universitari Doctor Peset, Neurology Department, Valencia, Spain, [2]Hospital Universitari i Politècnic La Fe, MS Unit - Neurology Department, Valencia, Spain, [3]Hospital Clínico Universitario, Unit of Neuroimmunology - Neurology Department, Valencia, Spain, [4]Hospital Universitari i Politècnic La Fe, Laboratory of Immunology, Valencia, Spain

Background: The presence of lipid-specific oligoclonal IgM bands (LS-OCMB) in the cerebrospinal fluid (CSF) has been related to a poorer response to first-line therapies. Fingolimod (FGM) is an antagonist of the sphingosine-1-phosphate receptor, licensed in Europe as second-line agent, although the pivotal studies were not intended to aggressive forms of multiple sclerosis (MS).

Objectives: To investigate whether the presence of LS-OCMB in the CSF influences the response to treatment with FGM in relapsing-remitting MS patients.

Methods: This is a retrospective analysis of 150 patients from 3 tertiary referral hospitals from Valencia (Spain), who began treatment with FGM, 89 of them followed-up ≥12 months. We finally selected those patients in which the presence or not of LS-OCMB was tested (n=50). Presence of attacks and the Expanded Disability Status Scale (EDSS) were assessed at least every 6 months. Demographic and baseline clinical and presence of further attacks or sustained EDSS worsening during follow-up were compared using nonparametric test. Survival curves to first attack after FGM therapy were obtained.

Results: In the final cohort, mean age was 34.1 years (SD 7.5), mean evolution time was 7.7 years (SD 6.3) and median follow-up time was 28.5 months (IQR 21.3). Median EDSS 12 months previous to treatment (EDSSpre) with FGM was 2.5 (IQR 1.5) and mean annualized relapse rate (ARR) in the year before FGM was 1.5 (SD 1.9). Nine patients were naïve patients (18%), 25 (50%) had previously received first-line therapy and 16 (32%) second-line therapy. LS-OCMB were present in 14 patients (28%). Baseline clinical characteristics differed between negative and positive LS-OCMB patients. Negative LS-OCMB patients started treatment at higher age (mean age 35.3 years [SD 7.5] vs 30.9 [SD 6.6], p=0.055), with higher EDSS (median 3.0 [IQR 2.0] vs 2.0 [IQR 0.5] p=0.008) and, although not stadistically significant, later (mean time to FGM start 8.1 years [SD 6.9] vs 4.4 [SD 3.7], p=0.243). Nevertheless, there were no statistically significant differences in the time to first attack after FGM or in the EDSS change after FGM related to the presence of LS-OCMB. Median global survival to first attack after FGM was 90 months.

Conclusions: There are no differences in the response to FGM therapy between negative and positive LS-OCMB MS patients. Differences in age and EDSS between negative and positive LS-OCMB are probably attributable to the former having longer times to failure to first-line therapies.

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miR-142-3p expression in multiple sclerosis cerebrospinal fluid is related to better cognitive performance

L Ramió-Torrentà[1,2], E Quintana[2], R Menéndez[2], R Robles-Cedeño[1,2], H Perkal[2], FJ Ortega[3], JM Fernández-Real[3], J Gich[1,2]

[1]Neuroimmunology and Multiple Sclerosis Unit, Dr. Josep Trueta University Hospital, Department of Neurology, Girona, Spain, [2]Girona Biomedical Research Institute (IDIBGI), Neurodegeneration and Neuroinflamation Group, Girona, Spain, [3]Endocrinology and Nutrition (UDEN), Girona Biomedical Research Institute (IDIBGI), and CIBER de la Fisiopatología de la Obesidad y la Nutrición (CIBERobn, CB06/03), Department of Diabetes, Girona, Spain

Background: Multiple sclerosis (MS) is associated with both physical and cognitive dysfunction that is present in 65% of patients and is characterized by memory, learning, attention and information-processing impairment. MicroRNAs (miRNAs) are small noncoding RNAs that regulate the gene expression. miRNAs are present in biological fluids and might be used as disease biomarkers. Some miRNAs (miR-21, miR-155, miR-146a and miR-142-3p) have been implicated in MS immune processes.

Objectives: To evaluate the association between the cerebrospinal fluid (CSF) expression of miR-21, miR-155, miR-146a and miR-142-3p and both clinical and cognitive impairment at the moment of MS diagnosis.

Methods: An observational cross-sectional study was designed. Circulating RNAs were extracted, retrotranscripted and preamplificated from CSF, and miRNAs were quantified in a real-time PCR. We administrated The Brief Repeatable Battery Neuropsychology Test, which included Selective Reminding Test, the 10/36 Spatial Recall Test, Paced Auditory Serial Addition Test, Symbol Digit Modalities Test (SDMT), Word List Generation. We also included Boston Naming Test, A and B version of Trail Making Test (TMT-A/B), Letter & Number and Digits of Wechsler Adult Intelligence Scale III Edition. Expanded Disability Status Scale (EDSS) score was obtained.

Results: 26 patients (76.9% were female) with a mean age of 39 ($\pm$9,7)years old and a mean EDSS score of 2,35 ($\pm$1,1) were analysed. None of the miRNAs analysed showed any correlation with the EDSS score. A negative correlation was found between mR-142-3p and TMT-A (r=-0.461, p=0.020), TMT-B (r=-0.511, p=0.011) and a positive correlation with 10/26 Spatial Recall Test (r=0.494, p=0.012) and 10/36 Spatial Recall Test-delayed recall (r=0.460, p=0.021). A tendency towards significance was found with SDMT (r=0.359; p=0.078). A negative correlation was found between miR-155 and TMT-B (r=-0.410, p=0.042) and a tendency towards significance with TMT-B (r=-0.367, p=0.065).

Conclusions: At baseline, some correlations between miRNAs in MS CSF and different cognitive domains were found. miR-142-3p appears to be related to better performance on complex attention, speed processing information, visuospatial learning and visuospatial delayed recall memory. More studies are needed to validate these findings and to understand the role of different miRNAs on cognitive impairment.

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Cytokines profile in the cerebrospinal fluid in chronic relapsing inflammatory demyelinating diseases of the central nervous system

M Simó-Castelló[1], F Pérez-Miralles[2], C Alcalá[2], L Navarro[2], F Gascón[3], A Navarré[3], R Alonso[1], I Cal[1], M Escutia[2], A Bernad[3], A Saiz[4], I Boscá[2], B Casanova[2], F Coret[3]
[1]Hospital Universitari i Politècnic La Fe, Laboratory of Immunology, Valencia, Spain, [2]Hospital Universitari i Politècnic La Fe, MS Unit - Neurology Department, Valencia, Spain, [3]Hospital Clínico Universitario, Unit of Neuroimmunology - Neurology Department, Valencia, Spain, [4]Hospital Clínic de Barcelona, MS Unit - Neurology Department, Barcelona, Spain

Background: The spectrum of chronic relapsing inflammatory demyelinating diseases (CRIDD) comprise, among other entities, Multiple Sclerosis (MS), Neuromyelitis Optica and related disorders (NMO) and Chronic Relapsing Inflammatory Optic Neuritis/Relapsing Optic Neuritis (CRION/RION). Sometimes the initial diagnosis can be difficult because optic neuritis and/or myelitis are clinical syndromes shared to all these medical conditions. Because cytokines (CK) profile could express different pathogenic processes, we have hypothesized that determination of CFS CK profile could help to distinguish among patients with different forms of CRIDD.

Objectives: To compare the CSF CK profile in 3 forms of CRIDD (MS, NMO and CRION/RION) and in a control group.

Methods: We have studied 72 patients: 7 control patients (non-inflammatory neurological diseases); 55 MS patients with nodular or diffuse spinal cord affectation; 5 NMO patients (all anti-NMO+) and 5 CRION patients (2 anti-MOG+). In all patients, the following CK have been determined by Luminex®: IL1β, IL1RA, IL2, IL4, IL5, IL6, IL8, IL9, IL10, IL12p40, IL12p70, IL13, IL17A, IL17F, IL18,IL21 IL22, IL23, IL27, IFN-γ, GM-CSF and TNF-α. One-way analysis of variance with Bonferroni's adjustment was performed to detect differences between control and CRIDD patients' groups. Adjusted significance level was set at p=0.0042.

Results: There were no significant differences in the CSF CK profile between control and CRIDD patients' groups, except for IL6 (p< 0.0001) and IL8 (p=0.0003). Bonferroni adjustment showed that the IL-6 and IL-8 CSF levels were significantly higher in NMO patients than in control and MS patients, and probably higher than in CRION/RION patients (IL6: p=0.001 NMO vs. control; p< 0.001 NMO vs. MS; p=0.008 NMO vs. CRION/RION), (IL8: p< 0.002 NMO vs. control; p< 0.001 NMO vs. MS; p=0.007 NMO vs. CRION/RION). There were not differences in IL6 and IL8 CSF levels between control, MS or CRION/RION patients.

Conclusions: IL6 has been related with NMO, and with spinal cord affectation in MS patients, but IL8, a CK related to the permeability of the blood brain barrier, has only been studied in cases of optico-spinal MS. Our results show that IL8 is at higher levels only in cases of NMO, and not in MS patients, despite we selected MS patients with nodular and diffuse spinal cord affectation. High levels of IL6 and IL8 in the CSF are restricted to NMO patients, and could help to distinguish between the different CRIDD in the diagnosis of initial optic neuritis/myelitis.

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Post-dural puncture headache is markedly reduced when 25 Sprotte needles are used

A Bertolotto[1], Y Motuzova[1], F Sperli[1], M Capobianco[1], M Malentacchi[1], A Pulizzi[1], S Malucchi[1]
[1]AOU San Luigi Gonzaga, Neurologia 2 - Centro Riferimento Regionale Sclerosi Multipla (CRESM), Orbassano, Italy

Background: AAN Guidelines (2005) suggest the use of 22 gauge (G) atraumatic Sprotte needle; however in clinical practice the 20G traumatic needle is the most used one. Moreover 25G needles have been used only in few experimental settings.

Objectives: To evaluate the frequency of post-dural puncture headache (PDPH) using four types of needles, on a prospective rater-blind study.

Methods: 365 lumbar punctures were performed using four different types of needles as follows: 39 with 20G Quincke traumatic

needle, 62 with 22G Sprotte needle, 133 with 25G Whitacre needle, 131 with 25G Sprotte needle. The patient was blinded for the needle used; a neurologist, blinded for the type of the needle, interviewed the patient for PDPH. Safety and time consuming were evaluated.

Results: PDPH developed in 35.9% using 20G Quincke needle, in 12.9% using 22G Sprotte needle, in 6.8% using 25G Whitacre needle and in 1.6% using 25G Sprotte needle. The incidence of PDPH with 25S was significantly lower than 20Q and 22S (p< 0.0001 and p< 0.002 respectively) and it approached significance with 25W (p=0.06). PDPH was not correlated with CSF volume collected, patient´s age, sex, body mass index, position during cerebrospinal fluid (CSF) collection, suspected diagnosis, and previous lumbar punctures (LP). The median expected pain was similar in the four groups, ranging from 7 to 8 in the Eleven Point Box Scale and the median experienced pain was definitively lower, ranging from 3 to 4 (p < 0.0001 for all needles). The experienced pain was similar with the 4 needles, unaffected by the introducer and CSF aspiration. The median time spent with 20Q was 3 min, shorter than with 22S (5 min), with 25W (15 min) and 25S (7 min). The median velocity of (CSF) efflux, spontaneous or aspired, was higher with 20Q (2.7 ml/min) and 22S (3 ml/min), than with 25S (2 ml/min) and 25W (0.8 ml/min). The volume of CSF collected ranged from 3 to 20ml, with median values 9, 15, 10 and 13 for 20Q, 22S, 25W and 25S, respectively. The amount of CSF was higher with Sprotte needles, both 22S and 25S.

Conclusions: PDPH is influenced by diameter and shape of the tip of the needles and indicated that 25S needle is associated with very low frequency of PDPH. Diagnostic LP with 25S needle is safe and it can be performed in everyday clinical practice but requires higher skill and more time than traditional LP.

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Oligoclonal bands predict multiple sclerosis in children with isolated optic neuritis: a retrospective multicenter cohort study

N Heußinger[1,2], E Kontopantelis[3], A Jenke[4], P Hofstetter[5], B Kornek[6], S Lutz[7], I Brecht[8], M Smitka[9], A Blaschek[10], K Rostasy[11], S Karch[12], R Trollmann[2], M Häußler[13], M Buttmann[8], German-Speaking Research Alliance for ChildrEn with MS (GRACE-MS)
[1]Children's Hospital Aschaffenburg, Aschaffenburg, Germany, [2]University of Erlangen, Department of Neuropediatrics, Erlangen, Germany, [3]University of Manchester, Institute of Population Health, Manchester, United Kingdom, [4]University of Witten/Herdecke, Centre of Paediatrics and Youth Medicine, Witten/Herdecke, Germany, [5]University of Frankfurt, Department of Neuropediatrics, Frankfurt, Germany, [6]University of Vienna, Vienna, Austria, [7]University of Essen, Department of Neuropediatrics, Essen, Germany, [8]University of Würzburg, Department of Neurology, Würzburg, Germany, [9]Carl Gustav Carus University Dresden, Dresden, Germany, [10]Julius-Maximilian-University Munich, Dr. von Haunersches Kinderspital, Munich, Germany, [11]University of Innsbruck, Department of Neuropediatrics, Innsbruck, Austria, [12]University of Heidelberg, Department of Neuropediatrics, Heidelberg, Germany, [13]University of Würzburg, Department of Neuropediatrics, Würzburg, Germany

Background: Isolated optic neuritis (ON) in childhood may remain a singular event or indicate the clinical beginning of multiple sclerosis (MS). Higher age and pathological cranial MRI at presentation were previously demonstrated as independent risk factors of conversion to MS.

Objectives: We set out to further evaluate potential MS risk factors, including cerebrospinal fluid findings, in children with isolated optic neuritis as a first demyelinating event.

Methods: Only children with isolated uni- or bilateral ON as a first demyelinating event below age 18 were included in this retrospective multicenter cohort study. The minimal follow-up (FU) for those not converting to MS according to McDonald 2010 was 2 years. Age (< 10 vs ≥ 10 years), sex, FU, laterality of ON, cranial MRI (no vs ≥ 1 MS-compatible lesion outside the optic nerves) and intrathecal oligoclonal IgG bands (OCB) were assessed as risk factors using simple and multiple logistic regressions.

Results: Of 183 included children 140 had uni- and 43 bilateral isolated ON. Median FU of patients not developing MS was 5.1 years (range 2.0 - 22.0). Univariate analyses revealed age (OR 1.37, 95% CI 1.20 - 1.57, p < 0.001), MRI positivity (OR 17.55, 95% CI 8.14 - 37.83, p < 0.001) as well as presence of OCB (OR 12.18; 95% CI 5.86 - 25.31, p < 0.001) as predictive factors, while the three other tested parameters were not significantly associated with conversion to MS. Multivariate analysis of all 6 factors confirmed age (OR 1.32, 95% CI 1.11 - 1.56, p = 0.001), MRI positivity (OR 9.46; 95% CI 3.35 - 26.72, p < 0.001) and OCB (OR 4.67; 95% CI 1.68 - 13.00, p = 0.003) as significant predictors of conversion. Further centers confirmed participation in this multicenter project. Accordingly, updated analyses will be presented.

Conclusions: Here we show for the first time that CSF examination in children with isolated ON as a first demyelinating event may help to predict the risk of conversion to MS.

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Intrathecal IgM index correlates with severe disease course in multiple sclerosis: clinical and MRI results

S Ozakbas[1], B Piri Cinar[2], P Özcelik[3], H Baser[3], G Kosehasanogullari[4]
[1]Dokuz Eylul University, Dept. of Neurology, Izmir, Turkey, [2]Giresun State Hospital, Giresun, Turkey, [3]Dokuz Eylul University, Izmir, Turkey, [4]Usak State Hospital, Usak, Turkey

Background: Intrathecally synthesised IgM can be seen not only in the cerebrospinal fluid (CSF) of infectious and inflammatory diseases of the central nervous system but also in the CSF of patients with multiple sclerosis (MS). In MS intrathecal IgM synthesis seems to correlated with an unfavorable disease course. In a cross-sectional study intrathecal synthesis of IgM (IgM index) found to be correlated with cranial magnetic resonance imaging (MRI) parameters.

Objectives: We aimed to determine the possible relationship between IgM index and MRI and clinical parameters.

Methods: A total of 81 patients with MS (58 female) patients in whom lumbar puncture was done included in the study. 51 patients had relapsing remitting (RR) disease course. 30 patients were SPMS. IgM was detected in paired CSF and serum specimens by ELISA. IgM index was calculated as follows: CSF IgM/serum IgM: CSF albumin/serum albumin. IgM index higher than 0.1

considered "increased". All patients had brain and whole spinal kord MRI.

Results: IgM index was normal in 43 out of 81 patients (53.1%) and increased in 38 (46.9%) patients. A significant correlation was found between IgM index and EDSS (r=0.638, p=0.001). Most of the patients with increased IgM index was SPMS patients: 28 patients had SPMS course. 10 patients had RRMS course. Only two patients with SPMS course had normal IgM index. EDSS score was significantly higher in patients with increased IgM index (EDSS 4.3 versus EDSS 2.8, p=0.000). All patients with EDSS >3 had an increased IgM index. All patients with higher than 0.2 IgM index values had SPMS course, and they were with EDSS >6. Time to the initiation of secondary progressive phase of the disease was found to be correlated with IgM index value (p=0.004). IgM index value was also correlated with T1 hypointense lesions (r=0.0431, p=0.008) and Gd enhancing lesions (r=0.0396, p=0.006). Patients with increased IgM index had more spinal lesions (p=0.000). There was no relation between increased IgM index and increased IgG index. There was also no relation with IgG oligoclonal band positivity. There was no correlation between valus of IgM index and IgG index.

Conclusions: According to our data, intrathecal IgM synthesis is associated with a worse long term prognosis. It correlates with a higher relapse rate, more disability, and worse MRI outcomes. Early observation of increased IgM index will be a helpful tool for clinicians to select patients for early immunomodulatory or immunosuppressant treatments.

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Lipid-specific oligoclonal IgM bands and cognition in early stages of multiple sclerosis

J Gich[1,2], R Menéndez[2], E Quintana[2], N Pueyo[2], R Robles-Cedeño[1,2], H Perkal[1], I Toboso[3], LM Villar[3], L Ramió-Torrentà[1,2]

[1]Neuroimmunology and Multiple Sclerosis Unit, Dr. Josep Trueta University Hospital, Department of Neurology, Girona, Spain, [2]Girona Biomedical Research Institute (IDIBGI), Neurodegeneration and Neuroinflamation Group, Girona, Spain, [3]Hospital Universitario Ramón y Cajal. Instituto Ramón y Cajal para la Investigación Sanitaria (IRYCIS), Departments of Immunology, Madrid, Spain

Background: Multiple Sclerosis (MS) is an inflammatory, demyelinating and neurodegenerative disease leading to both physical and cognitive impairment that can significantly impact patients' quality of life. The onset of cognitive deterioration can occur early in the disease and worsen over time. The clinical course is heterogeneous and some patients have a high active course of the disease. An association has been found between patients with severe clinical course of MS and the presence of lipid-specific oligoclonal IgM bands (LS-OCMB) in the cerebrospinal fluid (CSF), although most of clinical and radiological differences could only be detected after some years of follow-up. There are no previously data about the cognitive status in positive LS-OCMB patients.

Objectives: To evaluate the cognitive impairment at the beginning of the disease according to the presence of LS-OCMB in the CSF.

Methods: An observational, longitudinal and comparative study was designed. The Brief Repeatable Battery Neuropsychology

Test (BRB-N) was administered at baseline and 12 months. LS-OCMB were analysed in CSF and serum by isoelectric focusing and immunodetection. The cognitive performance of MS patients were classified as "normal", "mild", "moderate" or "severe" depending on the number of tests failed with 1 standard deviation lower than the average. We also classified cognitive evolution as "normal performance", "cognitive improvement" or "cognitive impairment" depending on the change in their performance at 12 month of follow-up.

Results: 50 patients were assessed at baseline and 19 patients at 12 months of follow-up. No significant differences were observed between patients with negative or positive LS-OCMB and cognitive performance at baseline and at 12 months, and the change in the cognitive status. No significant differences were also observed in cognitive domains between groups at baseline and at 12 months of follow-up.

Conclusions: No differences in cognitive performance and neuropsychological domains between patients with positive or negative LS-OCMB were observed in early stages of the disease. These results are in agreement with clinical and radiological data, where differences could not be observed at the onset of the disease. More follow-up studies are needed to evaluate if changes in cognitive performance in this two groups of patients appear over time.

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A retrospective study of the association between leucocytes, IgG-index, oligoclonale bands and age in demyelinating disease

M Bülow[1], JL Frederiksen[1]
[1]Glostrup Hospital, University of Copenhagen, Neurology, Glostrup, Denmark

Background: Multiple Sclerosis (MS) patients typically have a characteristic composition of the cerebrospinal fluid (CSF). There are no previous studies of the correlation between CSF composition and age in patients with MS.

Objectives: The study aims to analyze data on CSF including finding a possible link between leucocytes, IgG-index, oligoclonal bands, and age of MS in consecutive patients at the MS Clinic, Glostrup Hospital.

Methods: A retrospective study of all patients evaluated at the MS Clinic in the years 1999-2013. The inclusion criteria are known onset date, known date of lumbar puncture and one of the following diagnosis: MS, CIS or ON. In all 1471 patients. The statistical calculations are based on a CIS-ON group and a RRMS group where patients are subdivided into whether or not they have had ON at any time.

Results: A possible relationship between leukocyte count in CSF, IgG-index, OB and age was examined. White blood cell (WBC) counts and IgG index tended to be lower the older the patients were. There was no correlation between the presence of OB and age. Patients who have OB have higher WBC counts and higher IgG-index than those who do not have OB.

ON-CIS group: Mann-Whitney U test for WBC count showed Z = -5.02, p = .000. Median for ON = 2.0, CIS = 4.0. CIS group has a significantly higher WBC count in the CSF than ON group. For IgG-index Z = -4.00, p = .000. Median ON = .56, CIS = .62. CIS group has a significantly higher IgG index than the ON group.

Chi-square test for independence of OB showed Continuity Correction = 28.5 and Asympt.sig (2-sided) = .000. Since p < 0.05, there is a significant difference of OB in the CIS and the ON group.

RRMS group: Mann-Whitney U test for WBC Z = -.16, p = .87. For IgG-index Z = -.82, p = .41. Since p > 0,05, there is no statistical difference between the WBC counts and IgG index. Chi-square test for independence of OB showed Continuity Correction = .006 and Asympt.Sig (2-sided) = .94 (p > 0,05).

Conclusions: The trend is that the older the patients are the lower the WBC counts and the IgG-index. There is a tendency that the OB+ patients have higher WBC counts and higher IgG-index than the OB-. The CIS group has a statistically significant higher WBC and a higher IgG-index than the ON group. The presence of OB in the two groups is statistically significant. RRMS group: There is neither a signigicant difference in WBC, IgG-index nor in the occurrence of OB in terms of whether or not patients have had ON.

P214

Reduced level of sialylated IgG antibody in the CSF of patients with multiple sclerosis

T Curley[1], T Pointon[1], H Collins[1], K Dennison[1], G Im[1], M Graner[2], D Wagner[3], X Yu[1]
[1]University of Colorado School of Medicine, Neurology, Aurora, CO, United States, [2]University of Colorado School of Medicine, Neurosurgery, Aurora, CO, United States, [3]University of Colorado School of Medicine, Webb-Waring Center, Aurora, CO, United States

Background: A characteristic feature of the CNS inflammatory response in multiple sclerosis (MS) is the intrathecal synthesis of IgG and the presence of oligoclonal bands (OCBs). IgG form immune complexes with the antigen and generate negative feedback regulation through crosslinking the B cell receptor with the IgG inhibitory receptor FcγRIIB, which inhibits BCR signaling and thereby B cell activation and IgG Ab production. Recent studies showed that asialylated IgG antibody are proinflammatory and induced by the combination of T cell-dependent protein antigens and proinflammatory costimulation.

Objectives: To determine IgG antibody sialylation in the CSF and paired serum of patients with multiple sclerosis.

Methods: Purified IgG antibody in CSF and paired serum from 12 MS patients and 9 inflammatory CNS controls were quantified for sialic acid levels using immunoblots probed with biotinylated lectin Sambucus nigra agglutinin (SNA) specific for sialic acid, followed by detection with HRP-conjugated NeutrAvidin. Biotinylated anti-human IgG blots were used as background control.

Results: We found that there was a significant decrease of sialylated IgG in the CSF compared to paired serum (p=6.2^{-8}). In contrast, no significant difference of IgG sialylation was found in the CSF and serum of inflammatory controls (p=0.18) with other neurological diseases.

Conclusions: The significantly decreased level of IgG sialyaltion in MS CSF compared to paired serum may indicate the role of intrathecal antibody in disease pathogenesis.

P215

Cerebrospinal fluid markers of the course of multiple sclerosis

I Smagina[1], S Elchaninova[1]
[1]Altai State Medical University, Barnaul, Russian Federation

Background: The prediction of Multiple Sclerosis (MS) relapses and progression is important for determining the choice of therapeutic approach. In this context, the predictive biomarkers of the disease course are required for development.

Objectives: The study objective is to find out the Cerebrospinal Fluid (CSF) markers associated with the frequency of relapses and the rate of MS progression.

Methods: The cohort study involved 60 patients with MS (18 male, 42 female) at the age of 37.3±10.4, duration of the disease being 7.2±1.4 years, and disability status being 3.5±1.6 points on the Expanded Disability Status Scale (EDSS). Inclusion criteria: remittent type of the disease course, duration of the disease longer than 5 years, disability status not exceeding 6.5 points on the EDSS. Exclusion criteria: immunomodulatory therapy. The following parameters were measured in CSF by enzyme-linked immunosorbent assay: interleukin-1 level, tumour necrosis factor (TNF-α), C-reactive protein, protein S100, myelin basic protein (MBP), matrix metalloproteinase-2 (MMP-2), thrombomodulin, soluble VE-cadherin, von Willebrand factor, soluble platelet endothelial cell adhesion molecule -1 (sPECAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1). Albumin level was measured in blood plasma (BP) using bromocresol green method and in CSF using immunoturbidimetric method.

Results: Compared to remission period, the level of TNF-α was increased by 5.1 times (p=0.031), MBP - by 2.3 times (p=0.046), sPECAM-1 - by 4.3 times (p=0.024) and sVCAM-1 - by 3.7 times (p=0.035) during the relapse period. Besides CSF albumin compared to BP albumin as 0.010±0.001 vs 0.004±0.001 (p = 0.012). The risk of rapid progression of MS (annual disability progress is faster than 0.75 points on the EDSS) is increased when the level of sPECAM-1 exceeds 5 ng/ml (OR=4.2; 1.2-8.9; p=0.018), the level of sVCAM-1 exceeds 29 ng/ml (OR=3.3; 1.0-9.4; p=0.021), and the level of MMP-2 is higher than 49 ng/ml (OR=3.1; 2.3-4.4; p=0.023). The risk of recurrence of MS in the nearest three years is increased when the concentration of TNF-α exceeds 22 ng/ml (OR=3.1; 1.9-6.9; p=0.022), and MMP-2 is above 49 ng/ml (OR=2.3; 1.9-4.6 p=0.029).

Conclusions: The levels of sPECAM-1, sVCAM-1, MMP-2 and TNF-α in the CSF are suggested as predictive biomarkers of the course of MS.

Databases

P216

A visualization and analysis platform in the Swedish national MS registry for real-time data feedback

L Stawiarz[1], E Hagel[2], H Eriksson[3], J Hillert[1], Swedish MS Registry
[1]Karolinska Institutet, Clinical Neuroscience (CNS), Stockholm, Sweden, [2]Karolinska Institutet, Learning, Informatics, Management and Ethics (LIME), Stockholm, Sweden, [3]Carmona AB, Halmstad, Sweden

Background: MS patient registries with longitudinally collected data are increasingly important as a base for research and quality assurance of MS care. However, a common limitation of such registries is the insufficient ability to extract meaningful data, thus rendering registries' role to archiving tools, usably only by a small number of researchers.

Objectives: We set out to design and implement a Visualization and Analysis Platform (VAP) connected to the Swedish MS Registry (SMSreg) to allow all users the monitoring of their local data and results of care in comparison to national data, including immediate statistical analysis of selected outcome parameters using predefined graphical and table-form template reports.

Methods: A VAP was built in SQL and R language, using a large collection of R-libraries including a new and powerful web framework Shiny (© *RStudio, Inc.*). The platform is based on predefined types of analyses such as flexible tabular presentations, cross-sectional and longitudinal comparisons, linear models, comparisons between domains (spider diagrams) and advanced statistical analyses (e.g. locally weighted fitting to experimental data, survival analysis). A user interface with reactive programming was implemented to control the appearance of interactive graphs and tables, and to explore the changes in outcome parameters.

Results: A web-based platform for live visualization and interactive statistical analysis of data was developed and linked to SMSreg containing 15,000 patients and over 80,000 registered neurological visits. Operations are intuitively controlled via a flexible user interface, supported by different graphical selection tools. Automatic reports are functionally divided into subgroups customized for users' needs and access rights. They contain various types of analyses: SMSreg's content (quantity and density of data, descriptive statistics), clinical follow-up, quality assurance (access to MS care, effective investigation and monitoring of patients, adequate DMD treatment), annual reports, patients' reported outcomes and some analyses of research character, e.g. survival analysis of drugs. Selected tables and figures are open for the public on county and national levels.

Conclusions: VAP offers a range of visualization and analysis options for graphical and table-form reports applied in real-time on SMSreg's data. It fills a need of providing data back to clinicians, patients and researchers, thereby hopefully motivating registration, and increasing quality and density of data.

P217

Leveraging electronic health records for a phenome-wide examination of the comorbidity burden associated with multiple sclerosis disease outcome

M Goodman[1], B Healy[2], T Cai[3], HL Weiner[2], T Chitnis[2], PL De Jager[4,5], Z Xia[4,5]

[1]Harvard University, Department of Statistics, Cambridge, MA, United States, [2]Brigham and Women's Hospital, Department of Neurology, Boston, MA, United States, [3]Harvard School of Public Health, Department of Biostatistics, Boston, MA, United States, [4]Brigham and Women's Hospital, Program in Translational NeuroPsychiatric Genomics, Department of Neurology, Boston, MA, United States, [5]Harvard Medical School, Boston, MA, United States

Background: Comorbid conditions can impact disease outcome and course in multiple sclerosis (MS).

Objectives: To perform a phenome-wide association study (PheWAS) to identify comorbidities associated with severe MS disability. We hypothesize that such approach can uncover heretofore unknown associations.

Methods: Merging data from an algorithm-defined MS cohort derived from the Partners HealthCare electronic health record (EHR) system with a clinic-based, MS natural history cohort, we report an integrated analysis of all International Classification of Diseases (ICD)-9 codes from the EHR with all Expanded Disability Status Scale (EDSS) measures from a research database for each of the 3010 MS patients (72% female, 86% Caucasian). Each ICD-9 code is mapped to existing curated phenome-wide ontology. We set EDSS>=6 as a threshold to identify patients who had ever experienced severe disability (n=1010). Each ICD-9 code is tested for association with EDSS status (ever>=6 v. never) using logistic regression with EDSS as predictor, adjusting for sex, race, smoking, age at symptom onset, disease duration, and progressive course at onset.

Results: After Bonferroni correction, this PheWAS identified 38 unique ICD-9 codes. Consistent with expected disabilities, the strongest associations with ever EDSS>=6 are bladder dysfunction (e.g., functional bladder disorder: n=391, OR=4.4, p=2.2e-28), abnormal gait (n=167, OR=4.1, p=3.3e-13), and muscle spasm (n=75, OR=14.6, p=3.9e-13). Other expected associations include infections (e.g., urinary tract infection: n=337, OR=2.9, p=3.8e-14), mood disorders, osteoporosis, and adverse effects of adrenal cortical steroids. In addition, we found less obvious comorbidities: fever of unknown origin (n=178, OR=2.6, p=2.0E-07), disorders of fluid and electrolyte imbalance (n=102, OR=3.7, p=2.3e-7), venous embolism and thrombosis (n=61, OR=4.5, p=2.6e-6), and respiratory failure (n=31, OR=10.5, p=9.0e-6). Finally, we found intriguing associations with cardiac dysrhythmias (n=263, OR=1.8, p=0.00024), myocardial infarction (n=30, OR=3.8, p=0.0031), and type 2 diabetes (n=101, OR=2.2, p=0.0028), as well as inverse associations with benign skin neoplasm (n=248, OR=0.52, p=0.00018) and breast lump or mass (n=142, OR=0.44, p=0.00045) at a suggestive level of evidence.

Conclusions: The phenome-wide approach highlights clinically relevant parameters to monitor and improve in severe MS. Replication is ongoing, and associations will require further studies to elucidate their role in severe MS disability.

P218

Establishment of a global registry for multiple sclerosis patients on extended dose natalizumab schedules

J Herbert[1], L Zhovtis Ryerson[1], C Tornatore[2], J Foley[3], B Weinstock-Guttman[4], I Kister[1], K Pandey[5], D Hojnacki[4], G Remington[6], T Frohman[6], E Major[7], D Douek[8], S Qureshi[6], J Beh[6], D Okuda[6], P Utomo[1], T Hoyt[3], E Chamot[9], M Bucello[4], I Ahsan[4], C Kolb[4], E Frohman[6]

[1]NYU Langone Medical Center, Neurology - Multiple Sclerosis Comprehensive Care Center, New York, NY, United States, [2]Georgetown University Hospital, Neurology, Washington, DC, United States, [3]Rocky Mountain MS Clinic, Salt Lake City, UT, United States, [4]University of Buffalo, Neurology, Buffalo, NY, United States, [5]Barnabas Health MS Center, Neurology, Livingston, NJ, United States, [6]University of Texas Southwestern Medical Center, Neurology, Dallas, TX, United States, [7]National Institue of Neurological Disease and Stroke, Bethesda, MD,

United States, [8]National Institue of Allergy and Immunology, Bethesda, MD, United States, [9]University of Alabama at Birmingham, Birmingham, AL, United States

Background: Natalizumab (NTZ) is a highly effective treatment approved for management of relapsing forms of Multiple sclerosis (MS). However, its use is limited by susceptibility to progressive multifocal leukoencephalopathy (PML) in patients with serological evidence of exposure to JC virus, in whom PML risk ranges from 0.7% to 1.4% depending on their history of prior immunosuppression. Current therapeutic practice in adults is based on a standard 300 mg dose administered q4 weeks, aimed at maintaining maximal saturation of the α4β1 integrin receptor throughout the treatment cycle. We hypothesize that an extended dose (ED) NTZ schedule may result in sub-maximal receptor saturation thereby mitigating PML risk while maintaining therapeutic efficacy.

Objectives: To establish Natalizumab Extended Dose Registry (NEDR) - a global registry of MS patients on ED NTZ administration.

Methods: The Registry is maintained at NYU MS Center. Data is collected anonymously without patient identifiers. A standard questionnaire has been developed to pool clinical and radiological data for patients on ED schedule - requiring at least 3 consecutive NTZ doses administered q4.5 wks - 8.5 weeks, after ≥6-month initiation on standard q4wk schedule.

Results: The aims and structure of the Registry will be presented in detail as well as our preliminary 6-center experience with extended dosing, which encompasses 950 patient-years. Thus far, information on 601 patients has been obtained, with ED annualized relapse rate 0.12 and no cases of PML encountered over 680 JCV-antibody positive person-years (p=0.198).

Conclusions: To date excellent efficacy profile of the drug appears maintained. Absence of PML cases is encouraging, though a statistically significant decrease in PML has not yet been established, which may be due to low power of the study. Further patient recruitment and longer follow-up are required. We invite all interested MS practitioners worldwide to contribute cases to NEDR, in order to establish:

(1) short- and long-term efficacy of ED approach;
(2) short- and long-term safety;
(3) tolerability;
(4) to obtain sufficient statistical power to test the hypothesis whether PML risk is decreased with ED, and to plan:
(5) prospective study of different NTZ ED schedules;
(6) pharmacokinetic study of various ED NTZ schedules; and
(7) evidence-based guidelines for optimization and individualization of NTZ dosage and frequency.

P219

NMOBase is a Web-based, global observational registry for an 'orphan' disorder: neuromyelitis optica

I Kister[1], T Bacon[1], R Alroughani[2], C Boz[3], E Cristiano[4], G Iuliano[5], M Marriott[6], J Olascoaga[7], E Pucci[8], JI Rojas[4], B Taylor[9], M Terzi[10], S Vucic[11], J Herbert[1], H Butzkueven[6]

[1]New York University School of Medicine, Neurology, New York, NY, United States, [2]Amiri Hospital, Kuwait, Kuwait, [3]Karadeniz Technical University Farabi Hospital, Trabzon, Turkey, [4]Hospital Italiano, Buenos Aires, Argentina, [5]Ospedali Riuniti di Salerno, Salerno, Italy, [6]Royal Melbourne Hospital, Melbourne, Australia, [7]Hospital Donostia, Donostia-San Sebastian, Spain, [8]Generale Provinciale Macerata, Macerata, Italy, [9]Royal Hobart Hospital, Hobart, Australia, [10]Mayis University, Samsun, Turkey, [11]Westmead Hospital, Sydney, Australia

Background: Longitudinal study of a rare disease is challenging and usually based on case series from tertiary referral centers, which may have over-representation of the more severe cases and may not follow patients for routine care. Moreover, published Neuromyelitis Optica Spectrum Disorders (NMOSD) case series tend to originate in the developed countries, while this disease appears to be more prevalent in parts of the developing world. MSBase is a unique observational registry that can be freely joined by any neurologist in the world and used as a specialized electronic medical record for patients with neuroinflammatory disorders. MSBase allows for customized substudies to be created for specific subpopulations.

Objectives: To describe NMOBase, a Web-based, global observational registry within MSBase designed for the clinical care and study of patients with NMOSD.

Methods: We created NMOBase as a substudy of MSBase with specialized fields to capture NMO-specific information (eg NMO diagnostic criteria, NMO IgG serostatus) both at registration and follow-up visits. NMOBase allows clinicians to input detailed information about relapse history, disability, MRI changes, treatment switches, etc at each clinic visit and to analyze the data for individual patients as well as aggregates.

Results: Since its launch in 2013, 13 neurologists from 6 countries on 5 continents enrolled 46 patients with NMOSD into NMOBase; of whom 79% were women. The mean age at registration and mean disease duration were 41.4 ±12.3 and 9.2 ±8.6 years respectively. Caucasians constituted 44% of the cohort, followed by 18% Hispanics, 18% of Turkish and 13% of Asian descent. Median EDSS was 3 and 22% required ambulatory assistance. The most widely used therapy was Azathioprine, followed by oral Prednisone and Rituximab, but several patients were on Multiple Sclerosis disease-modifying therapies.

Conclusions: NMOBase allows any neurologist with Internet access to maintain a comprehensive electronic medical record on their NMOSD patients. Longitudinal data collected as part of routine care can then be used for evaluating outcomes in NMO and comparative studies of patients from different regions/ethnicities. NMOBase has the potential to become a sufficiently large and representative cohort to allow for statistically meaningful evaluation of treatments and outcomes. If successful, NMOBase can serve as model for the study of other orphan diseases.

P220

Argentinean registry of patients with relapsing remitting multiple sclerosis treated with fingolimod (REAL): design and results of interim analysis

G Seifer[1], GA Kuperman[1], A Villa[2], F Caceres[3], G Herrera[4], R Rey[5], M Parada Marcilla[2], C Calvo Vildoso[6], G Arguello[7], V Parisi[2], R Neme[8], V Sinay[9], JM Blasco[10], P Labal[11], M Burgos[4], N Deri[12], R Linares[13], S Vetere[14], M Jacobo[15], M Golberg[14], A Castronuovo[1], Real Study Group

[1]Novartis Argentina SA, Medical, Buenos Aires, Argentina, [2]Office, Buenos Aires, Argentina, [3]INEBA, Buenos Aires, Argentina, [4]Office, Salta, Argentina, [5]IADIN, Buenos Aires,

Argentina, [6]Office, Santa Fe, Argentina, [7]Office, Santa Cruz, Argentina, [8]Office, Mendoza, Argentina, [9]Fundacion Favaloro, Buenos Aires, Argentina, [10]Office, Mar del Plata, Argentina, [11]Office, Ushuaia, Argentina, [12]DIABAID, Buenos Aires, Argentina, [13]Office, Bahia Blanca, Argentina, [14]Office, La Plata, Argentina, [15]Office, Santiago del Estero, Argentina

Background: Once-daily oral fingolimod (Gilenya) is approved in Argentina for the treatment of relapsing multiple sclerosis (MS) since April 2011. Despite the fact that many registries provided real word data on fingolimod safety and efficacy, scarce data exists in South American countries. The aim of this registry in patients treated with fingolimod (REAL) is to prospectively study the safety and efficacy in patients treated with fingolimod in Argentina.

Objectives: To provide interim efficacy and safety data for patients enrolled in REAL.

Methods: REAL is a prospective 2 year open label study enrolling 200 RRMS patients in 30 centers in Argentina receiving fingolimod to treat the disease. All patients currently enrolled in the REAL registry were included. The study collects safety, efficacy and adherence data at baseline, first dose observation visit and every three months thereafter.

Results: 48 patients were analysed (2 patients were not included in the analysis but continued under fingolimod treatment). Mean age was 39 ± 6 years, 36 (75%) were women, mean EDSS at baseline was 2.7 ± 2.3 SD. Mean time since the disease was diagnosed was 9.1 ± 4.1 SD years. 72.9% of patients used previous DMTs. Mean time under fingolimod treatment was 8.5 ± 4.2 SD months up to this interim analysis. One patient presented a relapse that required steroids treatment with full recovery and another patient had an elevation of liver enzymes but no modification of treatment was needed. One serious adverse event was reported (severe pneumonia followed by death not related to fingolimod according to the investigator).

Conclusions: we present here preliminary real world data for patients treated with fingolimod in Argentina. REAL will provide long-term safety and efficacy data

P221

A Swedish nationwide pharmaco-epidemiological and genetic study (IMSE) of the long-term safety and efficacy of natalizumab

L Jonsson[1], C Holmén[1], J Hillert[1], P Nilsson[2], C Dahle[3], N Feltelius[4], A Sveningsson[5], J Lycke[6], A-M Landtblom[7], J Burman[7], F Walentin[8], C Martin[9], F Piehl[1], T Olsson[1]
[1]Karolinska Institutet, Department of Clinical Neuroscience, Stockholm, Sweden, [2]Lund University, Department of Neurology, Lund, Sweden, [3]Linköping University, Department of Clinical and Experimental Medicine, Linköping, Sweden, [4]Medical Products Agency, Uppsala, Sweden, [5]Umeå University, Department of Pharmacology and Clinical Neuroscience, Umeå, Sweden, [6]University of Gothenburg, Department of Clinical Neuroscience, Gothenburg, Sweden, [7]Uppsala University, Department of Neuroscience, Uppsala, Sweden, [8]Örebro University Hospital, Örebro, Sweden, [9]Danderyd Hospital, Department of Clinical Science, Stockholm, Sweden

Background: Natalizumab (NTZ) is a disease modulatory treatment for relapsing-remitting multiple sclerosis (RRMS) with high efficacy. However, post-marketing surveillance is important for the determination of long-term safety and efficacy outcome measures in the real-world setting. Therefore, when NTZ was launched in Sweden in August 2006, the "Immunomodulation and Multiple Sclerosis Epidemiology" (IMSE) study was initiated.

Objectives: To follow-up the long-term safety and efficacy of NTZ in a real-world setting.

Methods: MS patients in Sweden are registered into the nationwide web-based Swedish MS registry (SMSreg). The IMSE study includes descriptive data of AEs, extended disability status scale (EDSS), MS severity scale (MSSS), symbol digit modalities *test* (SDMT), MS impact scale (MSIS-29) and relapses obtained from SMSreg. Blood samples are collected at baseline, 6, 12 and 24 months.

The Wilcoxon Signed-Rank Test was used to assess changes in in efficacy scores.

Results: 2,368 patients have been included in the IMSE study until April 2014. 86% of the patients have RRMS (7.7% missing data on MS type). The mean treatment duration is 35 months, the mean age at treatment start is 36 years and 72% are female.

1,140 patients (48%) terminated treatment at some point, of which 237 later restarted. 1,356 patients are currently being treated with NTZ. The two main reasons for ending treatment are; anti-JC virus antibody positivity (JCV+) (39%) and pregnancy/planned pregnancy (17%). 23% of patients with ongoing treatment are JCV+.

In patients treated with NTZ continuously for ≥5 years (n=412), long lasting, significant, stabilization of disease activity are evident. EDSS scores improved with 10%, MSSS scores with 37%, MSIS-29 physical/psychological scores with 12% and 15%, respectively, and SDMT scores with 23% (mean values at 5 years of treatment compared to baseline values).

Serious AEs were rare (2.3%, 54 events), but included 7 non-fatal cases and 1 fatal case of progressive multifocal leukoencephalopathy (PML, 0.3%), with the latest case reported 2012-10-31. The proportion of JCV+ patients has been reduced over the last years as a result of JCV testing. This has reduced the rate of PML cases per patient years. A total of 11 patients (0.5%) have died for any reason.

Conclusions: SMSreg proves to function well as a post-marketing drug surveillance platform, providing long-term data regarding drug effects and AEs. NTZ is generally well tolerated with sustained efficacy, though the risk of PML is an important concern.

Diagnosis and differential diagnosis

P222

Transverse myelitis in neuro-Behcet's disease

HS Lee[1], HY Shin[1], BC Suh[2], SW Kim[3], SM Kim[1]
[1]Yonsei University College of Medicine, Neurology, Seoul, Korea, Republic of, [2]Kangbuk Samsung Hospital, Neurology, Seoul, Korea, Republic of, [3]Catholic University of Korea, Neurology, Seoul, Korea, Republic of

Background: Transverse myelitis (TM) can appear as the first manifestation in conditions such as multiple sclerosis (MS) and neuromyelitis optica (NMO). However a number of disorders including Behcet's disease (BD) may also cause TM. TM in Behcet's disease is rare and little is known about this. There are only a handful of case reports or series about this disorder.

Objectives: To describe the clinical and magnetic resonance imaging (MRI) characteristics of TM in BD.

Methods: From Jan 1984 to July 2012, there were 109 patients with BD who had neurological involvement. 60 (55.04 %) patients had parenchymal CNS involvement. TM was developed in 7 patients among 60 patients with parenchymal CNS involvement. The medical records and MRI of the 7 patients were reviewed retrospectively. All 7 patients fulfiled the diagnositic criteria for BD established by the International Study Group for Behcet's disease.

Results: TM was developed in 7 patients with BD. Four patients were male and three were women. The median age at onset of BD and TM was 29 year-old (range, 18 to 37 years) and 31 (range, 22 to 37 years) respectively. Two of 7 patients combined with brain stem lesion at the initial presentation of TM. Six patients were treated with corticosteroid. Among six patients treated with corticosteroid, four patients showed improvement after treatment. Other two had no response of the treatment and could not walk independently at the last visit. The median follow-up period was 8 years (range 5-23). Three of all seven patients had relapses. Two patients had one relapse as TM again and the other patient recurred twice (TM and rhombencephalitis). MRI showed confluent T2-weighted hyperintense lesions of the spinal cord in all seven patients. The median lengths of lesions were 7 vertebral bodies (range 1-15). In five patients, the involvement segment of spinal cord was longer than three vertebral bodies, i.e. longitudinal extensive transverse myelitis (LETM).

Conclusions: TM can be developed in patients with BD. LETM may be a relatively common and characteristic manifestation of TM in patients with neuro-Behcet's disease. Neuro-behcet' disease should be considered as a differential diagnosis of TM, especially in patients with LETM.

P223

Methionyl-tRNA formyltransferase (MTFMT) deficiency mimicking neuromyelitis optica

JA Pena[1,2], F Scaglia[3], TE Lotze[1,2]
[1]Baylor College of Medicine, Pediatric Neurology, Houston, TX, United States, [2]Texas Children Hospital, Pediatric Neurology, Houston, TX, United States, [3]Baylor College of Medicine, Department of Molecular and Human Genetics, Houston, TX, United States

Background: Neuromyelitis optica (NMO) is typified by optic neuritis and transverse myelitis, often with longitudinally extensive cord lesions. Brain MRI findings are otherwise atypical for multiple sclerosis. Rarely, mitochondrial diseases can present with features of an acquired demyelinating syndrome, such as NMO, to include optic neuropathy and longitudinally extensive transverse myelitis.

Objectives: We describe an adolescent male who was found to carry a homozygous mutation in the MTFMT gene linked to combined oxidative phosphorylation deficiency.

Methods: Case of MTFMT mimicking neuromyelitis optica.

Results: A 19 year old male presented with relapsing longitudinally extensive transverse myelitis, brainstem demyelination, and progressive optic neuropathy. NMO was initially considered due to gadolinium enhancement of long spinal cord lesions as well as white matter lesions in regions of high aquaporin expression to include the diencephalon and brainstem. In addition, there was clinical and radiographic improvement following treatment with corticosteroids and plasmapheresis. However, serum and CSF aquaporin antibodies were negative, and CSF lactate levels were persistently elevated. Whole exome sequencing was performed and demonstrated a pathologic mutation in the MTFMT gene.

Conclusions: Mitochondrial disease can present with features suggestive of NMO to include a relapsing clinical course, optic neuropathy, myelopathy associated with long cord lesions, and atypical brain MRI findings to include symmetric brainstem disease. Further investigations to include CSF lactate as well as related metabolic and genetic studies are appropriate in suspected NMO patients who are seronegative for aquaporin-4 antibodies. Whole exome sequencing can provide a cost effective method for discovering rare underlying genetic disorders that may mimic an acquired demyelinating syndrome.

P224

Characteristic retinal pathology in Susac syndrome detected by spectral domain optical coherence tomography differentiates from multiple sclerosis

M Ringelstein[1], P Albrecht[1], I Kleffner[2], J Harmel[1], B Bühn[1], A-K Müller[1], D Finis[3], R Guthoff[3], R Bergholz[4], M Krämer[5], F Paul[6], A Brandt[6], S Jarius[7], B Wildemann[7], H-P Hartung[1], J Dörr[6], O Aktas[1], European Susac Consortium (EUSAC)
[1]Heinrich-Heine University, Medical Faculty, Neurology, Düsseldorf, Germany, [2]University Hospital Münster, Neurology, Münster, Germany, [3]Heinrich-Heine University, Medical Faculty, Ophthalmology, Düsseldorf, Germany, [4]Charité - Universitätsmedizin Berlin, Ophthalmology, Berlin, Germany, [5]Alfried Krupp Hospital, Neurology, Essen, Germany, [6]Charité - Universitätsmedizin Berlin, NeuroCure Clinical Research Center, Berlin, Germany, [7]University Hospital Heidelberg, Neurology, Devision of Molecular Neuroimmunology, Heidelberg, Germany

Background: Susac syndrome (SuS) is a rare, presumably autoimmune-mediated vasculopathy, leading to microvessel occlusions in the brain, inner ear, and retina. The characteristic clinical triad consists of encephalopathy, sensorineural hearing deficits, and visual disturbances due to branch retinal artery occlusion (BRAO) detectable by fluorescein angiography (FA). Differentiation from Multiple Sclerosis (MS) can be challenging, since clinical and diagnostic findings may overlap.

Objectives: Evaluation of retinal layer pathology considering angiographic results in order to differentiate SuS from MS and healthy controls (HC).

Methods: Using spectral-domain optical coherence tomography (SD-OCT) with last generation automated segmentation procedures the total macular volume (TMV) and the mean peripapillary retinal nerve fiber layer (pRNFL), as well as the RNFL, ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), and outer nuclear layer (ONL) of the whole macula were studied in 17 SuS patients and

compared to each 17 age- and sex-matched relapsing remitting MS patients and HC. Statistical comparisons of the retinal parameters between groups were performed using generalized estimation equations correcting for within subject inter eye correlations and adjusting for age and sex.

Results: The pRNFL of our SuS patients was significantly reduced (p< 0.001) compared to MS patients and HC, while the TMV only differed significantly to HC (p< 0.001). The retinae of our SuS patients showed mainly peripherally scattered areas with severe pathology, in which the RNFL (p< 0.001), GCL (p< 0.001), IPL (p< 0.001), INL (p< 0.001), and OPL (p< 0.001), but not the ONL were significantly reduced compared to corresponding sectors in MS patients and HC. In retinal sectors without obvious pathology only the IPL was significantly reduced compared to HC and MS patients (p< 0.001 and p=0.008, respectively). Retinal OCT pathologies partly corresponded to angiographically proven BRAOs in our SuS patients.

Conclusions: In contrast to MS severe scattered inner retinal layer abnormalities in SuS patients sparing the ONL are detectable by SD-OCT, highlighting the retinal vascular pathogenesis of the disease. Interestingly, we observed alterations of the IPL in our SuS patients even in areas without obvious pathology possibly corresponding to a secondary pathology. SD-OCT represents a safe, non-invasive diagnostic tool for differentiating SuS from MS.

P225

Brain lesion location at onset helps differentiate neuromyelitis optica and multiple sclerosis

NH Kim[1], DE Kim[1], SH Woo[1], KH Lee[2], HJ Kim[3]
[1]Dongguk University Ilsan Hospital, Neurology, Goyang-si, Korea, Republic of, [2]Sungkyunkwan University Samsung Seoul Hospital, Neurology, Seoul, Korea, Republic of, [3]National Cancer Center, Neurology, Goyang-si, Korea, Republic of

Background: Neuromyelitis optica (NMO) is an inflammatory demyelinating condition of central nervous system mediated by antibodies to aquaporin-4 water channel. Making diagnosis of antibody-negative neuromyelitis optica spectrum disorder (NMOSD) is difficult because the more prevalent multiple sclerosis (MS) can present similarly. It is important to distinguish these two conditions because NMO needs long-term immunosuppression to prevent devastating relapses and beta-interferon for MS can worsen NMO. Hence we need other markers to help identify NMOSD and MS. Furthermore, in patients with history of multiple episodes, the discrimination using brain lesion is not easy because the cumulative multiple lesions from each episode can overwhelm and make obscure disease specific brain lesion distribution. So there is a need to evaluate brain lesion distributions of early phase to differentiate these two conditions.

Objectives: The objective of this study was to investigate disease specific locations in NMO and MS and to discriminate the diseases in early phase.

Methods: We compared brain lesion locations and frequencies in MS and NMO with brain MRI at onset. In this multicenter, retrospective study, clinical and magnetic resonance image (MRI) data at onset were collected for 93 seropositive NMO (or NMOSD) and 89 MS patients with brain involvement. By assessing brain lesions on fluid-attenuated inversion recovery (FLAIR) MRI, we generated lesion probability maps (LPMs) of brain lesions and

frequency. Voxel-wise analysis for comparing of LPMs were performed with a nonparametric permutation-based approach (p< 0.05).

Results: Patients with NMO showed lesion frequency in brainstem, pericallosal area, and corticospinal tract. Patients with MS had lesion frequency in several clusters of periventricular white mater and inferior temporal lobes. The voxel-wise analysis demonstrated NMO patients were significantly more likely to have lesions adjacent to fourth ventricle, involving corticospinal tract including midbrain cerebral peduncle and internal capsule, in optic radiation, and in pericallosal area than MS patients, while MS patients were significantly more likely to have lesions adjacent to posterior and temporal horn than NMO patients.

Conclusions: This work demonstrated disease specific brain lesion locations suggesting that focal pathology affects different regions in NMO and MS. Careful inspection of brain lesion distributions on MRI can help distinguish MS and NMO in early phase.

P226

Application of the 2010 McDonald criteria to a cohort of patients with clinically isolated spinal cord syndrome

A Vandendriessche[1], H Zéphir[2], O Outerrick[2], D Fetter[3], N Derache[4], G Defer[4], P Vermersch[2], J De Sèze[5], B Bourre[3]
[1]CHU Rouen, Neurologie, Rouen, France, [2]CHRU Lille, Lille, France, [3]CHU Rouen, Rouen, France, [4]CHU Caen, Caen, France, [5]CHU Strasbourg, Strasbourg, France

Background: Recently, the International Panel on Diagnosis of Multiple Sclerosis (MS) has proposed new Magnetic Resonance Imaging (MRI) criteria for the diagnosis of MS in patients with Clinically Isolated Syndrome (CIS). With the 2010 McDonald criteria, MS diagnosis can be settled on a single baseline cerebrospinal MRI by the demonstration of dissemination in space (DIS) and time (DIT).

Objectives: We aimed to evaluate the accuracy of the 2010 McDonald criteria for DIS and DIT, using a single baseline cerebro-spinal MRI, to predict conversion from Spinal Cord CIS (SC-CIS) to MS. We also evaluated whether CSF analysis was still relevant or not in this new set of criteria.

Methods: Patients with SC-CIS were recruited in the neurology departments of 3 French university hospitals (Lille, Strasbourg, Rouen). Data were collected prospectively in Lille and retrospectively in Strasbourg and Rouen.

Baseline cerebro-spinal MRI was peformed within the first 3 months after onset and patients were followed at month 3 and each 6 months. MS was diagnosed according to the 2005 McDonald criteria.

We applied the 2010 McDonald MRI criteria for dissemination in space (DIS 2010) and dissemination in time (DIT 2010).

A CSF analysis was performed searching intrathecal synthesis.

Results: 127 patients were included. After a mean follow-up of 7.9 years, 68 (53.5%) patients converted to MS. The sensitivity of the DIS 2010 criteria was 60.3% and the specificity 83.1%. The sensitivity of the DIT 2010 criteria was 27.9% and the specificity was 83.1%. All patients fulfilling the 2010 McDonald criteria had positive CSF (elevated IgG index or oligoclonal bands) while 29 (22.8%) had positive CSF without fulfilling neither 2005 nor 2010 McDonald criteria. Among them, 13 (44.8%) converted to MS.

Conclusions: We report the largest cohort of SC-CIS patients (127) evaluating the 2010 McDonald criteria.

The sensitivity of DIT 2010 criteria is lower than expected and the sensitivity of DIT 2010 is surprisingly low, while the specificity remains high. If changing the DIT criteria, including the symptomatic gadolinium-enhancing lesions, the sensitivity increased to 55.9% while maintaining a specificity of 81.4%. This definfion of DIT could consider the particular feature of SC-CIS. CSF analysis is important in patients fulfilling neither 2005 nor 2010 McDonald criteria to identify those at risk of conversion to MS.

P227

Aggressive multiple sclerosis

S Menon[1,2,3], SA Morrow[1,2,3], M Kremenchutzky[1,2,3]
[1]*Western University, Clinical Neurological Sciences, London, ON, Canada,* [2]*London Health Sciences Centre, London, ON, Canada,* [3]*Lawson Health Research Institute, London, ON, Canada*

Background: Multiple Sclerosis (MS) can demonstrate a benign or aggressive course, outcomes that are difficult to predict at onset.

Objectives: To study aggressive multiple sclerosis (AMS) in a natural history MS cohort.

Methods: Population based, treatment naive, clinically definite MS patients first seen between 1972-1984 and prospectively followed at the London MS Clinic were retrospectively analyzed by applying three different criteria for AMS: A1-Expanded Disability Status Scale (EDSS) 6 or greater within 5 years from onset; A2-EDSS 6 or greater by 40 years of age; A3-Secondary progressive (SP) MS within 3 years from onset. Patients fulfilling at least 1 criterion formed the combined AMS (C-AMS) cohort and those not satisfying any criteria formed the non-AMS (N-AMS) cohort. C-AMS and N-AMS were compared using multivariable logistic regression for baseline characteristics and Kaplan Meier survival analysis for age at mortality and time to EDSS 6 and 8 from symptom onset. For C-AMS, predictors of death and progression were analyzed using multivariable cox regression.

Results: Out of 1036 consecutive MS patients (males-34.5%, primary progressive (PP)-20.8%), A1 identified 172 (16.6%) patients (males-43.0%, PPMS-43.6%), A2 identified 283 (27.3%) patients (males-38.9%, PPMS-19.8%) and A3 identified 109 (10.5%) patients (males-44%). C-AMS included 372 (35.9%) unique patients (males-37.6%, PPMS-25.3%) and compared to N-AMS were more likely to be PPMS {adjusted odds ratio (AOR)=2.1; 95%CI:1.5-3.0}, younger at onset (AOR=0.96; 95%CI:0.95-0.98) and have brainstem/cerebellar (AOR=1.9; 95%CI:1.5-2.5) or cerebral hemispheric (AOR=1.9; 95%CI:1.2-3.2) onset. Median survival age at mortality and median time to EDSS 6 and 8 from onset were significantly reduced for C-AMS (64, 6, 16-years) when compared to N-AMS (75, 22, 32-years) (p< 0.0001). Among C-AMS, risk of dying young was greater in males {hazard ratio (HR)=1.5; 95%CI:1.0-2.1), cerebral hemispheric onset (HR=2.0; 95%CI:1.2-3.1) and younger onset age (HR=0.94; 95%CI:0.92-0.95). Faster conversion to SPMS was seen in those with older onset age (HR=1.05; 95%CI:1.03-1.06), spinal cord onset (HR=1.5; 95%CI:1.1-2.2) and males (HR=1.4; 95%CI:1.0-1.9).

Conclusions: Aggressive MS was identified in 10-36% patients in our natural history cohort. Features at onset associated with AMS were PPMS, brainstem/cerebellar or cerebral hemispheric onset and younger age. AMS patients reached disability end points 2-4 times faster and die up to 11 years younger than non-aggressive MS.

P228

Perivascular inflammation in Baló's concentric sclerosis - preliminary results from a 7T MRI study

JR Behrens[1], T Sinnecker[1,2], J Kuchling[1], L Harms[3,4], K Ruprecht[3,4], T Niendorf[5], J Dörr[1], F Paul[1,4,6], J Wuerfel[1,7]
[1]*NeuroCure Clinical Research Center, Charite - Universitätsmedizin Berlin, Berlin, Germany,* [2]*Asklepios Fachklinikum Teupitz, Department of Neurology, Teupitz, Germany,* [3]*Charité - Universitaetsmedizin Berlin, Department of Neurology, Berlin, Germany,* [4]*Clinical and Experimental Multiple Sclerosis Research Center, Charité - Universitaetsmedizin Berlin, Berlin, Germany,* [5]*Berlin Ultrahigh Field Facility (B.U.F.F), Max Delbrueck Center for Molecular Medicine, Berlin, Germany,* [6]*Experimental and Clinical Research Center, Charité - Universitaetsmedizin Berlin and Max Delbrueck Center for Molecular Medicine, Berlin, Germany,* [7]*Institute of Neuroradiology, University Medicine Goettingen, Goettingen, Germany*

Background: Baló's concentric sclerosis (Baló) is a rare variant of multiple sclerosis (MS) characterized by its particular multi-layered or onion-shaped lesions, often confused with malignancies. The pathogenesis of these bizarre and sometimes tumefactive lesions has remained puzzling, but hypoxia-like tissue injury has been hypothesized to contribute to their development.

MS brain lesions and their correlation to the cerebral vasculature can be visualized with very high anatomical details at 7 Tesla MRI (7T).

Objectives: To describe lesion morphology and vascular structures of Baló's concentric sclerosis at 7T in comparison to classical MS.

Methods: Four Baló's concentric sclerosis patients (age 23-45; three with a monophasic disease course, one with three relapses; one male; EDSS median 2.0) underwent 7T MRI. The imaging protocol included 2D highly resolving T2* weighted (T2*w) MRI (in-plane resolution 200μm x 200μm) and susceptibility weighted imaging (SWI, in-plane resolution 0.5mm x 0.5mm). Eight MS patients with relapsing-remitting disease course served as controls. We analyzed the lesion number, size and morphology with central vein and hypointense rim count on T2*w sequences, taking the SWI image as reference for detecting venous structures.

Results: In total, we detected 22 lesions in Baló patients (n=4), and 476 lesions in classical MS (n=8). Lesion morphology was concealed in one Baló patient due to damage caused by prior surgical resection. The other Baló's cases expressed at least one characteristically layered lesion. A central intralesional vein was clearly depicted within the inner layer in two Baló patients; in the third Baló patient's lesion, a central intralesional blood vessel was only faintly visible. A strong T2* hypointense rim was detectable at the edge of all layered Baló's lesions. When looking at other white matter lesions (n=18) in Baló patients, we observed a morphology and distribution of lesions comparable to our MS control cohort (hypointense rim count n=5, perivascular lesions count

n=17, periventricular lesions n=8). Cortical lesions, however, were not present in Baló patients.

Conclusions: Our findings support the hypothesis that Baló's concentric sclerosis is part of the MS disease spectrum and - despite unusual morphological features - shares the same pattern of perivascular inflammatory activity. A small intralesional vein and T2*w hypointense lesion rims are frequent findings in Baló plaques and in additional typical MS lesions.

P229

Aquaporin-4 antibody-seropositive myelitis initially biopsied due to suspected spinal cord tumors: diagnostic considerations

T Misu[1], D Sato[2], C Rocha[3], D Callegaro[4], I Nakashima[5], M Aoki[2], K Fujihara[6], MA Lana-Peixoto[7]
[1]Tohoku University, Multiple Sclerosis Therapeutics, Sendai, Japan, [2]Tohoku University School of Medicine, Neurology, Sendai, Japan, [3]Federal University of Minas Gerais, Belo Horizonte, Brazil, [4]University of São Paulo, São Paulo, Brazil, [5]Tohoku University School of Medicine, Sendai, Japan, [6]Tohoku University School of Medicine, Multiple Sclerosis Therapeutics, Sendai, Japan, [7]Federal University of Minas Gerais, Neurology, Belo Horizonte, Brazil

Background: Longitudinally extensive spinal cord lesions on the magnetic resonance imaging (MRI) are present in a variety of diseases, such as tumors, inflammation, compressive myelopathy, infections, arteriovenous malformations, ischemia, which could cause long T2-weighted hyperintense spinal cord lesions with swelling on the MRI. In some cases, the diagnosis can only be made by pathological analysis, despite the risks of surgical complications and sequelae.Antibody against AQP4 is an important diagnostic biomarker of NMOSD, though no assay is 100% sensitive and the test availability is limited in some regions. In fact, the AQP4-antibody positivity is crucial since immunosuppressive therapy is effective to reduce further attacks in NMOSD. If untreated, NMOSD carries a poor prognosis and thus its early diagnosis is warranted.Here we report the clinical, imaging and pathological features of two patients of AQP4-antibody-positive LETM, who initially underwent spinal cord biopsy due to suspected tumors.

Objectives: To consider clinical, MRI and neuropathological clues to the diagnosis of NMOSD in two cases of AQP4 antibody positive LETM initially biopsied due to suspected spinal cord tumors.

Methods: Two case reports with neuropathological analysis of biopsied tissues.

Results: Observations: We report 2 female patients (age 14 and 47) with acute severe transverse myelopathy. Spinal cord MRI showed T2-hyperintense longitudinally extensive lesions with swelling and contrast enhancement. The spinal cord biopsy excluded tumors, but no definitive diagnosis was made. Later, both patients were diagnosed as NMOSD because AQP4-antibody was positive. Pathological re-evaluation of the biopsied materials revealed that both cases had demyelinated lesions with thickened vessel walls and tissue rarefactions . The immunohistochemical staining showed findings compatible with acute NMOSD lesions such as astrocyte loss in the lesion center and the lack of AQP4 staining with relatively preserved myelinated fibers in one case.

The other case had findings of reactive astrogliosis with partially lacked AQP4, which is consistent with chronic NMOSD lesions.

Conclusions: Now we do not have to perform spinal cord biopsy to diagnose NMOSD without the diagnostic serum test of AQP4 antibody, we may encounter to such materials due to the investigation of spinal tumors.

NMOSD can be suspected in the biopsied material if some features such as cystic changes with vascular wall thickening and signs of astrocyte rarefaction are present.

P230

Artificial intelligence techniques in the diagnosis of clinically definite multiple sclerosis

G Dalla Costa[1], L Moiola[1], L Leocani[2], R Furlan[3], M Filippi[4], G Comi[1], V Martinelli[1]
[1]San Raffaele Hospital, Neurological Department, Milan, Italy, [2]San Raffaele Hospital, Neurophysiology Unit, Milan, Italy, [3]San Raffaele Hospital, Neuroimmunology Research Unit, Milan, Italy, [4]San Raffaele Hospital, Neuroimaging Research Unit, Milan, Italy

Background: The early identification of patients at risk of developing clinically definite multiple sclerosis (CDMS) represents the main purpose of diagnostic criteria and of clinicians in everyday clinical practice.

The integration of all risk factors observed at clinical presentation into an estimate of absolute risk should be therefore the starting point for an accurate and personalized risk management at the onset of the disease.

Objectives: The aim of the current study is to develop an artificial neural networks-based (ANNs) diagnostic model integrating both clinical and paraclinical baseline data.

Methods: Patients admitted to our Department within 3 months from the onset of a clinically isolated syndrome (CIS) have been included. We evaluated baseline clinical data as well as MRI, multimodal evoked potentials (EPs) and CSF data. A Multi Layer Perceptron with a Back Propagation algorithm was used to recognize a pattern for the early diagnosis and prediction of CDMS.

Results: 227 CIS patients have been identified, 71 (31%) developed CDMS at 24 months and 120 (52.9 %) during the entire follow up (6.82 yrs SD 2.78). 80% of the patients provided training data, 20% were assigned to the validation group for performance evaluation of the model. By changing the types of ANN and the number of input factors applied, we created models that demonstrated up to 87 % accuracy. The best accuracy was obtained with a neural networks topology of multilayer Perceptron with two hidden layers for models including both clinical, MRI, CSF and EPs data.

Conclusions: This study demonstrated the feasibility of using ANNs in medical decision support systems for predicting early conversion to CDMS by integrating baseline clinical and paraclinical data.

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MRI study of Leber's hereditary optic neuropathy and MS suggests common lesion pathology and an 83% risk of MS-like lesions in females with LHON

L Matthews[1,2], C Enzinger[3,4], F Fazekas[3], A Rovira[5], O Ciccarelli[6], MT Dotti[7], M Filippi[8], J Frederiksen[9], A Giorgio[7], W Kuker[1,2], C Lukas[10], M Rocca[8], N Stefano[7], A Toosy[6],

T Yousry[6], J Palace[1,2], on behalf of the MAGNIMS Network
[1]University of Oxford, Nuffield Department of Clinical Neurosciences, Oxford, United Kingdom, [2]Oxford University Hospitals NHS Trust, Department of Neurology, Oxford, United Kingdom, [3]Medical University of Graz, Department of Neurology, Graz, Austria, [4]Medical University of Graz, Department of Radiology, Graz, Austria, [5]Hospital Vall D'Hebron, Department of Radiology, Barcelona, Spain, [6]UCL Institute of Neurology, London, United Kingdom, [7]University of Siena, Department of Neurological and Behavioural Sciences, Siena, Italy, [8]Vita-Salute San Raffaele University, Neuroimaging Research Unit and Dept of Neurology, Milan, Italy, [9]University of Copenhagen, Glostrup Hospital, Copenhagen, Denmark, [10]St Josef Hospital Ruhr-University, Department of Radiology, Bochum, Germany

Background: Mitochondrial dysfunction may play an important role in the pathogenesis of MS lesions[1,2]. In support of this is the observation that the rare mitochondrial disease Leber's hereditary optic neuropathy (LHON) and an MS-like illness (LHON-MS) coexist more frequently than would be expected by chance[3,4]. The MRI brain appearances of MS are characteristic, and therefore if LHON-MS has common imaging features with MS it would lend weight to the idea that they are the same entity and therefore share a disease mechanism.

Objectives: The primary objective of our study was to compare the MRI features of MS, LHON and LHON-MS. A secondary aim was to observe the effect of female gender on the presence of white matter lesions in our cohort.

Methods: A blinded standardised study of MRI brain scans was conducted by three reviewers with expert experience in MS and MRI. There were 30 with MS, 31 with LHON (without an MS-like illness) and 12 with LHON-MS.

Results: All 12 patients with LHON-MS had an MRI scan rated as typical of MS by the expert reviewers. Two patients (6.5%) with LHON had an MRI scan consistent with MS, and six further patients (19.4%) had non-specific white matter lesions. The lesion morphology and location in MS and LHON-MS were very similar, and brain atrophy and T1 hypointensity were noted in both conditions. There was a high level of inter-rater agreement between the reviewers (94%, kappa = 0.88, p < 0.001).

Of the 12 females in total with LHON, eight had LHON-MS and three had asymptomatic T2 hyperintense white matter lesions. Ten of 12 females with LHON were rated as having brain lesions consistent with MS, compared to three of 30 males, equating to a relative risk of 8.3 (95% CI 2.8 to 25.1, p< 0.01).

Conclusions: The MRI brain features of MS and LHON-MS are indistinguishable to the expert eye providing evidence that these diseases are the same. Therefore they may share a common pathological mechanism, and further work into the role of mitochondrial dysfunction in the evolution of MS lesions should be encouraged. Future research should also explore the apparent synergistic effect of female gender and LHON on the risk of developing MS.

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P232

Diagnosing multiple sclerosis with a gait measuring system, an analysis of the motor fatigue, and machine learning

S Piérard[1], S Azrour[1], R Phan-Ba[2], V Delvaux[3], P Maquet[3], M Van Droogenbroeck[1]
[1]University of Liège, INTELSIG, Liège, Belgium, [2]University of Liège, Liège, Belgium, [3]University Hospital of Liège, Neurology, Liège, Belgium

Background: Walking impairment is frequent and appears early in the disease course of MS Patients (MSP). Last year, a new gait measuring system well suited for the clinical routine (GAIMS) has been introduced [Pierard ECTRIMS 2013]. The measures can be used to compute Gait Descriptors (GDs) averaging the gait characteristics, either over the total recorded test, or over any part of it. This allows to analyze the evolution of the gait over time, which is related to the motor fatigue. In [PhanBa PLoS ONE 7(4)], a statistical difference between MSP and Healthy People (HP) has been found on the walking speed evolution during a 500m walk test, but the corresponding discrimination power has not yet been investigated. Moreover, GAIMS provides more GDs, which opens new prospects.

Objectives: To show that the motor fatigue, given by the evolution of the gait characteristics measured by GAIMS during a single 500m walk test, can be used to discriminate MSP and HP.

Methods: 115 HP and 59 MSP (median EDSS 3.26) walked 500m (25 laps of an 8-shaped path) as fast as possible, and their gait was recorded with GAIMS. The measures taken over the total path, and 50 consecutive windows of 10m, have been analyzed. This led to 26 GDs for the total path, and for each window. A machine learning algorithm, named ExtRaTrees [Geurts Machine Learning 63(1)], was used to predict if the observed person is a MSP or a HP. We tried to feed it with two sets of values. The first set gathers the GDs computed on the total path while the second one is populated with the subtractions between the GDs computed on each window and the GDs computed on the first, the middle and the last window. In this way, the second set of values only takes into account the evolution of the GDs which is related to the motor fatigue.

Results: The results are obtained by leave-one-person-out: the class (HP or MSP) of each person is predicted using a model learned only from the data related to the other people. We obtained a maximum balanced accuracy (*ie* the arithmetic mean of the sensitivity and the specificity) on predictions of 89.8% and 82% respectively for the first and the second set of values.

Conclusions: Although the temporal evolution of the gait characteristics has a lower discrimination power than GDs averaged over the total test, the score obtained with the second set of values (82%) implies that the evolution of the gait characteristics, which is related to the motor fatigue, contains some useful information that can be taken into account for diagnosing MS.

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The diagnosis of multiple sclerosis: pinpointing the concept of "no better explanation"

M Calabrese[1], C Gasperini[2], C Tortorella[3], S Malucchi[4], P Ragonese[5], G De Luca[6], R Fantozzi[7], S Lo Fermo[8], L Boffa[9], D Paolicelli[10], A Gajofatto[1], I Pesci[11], P Annovazzi[12], C Cordioli[13], R Lanzillo[14], A Giorgio[15], A Gallo[16], E Cocco[17],

V Tomassini[18], G Frisullo[19], L Prosperini[20], ME Rodegher[21], C Solaro[22], The RIREMS Group (Rising Italian Researchers in Multiple Sclerosis)
[1]University Hospital of Verona, Dept. of Neurological and Movement Sciences, Verona, Italy, [2]San Camillo Hospital, Rome, Italy, [3]University of Bari, Bari, Italy, [4]Neurologia 2-CRESM, AOU San Luigi Gonzaga, Orbassano, Italy, [5]University of Palermo, Dept. of Experimental Medicine and Clinical Neurosciences, Palermo, Italy, [6]Ospedale SS Annunziata, Chieti, Italy, [7]Istituto Neurologico Mediterraneo, Pozzilli, Italy, [8]A.O.U. Policlinico-Vittorio Emanuele, Catania, Italy, [9]Tor Vergata, Dept. Neuroscienze Policlinico, Roma, Italy, [10]Univeristy of Bari, Dept of Basic Medical Sciences, Neurosciences and Sense Organs, Bari, Italy, [11]Ospedale Civile, Centro Sclerosi Multipla, Fidenza, Italy, [12]Ospedale S. Antonio Abate, Gallarate, Italy, [13]Azienda Ospedaliera Spedali Civili, Brescia, Italy, [14]University of Naples Federico II, Napoli, Italy, [15]University of Siena, Siena, Italy, [16]Second University of Naples, Napoli, Italy, [17]University of Cagliari., Public Health Clinical and Molecular Medicine, Cagliari, Italy, [18]Cardiff University, Cardiff, United Kingdom, [19]Policlinico Gemelli, Rome, Italy, [20]Azienda Ospedaliera S. Andrea, Rome, Italy, [21]Ospedale San Raffaele, Milano, Italy, [22]Ospedale PA Micone, Genova, Italy

Background: Since the first appearance of McDonald's diagnostic criteria for Multiple Sclerosis (MS), it was clear that beyond the demonstration of the disease dissemination in space and time, a crucial role in the diagnostic work up would have been played by the exclusion of other neurological diseases.

Objectives: Aim of this study is to provide an accurate picture of the main diseases that can mimic MS in the "real world" setting of a large number of specialist MS centres.

Methods: Prospective, observational clinical and radiological study Including all patients presenting with symptoms suggestive of MS, in which a further examination was required in order to exclude or confirm MS diagnosis. Each patient after a regular diagnostic workup (including magnetic resonance imaging, visual evoked potentials, blood and cerebrospinal fluid examinations) was included in a 2 years clinical and radiological follow up.

Results: In the first 2 months of recruitment, 300 patients were included and underwent clinical, imaging and paraclinical (blood and CSF) examinations. Among these patients, in 123 (41.3%) it has been possible to diagnose MS according to the most recently revised MS diagnostic criteria, in 55 (18.3%) a different diagnosis was made and in the remaining 121 (40.3%) patients a clinical and radiological follow up was required to clarify the diagnosis.

Among the 55 patients in which a MS diagnosis was excluded and other diagnoses were already possible, the most frequent diagnoses were migraine (in 15 cases), vascular encephalopathy including PTO (in 13 cases), recurrent optic neuritis (in 2 cases), systemic erythematous lupus (in 2 cases), dizziness (in 2 cases), neuroBechet's disease (in 2 cases), neuromyelitis optica (in 2 cases).

Conclusions: Our preliminary analysis confirm that according to the new diagnostic criteria, the MS diagnosis can be made at the end of diagnostic work-up after the first clinical evaluation in almost 40% of the patients presenting with symptoms suggestive of MS. Migraine and vascular encephalopathy are by far the most frequent alternative diagnosis, while, so far, no infective diseases have been observed. Results of our study will be helpful to recommend an appropriate diagnostic algorithm based on the most frequent conditions entering the differential diagnosis with MS.

P234
The thalamus and basal ganglia lesions in multiple sclerosis and primary angiitis of the central nervous system in southern Chinese people

Y Chen[1], MA Wu[2], QZ Lu[2], L Zhang[3], QY Shu[4], W Qiu[4], QX Hu[2]
[1]The First Affilated Hospital of Wenzhou Medical University, Neurolgical Department, Wenzhou, China, [2]The Third Affiliated Hospital of Sun Yat-sen University, Neurological Department, Guangzhou, China, [3]The Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, China, [4]The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: Deep gray matter lesions(DGMLs) and deep white matter lesions(DWMLs) in thalamus and basal ganglia have been reported in multiple sclerosis(MS) and primary angiitis of central nervous system (PACNS). Yet, no detailed investigation and comparison has been made on the magnetic resonance image(MRI) characteristics in these locations of the two diseases.

Objectives: To compare the features of thalamus and basal ganglia lesions on MRI between patients with MS and PACNS.

Methods: 49 MS patients, 16 PACNS patients with thalamus or basal ganglia lesions on MRI were enrolled. Clinical characteristics as well as MRI features were investigated and assessed.

Results: Among DGMLs and DWMLs, thalamus was more prone to be the target of MS(83.7%) in comparison with PACNS(43.8%) (p=0.002). Among the DGMLs in basal ganglia, putamen had significantly higher (P=0.037) involvement in PACNS than in MS. More importantly, larger lesion sizes in thalamus helps to distinguish PACNS(12.4±4.3) from MS(7.9±3.7)(p=0.006). DWMLs and other DGMLs in basal ganglia were useless in differentiating the two from each other.

Conclusions: MRI features of DGMLs in thalamus and basal ganglia differ in distribution and diameters in patients with MS and PACNS. It may be helpful in making a differential diagnosis.

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Patients with multiple sclerosis criteria subsequently displayed Behçet disease signs

L Ait Aissa[1], S Nouioua[1], N Hecham[1], MI Kediha[1], N Attal[2], M Tazir[1]
[1]Mustapha Bacha University Hospital, Neurology, Algiers, Algeria, [2]Institut Pasteur of Algeria, Immunology, Algiers, Algeria

Background: Multiple Sclerosis (MS) is the most common demyelinating disease of the young adult. However, the diversity of the clinical signs and the absence of biological and radiological markers are a real challenge for differential diagnosis with other MS mimicking disorders including Neuro-Behçet disease (NBD), a common condition in the Mediterranean and North African countries.

Objectives: To evaluate the sensitivity of various clinical and laboratory signs distinguishing between MS and NBD. Underscore the possibility of late onset extra neurological markers of Behçet´s disease.

Methods: We report on five patients diagnosed and treated as relapsing remitting MS (RRMS), who had subsequently developed extra neurological signs.

Results: Mean age of onset of neurological signs was 21 years. All the patients had the 2005 Mac Donald criteria for RRMS and all had oligoclonal IgG bands in cerebrospinal fluid. Other etiologic assessments were negative. Three of the patients were treated with interferon beta 1a and two with intravenous methyl prednisolone periodic pulses. Subsequently all the patients developed recurrent oral and genital ulcers, and a pseudofolliculitis with a positive pathergy test in one patient after a period of 3 to 15 years from onset of the neurological signs.

Conclusions: Multiple Sclerosis and Neuro-Behçet disease, two common inflammatory auto-immune disorders in the Mediterranean region, may be difficult to distinguish. Usually, extra-neurological signs such as oral and genital ulcers or other inflammatory signs precede neurological involvement, but in some cases, like those we present here, these specific NBD signs may be delayed, leading to misdiagnosis and inadequate treatment. The international MS criteria panel should consider and emphasize the possibility of Neuro-Behçet disease mimicking MS in the Mediterranean region.

P236
Non MS tumefactive inflammatory lesions: diagnosis and long term evolution of 10 patients in a multicentric study

A Siri[1], C Carra[2], S Pittion-Vouyovitch[1], M Debouverie[1], C Lionnet[2], F Viala[3], D Sablot[4], J-C Ouallet[5], A Ruet[5], B Brochet[5], L Taillandier[1], L Bauchet[2], X Ayrignac[2], N De Champfleur[2], N Derache[6], G Defer[6], J De Seze[7], P Labauge[2]
[1]Universitary Hospital, Nancy, France, [2]Universitary Hospital, Montpellier, France, [3]Hospital, Toulouse, France, [4]Hospital, Perpignan, France, [5]Universitary Hospital, Bordeaux, France, [6]Universitary Hospital, Caen, France, [7]Universitary Hospital, Strasbourg, France

Background: Isolated tumefactive inflammatory lesions can rarely reveal MS. Long term course of these atypical lesions is not well known. Diagnosis and treatment are no so far defined.

Objectives: Objectives of this study were describing clinical, MRI features and long-term follow-up of such patients and notably conversion to definite MS.

Methods: Inclusion criteria were as follow-up: 1) Isolated inflammatory lesions on MR examination with a size above 20 mm, involving the white matter, enhanced after gadolinium injection, with hyperintensity on Flair sequence, hypo intensity on T1 sequence. 2) Absence of other MS lesions on the first MR. 3) Exclusion of neoplastic and systemic disease.

Results: Ten patients (6 female and 4 male) were included. The mean age of onset was 40 years old (range: 26-65). Spinal cord MR was normal in all patients. CSF study showed oligoclonal bands in 6 out of 9 (66.7%). A cerebral biopsy was performed in 5 / 10 cases showing acute inflammatory demyelination. All patients but one were treated by steroids with improvement in all cases. The mean follow-up was 34.9 months (3-165). 4/10 patients converted to clinically definite MS. None of the remaining patients relapsed.

Conclusions: This study concerned diagnosis procedure and follow of patients with isolated tumefactive inflammatory lesion without any definite MS lesion on the first MR examination. Forty percent of patients converted to clinically definite MS.

P237
Magnetic resonance spectroscopy in cases of clinical conflict between multiple sclerosis, vasculitis and multiple lacunar infarcts of the brain

SS Salama[1], MA Ramadan[2], ME Reda[3], HM Marouf[4]
[1]Alexandria, Neurology, Alexandria, Egypt, [2]Alexandria, Alexandria, Egypt, [3]Alexandria, Radiology, Alexandria, Egypt, [4]Aexandria, Neurology, Alexandria, Egypt

Background: Proton MR spectroscopy (1H-MR spectroscopy) is a well-established method for the in-vivo investigation of the normal-appearing white matter (NAWM) in patients with multiple sclerosis (MS). Metabolic changes in NAWM are of special interest in patients with clinically isolated syndromes (CIS) suggesting a conflicting clinical diagnosis of MS, vasculitis or multiple lacunar infarcts

Objectives: The purpose of this study was to investigate metabolic alterations in NAWM in patients presenting by a first demyelinating attack with use of high-field 1H-MR spectroscopy to help differentiate between MS, vasculitis and multiple lacunar infarcts.

Methods: With use of a 1.5 T whole-body MR imaging system, multi -voxel 1H-MR spectroscopy (PRESS; TR: 1500 ms; TE: 30 ms and 135 ms) of the NAWM was performed in 30 patients presenting by a first attack of demyelinating disease (posing a conflict in their diagnosis between MS and vasculitis or MS and multiple lacunar infarcts) divided into three groups based on the suspected clinical diagnosis, suspected MS group sMS(n =16), suspected vasculitis group sVasc (n=10) and suspected lacunar infarcts group sMLI (n= 4) and ten controls of matching age and sex. Metabolite ratios of NAA/Cr (N-acetyl aspartate/ creatine), NAA/Cho (N-acetyl aspartate/ choline) and mIns/Cr (Myo-inositol/ creatine) were determined.

Results: Compared to the control, mean NAWM NAA/Cr and NAA/Cho concentrations were significantly reduced in the suspected MS group (1.82 ± 0.17 and 1.63 ± 0.15 versus 2.14 ± 0.20 and 1.88 ± 0.17, $P < 0.001$) but not in the suspected vasculitis and suspected multiple lacunar infarcts groups. Mean mIns /Cr ratios were significantly elevated in the suspected MS group (0.62 ± 0.04 versus 0.48 ± 0.07, $p < 0.001$) but not in the other two groups

Conclusions: A significant increase in the activity of the glial cells and axonal damage can only be observed in patients with CIS suggestive of MS but not in patients with suspected vasculitis or multiple lacunar infarcts.

P238
HTLV-1-associated myelopathy/tropical spastic paraparesis: a differential diagnosis in primary progressive multiple sclerosis

FJ Carod Artal[1], H Mourao Mesquita[2]
[1]Raigmore Hospital, Neurology, Inverness, United Kingdom, [2]Matsumoto Medical Center, Neurology, Brasilia, Brazil

Background: Human T-cell lymphotropic virus 1 (HTLV-1) associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a

progressive neurological disease caused by infection with HTLV-1. The retrovirus can be detected thought the world, although high endemic areas has been reported in Japan, Caribbean region, South American countries and Africa. It has been estimated that around 20 million people may be infected worldwide. Transmission can occur:

1) through sexual contact;
2) vertically by prolonged breast-feeding; and
3) via infected blood products.

Objectives: To study neurological symptoms, disability progression and magnetic resonance imaging (MRI) findings in a sample of TSP/HAM patients.

Methods: Cross-sectional descriptive study. During one year, patients affected by progressive paraparesis were screened for HTLV-1 infection. Diagnosis was done by ELISA and confirmed by western blot in both blood and CSF. Proviral load in peripheral blood mononuclear cells was measured. Patients were evaluated by means of the Expanded Disability Status Scale (EDSS), Kurtzke functional systems, Barthel index, Ashworth spasticity scale and SF-36. Patients performed brain and spinal cord MRI, and somatosensory evoked potentials.

Results: 246 patients affected by paraparesis were screened. Forty patients (65% females; mean age 49.8 years) were diagnosed as having HAM/TSP. Most patients presented with progressive spastic paraparesis and bladder dysfunction. Mean time since onset was 11.2 years. On neurological exam, lower limb briskly reflexes, bilateral ankle clonus and upgoing plantar responses (97.7%), lower limb sensory disturbance (80%), lower limb proximal muscle atrophy (28.6%), and cerebellar dysfunction (21.4%) were detected. Mean EDSS score was 6, and mean Barthel index was 65. Fifty percent of patients were wheel-chair restricted or had a domiciliary walk. Proviral load ranged between 198 and 24,464 copies. Brain MRI showed hyperintensity signal areas in the white matter in 42.8%. Spinal cord MRI showed thoracic spinal cord atrophy (66.7%), and T2 hyperintensities in the cervical and thoracic spine cord (21.4%).

Conclusions: TSP/HAM is a progressive neurological disorder that may mimic clinically and radiologically multiple sclerosis in endemic areas. Some patients may initially present with gait ataxia and cerebellar dysfunction. Proviral load may be helpful to differentiate HAM/TSP patients from primary progressive multiple sclerosis.

P239

Microscopic polyangiitis presenting with long extended tranverse myelitis (LETMS)

HÖ Köse[1], V Akdemir[2], Y Celik[2]
[1]*Kafkas University Medical Faculty, Neurology, Kars, Turkey,*
[2]*Trakya University, Edirne, Turkey*

Background: Microscopic polyangiitis (MPA) is a systemic inflammatory disease characterized by systemic small-vessel inflammation with the presence of serum myeloperoxidase-specific antineutrophil cytoplasmic antibody (MPO-ANCA). MPA often presented with rapidly progressive necrotizing glomerulonephritis or alveolar hemorrhage. Neurological findings are observed in 20 -50% of cases consisting of cranial and peripheral neuropathy, and central nervous system involvement including chronic hypertrophic pachymeningitis, pituitary gland involvement, intracerebral hemorrhage, multiple ischemic infarcts, subarachnoid hemorrhage and vasculitis during the disease and rarely as initial symptom.

Objectives: To report a case of Microscopic polyangiitis (MPA) as initial manifestation of longitudinally extensive transverse myelitis (LETM).

Methods: A case report demonstrating unique LETM presentation of MPA and review of the literature.

Results: 55 year old female who presented with paraparesis was diagnosed with LTME based on radiologically and clinical findings. She made a comlete recovery after a ten day course of high dose methyl prednisolone and was started on orally methyl prednisolone and azathiopurine.

Conclusions: We reported a 55-year-old woman who chronic spastic paraparesis a clinical picture of longitudinally extensive transverse myelitis (LETM). MPA should be considered as a differential diagnosis in cases of LETM

P240

Borrelia burgdorferi - infection agent - risk assessment in MS

H Hertmanowska[1], K Szepke[1], D Zielonka[1]
[1]*Outpatient Neurology Clinic MS Care Center Clinical Trials Site Hanka Hertmanowska, Plewiska, Poland*

Background: Borrelia burgdorferi (BB) is a bacterial species of the spirochete family. This bacteria is transmitted to a human via ticks of the genus Ixodes. The infection causes symptoms of different systems including the nervous system. The aim of this work is to evaluate the MS course in patients with history of tick bite.

Objectives: 22 patients aged 19-34 (26 +-7) with relapsing-remitting MS, duration of disease 1-5 years (3.5 +-0.7), time of tick bite exposure 2-7 years (4.3+-0.5), in which borreliosis and neuroborreliosis (NB) were excluded based on American Lyme Disease Foundation criteria. 18 patients received Interferon beta-1a (InfB1a) for 1 year treatment. 4 patients did not receive any immunomodulating or immunosuppressive treatment.

Methods: All patients were strictly monitored and underwent diagnostic tests. Blood tests: Western blot (WB), lymphocyte cluster of differentiation antigen 57 (CD57), lymphocyte transformation testing (LTT). Urine tests: spirochetal antigens test (LUAT): outer surface protein A, C (OspA, OspC), cell wall protein, associated with cilia antigen (p100), membrane protein A antigen (p39), decorin binding protein A antigen (p18). All patients underwent control cerebrospinal fluid specific IgG index test (IgG CSQrel.). In all patients this test revealed the value of up to 1.3, which excluded NB. The InfB1a treatment was terminated. Patients diagnosed with the presence of antibodies against BB in blood and BB antigens in urine, received antibiotics until normalization of CD57 and gained the reduction in the frequency of exacerbations to 1-2 per year. In case of exacerbation, Methyloprednisolone was administered.

Results: In 10 patients - exacerbations every 2 months, antibodies present in WB: in immunoglobulin M: OspC p25 in 6 patients, in immunoglobulin G (IgG): OspA p31 in 8 patients, OspC p25 in 10 patients, variable major protein-like sequence-expressed (VlsE) in 6 patients, decreased CD57 count and positive LUAT in all. In all 8 patients - exacerbations every 3 months, antibodies present in

WB: in IgG: OspC p25, OspA p31, p39, decreased CD57 lymphocyte count and positive LUAT.

In all 4 patients - 3 exacerbations a year - antibodies present in WB: in IgG: OspC p25, p30, positive LTT, normal CD57 lymphocyte count and negative LUAT.

Conclusions: Infection by BB spirochete may be the cause of frequent MS exacerbations and the failure of immunomodulating treatment. In each case of frequent exacerbations, tests for infection or re-infection of BB spirochete should be performed.

P241

Clinical course, radiologic features and treatment response in patients with tumefactive demyelinating lesions in Toronto

KM Krysko[1], L Lee[1,2], P O'Connor[1,3]
[1]University of Toronto, Division of Neurology, Toronto, ON, Canada, [2]Sunnybrook Health Sciences Centre, Division of Neurology, Toronto, ON, Canada, [3]St. Michael's Hospital, Division of Neurology, Toronto, ON, Canada

Background: Tumefactive demyelinating lesions (TDLs) occur in a rare subset of individuals with central nervous system demyelinating disease. These lesions differ from typical demyelinating lesions as they are greater than 2 cm in size, may display edema and mass effect, and often mimic tumors or abscesses. Clinical and radiologic features are different than in typical multiple sclerosis (MS), leading to difficulty in diagnosis and treatment.

Objectives: To describe the demographic and clinical features of individuals with TDLs to determine the course of disease, disability and the proportion with prior diagnosis of or subsequent development of MS. We also examine clinical and radiologic responses to treatment.

Methods: A retrospective observational multi-center study of 16 individuals [81% female; mean age 43.6 years] with TDLs in Toronto between 1999-2014. Data included demographic features, clinical course, disability (Expanded Disability Status Scale (EDSS)), radiologic features and treatment response.

Results: The mean age at TDL onset was 40.2 years and 75% had polysymptomatic onset with a mean EDSS of 5. The TDL was the first demyelinating event in 12 (75%), and 50% of these individuals were subsequently diagnosed with MS while the others remained clinically isolated syndrome. Three patients (18.8%) had recurrent TDL episodes. On imaging, most lesions enhanced (95%; 72% ring enhancing) and the maximum size ranged from 2 to 7.2 cm. At onset, MRI met McDonald criteria for dissemination in space in 50%. Most TDLs (90%) were treated initially with high-dose steroids and 70% improved. Five were treated with plasmapheresis and three with cyclophosphamide induction due to poor clinical and radiologic response to steroids. Two patients improved spontaneously without treatment. At mean follow up of 26 months, 10 (50%) TDL episodes had partial and 9 (45%) complete recovery, while one had not recovered (2 months after onset). Mean EDSS at follow up was 2. Radiologically, 95% of lesions decreased in size and 76% had complete resolution of enhancement. Pathology was available to confirm the diagnosis in 4 lesions (20%).

Conclusions: Individuals with TDLs remain a diagnostic challenge given atypical clinical and radiologic features with a range of presentations, but not all patients require biopsy. Treatment response is generally good. Many patients go on to develop more typical relapsing-remitting MS, but a subset has recurrent TDLs.

Disease biomarkers

P242

Glial and neuronal markers in CSF predict progression in multiple sclerosis

MA Mañé Martinez[1,2], B Olsson[3], L Bau[2], E Matas[2], A Cobo Calvo[2], U Andreasson[3], K Blennow[3], L Romero-Pinel[2], S Martínez-Yélamos[2], H Zetterberg[3,4]
[1]Department of Neurlogy, Joan XXIII University Hospital, Universitat Rovira i Virgili, Tarragona, Spain, [2]Multiple Sclerosis Unit, Department of Neurology, Bellvitge University Hospital, Universitat de Barcelona, L'Hospitalet de Llobregat, Spain, [3]Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Department of Psychiatry and Neurochemistry, Mölndal, Sweden, [4]Institute of Neurology, University College London, London, United Kingdom

Background: Several CSF biomarkers have been suggested as prognostic markers in Multiple Sclerosis (MS). In the present study, a broad range of glial and neuronal markers were evaluated as prognostic markers in MS and were compared head to head.

Objectives: To investigate glial and neuronal biomarkers in CSF samples from patients with relapsing-remitting MS and clinically isolated syndrome (CIS) suggestive of MS and to evaluate their ability to predict conversion from clinically isolated syndrome (CIS) to clinically definite MS (CDMS) and also disability progression in MS.

Methods: CSF levels of NFL, t-tau, p-tau, GFAP, S-100B, YKL-40, MCP-1, α-sAPP, β-sAPP, and Aβ38, Aβ40, Aβ42 were analyzed in 109 CIS patients and 192 relapsing-remitting MS patients. The mean follow-up time of these 301 patients was 11.7±6.4 years.

Results: High levels of NFL were associated with early conversion from CIS to CDMS. High levels of YKL-40 and GFAP were associated with earlier progression to Expanded Disability Status Scale (EDSS) 3 and high levels of YKL-40 were associated with earlier progression to EDSS 6.

Conclusions: CSF levels of NFL in CIS patients are an independent prognostic marker for conversion to CDMS. CSF levels of YKL-40 and GFAP are independent prognostic markers for disability progression in MS.

P243

Dicer and miRNA are differentially expressed and regulated in RRMS and SPMS

B Weinstock-Guttman[1], WJ Magner[2], M Ramanathan[3], D Hojnacki[4], R Ghazi[4], K Patrick[4], A Khan[4], TB Tomasi[2]
[1]SUNY University at Buffalo, Buffalo, NY, United States, [2]Roswell Park Institute, Buffalo, NY, United States, [3]SUNY University at Buffalo, Pharmaceutical Sciences, Buffalo, NY, United States, [4]SUNY University at Buffalo, Neurology, Buffalo, NY, United States

Background: miRNA-mediated regulation of gene expression is an important component of epigenetic gene regulation. The RNase

III enzyme, Dicer, mediates the cleavage that produces mature miRNA and can be acutely regulated by IFNb *in vitro*.

Objectives: To evaluate Dicer gene and protein expression levels and microRNA (miRNA) profiles in multiple sclerosis (MS) patients as biomarkers for disease status and response to interferon (IFN) b therapy.

Methods: We enrolled 100 subjects: 25 healthy controls (HC), 25 untreated MS (NT) and 50 MS patients on weekly IM IFNβ1a (25 good responders (GR), 25 poor responders (PR)). 79% of our patients were diagnosed as Relapsing Remitting Multiple Sclerosis (RRMS) and 20% as Secondary Progressive MS (SPMS). The PR had clinical (relapses and/or increased disability) and/or MRI activity on IFN therapy while GR patients were stable. Whole cell protein and total RNA were prepared from peripheral blood leukocytes (PBL). Dicer expression was analyzed by RT-qPCR and quantitative immunoblotting. True-seq small RNA libraries were sequenced on the Illumina HiSeq 2000 platform. Counts were normalized and examined for differential expression with miRanalyzer and edgeR software.

Results: 100 subjects were enrolled; average EDSS: 2.26 in GR, 3.30 in RRMS PR, 6.20 in SPMS PR, 3.03 in RRMS NT and 4.70 in SPMS NT. Decreased Dicer protein levels were found - 14.8, 11.2, 2.6 - in HC, RRMS NT and SPMS NT respectively. 48hrs after an Avonex dose, only Good Responders showed a significant enhancement in Dicer mRNA levels (2.3-fold: p=0.0013). Dicer protein levels appeared to increase in RRMS GR and possibly in SPMS PR (RRMS PR did not show any change) but levels did not achieve statistical significance.

Of ~600 miRNA identified in each group, several miRs appear to discriminate between RRMS and SPMS. miR-484 & miR-99a-5p show significantly decreased expression in SPMS NT patients and miR-107 with enhanced expression. Neither miR-342-3p nor miR-146b-5p was differentially expressed between healthy controls and RRMS patients; however, both were significantly decreased in SPMS.

Conclusions: The alterations in Dicer mRNA, protein and miRNA expression in MS and the restriction of specific responses to diagnostic subsets of patients suggests that Dicer and miRNA regulation may play a mechanistic role in MS. The identification of alterations in Dicer expression as well as restricted miRNA expression changes offer potential as diagnostic and prognostic markers.

P244

Interferon inducible transcriptional profile in secondary progressive multiple sclerosis patients

M Gurevich[1], G Miron[1], E Hanael[1], P Sonis[1], M Dolev[1], D Magalashvili[1], A Achiron[1]
[1]Sheba Medical Center, Multiple Sclerosis Center, Ramat Gan, Israel

Background: Interferon-beta is the recommended immunomodulatory treatment for the treatment of secondary progressive multiple sclerosis (SPMS) patients. Interferon inducible transcriptional signatures have been well characterized in relapsing remitting (RRMS) patients, however, information is sparse regarding gene expression profiles of interferon-treated SPMS patients. It is of importance to identify biomarkers that will characterize beneficial treatment response to interferon beta in SPMS patients. We hypothesize that this effect will be evident in patients with interferon inducible transcriptional profile.

Objectives: To assess interferon inducible transcriptional profile in a cohort of interferon treated SPMS patients.

Methods: Blood microarray gene expression analysis was performed in 105 MS patients including 50 SPMS patients (34 females, age 52.1± 1.1 years, EDSS 6.8± 0.1, 20 treated and 30 untreated) and 55 RRMS patients (27 females, age 37.5± 1.2 years, EDDS 2.4± 0.2, 25 treated and 30 untreated). All treated patients received Interferon beta 1a (Rebif, Merck Serono) for at least 12 months. First, interferon inducible gene expression profile was determined by finding differentially expressed genes between RRMS treated and untreated patients (p value < 0.01 after False Discovery Rate (FDR)). Next, unsupervised hierarchal clustering of SPMS patients was done based on the RRMS interferon inducible gene expression profile.

Results: Interferon induced transcriptional signature of Rebif treated RRMS patients included 101 differentially expressed genes. This expression signature was enriched by genes involved in Interferon Signaling pathway (p=7.4E-08) including MX1, OAS1, IFI 1/3/35 and IRF 7/9 genes. Hierarchical clustering of SPMS patients based on this interferon inducible signature resulted in 2 main clusters correlating with treatment status. 55% (11/20) SPMS patients had interferon induced signature and 9/20 SPMS patients, despite receiving treatment, were clustered together with untreated patients as they lacked an interferon induced signature.

Conclusions: Expression of interferon inducible genes may serve as biomarkers for selecting appropriate SPMS patients for treatment.

P245

Serum neurofilament light chain levels are increased in patients with a clinically isolated syndrome

G Disanto[1], R Adiutori[1], R Dobson[1], V Martinelli[2], G Dalla Costa[2], T Runia[3], E Evdoshenko[4], E Thouvenot[5], M Trojano[6], N Norgren[7], J Lorscheider[8], C Teunissen[9], L Kappos[8], G Giovannoni[1], J Kuhle[1,8], on behalf of the 'International Clinically Isolated Syndrome Consortium (iCIS)'
[1]Queen Mary University, London, United Kingdom, [2]Vita-Salute San Raffaele University, Milan, Italy, [3]Erasmus MC University Medical Center, Rotterdam, Netherlands, [4]City Clinical Hospital # 31, St Petersburg, Russian Federation, [5]Université Montpellier 1, Montpellier, France, [6]University of Bari, Bari, Italy, [7]Uman Diagnostics, Umea, Sweden, [8]University Hospital, Basel, Switzerland, [9]VU University Medical Centre, Amsterdam, Netherlands

Background: Neurofilaments (Nf) are highly specific structural elements of neurons. Cerebrospinal fluid (CSF) neurofilament light chain (NfL) levels represent a promising biomarker for axonal injury, but obtaining CSF is a relatively invasive procedure; this limits the potential use of Nf as biomarkers in MS.

Objectives: We investigated serum NfL levels in a large cohort of clinically isolated syndrome (CIS) patients and healthy controls (HC), and assessed their ability to predict conversion to clinically definite MS (CDMS) and their relation to other markers of disease activity.

Methods: A total of 1,047 CIS cases were collected across 33 centres located in 17 different countries. The median follow-up was 4.3 years (IQR=2.9-6.4), during which 623 patients (59.5%) converted to CDMS. We selected 100 patients with the shortest time of conversion to CDMS (fast converters (FC), median (interquartile range, IQR) conversion time: 110 days (73-139)) and 100 with the longest follow-up time in the absence of conversion (non-converters (NC), follow-up: 6.5 years (5.3-7.9)). Serum NfL concentration in these CIS samples and 92 British healthy controls (HC) were measured using our previously validated electrochemiluminescence immunoassay.

Results: NfL levels were higher in FC (median 24.1 pg/ml (IQR 13.5-51.8), odds ratio (OR)=5.9, 95%CI=2.6-13.0, p=1.5x10^{-5}) and NC (19.3 pg/ml (13.6-35.2), OR=7.0, 95%CI=2.9-17.3, p=2.3x10^{-5}) than in HC (7.9 pg/ml (5.6-17.2)). However, NfL levels were not associated with fast conversion (OR=1.4, 95%CI=0.7-2.7, p=0.37). Serum NfL concentration was positively associated with presence of gadolinium enhancing lesions (OR=2.7; 95%CI=1.1-6.4; p=0.026), larger T2 lesion load (OR=2.36; 95%CI=1.21-4.59; p=0.011), higher EDSS at baseline (OR=2.5; 95%CI=1.2-5.3; p=0.013), but not with the presence of oligoclonal bands in the CSF (OR=1.7; 95%CI=0.8-3.7; p=0.214).

Conclusions: Median serum NfL levels are abnormally high in CIS patients compared to healthy individuals, correlate with concurrent inflammatory MRI activity and disability and therefore represent a promising and easily accessible biomarker that deserves further exploration.

P246

Gray matter related proteins in cerebrospinal fluid differentiate between multiple sclerosis and other acquired demyelinating syndromes in childhood

V Singh[1], D van Pelt[1], M Stoop[1], C Stingl[1], I Ketelslegers[1], R Neuteboom[1], T Luider[1], R Hintzen[1]
[1]Erasmus MC, Rotterdam, Netherlands

Background: A few percent of all multiple sclerosis (MS) patients experience a first attack in childhood. In children, such a first acquired demyelinating syndrome (ADS) can remain monophasic. However, a significant part of these children will subsequently be diagnosed with MS. Currently exact risk prediction for future MS diagnosis is not possible. In the present study, we have analyzed cerebrospinal fluid (CSF) by high resolution and sensitive mass spectrometry in order to find CSF protein markers expressed during initial attack of CNS inflammation that can differentiate children with MS from those with monophasic ADS.

Objectives: Identification of CSF biomarkers for MS in children with an initial acquired central nervous system demyelinating syndrome (ADS).

Methods: We included 18 children with MS and 21 children monophasic ADS for proteomic analysis of trypsinised CSF (20 µl) by nano liquid chromatography Orbitrap mass spectrometry. Differentially abundant peptides between the groups were identified using univariate statistical analysis.

Results: A total of 2260 peptides corresponding with 318 proteins were identified from the total set of samples. A stringent filtering procedure was used for subsequent rigid positive of peptides. In this way, 88 peptides were significantly differentially abundant between children with MS and monophasic ADS (at p< 0.01 two

or more peptides identified). Peptides with increased abundance in MS were 53 that corresponded with 14 proteins, of which 12 linked to neuronal functions and structures such as synapse, axon, extracellular matrix proteases (for example Amyloid-like protein 2, Neurofascin, Carboxypeptidase E, Brevican, Contactin-2). Two of 14 were related to immune function. Thirty-five peptides were with decreased abundance in MS, which corresponded to 7 proteins. From these seven, five were linked specifically with the innate immune system (Haptoglobin, C4b-binding protein alpha chain) and Monocyte differentiation (antigen CD14) and the two other relate to inflammation.

Conclusions: monophasic ADS can be differentiated from MS in children primarily by gray matter proteins and immune related proteins. Further insight into the role of these proteins in childhood-onset MS can be useful for disease process understanding and might be useful as a future tool to differentiate children with MS from monophasic ADS.

P247

Global metabolomics identifies a metabolic profile of multiple sclerosis

P Bhargava[1], B Poore[2], C Nguyen[2], A Le[2], PA Calabresi[1]
[1]Johns Hopkins University School of Medicine, Neurology, Baltimore, MD, United States, [2]Johns Hopkins University School of Medicine, Pathology, Baltimore, MD, United States

Background: Multiple Sclerosis (MS) is a chronic demyelinating disorder of the central nervous system with inflammatory and degenerative components. Given that some metabolic changes have been reported by recent studies in models of MS, we hypothesized that metabolic pathway alterations in MS would be measurably different from healthy controls. The metabolic changes identified in MS could provide insight into pathogenesis of the disease, as well as enable the discovery of new biomarkers of disease progression and response to therapy.

Objectives: To examine the metabolic profile of subjects with MS and to compare this with healthy controls.

Methods: Plasma from 25 MS patients and 15 healthy controls was subjected to metabolic extraction using 1:2:0.8 of chloroform, methanol, and water buffer to generate aqueous, organic, and protein fractions. Normalization with protein concentration fraction was followed by data acquisition using the Agilent 6540 Quadrupole-Time-of-Flight (Q-TOF) mass spectrometer-Agilent 1290 HPLC. Data were then analyzed using Agilent Mass Hunter and Agilent Mass Profiler Professional and Qual software to determine the metabolic profile of each group. Samples were grouped according to disease status and differences in metabolite abundance between these groups. Statistical significance was determined using an unpaired t-test with a corrected Benjamini-Hochberg threshold of p=0.05. Furthermore, metabolic pathways were reconstructed and explored from metabolic data to identify pathway abnormalities.

Results: 2864 metabolites were identified in the negative aqueous layer, of which 84 showed differential regulation in MS subjects as compared to controls. Principal components analysis and unsupervised clustering demonstrated strong separation between MS and healthy controls. Among the metabolic pathways found to be altered, tryptophan metabolism and the tricarboxylic acid cycle stood out most profoundly. Metabolites in these pathways were

significantly different between MS and control samples. Further pathway analysis and metabolite identification is being performed.

Conclusions: Comparative global metabolic profiling revealed a distinct metabolic profile of MS as compared to healthy controls. This could serve as an important tool for biomarker discovery and provide new insights into the pathogenesis of the disease.

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CSF biomarkers of inflammation and neuronal damage in acute optic neuritis predict later development of MS and long-term disability

S Modvig[1], M Degn[1], JL Frederiksen[1], F Sellebjerg[2]
[1]Glostrup University Hospital, University of Copenhagen, Dept of Neurology, Glostrup, Denmark, [2]Danish MS Center, Rigshospitalet, University of Copenhagen, Dept of Neurology, Copenhagen, Denmark

Background: Cerebrospinal fluid (CSF) levels of inflammatory biomarkers have been suggested to predict multiple sclerosis (MS) development after clinically isolated syndromes, but there is a need for studies looking at the long-term prognosis.

Objectives: To assess the predictive ability of CSF biomarkers of inflammation and tissue-damage with regards to development of clinically definite MS (CDMS) and long-term disability.

Methods: 86 patients with acute optic neuritis (ON) as a first demyelinating event seen in our clinic between 1993 and 2002 were included retrospectively. Patients had undergone a lumbar puncture < 3 months from onset, CSF was stored at -80 C. Established MS-risk parameters (MRI, CSF leukocyte count, IgG-index and oligoclonal bands) were registered and CSF levels of chitinase-3-like-1 (CHI3L1), osteopontin, neurofilament light chain (NFL), myelin basic protein, CCL2, CXCL10, CXCL13 and matrix metalloproteinase-9 were measured by ELISA. Patients were followed up after a median time of 13.6 (range 9.6-19.4) years. 81.4 % were examined by the corresponding author incl. an EDSS and multiple sclerosis functional composit (MSFC) evaluation. 18.6 % were interviewed by phone, incl. an EDSS-questionnaire (Lechner-Scott et al, MSJ 2003). Time to CDMS was confirmed by collection of original charts from treating hospitals. Cox regression was used for time to CDMS, multivariate regression for multiple sclerosis severity score (MSSS) and Spearman correlation and linear regression for paced auditory serial addition test (PASAT).

Results: 46 of 86 (53.5%) developed CDMS between ON and follow-up. Of the established MS-risk parameters, MRI (p=0.0008) and leukocyte count (p=0.036) combined predicted MS development best. These two were then tested in a second model with the other CSF biomarkers, where MRI (p=0.0001) and CHI3L1 (p=0.017) combined predicted MS development best. NFL was the only significant predictor of long-term disability as assessed by the MSSS (p=0.0465). CHI3L1 predicted long-term cognitive impairment as assessed by the PASAT (r=-0.41, p=0.015).

Conclusions: NFL and CHI3L1 were significant predictors of long-term physical and cognitive disability. We have previously suggested these to be markers of tissue damage-related inflammation in ON, supporting these findings. Furthermore, CHI3L1 appeared to predict CDMS better than the CSF parameters

commonly used today. Thus, the two hold potential as clinically valuable biomarkers of future MS disease and disability after a first demyelinating event.

P249

Cerebrospinal fluid osteopontin and neurofilament levels mark different brain atrophy patterns in clinically isolated syndrome

V Direnzo[1], C Tortorella[1], S Zoccolella[1], M Ruggieri[1], M Mastrapasqua[1], D Paolicelli[1], F Dicuonzo[1], M Trojano[1]
[1]University of Bari, Bari, Italy

Background: MRI measures are known surrogate markers of disease activity and disability progression in patients with Clinically Isolated Syndrome (CIS) suggestive of Multiple Sclerosis (MS). Several studies prompt cerebrospinal fluid (CSF) Neurofilament light chain (NFL) and Osteopontin (OPN) as potential surrogate markers of inflammatory and neurodegenerative changes since the earliest stage of the disease.

Objectives: To evaluate the relationship between CSF NFL and OPN levels and MRI measures in patients with CIS.

Methods: Forty-one consecutive CIS patients were enrolled in the study. They underwent lumbar puncture (LP) and brain conventional MRI. CSF NFL and OPN were measured using a standard ELISA assay. Measures of brain volume [total brain volume (TBV), grey matter volume (GMV), peripheral grey volume (PGV), white matter volume (WMV), and ventricular volume] were obtained by SIENAX. Corpus callosum index (CCI) was also calculated. Measures of brain volume and CCI were categorized in "high" (above the median value) and "low" (below the median value) for the Anova analysis. Multivariate analysis was used to evaluate the relationship between CSF biomarkers and measures of brain volume.

Results: Patients with "low" GMV and "low" PGV showed higher CSF NFL levels compared to patients with "high" GMV [1770.8 (392,72-5587) vs 1094.65 (320.95-3112)] and "high" PGV [1945.3 (392,72-5587) vs 992.5 (320.95-3112)] (p=0.03 and p=0.01 respectively). In a multivariate analysis using GMV and PGV as predictors (covariates: age at LP, sex, number of T2 and enhancing lesions and number of CSF oligoclonal bands), CSF NFL levels were an independent predictors of GMV (R: -0.39; p= 0.01) and PGV (R: -0.41; p=0.008). Conversely, CSF OPN levels were the only significant predictors of CCI (R:-0.3 p=0.05).

Conclusions: These findings suggest that CSF NFL and OPN mark different patterns of brain damage in CIS patients tracking mainly grey matter and subcortical white matter damage respectively.

P250

The proteome profile of the urine is different in patients with neuromyelitis optica compared to multiple sclerosis and healthy subjects

HH Nielsen[1], LP Kristensen[2], HC Beck[2], J Reddy[3], Z Illes[1]
[1]Odense University Hospital, Department of Neurology, Odense C, Denmark, [2]Odense University Hospital, Center for Clinical Proteomics, Odense C, Denmark, [3]University of Nebraska-Lincoln, School of Veterinary Medicine and Biomedical Sciences, Lincoln, NE, United States

Background: The demyelinating diseases comprise a broad spectrum of diseases like multiple sclerosis (MS) neuromyelitis optica (NMO) and the NMO spectrum disorders (NMO-SD). Despite clear classification criteria, these diseases can be difficult to differentiate, especially early in the disease. However, early differentiation is of vital importance since misclassification can lead to deterioration of the condition due to incorrect medication.

Objectives: We hypothesized that analysis of "omics" in urine may have the capacity to yield quantitative biomarkers. In addition, MS and NMO/NMO-SD patients may exhibit specific differences in the molecular composition (proteins, posttranslational modifications) of the urine, which reflect the pathogenesis, and may enable early differentiation. Specifically, the hypothesis is tested by a thorough and unbiased analysis of the whole proteome.

Methods: Paired urine and plasma samples were collected from 7 age- and sex-matched patients with anti-AQP4^{+} NMO, 7 patients with MS and 7 healthy controls (HS). By using a liquid chromatography-based tandem mass spectrometry (LC-MS/MS), we quantitatively examined proteins in the urine.

Results: We identified 281 differentially altered proteins/peptides in the urine of patients with NMO compared to HS, and 289 proteins/peptides in MS. Out of these molecules, 110 of the NMO-specific peptides and 83 of the MS-specific peptides were also differentially expressed in the other group. Comparing those peptides, 50 overlapped between MS and NMO, but 33 were "truly MS-specific" and 50 "truly NMO-specific". Ontology annotation revealed molecules participating in regulation of biological processes, cell proliferation/communication and cell death among others.

Conclusions: Our results indicate that proteome profile of the urine is different in MS and NMO compared to healthy subjects and urine obtained from NMO and MS also differ. In the next phase, paired urine and plasma samples have been collected from additional patients with anti-AQP4^{+} NMO, MS and HS for validation and more thorough analysis of the proteome, and quantitative analysis of the individual molecules. Urine may be useful to identify biomarkers for MS and NMO.

P251

Diagnostic contribution of soluble CD163 to a panel of biomarkers in newly diagnosed patients with multiple sclerosis

M Stilund[1,2], MC Gjelstrup[2], T Petersen[1], HJ Møller[3], PV Rasmussen[1], T Christensen[2]
[1]Aarhus University Hospital, Department of Neurology, Aarhus C, Denmark, [2]Aarhus University, Department of Biomedicine, Aarhus C, Denmark, [3]Aarhus University Hospital, Department of Clinical Biochemestry, Aarhus C, Denmark

Background: Biomarkers for Multiple Sclerosis (MS) are needed for optimizing diagnosis, treatment and prognostic management. CD163 is a macrophage/microglial specific protein, which in its soluble form (sCD163) has been shown to be up-regulated in serum from patients with MS.

Objectives: The aim of this study is to investigate the potential diagnostic contribution of sCD163 together with other MS diagnostic biomarkers, both novel and well-known. The biomarkers will be correlated to the diagnosis, clinical status as well as the MRI status of each patient.

Methods: Paired samples of CSF and serum were collected from 125 patients suspected for MS at the Department of Neurology at Aarhus University Hospital, Denmark. All samples were frozen at -70°C and stored for subsequent analysis. For each patient, a MRI scan was performed and the revised diagnostic criteria for MS used. Based on these criteria, patients were divided into four groups: remitting- relapsing MS (n=44), primary progressive MS (n=15), clinically isolated syndrome (n=27), and a symptomatic control (SC) group (n=39) who had neurological symptoms yet a normal CSF and a normal neurological clinical examination. All samples were examined post-diagnosis with enzyme-linked immunosorbent-assays for sCD163 as well as a series of published MS biomarkers. Data were analyzed using Pearson correlation, and in an age adjusted linear regression model.

Results: Median levels of CSF/serum ratio of sCD163 levels were significantly elevated in patients with MS, especially patients with primary progressive MS (p < 0.001). Among the tested biomarkers, the sCD163 CSF/serum ratio correlated with Neurofilament light polypeptide (Nf-L) levels (r=0.39; p< 0.001), and median levels of Nf-L were significantly elevated (p< 0.001) in patients with newly diagnosed MS.

Conclusions: The preliminary results of this study suggest that sCD163 could contribute to the efficacy of biomarker panels in diagnosing patients with MS. Analyses of correlations to clinical measures and MRI, as well as the cumulative diagnostic proficiency of the extended panel are ongoing.

P252

A diagnostic test for MS leading to novel insights into pathogenesis: unique B-cell mutational patterns that create antibodies with unique CNS binding

B Greenberg[1], W Rounds[1], J Rivas[1], A Ligocki[1], M Levin[1], D Bigwood[2], E Eastman[2], L Cowell[1], N Monson[1]
[1]University of Texas Southwestern, Dallas, TX, United States, [2]DioGenix, Gaithersburg, MD, United States

Background: Multiple Sclerosis is known to be an autoimmune disorder that results in diffuse injury to the brain, spinal cord and optic nerves. Both a relapsing remitting version of the condition and a progressive form of the condition has been identified, but there is a lack of pathobiological understanding. Prior research has identified a unique pattern of somatic hypermutation in B cells from MS patients that is able to discriminate between MS and other neurologic disease. Yet, the biological implications of this pattern, until now, has not been well understood. Prior pathological studies have identified subtypes of MS in biopsy and autopsy specimens, but there has been no way to biologically separate MS into subtypes without tissue. Creating a new diagnostic test for MS, based in the underlying biology of the disease would be beneficial both for clinical practice and for advancing our understanding of pathogenesis.

Objectives: This study was designed to confirm the clinical validity of the B cell somatic hypermutation pattern found in MS patients and to determine the biologic relevance of this pattern.

Methods: CSF from over 300 patients being evaluated for MS was collected prospectively and handled in a uniform manner. Cells were isolated and next generation sequencing was used to amplify B cell sequences from the VH region. Patients were categorized as MS by an adjudication panel and the operating

characteristics of the diagnostic test were analyzed. A subset of patients had recombinant antibodies generated form the unique sequences and were subjected to staining studies on mouse and human tissue.

Results: Measurement of the somatic hypermutation frequency in MS patients yielded a diagnostic test for MS that was greater than 80% sensitive and specific. It was superior to conventional oligo-clonal band data as historically presented. Recombinant antibodies from patients within this study were created and found to bind to neurons and astrocytes with unique patterns. Specific mutations were associated with different staining patterns. Analysis of data for correlations with cognitive outcomes is ongoing.

Conclusions: Quantifying somatic hypermutation patters is a viable technology for the clinic and provides a useful tool for diagnosing multiple sclerosis patterns. Studies of the recombinant antibodies produced from these patients has yielded novel insights into the pathogenesis of MS with a predominance of neuronal and astrocytic binding patterns being observed.

P253
Peripheral blood cells from patients with benign multiple sclerosis are characterized by a TNF gene expression signature

NM Fissolo[1], R Nurtdinov[1], L Negrotto[1], S Malhotra[1], À Vidal-Jordana[1], J Castilló[1], X Montalban[1], M Comabella[1]
[1]Vall Hebron University Hospital, Multiple Sclerosis Centre of Catalonia, Neuroimmunology Department, Barcelona, Spain

Background: Multiple sclerosis (MS) is one of the leading causes of disability among young adults. In approximately 80-85% of MS patients, the disease follows a relapsing-remitting course (RRMS). Over time, the majority of these patients will enter a progressive phase (secondary progressive MS - SPMS). The remaining 15-20% of MS patients follows an essentially progressive course from the beginning and they are referred to as primary progressive MS (PPMS). MS disease course is highly unpredictable and disease activity biomarkers that may help in the distinction between MS patients with benign and aggressive disease courses are unfortunately lacking.

Objectives: In the present study, we aimed to identify the gene expression signatures associated with different clinical forms of MS and activity phases of the disease.

Methods: A total of 47 untreated MS patients and 19 healthy controls were included in the study. The MS group included 10 patients with early RRMS (in the first 5 years after disease onset), 10 patients with SPMS, 13 patients with PPMS, 10 patients with benign disease course (defined by EDSS ≤3 after 10 years from disease onset), and 4 patients with aggressive disease courses (defined by the presence over the last year of 2 or more relapses and increase of at least one point in the EDSS). The gene expression profiling was determined in peripheral blood mononuclear cells (PBMC) from MS patients and HC using microarrays (Affymetrix HG-U219 chip).

Results: PBMC from MS patients with benign disease course were characterized by an over-expression of TNF compared with cells from patients with other clinical forms and activity phases of the disease ($p=1.6\times10^{-7}$ vs. early RRMS; $p=1.5\times10^{-7}$ vs. SPMS; $p=8.2\times10^{-6}$ vs. PPMS; $p=1.9\times10^{-4}$ vs. aggressive MS) and HC ($p=4.5\times10^{-6}$). A large number of TNF-induced genes were also significantly up-regulated in PBMC from patients with benign MS, which included IL1B, CXCL2, CXCL3, CCL3, IER3, NFKBIA, and TNFAIP3 among others. Microarray findings were validated by real time PCR.

Conclusions: Unexpected results from clinical trials with anti-TNF therapies in MS patients together with the finding of a TNF signature in patients with benign course suggest that TNF, rather than being harmful to MS, could play beneficial roles in disease evolution.

P254
Cerebrospinal fluid proteome analysis reveals differentially abundant proteins in multiple sclerosis

J Füvesi[1], R Danielsson[2], K Bencsik[1], J Hanrieder[2,3], V Zsiros[1], C Rajda[1], P Håkansson[4], L Vécsei[1,5], J Bergquist[2,6]
[1]University of Szeged, Department of Neurology, Szeged, Hungary, [2]Uppsala University, Analytical Chemistry, Department of Chemistry-Biomedical Center, Uppsala, Sweden, [3]Chalmers University of Technology, Analytical Chemistry, Department of Chemical and Biological Engineering, Göteborg, Sweden, [4]Uppsala University, Department of Physics and Astronomy, Uppsala, Sweden, [5]MTA-SZTE Neuroscience Research Group, Szeged, Hungary, [6]Uppsala University, Science for Life Laboratory (SciLife Lab), Uppsala, Sweden

Background: Multiple sclerosis (MS) is a demyelinative disorder of the central nervous system that affects mainly young adults. Current diagnostic cerebrospinal fluid (CSF) tests examine the presence of oligoclonal bands and IgG index to support the diagnosis of MS.

Objectives: The aim of this study was to find differences in the CSF proteome of MS and control subjects or the different clinical forms of the disease.

Methods: Using liquid chromatography- Fourier transform ion cyclotron resonance - mass spectrometry (LC-FTICR MS) we analyzed tryptically digested CSF from MS (n=22) and control (n=15) subjects individually. CSF samples were obtained from diagnostic lumbar puncture (LP). The MS group included clinically isolated syndrome (CIS) (n=10), relapsing-remitting (R) (n=6) patient samples and a few samples from secondary and primary progressive clinical forms of the disease as well as a fulminant case. In case of the control subjects the presenting symptom was headache, but the routine CSF analysis gave normal values. Each sample was measured at least twice. The raw data was calibrated using mass and retention time values of human serum albumin peptides. Based on the combined mass and normalized retention time (net) values 2891 variables could be distinguished. These were compared to the mass and net values of a data base of proteins previously found in CSF by in silico digestion. The intensities of the well identified proteins were compared between the sample groups and expressed as ratios (CIS/C, R/C, CIS/R, MS/C).

Results: The mean age (year) at LP was 30.7 in the CIS, 35.2 in the R and 33.0 in the C group. The mean duration of the disease was 9.3 months in the CIS and 9.2 years in the R group. The mean EDSS was 1.6 points in the CIS and 2.4 in the R group, respectively.

Fifty proteins were identified with at least 20 % coverage of all possible hits in the SwissProt database. After further quality restrictions 15 proteins were considered to be well identified. Based on the

group median intensities all of these proteins were up-regulated in MS patients. Although the variation is high between individuals, there is a significant difference between the group means (p=0.002). Alpha-1-antichymotrypsin showed the highest increase in MS compared to the control group (MS/C ratio: 9.8).

Conclusions: Proteomic studies of CSF may lead to the development of more specific biomarkers that allow earlier diagnosis and distinction between clinical forms of the disease.

P255

Levels and age dependency of neurofilament light in healthy individuals and its relation to the brain parenchymal fraction

M Vågberg[1], N Norgren[2], A Svenningsson[1]
[1]Umeå University, Dept. of Pharmacology and Clinical Neuroscience, Umeå, Sweden, [2]Uman Diagnostics AB, Umeå, Sweden

Background: Neurofilament light (NFL) is an integral part of the axonal cytoskeleton and is released into the cerebrospinal fluid (CSF) in cases of axonal damage. Increased levels of NFL in CSF have therefore been used as a marker for ongoing axonal damage, for example in patients with multiple sclerosis. In order to interpret values of NFL in a diseased state, knowledge of NFL in the healthy is required. Another biomarker for neurodegeneration is the investigation of brain atrophy using magnetic resonance imaging (MRI), commonly measured as brain parenchymal fraction (BPF). Both brain atrophy and levels of NFL are associated with neurodegeneration, for example in the case of multiple sclerosis, where both are associated with increased disease activity. A potential correlation between levels of NFL and BPF in healthy individuals has not been investigated.

Objectives: This study aims to present the levels of NFL in healthy individuals stratified for age, and investigate if NFL is correlated to brain atrophy measured by MRI.

Methods: The level of NFL in CSF was analysed in 53 healthy volunteers aged 21 to 63. In addition, 48 of the volunteers underwent MRI and BPF was determined via a semiautomatic, relaxometry based technique.

Results: Mean (±SD) NFL of the whole study population was 355 (±214), mean BPF was 0.867 (±0.035). When divided into subgroups stratified for age, the mean NFL was: age 20 to 30 years: 186 (±50.0, n=17), age 30 to 40 years: 288 (±47.2, n=15), age 40 to 60 years: 491 (±170, n=18), age over 60 years: 834 (±356, n=3). Both the level of NFL and the BPF was significantly correlated with age and with each other, but the correlation between BPF and NFL did not retain statistical significance if controlled for age.

Conclusions: This study presents data on age-stratified levels of NFL in the CSF of healthy individuals. It is shown that levels of NFL increase with age. There was a significant correlation between the level of NFL and the BPF, which probably represents the association of both these variables with age related neurodegeneration.

P256

UP-regulation of Nod-like receptor signaling in multiple sclerosis

F La Rosa[1], F Piancone[1], I Marventano[1], L Mendozzi[1], D Caputo[1], M Rovaris[1], M Saresella[1], M Clerici[1,2]
[1]Fondazione Don C. Gnocchi ONLUS IRCCS, Laboratorio di Medicina Molecolare e Biotecnologie, Milano, Italy, [2]University of Milano, Milano, Italy

Background: Activation of the innate immune response is mediated the ligation of specialized receptors, including Toll-like receptors (TLR) and Nod-like receptors (NLR), and results in the production of inflammatory cytokines. IL-1b and IL-18, in particular, are secreted following the NLR-dependent activation of the inflammosome. NLRP3 upregulation was observed in CSF and serum of both Multiple Sclerosis (MS) patients and of mice during the development of Experimental autoimmune Encephalomyelitis (EAE).

Objectives: To better investigate the possible involvement of the inflammasome in MS.

Methods: we stimulated with LPS in association with MOG or MBP, peripheral blood mononuclear cells (PBMC) of 30 patients with a clinical and Magnetic Resonance Imaging (MRI) diagnosis of relapsing-remitting (RRMS), secondary progressive (SPMS), or benign (BEMS) MS. The expression of 84 genes involved in the inflammasome pathway was evaluated by RT-PCR; proinflammatory cytokines and caspase-1 were measured by ELISA in supernatants. Results were compared to those obtained in 20 age- and sex-matched healthy controls (HC).

Results: a number of genes, including the inflammasome components NLRP3 and Caspase-1, as well as and IL-1b and IL-18, are significantly up-regulated in MS patients compared to HC(p< 0.01), with the highest degree of up-regulation seen in SPMS patients. The concentration of IL-1b and IL-18 was similarly significantly augmented in SPMS, the increase being significant for IL-1b(p< 0.01).

Conclusions: These results indicate an involvement of the inflammasome pathway in MS and suggest the possible usefulness of therapeutic strategies targeting NPLR3 modulation in the therapy of this disease.

P257

Discovery of biomarkers reflecting progression pathophysiology for relapse remitting and primary progressive MS subtypes by multiplex aptamer approach

A Malekzadeh[1], J Killestein[2], J Kuhle[3], C Teunissen[1]
[1]VU University Medical Center, Clinical Chemistry, Amsterdam, Netherlands, [2]VU University Medical Center, Neurology, Amsterdam, Netherlands, [3]University Hospital Basel, Department of Biomedicine, Basel, Switzerland

Background: The patho-physiology of multiple sclerosis disease onset and progression remains undetermined. Understanding this is beneficial for prognosis, treatment strategies and for the development of new neuro-protective therapies.

Objectives: To unravel the patho-physiology of MS disease progression and possible identification of progression biomarkers, we performed proteomics on plasma of relapse-remitting MS (RRMS) patients with a benign disease course, RRMS patients with an aggressive disease course and primary progressive MS (PPMS) patients.

Methods: The proteomics assay is a multiplex aptamers platform (Somalogic). This highly sensitive assay allows detection of 1129 markers in body fluids of choice. A selection of patients based on their baseline and follow-up expanded disability status scale (EDSS) scores was performed. An exploratory phase was conducted on plasma of RRMS patients with a benign disease course

(n=10), aggressive disease course (n=10) and PPMS (n=10). Subsequently, to validate the exploratory data, a selection of patients with a comparable progression rates, age, gender and subtypes from an independent cohort was made. Moreover, for the validation cohort healthy controls (n=10) were included.

Results: Comparisons between RRMS-benign and RRMS-aggressive groups, for both independent runs, showed discovery of approximately 50 significant markers. These markers primarily associated with inflammatory and intracellular pathways. The validation run confirmed four out of the fifty markers. Comparisons between RRMS-all and PPMS for both runs, resulted in discovery of approximately 70 significant markers. This markers associated with cell cycle, apoptotic and metabolic pathways. Validation run confirmed five markers between these groups.

Conclusions: These findings support the idea that the disease progression of RRMS could be associated with immune related pathways, whereas the pathophysiology of the PPMS subtype could be represented by alterations in cell cycle and apoptosis related alterations and therefore follows a steady neurodegenerative course with no immune related exacerbations. Moreover, validations of the confirmed markers that potentially could be used as progression biomarkers are ongoing.

P258

Orbitrap proteomics analysis of cerebrospinal fluid to identify novel markers for progression after a first attack of demyelination

TF Runia[1], M Stoop[1], C Stingl[1], T Luider[1], RQ Hintzen[1]
[1]Erasmus MC, Neurology, Rotterdam, Netherlands

Background: In recent studies we have shown the validity of cerebrospinal fluid (CSF) proteomics studies for the detection of pathologically relevant proteins for multiple sclerosis (MS). Because the course of the disease after clinically isolated syndrome (CIS), the first presenting symptom of MS, is highly variable, there is a strong need for biomarkers in CIS patients.

Objectives: To identify novel markers for disease progression after CIS using advanced mass spectrometry techniques.

Methods: We included 47 CIS patients with CSF samples, clinical and MRI data collected within 2 months after symptom onset, and 64 controls. CSF samples were enzymatically digested and subsequently measured on a nanoLC-ESI-Orbitrap mass spectrometer. Using a 180 minute chromatographic gradient on a 50 centimeter C18 column the digested peptides were separated prior to measurement on the mass spectrometer to enable the identification of a maximum and unprecedented amount of proteins in one run. Machine performance was monitored by measuring a quality control sample after every six samples. The mass spectra were analyzed using specialized software (Progenesis LC-MS), and the identified proteins were analyzed for statistically significant abundance between groups.

Results: A total of 3009 peptides were identified, relating to 555 proteins. Only 2 proteins were significantly more abundant in CSF of CIS patients than in controls: chitinase 3-like protein 1, and Ig kappa chain VII region. 11 proteins were lower in CIS patients than controls (Voltage-dependent calcium channel subunit alpha-2/delta-1, Seizure 6-like protein 2, Calsyntenin-3, Neurosecretory protein VGF, Superoxide dismutase [Cu-Zn], Ribonuclease pancreatic, Trans-Golgi network integral membrane protein 2, Extracellular matrix protein 1, Transmembrane protein 132A, Cerebellin-3, Xylosyltransferase 1). There were no significant differences in protein levels between patients who did and did not reach a diagnosis of clinically definite MS. We also found no differences related to the number of MRI lesions, type of CIS or fatigue.

Conclusions: This confirms the earlier finding of chitinase 3-like 1 in the pathology of MS when compared to controls, but does not confirm its association with conversion to clinically definite MS. A striking finding is, that most found proteins were actually lower in CIS patients than in controls, which is counterintuitive but might lead to new insights into the pathophysiology of MS.

P259

Metabolomics of cerebrospinal fluid from progressive MS patients

F Mir[1], D Lee[1], H Ray[1], SA Sadiq[1]
[1]Tisch MS Research Center of New York, New York, NY, United States

Background: Identification of biomarkers for diagnosis and therapeutic monitoring of patients with multiple sclerosis (MS) has proven difficult due to the varied clinical course and complex pathophysiology associated with this autoimmune condition.

Objectives: The purpose of this study was to determine and compare the global metabolic profiles in human cerebrospinal fluid (CSF) associated with disease progression in multiple sclerosis (MS) and allow stratification of the two progressive disease subtypes.

Methods: CSF obtained from controls with no disease (n=15), patients with primary progressive multiple sclerosis (PPMS; n=15), and patients with secondary progressive multiple sclerosis (SPMS; n=15) were analyzed on the GC/MS and LC/MS/MS platforms conducted by Metabolon (Durham, NC).

Results: A total of 198 compounds of known identity were included in the analysis. 26 biochemicals were found to be significantly affected in the MS cohort as compared to the controls. Furthermore, the analysis also revealed differences between the primary progressive and secondary progressive populations (18 biochemicals). Of particular interest are the changes in carbohydrate metabolism, creatine and creatinine metabolism, ECM remodeling and neuroactive amino acids.

Conclusions: In conclusion, results from this global profiling study revealed perturbations in the CSF metabolome that were both consistent and different when comparing patients with PPMS or SPMS. We are currently validating these differential CSF signatures in an independent cohort. And believe they will aid in our understanding of progressive disease mechanisms in particular.

P260

Biomarkers in cerebrospinal fluid (Tau, phospho-Tau (181) and neurofilament light) in clinically isolated syndrome patients and healthy controls

E Koutsouraki[1], T Kalatha[1], E Hatzifilippou[1], P Gerasimidou[1], A Orologas[1], N Vlaikidis[2]
[1]Aristotle University, AHEPA Hospital, 1st Department of Neurology, Thessaloniki, Greece, [2]Aristotle University, Papanikolaou Hospital, 3rd Department of Neurology, Thessaloniki, Greece

Background: Several cerebrospinal fluid (CSF) proteins have been studied as potential predictors of clinically isolated syndrome (CIS) converted to multiple sclerosis (MS). Among the multitude of biomarkers which have been tested, neurofilaments and tau protein, markers of axonal and neuronal damage, seem to stand out for potential prognostic value.

Objectives: The aim of the present study was to evaluate CSF biomarkers indicating axonopathy and neuronal death in CIS compared with controls.

Methods: Total tau (tTau) and phosphorylated Tau 181 (pTau) were analyzed and determined using the Elisa technique in 68 CSF samples, of 55 MS patients (43±12) and 13 controls (40±12) who didn´t suffer from any inflammatory or degenerative disease of CNS. We used the diagnostic criteria of McDonald et al. MS patients were 44 females and 11 males, and controls were 4 females and 9 males. 18 (33%) of the patients suffered from CIS, 23 (42%) from relapsing/remitting MS (RRMS), 4 (7.3%) from primary progressive MS (PPMS), 5 (9.1%) from secondary progressive MS (SPMS), 3 (5.4%) from relapsing progressive type of MS (RPMS).

Neurofilament light (NFL) was analyzed and determined using the Elisa technique in 62 CSF samples of the same cohort. The group consisted of 49 MS patients (42±12) and 13 controls (41±12). MS patients were 40 females and 9 males, while the controls were 4 females and 9 males. 18 (36.7%) of the patients suffered from CIS, 21 (42.8%) from RRMS, 2 (4%) from PPMS, 4 (8%) from SPMS, 2 (4%) from RPMS.

We used the commercial available kits for the ELISA technique (Innogenetics, Belgium). Statistical analysis was performed using SPSS statistical package 17.0.

Results: Our results, regarding the comparison between CIS patients and healthy controls, indicated:

§ higher tTau concentration in CIS patients in comparison with the controls (U=69, z=-1.9, p=0.05)

§ significantly lower pTAU levels in CIS patients in comparison with the controls (U=230, z=-1.9, p=0,05) CIS patients demonstrated lower mean age (36.5+-11) than the controls (40+-12)

§ significantly higher concentrations of NFL in CIS patients when compared with the controls (Mann-Whitney: U=56, z=-2.4. p=0.014).

Conclusions: According to our results biomarkers of axonopathy such as tTAU and NFL, start to increase from the initial stage of MS demonstrating higher values compared with the healthy controls. Biomarkers of neuronal death like pTau were lower than the controls demonstrating the absence of brain atrophy during the initial stages of MS.

P261

Urine levels of 8-Isoprostane in relapsing-remitting and secondary progressive multiple sclerosis

P Kivisäkk[1], Y Hyvert[2], K Melo[1], S Cook[1], T Chitnis[1], HL Weiner[1]

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States; [2]EMD Serono Inc., Billerica, MA, United States

Background: 8-Isoprostane (8-iso-PGF$_{2\alpha}$ or 15-F$_{2t}$-IsoP) is a major lipid peroxidation product produced in the brain during oxidative stress (Roberts and Milne, 2009). Levels of 8-Isoprostane are increased in cerebrospinal fluid (CSF) from patients with multiple sclerosis (MS), with maximum levels in patients with secondary progressive MS (SPMS), and CSF levels of 8-Isoprostane were associated with disease activity (Mir, 2011; Sbardella, 2011). 8-Isoprostane can be detected in urine and levels have been reported to be dramatically (6-fold) increased in SPMS patients (Miller et al., 2011), but this finding has yet to be confirmed.

Objectives: To determine 1) if 8-Isoprostane urine levels are higher in patients with SPMS, and 2) if 8-Isoprostane urine levels can be used as biomarkers for disease activity and/or disease progression in MS.

Methods: We obtained random spot urine samples from 104 MS patients (90 RRMS/14 SPMS) and 23 healthy controls from the CLIMB Study (Comprehensive Longitudinal Investigation of MS at Brigham and Women´s Hospital) at Partners MS Center. Thirty-seven patients were untreated, while the remaining patients were treated with glatiramer acetate (n=26), interferon-β (n=22), natalizumab (n=11), or fingolimod (n=8). 8-Isoprostane was analyzed using a commercially available ELISA kit (Oxford Biomedical Research, Oxford, MI) after glucuronidase treatment to measure total urine output of 8-Isoprostane and results were normalized to creatinine levels (Oxford Biomedical).

Results: Patients with SPMS did not have elevated levels of 8-Isoprostane in urine (0.031±0.016; mean±SD) compared to relapsing-remitting (RR) MS patients (0.032±0.025) or healthy controls (0.027±0.023; p=0.84). Similar results were obtained when including all patients (shown) or patients without any immunomodulatory treatment (p=0.61). RRMS patients treated with fingolimod (0.029±0.013), glatiramer acetate (0.039±0.031), interferon-β (0.026±0.014), or natalizumab (0.023±0.013) had similar 8-Isoprostane levels in urine as untreated RRMS patients (0.034±0.029; p=0.60) suggesting that immunomodulatory treatment does not change 8-Isoprostane urine levels.

Conclusions: Our data failed to confirm the previously observed increase in 8-Isoprostane levels in urine from SPMS patients (Miller et al., 2011). Although we have only analyzed a limited number of SPMS patients this far, our data do not support the use of 8-Isoprostane urine levels as a marker of oxidative stress associated with neurodegeneration during the progressive phase of MS.

P262

Potential biomarkers of BIIB033 activity in phase 1 clinical studies

S Ray[1], J Tran[1], S Ciotti[1], Q Duong[1], R Huang[1], L Yang[1], D Cadavid[1]

[1]Biogen Idec, Inc., Cambridge, MA, United States

Background: BIIB033, a fully human IgG1 monoclonal antibody that binds with high affinity and specificity to LINGO-1 (leucine-rich repeat and immunoglobulin [Ig] domain-containing Nogo receptor-interacting protein-1) is an investigational product under evaluation for potential to lead to remyelination and functional recovery in multiple sclerosis (MS). Systemic intravenous (IV) doses of BIIB033 up to 100 mg/kg were well tolerated in 2 randomized, blinded, placebo-controlled, phase I studies, the single ascending dose (SAD; 0.1 to 100 mg/kg; n=72) study in healthy volunteers and the multiple ascending doses (MAD; 0.3 to 100 mg/kg IV; 2 doses separated by 14 days; n=47) study in

participants with RRMS or SPMS. One objective of these studies was to identify potential biomarkers of BIIB033 activity in the CNS among proteins, lipids, or carbohydrates produced during remyelination and secreted into the cerebrospinal fluid (CSF), blood, and/or urine. Leading candidates included markers of neuroaxonal damage, inflammation and remyelination such as neurofilament heavy and light chain (NF-H and NF-L), osteopontin, NCAM, beta amyloid peptides (a-beta) 1-40 and 1-42, and galactosyl sphingolipids (GalCers and sulfatides), as well as soluble LINGO-1 (sLINGO-1), a potential marker of BIIB033 target engagement.

Objectives: To determine whether potential biomarkers of BIIB033 activity in the CSF of participants in the SAD and MAD studies were modulated by 1 or 2 doses of BIIB033.

Methods: CSF was collected two weeks after the last dose from participants who received ≥10mg/kg BIIB033 in the SAD study and from all cohorts in the MAD study. sLINGO-1, NF-H and L, NCAM, osteopontin and a-beta 40 and 42 were measured by ELISA. GalCer and Sulfatide levels were measured using LC MS/MS methods and BIIB033 levels in CSF were measured using immuno-PCR.

Results: Compared with baseline, CSF levels of BIIB033 were increased dose-dependently in both healthy volunteers and participants with MS. In participants from both the SAD and MAD studies who received doses of ≥10 mg/kg, sLINGO-1 levels were also increased. Differences in levels of several CSF analytes were observed between healthy volunteers and participants with MS demonstrating disease manifestation, but none were identified as modulated by 1-2 doses of BIIB033.

Conclusions: These data support BIIB033's entry into the CNS and target engagement within the CNS. Potential biomarkers of intrathecal pharmacodynamics activity of BIIB033 were not identified in these Phase 1 studies.

P263

Correlation of neurofilaments and nitrotyrosine with retinal nerve fiber layer thickness and disability in different phases of multiple sclerosis

C Uzunköprü[1], N Yuceyar[1], D Taskiran[2], S Guven Yilmaz[3], F Afrashi[3], O Ekmekci[1]
[1]Ege University Medical School of Hospital, Neurology, Izmir, Turkey, [2]Ege University Medical School of Hospital, Physiology, Izmir, Turkey, [3]Ege University Medical School of Hospital, Ophthalmology, Izmir, Turkey

Background: Neurofilaments (Nf) are promising candidate to be a reliable biomarker of axonal degeneration in multiple sclerosis (MS).The measurement of retinal nerve fiber layer (RNFL) has been also proposed as a way to verify axonal loss.

Objectives: The aim of the study is to confirm the potential of Nf as an early biomarker of axonal degeneration in MS and to assess its relationship with other biomarker; nitrotyrosine(NT)and with RNFL thickness. We also investigate their correlation with disease duration and neurological impairment.

Methods: NF heavy chain (NfH) and NT were analyzed by ELİSA in serum and cerebrospinal fluid(CSF) of 30 relapsing remitting MS patients(RRMS)(mean age 30,5±6.1years) fulfilling the McDonald 2010 criteria (in whom 23 patients evaluated after their first demyelinating event) and in serum of secondary

progressive MS(SPMS) patients(mean age 40±6.8years). 30 healthy subjects and non-inflammatory neurological patients matched for age and gender were served as controls. The thickness of RNFL was measured in both eyes by optical coherence tomography (OCT) in all subjects. Multiple Sclerosis Functional Composite(MSFC), Expanded Disability Status Scale (EDSS) and cognitive test battery were also performed to all subjects.

Results: RRMS and SPMS patients exhibited highly significantly increased serum and CSF levels of NfH and NT compared with controls(P= 0,002; P< 0,001 respectively).SP-MS patients had significantly higher levels of both biomarkers than RRMS(p< 0,05) Irrespective of optic neuritis history, all MS patients exhibited significantly lower RNFL thickness of each eyes compared with controls (p< 0,05).The difference between the two stages of MS was also significant. RNFL thickness was significantly correlated with serum and CSF NfH/NT levels except for CSF NT levels in RRMS(p< 0,05). Disease duration and EDSS scores of MS patients correlated significantly with the levels of NfH, NT and thickness of RNFL. However, serum levels of NfH and RNFL thickness were better correlated with cognitive decline and cognitive component of MSFC than CSF NfH and serum/CSF NT levels.

Conclusions: Axonal degeneration occurs at the very early stage of MS. We confirmed that NfH and NT are promising biological marker for axonal damage and oxidative stress in MS, giving us information on different phases of axonal pathology. OCT as a noninvasive technique is reliable indicator of axonal loss as it reflects cognitive and physical disability in MS.

P264

Correlation of mRNA expression in the blood with multiple sclerosis disease activity on MRI

JW Lindsey[1], EY Lu[2], JT Chang[3]
[1]University of Texas Health Science Center at Houston, Neurology, Houston, TX, United States, [2]University of Texas Health Science Center at Houston, Biomedical Informatics, Houston, TX, United States, [3]University of Texas Health Science Center at Houston, Integrative Biology and Pharmacology, Houston, TX, United States

Background: Exacerbations or relapses are a typical clinical feature of multiple sclerosis (MS). Some relapses follow infections, but most occur without an apparent precipitating factor. Serial MRI scans in MS demonstrate frequent but intermittent disease activity. Discovery of changes in immune function in the blood that precede MS disease activity in the brain would lead to a better understanding of the disease pathogenesis.

Objectives: To assess whether there are measurable alterations in mRNA expression in the blood preceding MS disease activity on MRI.

Methods: Subjects had blood drawn in PAXgene RNA tubes every two weeks and gadolinium-enhanced MRI scans of the brain every 4 weeks for a total of 16 weeks. MRI scans were analyzed for gadolinium-enhancing (Gd) lesion number and volume, and for T2 lesion number and volume. RNA was extracted from five subjects with MRI activity, and gene expression was measured using Illumina human microarrays. The transcripts with greater than 2-fold change during the study were analyzed for correlation with the MRI measures. Pearson correlation was

calculated for blood collected at the same time as the MRI, and for specimens collected 2 and 4 weeks preceding the MRI.

Results: Among the 5 subjects, there were 132 nominally significant correlations (p< 0.05) between mRNA expression and MRI activity. The largest number (63) of the correlations occurred 4 weeks before MRI. There were 70 distinct transcripts, which included 45 documented protein coding genes. Seven of these are proteins induced by interferon. Ten transcripts were changed in more than one subject, but only two (RPL9 and TELO2) were altered in the same direction at the same time point.

Conclusions: Changes in gene expression in the blood occur most often at 4 weeks before MRI activity. Many of the altered transcripts are regulated by interferon. The number of subjects studied is small, but the results suggest immune changes before MS activity will differ widely between individuals.

P265

Identification of multiple sclerosis cerebrospinal fluid biomarkers using nuclear magnetic resonance spectroscopy

MA Pawlak[1], E Jodlowska[1], B Gierczyk[2], L Popenda[3,4], S Jurga[3,5], R Kazmierski[1]
[1]Poznan University of Medical Sciences, Department of Neurology and Cerebrovascular Disorders, Poznan, Poland, [2]Adam Mickiewicz University, Faculty of Chemistry, Supramolecular Chemistry, Poznan, Poland, [3]Adam Mickiewicz University, NanoBioMedical Centre, Poznan, Poland, [4]Polish Academy of Sciences, Institute of Bioorganic Chemistry, Poznan, Poland, [5]Adam Mickiewicz University, Department of Macromolecular Physics, Poznan, Poland

Background: Nuclear Magnetic Resonance (NMR) spectroscopy identifies metabolites of small molecular weight present in cerebrospinal fluid (CSF). Diagnosis of multiple sclerosis (MS) and clinically isolated syndrome (CIS) is based on a combination of symptoms, laboratory tests and MRI results, and sometimes is not conclusive especially early in the disease process. Previous studies that employed NMR to examine the CSF of patients with CIS and MS focused mainly on differences and did not use receiver operator characteristics (ROC) curves statistics to assess the peaks. Additionally they usually involved sample pH adjustment that could influence the metabolites and their stability.

Objectives: To identify CSF metabolites differentiating CIS and MS from other non-inflammatory neurological diseases using ROC curves and area under the curve (AUC) >0.6

Methods: Patient population consisted of 17 MS patients and 26 CIS patients. They were compared to 42 control patients with headaches and other non-inflammatory neurological disorders. CSF samples were stored at -80C until further analysis. We did not use pH adjustment prior to the acquisition using 800Hz Agilent NMR spectrometer. The spectra were phase- and baseline corrected, normalized and the peaks were manually integrated and scaled relative to glucose using MestReNova software. Statistical analysis was performed using R-CRAN environment, package ChemoSpec, ExpDes and ROCR packages were used for ANOVA and ROC analysis.

Results: ANOVA identified significant associations at the chemical shift of 1.70, 2.10, 3.35, 3.60, 3.65, 3.68 and 3.75 ppm. ROC curve AUC for MS vs. control for 2.10 ppm was equal to 0.79.

CIS vs. control group for 3.65 ppm AUC was 0.76. Joint analysis for CIS+MS vs. control group identified 8 associations: 3.75, 3.68, 3.25, 2.95, 1.20, 1.00 and 0.75 ppm. ROC characterized by AUC> 0.60 was identified for 1.00 (AUC 0.69), 1.20 (0.64), 2.1 (0.64), 2.95 (0.66), 3.3 (0.64), 3.25 (0.63), 3.68 (0.64), 3.75 (0.63).

Conclusions: Application of ROC curves to assess the predictive value of individual NMR peaks can identify individual spectral features useful in CSF metabolomics. Lack of differences between the CIS and MS groups indicates a common biochemical basis of those conditions. The differences between MS+CIS and controls indicate potential for small molecular weight biomarkers in diagnosis of early phase demyelinating disease. Further studies are needed to validate our findings and identify chemical compounds associated with the identified peaks.

P266

Next generation sequencing of microRNA in the CD4+ T-cells of secondary progressive multiple sclerosis individuals

KA Sanders[1,2], RA Lea[2], SE Agland[3], RJ Scott[2,4], J Lechner-Scott[2,3], L Tajouri[1]
[1]Bond University, Faculty of Health Sciences and Medicine, Gold Coast, Australia, [2]Hunter Medical Research Institute, Centre for Information-Based Medicine, Newcastle, Australia, [3]John Hunter Hospital, Department of Neurology, Division of Medicine, Newcastle, Australia, [4]Hunter Area Pathology Service, Division of Molecular Genetics, Newcastle, Australia

Background: The role of microRNAs (miRNA) in multiple sclerosis extends beyond their use as biomarkers for diagnosis and prognosis. These non-coding RNAs are significant regulators of gene expression, and understanding the impact of their differential expression on specific immune cell behaviour during pathogenesis and progression will further our understanding of MS. The total coverage approach of next generation sequencing (NGS) can identify known miRNA not seen with other techniques and may identify novel miRNA sequences associated with MS.

Objectives: The objective of this study was to determine the miRNA expression patterns of CD4+ T-cells from secondary progressive MS (SPMS) individuals versus healthy controls (HC) using NGS. Our aim was to identify deregulated miRNAs in SPMS CD4+ T-cells and determine their impact in MS progression.

Methods: The study included 24 subjects: 12 untreated SPMS individuals (9 females) and 12 age- (±5 years), gender-matched HCs. PBMCs were isolated by density gradient centrifugation on lymphoprep. CD4+ T-cells were negatively selected using EasySep technology (StemCell), and purity determined by flow cytometry (>90%). Total RNA was isolated from CD4+ T-cells and integrity measured on a Bioanalyzer 2100 (Agilent Technologies). NGS of miRNA was performed using the TruSeq Small RNA sample preparation kit on a HiSeq2500 Rapid system (Illumina) with 50bp fragment length. All reads were adapter trimmed and aligned against the human genome and miRBase v20. miRNA differential expression between SPMS and HC were identified and RT-qPCR used to confirm the most deregulated miRNA candidates.

Results: The extracted RNA performed exceptionally well in QC experiments and RNA integrity number scores ranged from

8.6-9.6. All samples yielded >1ug of RNA; sufficient for NGS and confirmatory experiments. NGS performed above average (4-9 million reads/sample) and is suitable for expression profiling and novel small RNA discovery. Preliminary analyses of the sequencing data identified >300 miRNA expressed in the CD4+ T-cells of SPMS individuals and HCs.

Conclusions: Prediction algorithms will determine the likely mRNA targets of differentially expressed miRNAs in the CD4+ T-cells of SPMS individuals. The potential effects of these miRNA on cellular behavior in MS can then be determined. Future functional studies on these miRNA in CD4+ T-cells will confirm these targets and further inform our understanding of the clinical relevance of miRNA-dependent regulatory mechanisms in MS progression.

P267

MicroRNA-572 expression in serum of multiple sclerosis patients with different patterns of disease progression

S Agostini[1], R Mancuso[1], A Hernis[1], M Rovaris[1], D Caputo[1], M Clerici[1]
[1]Don C. Gnocchi Foundation, Lab Molecular Medicine, Milano, Italy

Background: Clinical progression of multiple sclerosis (MS) is correlated to accumulation of impairment due to demyelination, and failure of remyelination is one of the mechanism involved in the axonal degeneration. A higher remyelination capacity has been observed in the brain of primary progressive (PPMS) compared to secondary progressive (SPMS) patients. The identification of biomarkers for remyelination represents an important scientific challenge; in particular the discover of circulating microRNAs (miRNAs) associated to this process may represent the first key step toward the development of in vivo non-invasive blood-based molecular test. A recent microarray study evidenced 7 dysregulated miRNAs in serum of MS patients compared to HC. A predicted target of one of these (miR-572) is neural cell adhesion molecule (NCAM-1): this cell membrane glycoprotein mediates adhesion between neuronal and glial cells; consequently different level of this miRNA could be related to different remyelination capacity.

Objectives: To verify the presence and expression level of a particular miRNA (miR-572) in serum from patients with different form of MS and from HC.

Methods: A group of 27 chronic progressive (14 PP- and 13 SP-) and 31 relapsing remitting (RR-) MS patients and, a group of 15 sex/age matched healthy controls were included in the study. miRNA isolation from serum was performed with a column based kit (miRNeasy Mini KIT- QIAGEN). Specific LNA™-individual microRNA assays (Exiqon) were used to qPCR detection of miR-572 in sera. The relative fold expression levels (2^{-DDCt}) were calculated using synthetic *C.el* miR-39 for normalization of data.

Results: miR-572 expression level was reduced in serum of MS patients (0.01 fold; $p< 0.05$) compared to HC; significant differences were observed in SPMS (upregulated of 3.75 fold) and in PPMS (down-regulation of 0.01 fold) compared to HC; level of expression correlated to EDSS score ($r=0.491$; $p< 0.05$). The area under the receiver operating characteristic curve (ROC) (72%, 95%CI: 0.598-0.815%) suggests that this miRNA has a good predictive value, in particular to distinguish for SPMS (AUC:92%;95%CI: 0.611-0.933) and PPMS (AUC:88%;95%CI: 0.713-0.973) from HC.

Conclusions: As miR-572 upregulation could correspond to reduced remyelination capacity, observed changes in serum of MS patient in different clinical form as well as correlation to disability score suggest that this miRNA may serve as potential non invasive biomarker for remyelination.

P268

Uric acid levels are reduced in multiple sclerosis

M Moccia[1], R Lanzillo[1], R Palladino[2,3], C Russo[1], A Carotenuto[1], M Massarelli[1], G Vacca[1], V Vacchiano[1], V Brescia Morra[1]
[1]University Federico II, Department of Neurosciences, Napoli, Italy, [2]Imperial College, Department of Primary Care and Public Health, London, United Kingdom, [3]University Federico II, Department of Public Health, Napoli, Italy

Background: Multiple sclerosis (MS) pathogenesis represents a significant challenge in consideration of subsequent therapeutical approaches. Considering the possible role of reactive oxygen and nitrogen species in inflammation, demyelination and axonal injury, natural scavengers, such as uric acid (UA), have been widely investigated. In particular, serum UA levels have been studied in relation to MS risk, clinical picture, neuroradiological activity, and treatments. However, there is poor accordance within different studies, possibly due to small sample size.

Objectives: We mainly aim to evaluate differences in UA levels between MS subjects and controls. A secondary endpoint is the possible relationship between UA levels and MS activity.

Methods: We consecutively recruited 415 MS subjects (245 females, 170 males) at the Center for Multiple Sclerosis of the University Hospital "Federico II" from January to December 2013. MS subjects were matched for age and gender with 111 healthy subjects (63 females, 48 males). MS subjects and controls were evaluated for UA levels, and for concomitant diseases or treatments possibly modifying UA values. MS subjects were classified according to EDSS score (3.9±1.4), disease modifying treatment, and current clinical picture (297 relapsing remitting MS, 118 secondary progressive MS).

Results: At t-test, MS subjects presented significantly lower UA levels (253.6±3.0 mmol/L) than controls (269.2±6.6 mmol/L) ($p=0.022$). The latter result was confirmed by analysis of variance with post-hoc Bonferroni correction ($p=0.026$). EDSS score, disease modifying treatment, and current clinical picture were not related to UA levels.

Conclusions: Our large cross-sectional study indicates that lower UA levels may differentiate MS subjects from controls. Therefore, UA should be considered an easily detectable marker of MS.

Further investigations should be addressed to clarify the relationship between UA levels and MS activity with longitudinal models considering UA variability within subjects.

P269

Search of biomarkers associated with disability progression by means of gene expression profiling in patients with progressive multiple sclerosis

R Nurtdinov[1], C Tur[1], S Malhotra[1], J Sastre-Garriga[1], X Montalban[1], M Comabella[1]

[1]*Vall Hebron University Hospital, Multiple Sclerosis Centre of Catalonia, Neuroimmunology Department, Barcelona, Spain*

Background: Multiple Sclerosis (MS) is a neurodegenerative immune-mediated disease of the central nervous system. An important proportion of MS patients suffers from a progressive course of the disease, with sustained neurological deterioration and without options of receiving effective therapies to halt progression. In this scenario, a more in-depth understanding of the prognostic factors that make MS patients to progress slower or faster in their disability will be critical to stratify them according to disease evolution.

Objectives: We aimed to identify genes associated with disability progression in peripheral blood mononuclear cells (PBMC) from patients with primary progressive MS (PPMS).

Methods: Patients with PPMS were classified according to worsening of disability over a two-year period. Disability progression was defined as a confirmed increase in the EDSS score of at least 2 points during the two-year follow-up period. Ten PPMS patients were included in the study, 5 patients with disability progression and 5 patients whose EDSS scores remained stable over the follow-up period. In these patients, the gene expression profiles were determined in PBMC at baseline and after two years of follow-up by means of the Affymetrix GeneChip® Human Transcriptome Array 2.0.

Results: Gene expression profiling study using microarrays in PPMS patients with and without worsening of disability led to the identification of a number of differentially expressed genes associated with disability progression. The most differentially expressed gene between patients with and without disability progression corresponded to SH2B3 (SH2B adaptor protein 3). At baseline, SH2B3 expression levels were significantly lower in PPMS patients with disability progression compared to patients without disability progression (p=0.014), and differences remained significant over the two-year follow-up period (group effect: p=2.1x10-6). A significant time effect in SH2B3 expression was observed in PPMS patients with disability progression, and SH2B3 expression levels decreased over time (p=1.9x10-3) in this group of patients whereas remained statistically non-significant in patients with stable EDSS scores.

Conclusions: The SH2B3 gene encodes a key negative regulator of cytokine signalling that has been associated with susceptibility to several autoimmune disorders including MS. These findings may point to SH2B3 as a disease activity biomarker associated with disability progression in PPMS patients.

P270
Neurofilament light subunit as an independent biomarker in clinically isolated syndromes

<u>G Arrambide</u>[1], C Espejo[1], LM Villar[2], JC Álvarez-Cermeño[2], C Picón[2], H Eixarch[1], E Simón[1], M Comabella[1], J Sastre-Garriga[1], J Río[1], À Vidal-Jordana[1], J Castilló[1], I Galán[1], F Palavra[1], C Nos[1], L Negrotto[1], C Auger[3], Á Rovira[3], X Montalban[1], M Tintoré[1]

[1]*Vall Hebron University Hospital, Multiple Sclerosis Centre of Catalonia, Neuroimmunology Department, Barcelona, Spain, [2]Hospital Ramón y Cajal & Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Neurology and Immunology Department-Multiple Sclerosis Unit, Madrid, Spain, [3]Vall*

Hebron University Hospital, Magnetic Resonance Unit, Neuroradiology Department, Barcelona, Spain

Background: Neurofilament light (NfL) subunit levels in cerebrospinal fluid (CSF) are significantly higher in patients with clinically isolated syndromes (CIS) who convert to multiple sclerosis (MS) in comparison to those who remain as CIS.

Objectives: To validate NfL levels as independent predictors of conversion to MS and to evaluate NfL levels with expanded disability status scale (EDSS) and magnetic resonance (MR) inflammation variables.

Methods: Clinical, CSF and MR data were acquired from two CIS cohorts: Vall d´Hebron (N=93) and Ramón y Cajal (N=62) hospitals. NfL levels were determined using a commercial ELISA kit. A 900 ng/L cut-off was obtained from a control group of patients with other non-inflammatory neurological disorders. Primary endpoints were conversion to clinically definite (CD) MS and 2010 McDonald MS according to NfL status (positive/negative). Uni- and multivariate analyses were performed for NfL levels as a continuous value and evaluated with oligoclonal bands and T2 lesion number on baseline MR. Disease modifying treatment (DMT) and hospital were considered covariates. NfL levels were compared in terms of disability (EDSS >=3.0). Correlations with MR inflammation variables at baseline and on follow-up were determined.

Results: In total, 155 patients were evaluated: 101 (65.2%) were female with a mean age (SD) of 33.6 (8.8) years and a follow-up of 44.2 (27.3) months; 48 (31.0%) converted to CDMS. DMT was started before CDMS in 46 (29.7%) patients. Median (IQR) NfL levels were 1238.3 (1782.1) for CDMS and 555.8 (825.5) ng/L for CIS. With the cut-off 900, 63 (40.6%) patients were NfL positive: 28/63 (44.4%) with positive and 20/92 (21.7%) with negative NfL converted to CDMS (log rank p=0.004), whereas 43/63 (68.2%) with positive and 31/92 (33.7%) with negative NfL fulfilled McDonald MS (log rank < 0.0001). NfL levels were predictors of both CDMS (HR 1.009, 95%CI 1.005-1.014, p< 0.0001) and McDonald MS (HR 1.009, 95%CI 1.005-1.013, p< 0.0001). The adjusted HR (aHR) of NfL levels for conversion to CDMS remained significant in the multivariate analysis (aHR 1.005, 95%CI 1.000-1.011, p=0.040). Although mean NfL levels were higher in cases with EDSS >=3.0 than for lower scores, the difference was not significant (p=0.172). Finally, significant correlations with MR inflammation variables were found.

Conclusions: NfL levels appear to be independent predictors for conversion to CDMS and have strong correlations with MR inflammation variables.

P271
Subanalysis of a multicentric cross-sectional study of CSF-GFAP in the diagnosis of inflammatory demyelinating diseases

<u>S Nishiyama</u>[1], T Misu[1], Y Shimizu[2], K Yokoyama[3], T Kageyama[4], Y Takai[1], R Takano[1], T Takahashi[5], J Fujimori[6], S Sato[7], I Nakashima[1], K Fujihara[8], M Aoki[1]

[1]*Tohoku University, Department of Neurology, Sendai, Japan, [2]Tokyo Women's Medical University, Department of Neurology, Tokyo, Japan, [3]Juntendo University, Department of Neurology, Tokyo, Japan, [4]Tenri Hospital, Department of Neurology, Tenri, Japan, [5]Yonezawa National Hospital, Department of Neurology,*

Yonezawa, Japan, [6]Tohoku Pharmaceutical University Hospital, Department of Neurology, Sendai, Japan, [7]Konan Hospital, Department of Neurology, Sendai, Japan, [8]Tohoku University, Department of Multiple Sclerosis Therapeutics, Sendai, Japan

Background: Neuromyelitis optica (NMO) is characterized by severe optic neuritis and transverse myelitis. The extensive loss of AQP4 and glial fibrillary acidic protein (GFAP) were revealed in pathological studies in NMO, especially in the perivascular regions with complement and immunoglobulin depositions. We revealed elevated CSF-GFAP in NMO patients in the past study, but the clinical significance of tissue damage and the relation with other inflammatory demyelinating disease are unknown. Also, comprehensive study of CSF biomarkers including GFAP and myelin basic proteins (MBP) in inflammatory demyelinating diseases is still lacking.

Objectives: To clarify the usefulness of CSF biomarkers including GFAP and MBP in the diagnosis and the prognosis of inflammatory demyelinating diseases (e.g.: NMOsd, seronegative NMO, Multiple Sclerosis (MS), Tumefactive demyelinating disease (TDD), Neuro-Behcet's disease).

Methods: We conducted multicentric cross-sectional study in Japan from January 1999 to December 2012 including 129 patients who diagnosed as inflammatory demyelinating diseases and 12 healthy control cases. CSF-GFAP and CSF-MBP were measured by sandwich ELISA kit. The corrected data was analyzed by Graphpad Prism 5.

Results: CSF-GFAP/MBP ratio in seropositive NMOsd showed significantly higher than that in MS (cut-off: 0.082, sensitivity 86.84%, specificity 96.15%). In spite of the relative low prevalence of CSF-GFAP of NMOsd in optic lesion (47%), CSF-GFAP/MBP ratio improved the positivity in optic lesion (73%). The prevalence of CSF-GFAP/MBP ratio of NMOsd in cerebral lesion and spinal cord lesion is high as well as CSF-GFAP (100% and 90%, respectively). CSF-GFAP level is tend to decrease in accordance with the duration of CSF-collected day from estimated relapse day. On the other hand, CSF-MBP level is no tendency of decrease, which may reflect the difference in the time course of cytotoxic events between astrocytes and oligodendrocytes. There is no correlation between CSF-GFAP and serum anti-AQP4 antibody titers.

Conclusions: Elevated CSF-GFAP levels in the inflammatory demyelinating diseases, such as NMOsd, reflect acute astrocytic destructive damages. CSF-GFAP level itself in the relapse of optic neuritis in NMOsd is relatively low prevalence than cerebral lesion or myelitis, but CSF-GFAP/MBP ratio may improve the sensitivity. Obtaining CSF in the acute phase of NMO relapse is preferable for making precise diagnoses by CSF-GFAP.

P272
CSF fetuin-A is a biomarker of subclinical disease activity in progressive MS

VK Harris[1], M Landy[1], S Chirls[1], I Londono[1], SA Sadiq[1]
[1]Tisch MS Research Center of New York, New York, NY, United States

Background: There is a need for accurate and predictable biomarkers for the effective stratification of treatment for individual MS patients. In particular, biomarkers measuring disease activity in progressive MS would be particular useful since disease worsening is difficult to quantify using standard imaging metrics. We recently identified Fetuin-A as a CSF biomarker that was elevated in relapsing remitting (RRMS) patients with active disease. In addition, reduced CSF Fetuin-A in RRMS patients treated with natalizumab for one year correlated with therapeutic response to the drug. A direct role for Fetuin-A in MS pathogenesis is supported by EAE animal studies which showed that Fetuin-A contributed to disease severity, and its expression was markedly upregulated in demyelinated areas and in gray matter within human MS and mouse EAE brain tissue.

Objectives: To determine if Fetuin-A levels in CSF correlate with disease progression/activity in patients with progressive MS.

Methods: Patients with clinically definite secondary progressive (SPMS) (n=75) and clinically definite primary progressive (PPMS) (n=40) were classified as having disease activity on the basis of patient self-reporting, EDSS, and MRI over a period of 24 months. CSF Fetuin-A was determined by ELISA in all patients. All samples and clinical information were obtained with IRB approval and informed consent.

Results: There was no significant correlation between MRI findings and change in EDSS or disease worsening as self-assessed by the patient. CSF Fetuin-A levels were significantly higher in patients who reported worsening or in patients who had EDSS change of greater than 0.5 over the study period in comparison to patients with stable EDSS.

Conclusions: In patients with progressive disease, standard MRI is a poor determinant of disease activity. CSF Fetuin-A levels may provide a quantifiable biomarker of disease activity and appears to correlate with clinical findings. If validated, our findings could help in objectively determining therapeutic efficacy in patients with progressive disease.

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Lipidomics analysis reveals low levels of phosphatidylcholines and sphingomyelins in cerebrospinal fluid of multiple sclerosis patients

D Pieragostino[1,2], M D'Alessandro[1,2], M Di Ioia[2,3], M Zucchelli[2,4], A Lugaresi[3], P Sacchetta[1,2], P Del Boccio[1,2]
[1]University 'G. d'Annunzio', Experimental and Clinical Sciences, Chieti, Italy, [2]Centre of Investigation on Aging (Ce.S.I.), Analytical Biochemistry and Proteomics Unit, Chieti, Italy, [3]University 'G. d'Annunzio', Neurosciences and Imaging, Chieti, Italy, [4]University "G. d'Annunzio", School of Medicine and Health Sciences, Chieti, Italy

Background: A very active field of research in MS relates to novel feasible biomarkers that should help to understand aethiopathogenesis, to make an early and definite diagnosis, to predict prognosis and response to treatment and finally to develop new treatments. Recent studies suggest lipid mediators in the autoimmune process and describe an alteration of lipid metabolism in CNS. Lipidomics based on mass spectrometry is considered an useful and innovative approach to characterize the metabolic dyshomeostasis in multifactorial diseases, such as MS, since it allows to photograph the alteration of many metabolites simultaneously.

Objectives: To identify specific lipids pattern in CSF that segregate MS vs OND patients in order to discover new candidate biomarkers and new promising therapeutic targets for MS.

Methods: The study was carried out on twenty patients with definite MS and Seventeen patients with other neurological diseases (OND). Total lipids were extracted from 200 uL of CSF per patient by using Methyl tert-butyl ether as organic solvent for liquid-liquid extraction.

Lipids were analyzed by LC-MS/MS. Elution was obtained using a column Atlantis HILIC by a linear gradient of formic acid 0.1% and ACN. The LC system was coupled on-line with an ESI-triple quadrupole mass spectrometer. The profile of biological phosphatidylcholines (PCs) and sphingomyelins (SMs) in CSF was obtained by parent ion scan mode following the signal at m/z=184 Da corresponding to the polar head of this classes of phospholipids.

Partial least squares discriminant analysis using SIMCA-P+ was employed for data processing in order to find differential lipids in two analyzed groups. The significant metabolites were identified using Lipidmaps and Human Metabolome Database. Correlation analysis between clinical parameters and lipid levels were performed by using Statistica 7.0.

Results: Data of phospholipids profiling in CSF were processed by multivariate analysis (PLS-DA) obtaining 14 lipids that significantly ($p < 0.05$) segregate the two clinical groups analyzed. In particular we found 13 lipid species (11 PCs and 2 SMs) that are down regulated in MS, four of which correlated with clinical parameters ($p < 0.05$), particularly with barrier index, disease duration and Link Index.

Conclusions: Our data show evidences of a distinctive lipidomics "fingerprinting" for MS, opening the route for new candidate biomarkers and therapeutic targets. These results add a piece in the understanding of the molecular mechanisms underlying the disease.

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Metabolomic profile of multiple sclerosis patients

E Cocco[1], L Lorefice[1], F Murgia[1], L Barberini[1], J Frau[1], G Fenu[1], G Coghe[1], MR Murru[2], R Murru[1], S Poddighe[1], L Atzori[1], MG Marrosu[1]
[1]University of Cagliari, Cagliari, Italy, [2]ASL8, Cagliari, Italy

Background: Multiple sclerosis (MS) is a chronic disease of the central nervous system characterized by a high level of heterogeneity in pathological, clinical, radiological features and drugs responses. Consequently, the availability of biomarkers that reliably capture the different aspects of the disease could be extremely useful in MS understanding and its management. Metabolomics is based on detailed analysis of metabolites in bio-fluids and tissues; it involves a non-selective approach to identify all metabolites in a biological system and has the potentiality to discover new biomarkers.

Objectives: To investigate the metabolomic profile of MS patients and to define the metabolic differences between MS patients and the healthy control population. Moreover we would like to search the metabolic pathways potentially related to MS pathogenesis.

Methods: Blood samples were obtained from 73 (27 males and 46 females) MS patients and a group of 88 (27 males and 61 females) healthy controls (HC) demographically and ethnically matched. All the patients were therapy free from at least 90 days.

Samples were analyzed with a 500 MHz Varian spectrometer; multivariate statistical techniques were used for data interpretation.

Initially data analysis was conducted with principal component analysis (PCA) then a supervised analysis (orthogonal partial least squares discriminant analysis [OPLS-DA]) was applied. To evaluate the goodness of the models the variance and the predictive ability (R2X, R2Y, Q2) were calculated. Metabolites were identified and quantified using Chenomx software and data available in the literature.

Results: The model obtained by OPLS-DA analysis revealed metabolic differences between MS patients and HC samples (R2X=0.615, R2Y=0.619, Q2=0.476; $p < 0.001$). Metabolites driving this difference between MS and HC were: Glucose, 5-OH-tryptophane, tryptophan (lower in MS) and 3-OH-butyrate, acetoacetate, acetone, alanine, choline (higher in MS group). The model was, then, validated by introducing blindly 10 MS and 10 HC samples, in this case the average value of predictivity was 100% for HC and 83% for MS patients.

Conclusions: The metabolic model obtained in our study was able to blindly discriminate patients versus HC. Therefore, a specific metabolomic profile of MS patients was defined.

Metabolomic analysis appears to be a promising non-invasive approach to study MS. Our results are preliminary and need to be replicated in other samples.

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Metabolomics analysis of cerebrospinal fluid reveals a distinctive biochemical alteration associated with multiple sclerosis

M di Ioia[1], D Pieragostino[1], M D'Alessandro[1], C Rossi[1], M Zucchelli[1], A Lugaresi[1], V Di Tommaso[1], D Farina[1], D Travaglini[1], P Sacchetta[1], P Del Boccio[1]
[1]G. d'Annunzio, Chieti, Italy

Background: Multiple Sclerosis (MS) is a disease due to an autoimmune attack against myelin components in which non proteic mediators may play a role. Recent research in Metabolomics and Lipidomics has been driven by rapid advances in technologies such as mass spectrometry and computational methods. They can be used to study multifactorial disorders like MS, highlighting the effects of disease on metabolic profiling, regardless of the multiple trigger factors.

Objectives: To identify metabolic alterations specific of MS, employing a combined targeted/untargeted mass spectrometry based metabonomics platform.

Methods: A targeted metabolic fingerprint strategy was performed by Direct Infusion Mass Spectrometry (DIMS) to evaluate amino acids, free carnitines and acylcarnitines levels in cerebrospinal fluid (CSF) of patients with MS and other neurologic diseases (ONDs). Untargeted analysis for lipids profiling in CSF was performed with an Autoflex Speed MALDI-TOF-TOF mass spectrometer (Bruker Daltonics, Bremen, Germany) in the mass range 0.8-3 kDa. The lipids were identified by fragmentation analysis and by database search ("Lipid Map" and "Human Metabolome" databases). A multivariate statistical analysis based on supervised and non-supervised techniques (PLS-DA, PCA) was performed in order to identify, comparing MS with OND patients, potential biomarkers of MS. Correlation analysis between clinical parameters, lipids, Carnitines and AminoAcids levels were performed by using Statistica 7.0 (StatSoft DemoVersion).

Results: Ten metabolites significantly (p< 0.05) segregate the two clinical groups. The most relevant result was the alteration of phospholipids levels in MS and the correlation between some of them with clinical data. In particular lysophosphatidylcholines (m/z=522.3, 524.3) and an unidentified peak at m/z=523.0 correlated to the Link index, lysophosphatidylinositol (m/z=573.3) correlated to EDSS and phosphatidylinositol (m/z=969.6) correlated to disease duration. We also found high levels of glutamate in MS.

Conclusions: Taken together these metabolites could be considered as promising candidate biomarkers and/or new therapeutic targets for the disease.

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Increased production of superoxide anion, antioxidative enzyme activity and oxidative damage in multiple sclerosis patients during relapse

D Obradovic[1], M Jovanovic[1], A Jovicic[1]
[1]Military Medical Academy, Belgrade, Serbia

Background: Oxidative stress is proposed as one of possible mechanisms of central nervous system damage in multiple sclerosis (MS).

Objectives: It was our aim to investigate free radicals production, by measuring superoxide anion (O2·), activity of antioxidative enzymes: superoxide dismutase (SOD) and glutathione reductase (GSH-R) and presence of oxidative damage by measuring index of lipid peroxidation (ILP), during relapse in relapsing-remitting (RR) MS patients.

Methods: The research included 40 RRMS patients, 24 female and 16 male, average age 35.6±11.4 years, MS duration 7.3±3.4 years, average EDSS 4.6±1.7.Control group consisted of 17 patients with suspected and confirmed non-inflammatory neurologic disease. In the samples of blood, O2· production was measured and activity of SOD and GSH-R in erythrocyte hemolysate, while the ILP was measured in plasma and CSF.

Results: We found significant difference in O2· production between MS patients and control group (2.28 vs 0.004μmolNBT/mgHb/min), as well as significantly higher activity of SOD and GSH-R in MS group compared to controls (786.56 vs 382.08U/mgHb) and (17.34 vs 4.92 μmolNAD+/mgHbh) respectively. ILP was higher, both in plasma and CSF, in MS patients group compared to controls (plasma:10.08 vs 5.11 μmolMDA/ml and CSF:1.73 vs 0.511 μmolMDA/ml). No correlation was found between age, gender, disease duration, EDDS and examined parameters of oxidative stress.

Conclusions: There is significant increase of O2· production, but also significant increase of antioxidative enzymes activity in erythrocyte hemolysate during MS relapse. Furthermore, increased ILP was found both in plasma and CSF during MS relapse.

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Oxidation and axonal degeneration: early oxidation state can be a long term disability biomarker. Results from a 12-years study

JL Ruiz Peña[1], M Lucas[1], G Izquierdo Ayuso[1]
[1]Hospital Virgen Macarena, Seville, Spain

Background: Interferon therapy decreases the plasma concentration of reduced sulfhydryl after treatment, suggesting that the concentration of reduced sulfhydryl groups is a biochemical marker of oxidation state in MS.

Objectives: To assess the usefulness of the oxidation state as a marker of long-term disability in Relapsing Remitting Multiple Sclerosis (RRMS) treated patients.

Methods: 31 patients (9 man and 22 women) with RRMS and a Kurtzke Expanded Disability Scale Score (EDSS) of 0-5.5 were recruited in 4 MS Clinics and included in a prospective, longitudinal study of Intra muscular Interferon (IM IFN) beta-1a in RRMS. All patients were followed up for a period of 2 years and the patients from Seville's MS Clinic for 12 years. Every three months disability was assessed by different neurological scale. Measure of the oxidation state and H-MRS were performed at baseline, 12 and 24 months. At the beginning of the study MRI and H-MRS were also performed on 10 healthy, age matched control subjects with not known systemic or neurological disease.

Results: There is a relationship between the change in NAA in the first 24 months after treatment and changes in sulfhydryl groups in the first 12 months following the introduction of treatment (r = - 0.8, p = 0.02). Loss of choline after two years of treatment is related to the loss of sulfhydryl groups in the first 12 months following the introduction of treatment (r = - 0.9, p = 0.001). There is a relationship between the evolution of the oxidative environment during the first year of treatment and subsequent disability. It was obtained a statistically significant correlation between the loss of sulfhydryl groups during the first quarter of treatment and different levels of disability; EDSS 24 m (r = 0.6, p = 0.017), EDSS 36 m (r = 0.6, p = 0.032), EDSS 48 m (r = 0.7, p = 0.003), EDSS 60 m (r = 0.7, p = 0.005), EDSS 72 m (r = 0.6, p = 0.024), EDSS 84 m (r = 0.6, p = 0.014), EDSS 96 m (r = 0.6, p = 0.014).

Conclusions: The redox levels immediately following the introduction of immuno-modulating medication can play an important role in the disability developed during the evolution of the disease and its monitoring could predict treatment response in regards to this disability.

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Elevated CSF lipocalin-2 levels at diagnosis predict faster disability progression in RRMS patients

AM Menezes[1], S Xavier[1], S Neves[1,2,3], F Marques[1,2,3], JJ Cerqueira[1,2,3]
[1]School of Health Sciences, University of Minho, Braga, Portugal, [2]Life and Health Sciences Research Institute, University of Minho, Braga, Portugal, [3]ICVS/3B's Associated Laboratory, Braga, Portugal

Background: Lipocalin-2 (LCN2) is small molecule secreted by neutrophils and involved in innate immunity and iron metabolism. Recent data, including from our group, highlighted the involvement of LCN2 in the murine experimental auto-immune encephalomyelitis (EAE) model of multiple sclerosis (MS), by showing that its expression in the brain parenchyma, the choroid plexus and the CSF increases during relapse, decreases during remission and is abrogated by natalizumab treatment. In addition, LCN2 knockout mice displayed a different EAE phenotype, with more animals developing a chronic/progressive course associated to increased parenchymal inflammation. Importantly, these results

seemed relevant for the human disease, as, in a preliminary study, CSF LCN2 levels were increased in MS cases compared with controls.

Objectives: The aim of the present study was to assess whether CSF LCN2 levels at diagnosis were associated with clinical severity in a multiple sclerosis cohort followed in our clinic.

Methods: Normal 0 21 false false false PT X-NONE X-NONE MicrosoftInternetExplorer4 Patients performing lumbar puncture as part of their initial diagnostic workup for suspected MS gave informed consent to participate on a longitudinal prospective study, ongoing in our centre since 2008 (MIND-MS). Upon collection, CSF was immediately aliquoted and frozen until analysis. LCN2 levels were determined with an ELISA assay developed in-house, validated against a commercially available kit (R&D systems). Patients were then prospectively followed every 6 months, and clinical information recorded on a longitudinal database. The local ethics committee approved all procedures.

Results: We collected data on 37 patients (68% female) with confirmed relapsing remitting MS according to McDonald 2005 criteria and followed for an average of 4 years (range 2 - 5). At time of LP, patients had a mean age of 33 years and a median EDSS of 1,5 (range 1-3). All patients received treatment with interferon beta (70%) or glatiramer acetate (30%). Mean LCN2 levels in CSF were 1,72 ng/mL (+-0,97) and were not related with CSF leucocyte number or detection of oligoclonal bands or number of Barkhoff criteria or presence of gadolinium enhancing lesions in the MRI at the time of CSF collection. More importantly, LCN2 levels above average predicted a faster disease progression to an EDSS of 3 or higher (Cox regression p=0,015 OR=0,249).

Conclusions: Our results suggest that higher lipocalin-2 levels might predict a faster disease progression.

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Expression of miRNAs in multiple sclerosis cerebrospinal fluid and their relation to MR activity

E Quintana[1], B Beltrán[2], S Valverde[3], R Robles-Cedeño[1,4], H Perkal[1], X Lladó[3], JM Fernández-Real[5], L Ramió-Torrentà[1,4]

[1]Girona Biomedical Research Institute (IDIBGI), Neurodegeneration and Neuroinflamation Group, Girona, Spain, [2]IDI MRI-Unit, Radiology Department, Dr. Josep Trueta University Hospital, Girona, Spain, [3]University of Girona, Department of Computer Architecture and Technology (VICOROB Group), Girona, Spain, [4]Neuroimmunology and Multiple Sclerosis Unit, Dr. Josep Trueta University Hospital, Department of Neurology, Girona, Spain, [5]Endocrinology and Nutrition (UDEN), Girona Biomedical Research Institute (IDIBGI), and CIBER de la Fisiopatología de la Obesidad y la Nutrición (CIBERobn, CB06/03), Department of Diabetes, Girona, Spain

Background: Multiple Sclerosis (MS) is an inflammatory, demyelinating and neurodegenerative disease leading to both physical and cognitive impairment. Magnetic resonance (MR) is the most sensitive tool to investigate the brain tissue damage occurring in MS and it is the most used biomarker for the diagnosis and follow-up. MicroRNAs (miRNAs) are small noncoding RNAs that regulate the gene expression. miRNAs are present in biological fluids and might be used as disease biomarkers. Some miRNAs (miR-21, miR-155, miR-146a and miR-142-3p) have been implicated in MS immune processes.

Objectives: To evaluate the association between the cerebrospinal fluid (CSF) expression of miR-21, miR-155, miR-146a and miR-142-3p and different MR parameters in MS patients.

Methods: An observational cross-sectional study was designed. Circulating RNAs were extracted, retrotranscripted and preamplificated from CSF, and miRNAs were quantified in a real-time PCR. MR parameters analysed were: number of lesions in T2, number of gadolinium enhancing lesions (Gd+) in T1, presence of hipointense T1 lesions (hipoT1), and brain parenchymal fraction (BPF).

Results: 29 patients (79.30% were female) with a mean age of 40 (± 10.22) years old were analysed. Positive correlations were observed between Gd+ and miR-21 expression (r=0.418, p=0.030) and BPF with both miR-155 and miR-142-3p expression (r=0.541, p=0.021 and r=0.602, p=0.010 respectively). A downregulation of miR-142-3p in patients with hipoT1 compared with those without (0.016 vs. 0.067; p=0.017) and an upregulation of miR-146a in patients with ≥9 lesions in T2 compared with those with < 9 lesions (0.325 vs. 0.197; p=0.021) were also found.

Conclusions: miR-21 and miR-146a upregulation were found related to MR activity. miR-155 and miR-142-3p, which are related to inflammation, were found associated to less brain atrophy. The differential expression of miRNAs involved in the immune system regulation in CSF of MS patients is associated to different MR parameters.

Disease therapy

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Natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis: a prospective observational study of 197 patients

D Baroncini[1], A Ghezzi[2], C Stefanin[2], M Zaffaroni[2], P Annovazzi[2], S Baldini[2], G Comi[1]

[1]Centro Studi Sclerosi Multipla and H. San Raffaele, Gallarate-Milan, Italy, [2]Centro Studi Sclerosi Multipla, Gallarate, Italy

Background: Comparative data are not available on the effectiveness of natalizumab (NAT) versus fingolimod (FTY) in active relapsing-remitting multiple sclerosis (RR-MS).

Objectives: Aim of our study was to compare the clinical and MRI outcomes in a cohort of RR-MS patients (pts) treated with NAT or FTY in a clinical setting.

Methods: All consecutive RR-MS pts who started NAT or FTY before January 1st 2013 (after first line treatment or as first therapy according to EMA's prescription rules) were included in the study. Clinical and MRI data were collected prospectively. Pts without any clinical or MRI activity during the observation period were considered "disease-free".

Results: 160 pts. treated with NAT and 37 with FTY were enrolled in the study: females 67% vs 73% (p=0.47), mean age 37.5±9.1 vs 39.4±7.7 years (p=0.239), mean MS duration 10.1±6.0 vs 11.6±7.9 years (p=0.345), mean baseline EDSS score 2.5±1.5 vs 2.1±1.1 (p=0.199), mean annual relapse rate (ARR) in the year prior to NAT or FTY treatment 1.2±0.8 vs 1.2±0.5 (p=0.918). A total of 180 pts had been treated for 1 year (NAT=144, FTY=36) and 131 pts for 2 years (NAT=112, FTY=19). Four pts stopped FTY because of sustained bradycardia (1), pregnancy (1), minor

adverse event (AE) (1) and lack of efficacy (1). Thirty-eight pts dropped out from NAT because of AE (3), presence of neutralizing antibody (8), positivity to JC virus antibodies (22), pregnancy (4), and lack of efficacy (1).

In pts treated with NAT and FTY the ARR was 0.03 ± 0.20 vs 0.3 ± 0.7 (p< 0.001) after 1 year, and 0.04 ± 0.15 vs 0.26 ± 0.42 (p< 0.001) after 2 years of treatment respectively; the proportion of clinically active patients was 3% vs 22% (p< 0.001) after 1 year and 8% vs 32% (p=0.003) after 2 years of treatment respectively; the proportion of disease-free pts 97% vs 45% (p< 0.001) after 1 year and 93% vs 42% (p< 0.001) after 2 years of treatment respectively. The EDSS score was 2.1 ± 1.4 vs 2.0 ± 1.2 (p=0.971) after 1 year and 2.3 ± 1.5 vs 2.1 ± 1.2 (p=0.736) after 2 years of follow up.

Conclusions: Both NAT e FTY reduced clinical and MRI activity in RRMS pts, but the effect was stronger in those treated with NAT compared to FTY. The number of drop-outs was higher in NAT compared to FTY treated pts (24% vs 11%), mainly due to PML concern (58%).

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The influence of immunomodulatory treatment on the clinical course of multiple sclerosis

A Kavaliunas[1], L Stawiarz[1], A Glaser[1], J Hillert[1]
[1]Karolinska Institutet, Clinical Neuroscience, Stockholm, Sweden

Background: One of the major questions concerning the clinical progression of multiple sclerosis (MS), still insufficiently elaborated or confirmed, is if it can be slowed down or augmented by external factors such as disease modifying drugs (DMDs) beyond the 2 years of a typical randomized controlled trial.

Objectives: The aim of the study was to investigate if DMD treatment affects the long term clinical progression of MS, measured as time from diagnosis to scores of 4 or higher of Expanded Disability Status Scale (EDSS).

Methods: Longitudinal, prospective data concerning treatment status and EDSS are collected by health professionals in the Swedish MS Registry. This study cohort comprised newly diagnosed MS patients at the Karolinska University Hospital (Stockholm, Sweden) between 2001 and 2005.

Survival analysis adjusted for suspected confounders was performed with the outcome variable time in months from the baseline EDSS at diagnosis to EDSS ≥4 in a comparison of patients selected for treatment early or late after onset of disease.

Results: Patients were divided into two groups, i.e. those with early (205 patients that received the first treatment within 24 months from MS onset) or delayed treatment (299 patients that received the first treatment after 24 months from MS onset).

Univariate Kaplan-Meier analysis showed a statistically significant difference for time to reach EDSS ≥4 between early and delayed treatment groups (p > 0.001) with those treated late doing worse (hazard ratio of 1.77 (95% CI: 1.15−2.73) to reach EDSS ≥4). The difference remained statistically significant after adjusting for covariates (age at onset, the baseline EDSS and gender).

However, further analysis revealed that the early and delayed treatment groups were very different at the mean of age at diagnosis (32.2 and 39.1 years respectively). When we chose to include age at diagnosis instead of age at onset in the Cox proportional hazard model, significance was lost (95% CI for hazard ratio to reach EDSS ≥4 were 0.94-2.35).

Interestingly, gender was not a significant covariate in either model while the baseline EDSS remained significant in both analyses.

Conclusions: Different approaches to analyze the clinical course of MS, expressed in increase of EDSS score, show the importance of chosen confounders. Thus, we cannot confirm the beneficiary effect of early treatment in a cohort of this size in spite of a follow-up time of at an average of 10 years.

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Mechanism of action and safety implications of differently manufactured glatiramer acetates: gene expression studies of a human monocyte cell line

SE Kolitz[1], T Hasson[2], F Towfic[1], JM Funt[1], S Bakshi[2], KD Fowler[1], D Laifenfeld[2], MN Artyomov[1], R Schwartz[2], A Komlosh[2], L Hayardeny[2], D Ladkani[2], MR Hayden[2], B Zeskind[1], I Grossman[2]
[1]Immuneering Corporation, Cambridge, MA, United States,
[2]Teva Pharmaceutical Industries Ltd., Petach Tikva, Israel

Background: Since the 1990s, branded glatiramer acetate (GA) has provided a safe and effective treatment option for multiple sclerosis patients. Decades of study have yielded considerable insight into GA's mode of action, yet the precise mechanism remains to be fully characterized. GA has a highly complex colloidal composition in solution, so small manufacturing differences can have significant impact. Prior research in animal models published by our group strongly indicated that differently manufactured GAs give rise to altered gene expression profiles, raising concerns for compromised patient safety.

Objectives: To further the scientific understanding of GA's mechanism of action by analyzing gene expression profiles of human antigen presenting cells upon exposure to differently manufactured GAs, and explore the safety implications.

Methods: Cells from a human monocyte cell line (THP-1) were stimulated with either branded GA, purported generics from several manufacturers, or vehicle controls. RNA was extracted and expression profiled at various timepoints post exposure using Affymetrix U133 plus 2.0 chips. Differentially expressed genes (adj.p < 0.05 by LIMMA) were identified across different conditions, followed by analysis of pathway enrichment. The expression level of top resulting genes was independently assessed by qRT-PCR.

Results: Branded GA significantly modulated many pathways in human monocytes, including cytokine-cytokine receptor interactions, and regulation of immune processes. These findings were concordant with previously reported effects of GA (e.g. increasing expression of anti-inflammatory IL10), and support the validity of the study design. Significant differences between gene expression profiles induced by branded GA and various purported generics were observed and confirmed by qRT-PCR. For Probioglat, these differences impact key genes (e.g. CCL5, adj.p < 4.1×10^{-5}) in pro-inflammatory pathways (e.g. response to lipopolysaccharide, adj.p = 2.86×10^{-3}), raising safety concerns that warrant further studies, especially given that Probioglat is in clinical use in Mexico where healthcare providers have already reported different responses to treatment.

Conclusions: Gene expression studies in human monocytes demonstrate the complex mechanism of action of branded glatiramer

acetate, and identify significant differences from purported generics. Further investigation is warranted in order to ensure the safety of multiple sclerosis patients.

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Rituximab following natalizumab withdrawal in relapsing remitting multiple sclerosis

BE Beaber[1], G Mallari[1], D Le[1], AM Langer-Gould[1,2]
[1]Southern California Permanente Medical Group, Los Angeles Medical Center, Neurology, Los Angeles, CA, United States, [2]Kaiser Permanente Southern California, Research & Evaluation, Pasadena, CA, United States

Background: Withdrawal from natalizumab treatment in relapsing-remitting multiple sclerosis (RRMS) often leads to an increase in disease activity peaking around 4 months after discontinuation. The optimal post-natalizumab treatment for patients with previously aggressive MS disease is unknown.

Objectives: To gather preliminary evidence whether switching to rituximab after discontinuation of natalizumab decreases the risk of withdrawal relapses.

Methods: We conducted a retrospective cohort study of RRMS patients who discontinued natalizumab at least 6 months prior to chart abstraction from the membership of Kaiser Permanente Southern California 2007-2013. Data were abstracted from the complete electronic health record. Data were analyzed using Cox proportional hazards adjusted for age at time of discontinuation and natalizumab treatment duration.

Results: We identified 63 patients who had RRMS at the time natalizumab treatment was initiated. The majority had started natalizumab due to continued relapse activity despite treatment with other agents. 13 had transitioned to SPMS at the time of natalizumab discontinuation. Of the 50 patients that still had RRMS, the majority (37/50) were stopped due to testing positive for JC virus antibody. Seventeen (34%) were treated with rituximab 2-8 weeks after the last natalizumab infusion. 14 received 1000mg iv two weeks apart and 3 received lower doses. 18 patients were not started on any treatment in the first 6 months following natalizumab discontinuation. Fifteen (88%) of the rituximab-treated patients were relapse-free at 9 months of follow-up compared to only 44% of those untreated HR=0.09, 95%CI 0.01-0.80; p=0.03). Patients treated with rituximab were younger on average than those that were untreated. Younger age at the time of natalizumab treatment discontinuation was associated with an increased risk of natalizumab withdrawal relapses.

Conclusions: This study provides preliminary [level 3b] evidence for the effectiveness of rituximab for preventing natalizumab withdrawal relapses in individuals with RRMS.

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Comparison of fingolimod versus interferon beta/ glatiramer acetate as second-line therapy in active multiple sclerosis

A He[1], T Spelman[1], V Jokubaitis[2], A Lugaresi[3], G Izquierdo[4], M Trojano[5], P Grammond[6], J Lechner-Scott[7], P Duquette[8], M Girard[8], E Pucci[9], M Slee[10], F Grand'Maison[11], C Oreja-Guevara[12], C Boz[13], R Fernandez-Bolanos[14], S Hodgkinson[15], J Sanchez-Menoyo[16], G Iuliano[17], M Barnett[18], F Moore[19], H Butzkueven[20], T Kalincik[2,21], MSBase Study Group

[1]Royal Melbourne Hospital, Melbourne, Australia, [2]University of Melbourne, Department of Medicine, Melbourne, Australia, [3]University 'G. d'Annunzio, Chieti, Italy, [4]Hospital Universitario Virgen Macarena, Sevilla, Spain, [5]University of Bari, Bari, Italy, [6]Hotel-Dieu de Levis, Quebec, QC, Canada, [7]John Hunter Hospital, Newcastle, Australia, [8]Hôpital Notre Dame, Montreal, QC, Canada, [9]Ospedale di Macerata, Macerata, Italy, [10]Flinders University and Medical Centre, Adelaide, Australia, [11]Hôpital Charles LeMoyne, Quebec, QC, Canada, [12]University Hospital San Carlos, Madrid, Spain, [13]Karadeniz Technical University, Trabzon, Turkey, [14]Hospital Universitario Virgen de Valme, Sevilla, Spain, [15]Liverpool Hospital, Liverpool, Australia, [16]Galdakao Hospital, Vizcaya, Spain, [17]Ospedali Riuniti di Salerno, Salerno, Italy, [18]Brain and Mind Research Institute, Sydney, Australia, [19]Jewish General Hospital, Montreal, QC, Canada, [20]University of Melbourne, Melbourne, Australia, [21]Royal Melbourne Hospital, Department of Neurology, Melbourne, Australia

Background: Fingolimod has been demonstrated to be superior (i) to placebo as well as intramuscular interferon beta-1a in reducing relapse rates and (ii) to placebo in reducing disability progression in two landmark clinical trials. The relative effectiveness of switching from interferon beta or glatiramer acetate (IFN/GA) to fingolimod versus switching between IFN/GA preparations in patients experiencing on-treatment relapses has not yet been investigated.

Objectives: To compare the effectiveness of and persistence on fingolimod versus IFN/GA as second-line therapy after on-treatment relapse in multiple sclerosis.

Methods: Data was extracted from MSBase, an international observational multiple sclerosis registry. Patients previously treated with IFN/GA for a minimum of 6 months who experienced on-treatment relapse within previous 12 months and switched to either fingolimod or another IFN/GA product were identified. Propensity score matching with a variable ratio of up to 1:6, using nearest neighbour matching without replacement and a caliper of 0.1was used to match patients in each treatment arm on baseline clinical and demographic characteristics. In order to eliminate attrition bias, pairwise censoring was applied (with the exception of the treatment persistence analysis). Weighted paired t-test and weighted frailty Cox proportional hazards model were used to evaluate differences in disease outcomes.

Results: Amongst the 692 (IFN/GA) and 206 (fingolimod) patients eligible for matching, the switch to fingolimod was associated with relatively longer MS duration, lower number of pre-treatment relapses (but higher number of steroid-treated relapses), higher number of previous treatment starts and residence in Australia or Turkey. The 477 (IFN/GA) and 149 (fingolimod) matched patients differed only in the year of treatment switch. Median pairwise-censored on-treatment follow-up was 11 months. Patients in the fingolimod group had an annualised relapse rate of 0.31 compared to 0.59 in the IFN/GA group (p=0.01) and a lower hazard of relapse (hazard ratio 0.50). There was no difference in the post-switch disability between the two groups. Persistence on fingolimod was better compared to IFN/GA (hazard ratio 0.39). Sensitivity analyses confirmed the results of the primary analysis.

Conclusions: Following an on-treatment relapse on IFN/GA, switching to fingolimod is associated with lower hazard of relapses and increased treatment persistence compared with switching to another IFN/GA preparation.

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Clinical markers of long-term disability in RRMS patients treated with interferon beta

J Río[1], S Otero-Romero[1,2], M Tintoré[1], M Comabella[1], C Nos[1], L Negrotto[1], I Galán[1], À Vidal-Jordana[1], J Castilló[1], F Palavra[1], E Simón[1], G Arrambide[1], J Sastre-Garriga[1], X Montalban[1]
[1]Vall Hebron University Hospital, Multiple Sclerosis Centre of Catalonia, Neuroimmunology Department, Barcelona, Spain, [2]Vall Hebron University Hospital, Preventive Medicine and Epidemiology Department, Barcelona, Spain

Background: Clinical markers of long-term disability in RRMS patients treated with interferon beta
Objectives: To investigate the association between early clinical activity during interferon beta therapy (IFNβ) and long-term disability outcomes in patients with relapsing-remitting multiple sclerosis (RRMS).
Methods: A prospective and longitudinal 12-year follow-up study of patients with RRMS treated with IFNβ was conducted. All patients included underwent a neurological evaluation every 3 or 6 months for assessing disability (EDSS score) and relapses. Disease activity during the first 2 years was defined as: presence of at least 1 relapse, presence of at least 2 relapses, confirmed increase of at least 1 EDSS point and confirmed increase of 1 EDSS point plus relapses. Hazard ratios were calculated for early disease activity predicting severe long-term disability outcomes (5-step EDSS worsening, wheel-chair bound or secondary progressive stage of the disease) during the 12-year interval.
Results: From an original prospective cohort of 1450 patients treated with IFNβ, we included 234 patients with a follow-up of at least 12 years. One hundred and twenty patients (51%) were clinically active during the first 2 years of treatment, ranging from 18% for patients with a confirmed increase of 1 EDSS point plus relapses to 46% for patients experiencing at least 1 relapse. Persistent disease activity during the first 2 years of therapy predicted severe long-term disability worsening: confirmed increase of 1 EDSS point (HR 9.1; 4.1-22.6), at least 1 relapse (HR 4.4; 1.7-11.7), at least 2 relapses (HR 3.6; 1.6-8.1), and confirmed increase of 1 EDSS point plus relapse (HR 11.7; 5.3-26) for patients wheel-chair bounded; confirmed increase of 1 EDSS point (HR 10.2; 5.7-18.6), at least 1 relapse (HR 3.8; 2-7.1), at least 2 relapses (HR 3.9; 2.1-7.1), and confirmed increase of 1 EDSS point plus relapse (HR 9; 4.9-16.4) for patients with 5-step EDSS worsening; confirmed increase of 1 EDSS point (HR 9.4; 4-22.5), at least 1 relapse (HR 2.2; 1.2-4.2), at least 2 relapses (HR 2.1; 1-4.7), and confirmed increase of 1 EDSS point plus relapse (HR 6.9; 2.7-18.1) for patients evolving to secondary progressive MS.
Conclusions: Disease activity during the first two years of treatment with IFNβ is associated with worse long-term outcomes. The results provide rationale for close clinical monitoring of IFNβ-treated patients, and eventually for therapy switch and/or escalation in patients with active disease.

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Rituximab in the treatment of secondary-progressive multiple sclerosis

C Perrone[1], I Berriosmorales[1], B Beretich[2], P Riskind[1], C Ionete[1]
[1]University of Massachusetts Medical School, Worcester, MA, United States, [2]Maine Medical Center, Portland, ME, United States

Background: While mitoxantrone is the only FDA-approved drug to treat secondary-progressive multiple sclerosis (SPMS), its use is limited by high toxicity. A safer and more effective therapy is needed. With a growing understanding of B cell involvement in SPMS pathophysiology and safety demonstrated in phase I and phase II studies for relapsing-remitting MS, targeting this cell population with rituximab may alter the disease course.
Objectives: The goal of this study is to evaluate clinical outcomes in SPMS patients treated with rituximab compared to a control group.
Methods: Expanded Disability Status Scale (EDSS), 25-ft walk, and nine-hole peg test scores were evaluated for 40 SPMS patients treated with rituximab and a control group of 40 SPMS patients, matched for age and disease duration, on second-line immunosuppressive agents. Progression was first observed with respect to EDSS and composite scores. The differences in EDSS at -2, -1, +1, and +2 years relative to rituximab initiation were compared to differences over a 4-year follow-up period for control patients. To account for dilutional effects, patients on rituximab were also grouped by response (improvement, stable, progression). Mean differences between time periods were compared using a one-way, multiple comparison ANOVA. MRI data and adverse reactions were monitored for safety of the treatments.
Results: The control group showed greater interval progression when compared to patients treated with rituximab after 2 years (p=0.0162). Subgroup analysis demonstrated that 45% of patients improved on rituximab. With an additional 38% demonstrating stability, over 80% of patients on rituximab achieved the goals of disease-modifying therapy, halting progression and promoting improvement. After two years of rituximab therapy, patients with stability or improvement had significantly lower EDSS scores relative to patients in the control cohort and non-responders who progressed. No changes in MRI activity were observed for patients through their course of treatment, except for one non-enhancing lesion in one patient, and the adverse reactions reported were only mild to moderate.
Conclusions: B cell depletion through rituximab use could have important therapeutic benefit for SPMS patients. However, our results suggest the need for more prospective randomized controlled trials using B cell depletion therapies, including investigation into a biomarker for detection of clinical response.

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Efficacy of Natalizumab extended dosing in multiple sclerosis: a retrospective multicenter analysis

L Zhovtis Ryerson[1], J Herbert[1], C Tornatore[2], J Foley[3], B Weinstock-Guttman[4], I Kister[1], K Pandey[5], D Hojnacki[4], G Remington[6], T Frohman[6], E Major[7], D Douek[8], S Qureshi[6], J Beh[6], D Okuda[6], P Utomo[1], T Hoyt[3], E Chamot[9], M Bucello[4], I Ahsan[4], C Kolb[4], E Frohman[6]
[1]NYU Langone Medical Center, New York, NY, United States, [2]Georgetown University Hospital, Neurology, Washington, DC, United States, [3]Rocky Mountain MS Clinic, Salt Lake City, UT, United States, [4]University of Buffalo, Neurology, Buffalo, NY, United States, [5]Barnabas Health MS Center, Neurology,

Livingston, NJ, United States, [6]University of Texas Southwestern Medical Center, Neurology, Dallas, TX, United States, [7]National Institute of Neurological Disease and Stroke, Bethesda, MD, United States, [8]National Institute of Allergy and Immunology, Bethesda, MD, United States, [9]University of Alabama at Birmingham, Birmingham, AL, United States

Background: Natalizumab (NTZ) is a highly-effective agent approved for the management of relapsing forms of Multiple Sclerosis (MS). However, its use is limited by susceptibility of NTZ-treated patients to a serious viral disease of the central nervous system (CNS) - Progressive Multifocal Leukoencephalopathy (PML). In an attempt to mitigate risk of PML we have begun to explore the effect of extended dosing schedules (ED) for NTZ. We hypothesize that less frequent NTZ dosing may result in sub-maximal $\alpha4\beta1$-integrin receptor saturation, adequate to exclude autoreactive T cells from entry into CNS ('MS-protective') but nevertheless sufficiently permissive to enable normal CNS lymphocyte scavenging of JC-virus to occur ('PML-protective').

Objectives: To investigate efficacy of various duration NTZ ED schedules.

Methods: We conducted a retrospective review of charts and MRI scans of NTZ-treated patients from 6 U.S. MS centers. Patients were stratified into 4 groups based on NTZ treatment schedule after an initial 6-month initiation period with q4wk infusion: (1) group 1 - standard dosing (SD) every 4 weeks from onset; (2) group 2 (n= 222) - early extended dosing (EED) q4w3d-6w6d; (3) group 3 (n=221)- late extended dosing (LED) q7 - 8.5wks; (4) group 4 (n=158) - variable extended dosing (VED) - includes patients who alternated between EED and LED, in any sequence. For each group we calculated adjusted annualized relapse rate (ARR), incidence of steroid usage, new T2 lesions, T1 enhancing lesions, and disease free rate (No Evidence of Disease Activity, NEDA).

Results: ARR for all ED groups (groups 2-4) remained remarkably low (0. 08 - 0.18), comparable to SD (group 1) and to those reported in 2 pivotal NTZ studies and the TOPS post-marketing database. Discontinuation rate for total ED cohorts was 32%, primarily due to safety concerns. NEDA including both clinical and MRI criteria ranged from 49% in VED, 57% in EED to 77% in LED. AAR and NEDA were significantly better in LED compared to EED and VED, possibly reflecting selection bias.

Conclusions: Following an initial NTZ q4wks initiation period for at least 6 months, ED of NTZ up to q8.5wks appears to maintain the excellent efficacy profile of the drug both clinically and radiologically. Further efficacy and safety monitoring in these cohorts are ongoing. A large prospective study of ED NTZ schedules in MS is warranted.

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Comparative efficacy of switch to natalizumab or fingolimod in active relapsing-remitting multiple sclerosis

T Kalincik[1,2], D Horakova[3], T Spelman[2], V Jokubaitis[1], M Trojano[4], A Lugaresi[5], G Izquierdo[6], C Rozsa[7], P Grammond[8], R Alroughani[9], P Duquette[10], M Girard[10], E Pucci[11], J Lechner-Scott[12], M Slee[13], R Fernandez-Bolanos[6], F Grand'Maison[14], R Hupperts[15], F Verheul[16], S Hodgkinson[17], C Oreja-Guevara[18], D Spitaleri[19], M Barnett[20], M Terzi[21], R Bergamaschi[22], P McCombe[23], J Sanchez-Menoyo[24], M Simo[25], T Csepany[26], G Rum[27], C Boz[28], E Havrdova[3], H Butzkueven[1], MSBase Study Group
[1]University of Melbourne, Department of Medicine, Melbourne, Australia, [2]Royal Melbourne Hospital, Department of Neurology, Melbourne, Australia, [3]Charles University in Prague, Prague, Czech Republic, [4]University of Bari, Bari, Italy, [5]University 'G. d'Annunzio', Chieti, Italy, [6]Hospital Universitario Virgen Macarena, Sevilla, Spain, [7]Jahn Ferenc Teaching Hospital, Budapest, Hungary, [8]Hotel-Dieu de Levis, Quebec, QC, Canada, [9]Amiri Hospital, Kuwait, Kuwait, [10]Hôpital Notre Dame, Montreal, QC, Canada, [11]Ospedale di Macerata, Macerata, Italy, [12]John Hunter Hospital, Newcastle, Australia, [13]Flinders University and Medical Centre, Adelaide, Australia, [14]Hôpital Charles LeMoyne, Quebec, QC, Canada, [15]Orbis Medical Center, Sittard, Netherlands, [16]Groen Hart Ziekenhuis, Gouda, Netherlands, [17]Liverpool Hospital, Liverpool, Australia, [18]University Hospital San Carlos, Madrid, Spain, [19]AORN San Giuseppe Moscati, Avellino, Italy, [20]Brain and Mind Research Institute, Sydney, Australia, [21]19 Mayis University, Samsun, Turkey, [22]National Neurological Institute C. Mondino, Pavia, Italy, [23]Royal Brisbane and Women's Hospital, Brisbane, Australia, [24]Galdakao Hospital, Vizcaya, Spain, [25]Semmelweis University, Budapest, Hungary, [26]University of Debrecen, Debrecen, Hungary, [27]Petz A. County Hospital, Gyor, Hungary, [28]Karadeniz Technical University, Trabzon, Turkey

Background: Patients suffering from breakthrough disease despite treatment with interferon β or glatiramer acetate often escalate therapy to either natalizumab or fingolimod. However, no studies have directly compared the outcomes of escalation to either of these two agents.

Objectives: To compare treatment outcomes between escalation to natalizumab or fingolimod due to active multiple sclerosis (MS) on injectable immunomodulatory agents.

Methods: Using MSBase, an international, observational MS registry, we identified patients with relapsing-remitting MS experiencing on-treatment relapses or disability progression within the 6 months preceding escalation to natalizumab or fingolimod. Propensity score matching (variable 1:6 ratio, nearest neighbour matching without replacement, caliper 0.1) was used to select subpopulations with similar baseline demographic and clinical characteristics. In order to eliminate attrition bias, pairwise censoring was applied. Relapse and disability outcomes were compared in paired analyses adjusted for baseline MRI.

Results: Among the 792 included non-matched patients, escalation to natalizumab was associated with more severe disability, more frequent relapses, younger age and country of residence at baseline compared to fingolimod. The matched subsets of 407 (natalizumab) and 171 (fingolimod) patients did not differ in the recorded baseline parameters. Mean on-study follow-up was 12 months. The annualised relapse rates decreased from 1.5 to 0.2 on natalizumab and from 1.3 to 0.4 on fingolimod, with 50% relative post-switch difference in relapse hazard (p< 0.001). The changes in disability burden (quantified as area under disability-time curve) were -0.12 on natalizumab and 0.04 on fingolimod (Expanded Disability Status Scale step/year, p=0.002). The rate of 6-month confirmed disability regression was 67% higher after switch to natalizumab versus fingolimod (p=0.03) with no difference in the rate of 6-month confirmed disability progression.

Conclusions: In patients with active MS during treatment with injectable disease modifying therapies, escalation to natalizumab or fingolimod leads to significantly decreased relapse rates. Patients escalating to natalizumab are relatively less likely to experience on-treatment relapses. Switch to natalizumab increases the probability of reduction of disability compared to fingolimod and may lead to decrease in the overall disability burden. The probability of disability progression events is similar between the two escalation strategies.

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Persistence with fingolimod versus dimethyl fumarate in patients with multiple sclerosis: retrospective analysis of US open source pharmacy data

N Bergvall[1], R Lahoz[1], T Nazareth[2], JR Korn[3]
[1]Novartis Pharma AG, Basel, Switzerland, [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States, [3]IMS Health, Waltham, MA, United States

Background: Persistence with disease-modifying therapies (DMTs) improves clinical outcomes in multiple sclerosis (MS). No studies have compared persistence among patients receiving the recently approved oral DMTs, fingolimod and dimethyl fumarate (DMF).

Objectives: To compare 6-month persistence rates among patients with MS initiating fingolimod or DMF using mail-order pharmacy data from the US open-sourced LRx™ database.

Methods: A retrospective analysis was conducted on mail-order pharmacy claims data from the IMS longitudinal LRx database. Patients with >=1 prescription for fingolimod or DMF between 1 April 2013 and 31 July 2013 were included (index DMT). Patients were at least 18 years old, were naive to fingolimod and DMF, and had not received multiple DMTs on the date of first index DMT claim (index date). Prescription records were collected from pharmacies that had supplied at least 1 claim for index DMT between the first month from the index date and the last month of follow-up. Persistence was assessed as the time from initiating index DMT until discontinuation (a gap of >=60 days), receipt of another DMT or the end of the 6-month follow-up period. The risk of discontinuing index DMT was assessed using a Cox proportional hazards model controlling for age, gender, and region, and time to index DMT discontinuation was estimated using a Kaplan-Meier analysis.

Results: The study included 9546 patients (fingolimod: n=1390; DMF: n=8156). The proportion of patients discontinuing index DMT was significantly lower for patients taking fingolimod (23.3%) compared with those taking DMF (36.6%; $p< 0.0001$). The risk of discontinuation was 1.6-fold higher in patients taking DMF compared with those taking fingolimod (hazard ratio, 95% confidence intervals: 1.58, 1.41-1.77; $p< 0.0001$) and time to discontinuation was significantly longer with fingolimod compared with DMF ($p< 0.0001$). Similarly, the fingolimod cohort was persistent with index DMT for longer than the DMF cohort (mean number of days ± standard deviation: 152±53 days versus 135±62 days, respectively). Similar results were seen when discontinuation was defined as a gap of >=30 days ($p< 0.0001$ for all outcomes).

Conclusions: This analysis of US pharmacy data provides the first insight into short-term persistence rates with oral DMTs. In a real-world setting, fingolimod was associated with a lower risk of discontinuation over 6 months than DMF in patients initiating these therapies.

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Including threshold rates of brain volume loss in the definition of disease-activity-free in multiple sclerosis using fingolimod phase 3 data

N De Stefano[1], T Sprenger[2,3], MS Freedman[4], B Cree[5], MP Sormani[6], DA Häring[7], G Francis[8], D Piani Meier[7], D Tomic[7], L Kappos[9]
[1]University of Siena, Department of Medicine, Surgery and Neuroscience, Siena, Italy, [2]University Hospital Basel, Medical Image Analysis Centre, Basel, Switzerland, [3]University Hospital Basel, Department of Neurology and Division of Neuroradiology, Basel, Switzerland, [4]University of Ottawa and the Ottawa Hospital, Research Institute, Ottawa, ON, Canada, [5]University of California San Francisco, Department of Neurology, San Francisco, CA, United States, [6]University of Genoa, Biostatistics Unit, Department of Health Sciences, Genoa, Italy, [7]Novartis Pharma AG, Basel, Switzerland, [8]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States, [9]University Hospital Basel, Basel, Switzerland

Background: Brain volume loss (BVL) is an established marker of neurodegeneration. The reported mean annual rate of age-related BVL in healthy individuals (HIs) is 0.1-0.3%, whereas in patients with relapsing-remitting multiple sclerosis (RRMS), mean annual BVL is accelerated (0.5-1.35%). However, BVL is omitted from the current composite measures of disease activity and progression in RRMS, which rely on focal lesion-, relapse- and disability-related measures. Inclusion of BVL should provide a more comprehensive and stringent definition of disease-activity-free (DAF) or no evidence of disease activity (NEDA) for the assessment of treatment success.

Objectives: To evaluate a range of BVL thresholds using data from a population of patients with relapsing MS pooled from two 2-year, placebo-controlled, phase 3 trials (FREEDOMS and FREEDOMS II) in order to identify an appropriate BVL cut-off for inclusion in a revised DAF definition.

Methods: Percentage brain volume change (PBVC) from baseline to month 24 was assessed with Structural Image Evaluation, using Normalization, of Atrophy (SIENA). Different BVL thresholds were specified across mean ranges reported in HIs and MS patients (annual PBVC, −0.2%, −0.4%, −0.6%, −1.0%, and −1.2%). Among those in the pooled patient population with BVL above these thresholds, the proportions receiving fingolimod 0.5 mg (n = 783) or placebo (n = 773) were compared.

Results: In the pooled population, the mean annual PBVC with fingolimod was −0.43% (standard deviation [SD], 0.65%; median, −0.35%) compared with −0.66% with placebo (SD, 0.77%; median −0.51%; $p < 0.0001$). Irrespective of the chosen threshold, more fingolimod- than placebo-treated patients had BVL that remained below the threshold tested (PBVC threshold: % patients fingolimod vs placebo; −0.2%: 29.1% vs 20.0%; −0.4%: 37.2% vs 26.7%; −0.6%: 45.4% vs 32.8%; −1.0%: 61.6% vs 49.8%; −1.2%: 66.3% vs 55.5%; all $p < 0.001$).

Conclusions: This analysis provides BVL thresholds from which a candidate may be selected to allow more stringent

differentiation of patients categorized as DAF across treatment groups. Further analyses are required to confirm the BVL threshold most suitable for inclusion in a comprehensive DAF composite (BVL, lesional disease activity and disability progression).

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Comparison of survival of interferon beta-1b treated MS patients across two populations: the limitation of using propensity score matching

N Koch-Henriksen[1,2], G Suarez[3], A Reder[4], M Magyari[2]
[1]University of Aarhus, Dept. of Clinical Epidemiology, Aarhus, Denmark, [2]The Danish MS Research Centre, The Danish Multiple Sclerosis Registry, Copenhagen, Denmark, [3]Bayer HealthCare Pharmaceuticals, New Jersey, NJ, United States, [4]University of Chicago Medical Center, Dept. of Neurology, Chicago, IL, United States

Background: The 21-year long-term follow-up of survival in patients, originally enrolled in the North American (NA) pivotal 1993-interferon beta-1b (IFNb-1b)-study, showed significantly better long-time survival in patients from the two treatment arms, IFNb1b 50 and 250 mcg every other day (internal replication cohorts), compared with the placebo arm. In 1996 treatment with IFNb-1b 250 mcg was approved in Denmark. It was offered free to all MS-patients who fulfilled the same criteria as in the pivotal study: RRMS, age 18-55, EDSS ≤ 5.5, and at least two relapses in the preceding two years. All treated patients are registered in a permanent database, The Danish MS Treatment Register, and the Danish Civil Registration System which enables complete follow-up as to vital status for all the citizens at any time.

Objectives: To test the validity of regression analyses and Propensity Score Matching (PSM) when comparing long-term survival in the two selected treatment cohorts of MS patients from different geographical locations.

Methods: Patients from the INFb-250 mcg arm of the NA pivotal study and patients from the Danish MS Treatment register who started INFb-250 mcg treatment in the period 1996-2001 were included. The NA follow-up was truncated at 18 years to match the maximum observation time of the Danish Cohort, and the Danish cohort was adjusted to the same age range as the NA patients.

Results: NA patients (N=124, 250mcg group) showed a survival numerically better than treated Danish patients (N=415): The hazard ratio (HR) for death (North Americans vs. Danes) was 0.56 (95% CI 0.30-1.04; p=0.068). After adjusting for sex, age at start of therapy, duration of MS, MS Severity Score, and relapses in two years prior to treatment start, the Cox regression analyses changed nothing. PSM ("nearest neighbour" 1:1 matching"; exact for sex) increased the difference with a HR for survival of 0.421 in favor of the NA group (95% CI 0.20-0.88; p=0.022).

Conclusions: Cox Regression analysis and PSM, adjusted for possible clinical and demographic confounders, failed to remove an apparent but probably non-existing biological difference in treatment effect in terms of survival between the cohorts. These results demonstrate the difficulties when comparing cohorts with different characteristics such as social-economic factors, geographic location, follow-up periods, and patient and prescribing behaviors outside of a controlled clinical trial.

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A six-year clinical follow-up study of patients with multiple sclerosis who started natalizumab

L Prosperini[1], P Annovazzi[2], M Capobianco[3], F Buttari[4], V Barletta[1], C Gasperini[5], S Galgani[5], D Centonze[4], A Bertolotto[3], C Pozzilli[1], A Ghezzi[2]
[1]Sapienza University, Neurology and Psychiatry, Rome, Italy, [2]S. Antonio Abate Hospital, Multiple Sclerosis Centre, Gallarate, Italy, [3]San Luigi Gonzaga University-Hospital, Regional Multiple Sclerosis Centre, Orbassano, Italy, [4]Tor Vergata University, Neurosciences, Rome, Italy, [5]S. Camillo-Forlanini Hospital, Neurosciences, Rome, Italy

Background: Natalizumab is a very effective treatment to prevent relapses and accumulation of disability due to multiple sclerosis (MS), as shown in both pivotal trials and real-life studies. However, there are only few data on its long-term impact and consequences of its discontinuation.

Objectives: To investigate the long-term clinical outcomes of patients with MS who started natalizumab soon after the authorization by the Italian Pharmaceutical Agency.

Methods: Data on patients having a 6-year follow-up after starting natalizumab were collected. They were divided into 3 groups: continuing, temporarily interrupting (for at least 3 months) or discontinuing treatment. Logistic regression analyses were performed to ascertain the effect of final treatment status on the odds of either 1-step increase (disability worsening) and 1-step decrease (disability reduction) in Expanded Disability Status Scale (EDSS) score, controlling by baseline patients' characteristics.

Results: A total of 378 patients (259 F, 119 M) with mean (SD) age of 35.1 (8.9), and median EDSS score of 3.0 (range: 1.0-7.0) were considered. Continuing, temporarily interrupting and discontinuing groups accounted for 125 (34%), 75 (20%) and 170 (46%) patients, respectively; 8 patients were lost to follow-up. Safety concerns for PML risk mainly led to discontinuation (110) and temporary interruption (66) of natalizumab.

Disability worsening was observed in 8 (6%) continuing, 17 (23%) temporarily interrupting, and 66 (39%) discontinuing patients. Disability reduction was observed in 37 (30%) continuing, 15 (20%) temporarily interrupting, and 12 (7%) discontinuing patients.

Discontinuing and interrupting patients were 9.3 and 4.3 times more likely to experience disability worsening than continuing ones (p< 0.001 and p=0.001, respectively); discontinuation implied a 2.2-fold increased risk of disability worsening even respect to temporary interruption (p=0.015).

Discontinuing patients were less likely to experience disability reduction than continuing (OR=0.21, p< 0.001) and temporarily interrupting ones (OR=0.35, p=0.014). Finally, the odds of disability reduction did not differ between continuing and temporarily interrupting patients (p=0.21).

Conclusions: Our findings support the notion of high and sustained clinical effectiveness of ongoing natalizumab treatment. Either discontinuation and temporary interruption make patients at risk of disability worsening; however, temporary treatment interruption did not preclude the occurrence of disability reduction.

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Real life use of natalizumab and fingolimod in Austria: benefit-risk data from the Austrian Multiple Sclerosis Treatment Registry

M Guger[1], C Enzinger[2], F Leutmezer[3], J Kraus[4], T Berger[5]
[1]General Hospital Linz, Department of Neurology and Psychiatry, Linz, Austria, [2]Medical University of Graz, Department of Neurology, Graz, Austria, [3]Medical University of Vienna, Department of Neurology, Vienna, Austria, [4]Paracelsus Medical University of Salzburg, Department of Neurology, Salzburg, Austria, [5]Innsbruck Medical University, Clinical Department of Neurology, Innsbruck, Austria

Background: High efficacy of Natalizumab and Fingolimod in the treatment of relapsing-remitting multiple sclerosis (MS) has been proven in randomized trials. However, such trials do not necessarily reflect real-life situations faced in everyday practice.

Objectives: The Austrian MS Treatment Registry (AMSTR), established in 2006 and extended in 2011 to maintain quality control and comply with reimbursement regulations of the Austrian sick funds, allows to obtain such data, to assess indications, the clinical profiles of the treated populations and to monitor safety in a real life setting.

Methods: The baseline documentation within the AMSTR includes duration of disease, relapses within the last 12 months, EDSS, MRI activity and previous disease modifying therapies. Entry of follow up data (relapses, EDSS, adverse events) is required at 3 months intervals.

Results: As of April 23rd 2014, the registry comprised 1208 patients treated with Natalizumab (70.3% female) and 312 patients treated with Fingolimod (71.8% female). At baseline, their mean age was 35.6 (16-67) years in the Natalizumab and 38.3 (18-64) years in the Fingolimod group, with disease durations of 7.8 (0-40) years and 8.9 (0-32) years, respectively. The relapse rate in the year before start of respective drugs was 2.3 with Natalizumab and 1.8 with Fingolimod. For those treated for at least one year, the subsequent annualized relapse rates decreased to 0.35 (Natalizumab) and 0.40 (Fingolimod). At baseline, the EDSS was 3.2 (0-8.5) in the Natalizumab and 2.6 (0-7.5) in the Fingolimod treated group. EDSS stabilization or improvement was observed in 85% (Natalizumab) and 78% (Fingolimod). 40% of Natalizumab patients and 41% of the patients receiving Fingolimod stopped therapy according to the following reasons - patient's wish, adverse events (AEs), continuing disease activity, pregnancy or intended pregnancy.

Conclusions: For more than 7 years, the AMSTR has proved valuable to measure quality of care and monitor treatment, providing neurologists with highly relevant information for clinical practice. Continuous optimization and extension of this registry represents an unanimous goal and necessity. The availability of an increasingly broad treatment armamentarium with its consequences for daily practice (e.g. monitoring long-term benefit/risk profiles of individual drugs but also of their sequential use) emphasizes the need and the crucial importance of this registry for improved real life management of MS patients in Austria.

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Comparison of dropout rates of disease modifying therapies in multiple sclerosis

M Kurtuncu[1], S Yildiz Celik[1], A Coban[1], E Shugaiv[1], M Pehlivan[1], G Akman-Demir[2], M Eraksoy[1]
[1]Istanbul University Istanbul Medical Faculty, Neurology, Istanbul, Turkey, [2]Istanbul Bilim University, Neurology, Istanbul, Turkey

Background: There is an obvious need for head-to-head treatment studies in multiple sclerosis (MS). The lack of drug comparison trials may at least be partially compensated by real-life experience.

Objectives: The adherence of disease modifying treatments (DMT) depends not only on the side effects but also on the effect of a particular drug. Therefore, we can postulate that the treatment durations may give a reflection on the effectiveness of DMTs.

Methods: All MS patients with a DMT in a large database of 7300 patients with a demyelinating disease were included in the study. Cox´s proportional hazards analysis was performed to assess the impact of several covariates such as gender, disease duration, age of onset, age at the starting of the treatment, body mass index (BMI), oligoclonal band status, and treatment choices on the duration of treatments.

Results: A total of 1805 MS patients (1670 female, 702 male) were included in the study. The number of patients exposed to DMTs were as follows: 525 patients with interferon (IFN) beta1-a i.m., 494 patients with IFN beta1-b s.c., 590 patients with IFN beta1-a s.c., 442 patients with glatiramer acetate (GA) s.c., 139 patients with natalizumab, and 182 patients with fingolimod. According to the Cox regression analysis, only the treatment choice made a unique statistically significant effect on the treatment duration (p< 0,01) with IFN beta1-a i.m. having the highest dropout rate. Compared to IFN beta1-a i.m., the hazard ratios of the DMTs are as follows: IFN beta1-b s.c. 0,45 (95% CI 0,28-0,73; p=0,001), GA 0,53 (95% CI 0,33-0,85; p=0,009), IFN beta1-a s.c. 0,56 (95% CI 0,36-0,88; p=0,012), fingolimod 0,50 (95% CI 0,15-1,70; p=0,3), natalizumab 0,18 (95% CI 0,06-0,60; p=0,005). Subgroup analysis revealed that BMI had a significant impact on the treatment duration of GA with a hazard ratio of 0,89 (95% CI 0,79-0,60; p=0,99) without any effect to the treatment durations of other DMTs.

Conclusions: This long term, real-life study clearly shows that the dropout rates differ between DMTs. Despite the fact that natalizumab is used mostly in treatment refractory MS patients, its dropout rate is much less than the first line DMTs. Interestingly, BMI may affect the treatment duration of GA with higher dropout rates in underweight patients.

P295

Consensus opinion of US neurologists on practice patterns in radiologically and clinically isolated syndrome and relapsing-remitting MS

C Tornatore[1], JT Phillips[2], O Khan[3], A Miller[4], A Ally[5]
[1]Georgetown University, Washington, DC, United States, [2]Baylor Research Institute, Dallas, TX, United States, [3]Wayne State University, Detroit, MI, United States, [4]Mount Sinai School of Medicine, New York, NY, United States, [5]CVS Caremark Inc., Woonsocket, RI, United States

Background: A robust, up-to-date treatment algorithm for multiple sclerosis (MS) based on class I evidence has not been established. Appropriate management and selection of therapy is critical to optimize patient benefit.

Objectives: A modified Delphi process was used to assess practice patterns of recognized experts in the management and treatment of patients with MS or signs and symptoms suggestive of MS.

Methods: MS specialists from the Consortium of Multiple Sclerosis Centers (CMSC) were invited to participate. A steering committee of MS experts developed 2 surveys assessing treatment practices and factors influencing treatment decisions, administered between December 2013 and April 2014. They included patient scenarios detailing key clinical and magnetic resonance imaging (MRI) findings. Consensus opinion was defined a priori as 75% agreement.

Results: From geographically diverse US academic (49%) and community (51%) treatment centers, 107 respondents completed the first survey. Overall, there were 43 (46%) points of consensus, 21 of which were related to use of MRI. In all patient scenarios presented, there was consensus on when to initiate treatment but not on choice of therapy. A trend toward earlier, more aggressive treatment was observed: 70% would initiate treatment in a radiologically isolated syndrome case if 1 gadolinium-enhancing lesion was observed; 73% would treat clinically silent, but MRI-defined active disease in a patient with relapsing-remitting MS. Over 99% recommended a follow-up MRI within 12 months of presentation irrespective if treatment was initiated or not. In clinically stable RRMS patients, a change of therapy would be considered on the appearance of a single new Gd+ lesion (56%) or 2-4 T2 lesions (65%); there was consensus for continuing therapy in RRMS patients who remain stable by clinical and MRI measures for 5 years. Differences in opinion were observed regarding the best options for transitioning between treatments and duration of washout (except for the consensus that no washout is required for interferons and glatiramer acetate).

Conclusions: These compelling findings show considerable conformity in treatment practices among US physicians who are adopting a more aggressive approach to early treatment of MS, although variations in therapy selections are potentially influenced by payer formulary coverage. The completed consensus guidelines may offer key insights into harmonizing MS care without increasing overall healthcare cost.

P296

Assessing tolerability of interferon beta-1a intramuscular injections with a 30 gauge needle

AC Neal[1], LO Tuttle[1], JA Ruiz[1], BM Anderson[1], PB Wade[1]
[1]Mount Sinai Rehabilitation Hospital, Mandell Center for Multiple Sclerosis, Hartford, CT, United States

Background: Interferon Beta-1a (IFNB-1a) is routinely prescribed to persons with multiple sclerosis (PwMS). Clinicians have an option for choosing the needle gauge (G) for intramuscular injection when prescribing IFNB-1a. Options include 23G, 25G or 30G, with the 30G having the smallest diameter. In 2008, Freedman et al reported a decrease in anxiety and pain using 25G versus 23G needles for IFNB-1a injection. No studies have examined patient perception of 30G needles for IFNB-1a injection.

Hypothesis: PwMS will report less pain and anxiety using 30G compared to 25G needles for IFNB-1a injection.

Objectives: To evaluate perceived anxiety, pain and tolerability of the 30G needle for IFNB-1a injection.

Methods: Twenty patients with relapsing remitting multiple sclerosis using IFNB-1a with a 25G needle as part of routine care without prior use of a 30G needle were enrolled in this five week study. Participants self administered their normal dose of IFNB-1a weekly at home, alternating thighs, and filled out questionnaires pre and post injections. Week 1, participants used their own 25G needle and practiced completing the questionnaires; this data was not analyzed. Participants were provided 30G needles for weeks 2 and 3 and 25G for weeks 4 and 5. Participants were blinded to needle G. Pre-injection outcomes included Visual Analog Scales (VAS) for anxiety and pain and a Fear of Injection Questionnaire (FIQ). Post-injection outcomes included VAS pain, VAS anxiety and a Perception of Needle Questionnaire (PNQ). Data were analyzed using Wilcoxon Signed Ranks tests in SPSS version 18.

Results: Participants were 75% female, with a mean age of 48.60±10.41 years (yr), disease duration of 13.00 ±7.86 yr, and length of time on IFNB-1a of 9.70 ±6.28 yr. Mean VAS pre-injection anxiety was significantly higher for the 30G needle (M=2.28 cm, SD=2.73) than the 25G needle (M=1.58 cm, SD=2.25), p=0.030. There was no difference in fear of injection. A significant decrease in VAS pain post-injection using the 30G needle (M=0.764 cm, SD=0.93) compared to the 25G needle (M=1.201 cm, SD=1.22), p=0.035 was reported. Analysis of the PNQ indicated participants favored the 30G needle (M=1.94, SD= 0.858) over the 25G needle (M=2.58, SD=0.914), p=0.005.

Conclusions: PwMS reported increased anxiety prior to using the 30G needle but felt less pain and reported a more favorable perception after injection compared to the 25G needle when injecting IFNB-1a.

P297

Influence of treatments on multiple sclerosis disability: a cohort study

E Cocco[1], C Sardu[1], G Spinicci[2], L Musu[2], R Massa[2], J Frau[1], L Lorefice[1], G Fenu[1], G Coghe[1], S Massole[2], MA Maioli[2], R Piras[1], M Melis[1], G Porcu[1], E Mamusa[2], N Carboni[1], P Contu[1], MG Marrosu[1]
[1]University of Cagliari, Cagliari, Italy, [2]ASL8, Cagliari, Italy

Background: Multiple sclerosis (MS) is a disease of the CNS that causes severe neurological disability in young adults and relevant health and social costs. The actual therapeutic landscape consists of the disease-modifying drugs (DMD) that act by reducing the inflammatory activity but conflicting results exist on their effect on disability in the long term.

Objectives: The aims of this study were to understand the effect of common DMD in the long-term risk of disability and whether the effect is related to disability at start of treatment.

Methods: We analysed a cohort of 3060 patients from the MS Clinic of Cagliari (Italy) database. The median time of the follow-up was 12 years, accounting for 42025 person-years. Disability was assessed using the EDSS. Complete data on therapy were available for 2516 individuals. Among these patients, 1429 were treated with immunomodulants (IMT), 165 were treated with immunosuppressants (IST), 385 were treated with both, and 537 were not treated (UT). The median duration of treatment was 6.0 years. The effect of therapy on progression to EDSS 3 and EDSS 6 from onset was analysed in treated *vs* untreated patients using

Cox regression analysis adjusted for propensity score and immortal time bias.

Results: The risks of EDSS 3 were 94% (HR= 0.06, p< 0.001) and 73% (HR= 0.27, p< 0.001) lower in 1306 IMT patients and in 98 IST patients, respectively, than in untreated patients. The risk of EDSS 6 in 1389 IMT patients was 86% lower than in UT (HR= 0.14, CI 95% 0.08-0.25, p< 0.001), whereas in 140 IST patients, the risk did not significantly differ. The risk of EDSS 6, analysed in 1275 IMT patients before they progressed to EDSS 3 was 91% lower than in 539 UT (HR= 0.09, 95% CI 0.04-0.19, p< 0.001). Similarly, in 114 patients who started IMT after they progressed to EDSS 3, the risk was 75% lower than in UT (HR= 0.25, 95% CI 0.12-0.51, p< 0.001). The risk of EDSS 6 was higher in patients who started therapy after EDSS 3 than in patients who started therapy before EDSS 3 (HR= 4.42, 95% CI 2.64-7.39, p< 0.001).

Conclusions: These results demonstrate, despite the observational design of this study, a benefit of common DMD in delaying long-term disability in MS patients treated either in the early or, to a lesser extent, in the later phase of the disease. Thus, the window of therapeutic opportunity is relatively extended, assuming that early treatment is better than late treatment, but late treatment is better than never.

P298
Safety and efficacy of treosulfan in 21 patients with active secondary progressive multiple sclerosis after treatment with mitoxantrone

A Deiß[1], S Bräuninger[1], H Wiendl[2], M Buttmann[1]
[1]University of Würzburg, Department of Neurology, Würzburg, Germany, [2]University of Münster, Department of Neurology, Münster, Germany

Background: Immunotherapy of patients with active secondary progressive multiple sclerosis (SPMS), after having reached the maximal cumulative dose of mitoxantrone, represents a therapeutic challenge. Treosulfan, a well-tolerated alkylating agent approved for ovarian cancer, was previously found to be effective and safe in 11 patients with active SPMS in a non-randomised, open-label trial. However, none of these patients had previously received immunosuppressive therapy.

Objectives: To report on 21 patients with active SPMS, who received treosulfan in a clinical routine setting after previous treatment with mitoxantrone.

Methods: Retrospective single center case series.

Results: Fourteen patients (67%) were women. At treosulfan initiation, mean age was 46 (SD 10.6, range 26-69) years. Ten patients had SPMS without and 11 with superimposed relapses. Mean time since diagnosis was 13.5 (SD 6.1) years. Median duration of the secondary progressive phase was 5 (range 1-22) years. All patients had previously received mitoxantrone (mean cumulative dose 97.2 mg/m^2, SD 36.9). All had clinically active disease as assessed by EDSS progression, clinical relapses and MRI activity markers. Median EDSS at baseline was 6.5 (range 4.0-8.0). Most often, treosulfan was intravenously administered at a standard dose of 7 g/m^2 for 4 monthly cycles, followed by quarterly infusions − with dose adjustments according to blood counts (mean 6.7 cycles, SD 2.8; mean cumulative dose 45.5 g/m^2, SD 21.2). An improvement of the EDSS score during treosulfan treatment was observed in 2 patients, EDSS stability was noted in 15

patients and 3-month sustained EDSS progression was seen in 4 patients. Treatment of 2 patients had to be stopped due to serious adverse events, including urosepsis followed by deep vein thrombosis and pulmonary embolism in one patient, as well as severe pneumonia requiring assisted ventilation in the other. Both patients fully recovered from these complications. Another patient´s treatment was discontinued due to incompliance and suspected self-harming behaviour. Mostly mild to moderate adverse events leading to dose or interval alterations included leukocytopenia, thrombocytopenia and infections. No haematologic malignancy was observed (mean follow-up 44 months, SD 19.4). Overall, treatment with treosulfan was well tolerated.

Conclusions: Treosulfan could be considered as a rescue therapy in mitoxantrone-pretreated patients with active SPMS after stringent benefit-risk assessment. Further study is warranted.

P299
Improving adherence in pediatric MS: feasibility of a randomized-control trial with a remote motivational interviewing intervention

AE Sye[1], CE Schwartz[2,3,4], E Quon[1], EA Yeh[1,5]
[1]Hospital for Sick Children, Neurosciences and Mental Health, Toronto, ON, Canada, [2]DeltaQuest Foundation, Concord, MA, United States, [3]Tufts University Medical School, Boston, MA, United States, [4]Oslo and Akershus University College of Applied Sciences, Oslo, Norway, [5]Hospital for Sick Children, Neurology, Toronto, ON, Canada

Background: Poor medication adherence occurs in approximately ¼ to ½ of children with MS. Most interventions to improve medication adherence to date have relied on face-to-face contact. The relative rarity of the condition and need to travel great distances for specialist care suggests the need for remotely-administered interventions in this population. The feasibility of a remote behavioral intervention in this population has not been assessed, nor have rigorous evaluations of enrollment methods and retention of pediatric MS patients in behavioral intervention studies been performed.

Objectives: To evaluate the feasibility of implementing a remote motivational interviewing (MI) intervention combined with web-based outcome measures in a pediatric MS patient population.

Methods: We evaluated enrollment and retention at a single tertiary-care centre in a prospective trial of medication adherence in pediatric MS. Feasibility was assessed by examining patient recruitment, retention, intervention compliance and satisfaction, and completion of web-based questionnaires. We also evaluated strategies to retain and recruit trial participants. Recruitment strategies included pairing the enrollment visit with a clinic visit, minimizing travel distances by offering online questionnaires and a remote intervention, and offering a parking voucher. Retention strategies included building strong relationships with the study coordinator and staff, contact between study visits via email and telephone reminders, scheduling night and weekend appointments, and financial incentives. Ethics approval from SickKids' Research Ethics Board was obtained.

Results: Thirteen of 14 patients invited agreed to participate in the study. One patient withdrew due to psychiatric issues; two were ineligible, yielding a total of ten retained. Average commute to hospital was 78 minutes. All patients and parents were able to

complete their respective initial web-based questionnaire, taking about 20 minutes to complete. All planned remote MI intervention sessions were completed by participants. All participants reported being highly satisfied with the intervention and 2/3 reported it to be very helpful for them to remember to take their medication regularly.

Conclusions: Enrollment and retention rates were high in this pilot study. The current study demonstrates (1) feasibility of enrollment of pediatric MS patients in a trial involving a remote intervention and (2) feasibility of offering motivational interviewing remotely to clinical populations.

P300

Comparative tolerability and efficacy of dimethyl fumarate and fingolimod in multiple sclerosis

S Cohn[1], R Bermel[2], C Hara[2], C Hersh[2], RJ Fox[2], J Cohen[2], D Ontaneda[2]

[1]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, United States, [2]Cleveland Clinic Mellen Center, Cleveland, OH, United States

Background: Fingolimod (FTY) and dimethyl fumarate (DMF) are two commonly used oral disease modifying therapies (DMT) for relapsing multiple sclerosis (MS). Phase 3 clinical trials established the efficacy and tolerability of both but the comparative efficacy, safety and tolerability of these medications is unknown.

Objectives: To compare the real-world efficacy, safety, and tolerability of dimethyl fumarate (DMF) and fingolimod (FTY) in patients with MS.

Methods: Patients prescribed DMF or FTY at our center were identified. Patient and clinician-reported outcomes, MS disease history, prior DMT use, screening laboratory studies, relapse data, MRI data and follow-up data was abstracted and entered into a secure REDCap database. Propensity score methods based on clinical and imaging data were used to improve balance of baseline characteristics between the treatment groups, including both 1:1 Greedy matching without replacement and Average Treatment effect on the Treated (ATT) weighting approaches. Primary outcomes included discontinuation rate at 3 months for tolerability and proportion of patients with MRI activity or relapses by 3 month follow-up for efficacy.

Results: 426 patients initiated DMF therapy and 317 initiated FTY (total n=743). ATT weighting on the linear propensity score achieved better covariate balance compared to 1:1 matching and was used to obtain adjusted estimates for each outcome. Discontinuation of DMF occurred in 18% of subjects compared to 8% of those on FTY. Patients on DMF had a statistically significantly higher rate of drug discontinuation at 3 months (OR 3.43, 95% CI 1.69 to 6.97, p< 0.001) compared to FTY. The leading causes of discontinuation in DMF patients were gastro-intestinal and dermatological (flushing) symptoms. Patients on DMF showed a trend for higher odds of relapse in the first 3 months of therapy (OR 2.04, 95% CI 0.78 to 5.37, p,>0.05) when compared to FTY. There was no significant difference in rates of MRI activity between DMF and fingolimod patients at 3 months (OR 1.05, 95% CI 0.42 to 2.65, p>0.05).

Conclusions: Patients using DMF were three times more likely to discontinue medication than those starting FTY. Gastrointestinal and flushing symptoms adversely affected the overall tolerability

of DMF. Efficacy was not statistically different between FTY and DMF at 3 months however the follow-up may be too short to detect a difference. The comparative efficacy and tolerability of FTY and DMF will need to be considered when using selecting between these medications.

P301

Suboptimal response to therapy in disease-free MS patients: a paradox?

FFA Figueira[1], GMA Figueira[1], PV Soares[1]

[1]Hospital São Francisco, Neurology, Rio de Janeiro, Brazil

Background: Current MS therapies target inflammatory activity of disease, defined by clinical relapses and EDSS progression, besides with absent T1W contrast enhancing lesions as well as no new or enlarging T2W lesions on MRI, in a way to impact disability development. So, the absence of clinical and MRI activity are accepted paradigms of disease free status in treated patients. Nevertheless, axonal loss seems to be a major determinant of disability, and may occur with lacking clinical expression and sophisticated MRI requirements. In this paper, we discuss current concept of disease free applied in real world, and propose that measures of atrophy be used in daily practice as a tool for optimal therapy.

Objectives: Axonal loss is an early finding in MS and relates to disability. So we propose its use as a marker for treatment optimization.

Methods: Our group studied 206 consecutive non-selected patients with relapsing-remitting MS diagnosed according to 2001 McDonald criteria, on regular immunomodulatory treatment. They were submitted to serial clinical examinations and conventional MRI evaluation focus on relapses, EDSS progression and the presence of T1W Gd enhancing or T2W new/enlarging lesions. On conventional MRI sequences, we studied brain parenchymal fraction (BPF) and corpus callosum index (CCI), annually comparing results with data from a control group, composed by non-inflammatory diseases.

Results: After 5 year, 56.7% patients presented with some evidence of disease activity: all but two patients showed worsening scores in BPF and CCI. On the other hand, 43.2% fulfilled accepted criteria for free of disease status, despite 48.3% of them showed a progressive reduction on BPF and CCI, comparable with those stratified as suboptimal responders.

Conclusions: Our data demonstrates that axonal loss can be detected on follow up using corpus callosum index using conventional MRI sequences, even among apparently stable patients. We propose this parameter to be included as one requirement for "disease free" patient concept.

P302

Patient-reported adverse events of high-dose intravenous methylprednisolone for relapse treatment in multiple sclerosis (FEEL study)

I Stavrakaki[1], ELJ Hoogervorst[2], P Pop[3], E van Munster[4], WHJP Linssen[5], R Hupperts[6], LGF Sinnige[7], JJ Kragt[8], WIM Verhagen[9], LH Visser[10], R van der Kruijk[11], HM Schrijver[12], J Koeman[13], F Verheul[14], JBS Boringa[15], EPJ Arnoldus[16], W Gladdines[1], F Lönnqvist[1], PJ Gaillard[1], PJ Jongen[17]

[1]to-BBB Technologies BV, Leiden, Netherlands, [2]St Antonius

Ziekenhuis, Utrecht, Netherlands, ³Viecuri Medisch Centrum, Venlo/Venray, Netherlands, ⁴Jeroen Bosch Hospital, Den Bosch, Netherlands, ⁵Sint Lucas Andreas Ziekenhuis, Amsterdam, Netherlands, ⁶Orbis Medical Center, Sittard, Netherlands, ⁷Medisch Centrum Leeuwarden, Leeuwarden, Netherlands, ⁸Reinier de Graaf Groep, Delft, Netherlands, ⁹Canisius-Wilhelmina Ziekenhuis, Nijmegen, Netherlands, ¹⁰St. Elisabeth Ziekenhuis, Tilburg, Netherlands, ¹¹Slingeland Ziekenhuis, Doetinchem, Netherlands, ¹²Westfriesgasthuis, Hoorn, Netherlands, ¹³Admiraal De Ruyter Ziekenhuis, Goes, Netherlands, ¹⁴Groene Hart Ziekenhuis, Gouda, Netherlands, ¹⁵Meander Medisch Centrum, Amersfoort, Netherlands, ¹⁶Tweesteden Ziekenhuis, Tilburg, Netherlands, ¹⁷MS4 Research Institute, Nijmegen, Netherlands

Background: Pulses of high dose intravenous methylprednisolone (IVMP) 500-1000 mg/day for 3-5 days is the mainstay of relapse treatment in multiple sclerosis (MS). Despite IVMP being generally considered as well tolerated in this patient group, patient-reported adverse events (AEs) are scarcely studied.

Objectives: The FEEL study is an observational study designed to assess the frequency, severity and impact of patient-reported AEs during and shortly after IVMP treatment in patients with relapsing-remitting MS (RRMS) and clinically isolated syndrome (CIS).

Methods: 80 RRMS and CIS patients (median age 45 y) diagnosed with a relapse and planned to be treated with IVMP were enrolled at 15 hospitals in the Netherlands from January 2013 until 10 March 2014 (cut-off). The patients completed a questionnaire assessing the frequency, severity and impact of IVMP AEs on a 4-point Likert scale (a lot, quite a lot, a little, not at all) at 4 time points: before start of treatment, during treatment and 1 and 7 days after end of treatment. AEs were defined as any worsening of pre-existing symptom or the occurrence of any new symptom after start of treatment. AEs were considered as severe when one of the two highest points were chosen at least once. Preliminary data regarding frequency and severity from 60 patients (17 drop outs, 3 didn't complete baseline) who completed baseline and at least one follow up questionnaire are shown here.

Results: Patients reported the following AEs: taste alteration (55%), facial flushing (53%), nausea/stomach pain (50%), insomnia (38%), agitation (33%), changes in appetite (32%), behavioral changes (30%), muscle weakness (28%), anger (27%), palpitations (27%), depression (22%), euphoric feelings (20%), acne (20%), skin changes (20%) and muscle cramps (17%). The median number of AEs per patient was 4 (range 0-12). The CNS-related AEs considered severe and experienced by at least 10% of the patients were insomnia (27%), agitation (18%) and depression (10%). As regards severe non-CNS-related AEs, nausea/stomach pain (20%), muscle weakness (20%), metallic taste (15%) and facial flushing (12%) were most commonly reported.

Conclusions: MS patients treated with high-dose IVMP for a relapse experience a median number of 4 AEs during and shortly after treatment. Severe CNS-related and non-CNS-related AEs occur in up to 27% and 20% of the patients respectively, and add to the MS-related symptoms. These data show that from a patient perspective, there is room for improvement in the treatment of MS relapses.

P303

Safety and efficacy of dimethyl fumarate in patients with multiple sclerosis - real world experience

C Chaves[1], R Ganguly[1], C Dionne[1], A Camac[1]
¹Lahey Clinic/Tufts University, Neurology, Lexington, MA, United States

Background: Dimethyl fumarate (DMF) is a new oral disease modifying agent (DMA) recently approved to treat relapsing remitting multiple sclerosis (RRMS). Its safety and efficacy were demonstrated in two phase III clinical trials. However, its benefit in real world MS patients is still not well known.

Objectives: To report on the safety and efficacy of DMF in RRMS patients followed at the Lahey Clinic MS Center.

Methods: We retrospectively selected all RRMS patients treated with DMF from our MS database. Potential side effects and number of clinical relapses were reviewed.

Results: We had 145 patients, 103 women (71%) and 42 men (29%), with a mean age of 49 years. Patients were followed for a median of 8.7 months. Side effects from prior DMA (43%) were the most frequent cause for starting DMF followed by lack of efficacy (23.5%) to other agents. The most common side effects were flushing and gastrointestinal (GI) symptoms. Flushing was reported by 57.3% of the patients in the first month of treatment, 34.6% by the 3rd month and 45 % and 71.4 % by the end of the 6th and 9th months. GI side effects occurred in 53% of patients in the first month, but declined to 18%, 13.9% and 10.7 % by the end of the 3rd, 6th and 9th months. Decrease in the number of white blood cells and/or lymphocyte counts were detected in 26.5%, 50.7% and 62% of patients at months 3, 6 and 9, with grade II leucopenia and/or grade III lymphopenia occurring in 2%, 4.5% and 6.9% patients, respectively. Five patients (3.4%) developed serious infections while on DMF, two of them in the setting of severe leucopenia and/or lymphopenia. Transaminitis was seen in 13.3% of patients at month 3, 19.4% at month 6 and 13.8% at month 9; all, except one, had levels below three times baseline. One patient (0.7 %) was diagnosed with adenocarcinoma of the lung during treatment. Eight patients (5.5%) had exacerbations within the first 7 months of starting DMF, four of them occurring within the first 3 months of treatment. DMF was discontinued in 23 patients (15.9%), the majority due to GI side effects followed by clinical relapse.

Conclusions: In our study, the side effects from DMF were similar to phase III studies, however, flushing occurred more frequently and lasted longer than previously reported. In addition, decrease in white blood cell and/or lymphocyte count were detected in more than 50% of the patients, as many as 6.9% with severe abnormalities. During this study, 5.5% of patients had exacerbations, most of them within the first few months of treatment.

P304

Time to relapse among propensity score matched patients receiving disease modifying therapy for multiple sclerosis

BH Johnson[1], MM Bonafede[1], C Watson[2]
¹Truven Health Analytics, Outcomes Research, Cambridge, MA, United States, ²Biogen Idec Inc., HE&OR, Global Market Access, Cambridge, MA, United States

Background: A recent study conducted using multiple sclerosis (MS) registry data mainly from Europe found that natalizumab significantly delays time to relapse compared to platform therapy (interferon beta/glatiramer acetate) in patients who switch therapies.

Objectives: To examine relapse rates and time to relapse among propensity score matched MS patients treating with platform therapy or natalizumab using United States administrative claims data.

Methods: Adults with a diagnosis of MS (ICD-9-CM code 340) receiving platform therapy or natalizumab between January 1, 2009 and April 1, 2012 were identified in the Truven Health MarketScan Research databases; the first claim was the index date. Patients were required to have 12 months of continuous enrollment before [pre-period], with no prior non-index MS therapy, and after [post-period] the index date and remain on their index drug for 12 months. Nearest neighbor propensity score matching was conducted on the probability of a patient receiving natalizumab, including the following match characteristics: age, gender, region, health plan type, index year, selected comorbid conditions and concomitant medications, MS severity, pre-period relapse and pre-period expenditures. Relapse was defined as the presence of an MS-related inpatient (IP) admission, IV or oral corticosteroid use during the 12 month post-period. Time to relapse was evaluated using a Cox Proportional Hazard model controlling for all available baseline demographic and clinical characteristics.

Results: A total of 882 natalizumab patients (mean age 45 years, 70% female) were matched 1:1 to 882 platform therapy patients (standardized difference < 10 on all matching measures). Post-period relapse was significantly less among natalizumab patients compared to platform therapy (26.5% vs. 35.5%, p< 0.001); natalizumab patients had 25 more days without relapse during the 12 month post-period (308 vs. 283 days, P< 0.001). Natalizumab patients had lower post-period rates of MS-related IP admissions (1.0% vs. 2.6%), IV-corticosteroid use (15.6% vs. 19.0%) and oral corticosteroid use (15.4% vs. 23.1%) (all p< 0.001). Natalizumab patients had a significantly lower risk of relapse (hazard ratio=0.69, 95% [CI: 0.59, 0.82]) during the 12 month post-period after controlling for baseline characteristics.

Conclusions: Initial natalizumab treatment was associated with significantly lower risk of relapse compared to interferon beta/glatiramer acetate initiation.

P305

Adherence project with German MS-patients: can an approach of individualized patient counseling improve adherence?

M Mäurer[1], R Voltz[2], Y Begus-Nahrmann[3], B Schmid[4], G Niemczyk[4], BC Kieseier[5]

[1]Caritas Hospital, Department of Neurology, Bad Mergentheim, Germany, [2]University Hospital of Cologne, Department of Palliative Medicine, Cologne, Germany, [3]Konzept Pharma Service GmbH, Freden, Germany, [4]Biogen Idec GmbH, Ismaning, Germany, [5]Heinrich-Heine University, Department of Neurology, Düsseldorf, Germany

Background: Patients with multiple sclerosis (MS) frequently discontinue treatment with therapy, although beneficial effects are evident in the long-term. Patient counseling programs (PCP) should not only help in the understanding of MS but also to stay adherent to a given therapy and follow medical recommendations.

Objectives: To evaluate, whether an individualized PCP based on the statistical analysis of a patient survey to identify current adherence risk factors can improve adherence and provide an effective system to stay adherent.

Methods: In an open-label survey, German MS patients completed an anonymous web-based questionnaire regarding adherence factors. 4000 patients were invited, 1883 participated. Statistical analysis consisted of contingency tables and Chi-Square test. In February 2014, the PCP based on these results for patients treated with dimethyl fumarate (DMF) including amongst others differentiated information for 3 patient subtypes and a smartphone application started. DMF patients which were not included in the PCP serve as controls.

Results: Demographic parameters from the survey were comparable to the German MS-register. While 87% of these patients were currently treated with disease-modifying drugs, 35% stated to have problems with adherence. Demographic factors did not act as reliable parameter predicting adherence risk factors while experience with MS therapies did. There is a positive correlation with adherent behavior in patients having realistic expectations of therapeutic outcome, good self-management, and reliable information sources.

As of April 2014, 1701 DMF patients registered in the PCP. Approximately 75% of patients had experience with at least one therapy while the rest was newly diagnosed in both cohorts. The primary reason for transitioning to DMF in both groups was sensed ineffectiveness of prior therapy. Approximately a third of patients in the PCP reported adverse events (AE). Flushing was the most common AE, so far. Close contact between PCP and patients lead to effective AE management and most of the symptoms could be handled and improved. To retain adherence individual intake procedures were defined and the application with a reminder function was distributed.

Conclusions: Reduction of AEs and thereby initial adherence could be achieved by the individualized PCP. Qualitative and quantitative measurements of adverse effects reduction and adherence will show if this initial approach will also be useful for long-term adherence.

P306

Reduced frequency and severity of injection site reactions with glatiramer acetate 40mg/mL three times weekly dosing

JS Wolinsky[1], Y Sidi[2], JR Steinerman[3], V Knappertz[3,4], S Kolodny[5], The GLACIER Study Group

[1]University of Texas, Health Science Center at Houston, Houston, TX, United States, [2]Teva Pharmaceutical Industries, Netanya, Israel, [3]Teva Pharmaceutical Industries, Frazer, PA, United States, [4]Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany, [5]Teva Pharmaceutical Industries, Cleveland, OH, United States

Background: Injection site reactions (ISRs) are the most common treatment (Tx)-related adverse events (AEs) associated with subcutaneous glatiramer acetate (GA) use in RRMS patients (pts). GA 20mg/mL daily (GA20) and 40mg/mL 3 times weekly (GA40) dosing regimens are shown to be safe and well tolerated in RRMS

pts. Reducing GA injection frequency may alter ISR rate and severity.

Objectives: To compare ISR frequency and severity with GA40 vs. GA20 in RRMS pts in the open-label phase IIIb **GL**atiramer **A**cetate low frequen**C**y safety and pat**I**ent **E**xpe**R**ience (**GLACIER**) study.

Methods: Pts ≥18 years (yrs) old with confirmed RRMS (McDonald, 2010) and EDSS score 0-5.5 treated with GA20 for ≥6 months before screening were eligible. Pts were randomized 1:1 to continue GA20 therapy or to convert to GA40 for a 4-month active Tx period. Pts were evaluated at baseline (BL) and months 1, 2, and 4. Pt-reported ISRs were recorded on a daily diary card and classified as mild (easily tolerated), moderate (interferes with normal daily activity), or severe (prevents normal daily activity). All ISRs occurring in the active Tx phase were coded to MedDRA-preferred terms. ISR frequency was measured as annualized event rate; ie, total number of ISR events/pt-yr of drug exposure. The risk ratio (RR) for annualized ISR rate with GA40 vs GA20 was derived from a BL-adjusted quasi-likelihood (over-dispersed) Poisson regression.

Results: Most pts (GA40 n=108, GA20 n=101) were female (82%) and Caucasian (94%). Mean (±SD) age was 50.7 (10.2) yrs. Exposure to GA40 was 32.4 pt-yrs and to GA20 was 30.6 pt-yrs. Adjusted mean (±SE) annualized ISR rate was reduced 50% in the GA40 group: 35.2 (7.2) vs. 70.4 (12.0); RR=0.50 (95%CI 0.34, 0.74), *p*=.0006. Unadjusted event rates per pt-yr for common ISRs were substantially reduced in the GA40 group vs. GA20: pain (24.8 vs. 55.3), erythema (21.4 vs. 43.5), mass (11.8 vs. 21.9), pruritus (7.8 vs. 13.0), urticaria (5.4 vs. 12.3), and swelling (5.3 vs. 19.4). The total number of individually reported ISRs in GA20 was 5537, and in GA40 was 2610; of these, moderate or severe reactions were less frequent in GA40-treated pts (9%) than in GA20-treated pts (15%).

Conclusions: The frequency of all ISRs was substantially reduced with GA 40mg/mL 3 times weekly compared with GA 20mg/mL daily. ISRs with GA40 were less likely to interfere with or prevent daily activity.

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Real-world titration of disease modifying therapies in the treatment of multiple sclerosis: findings from a survey of neurologists

T Nazareth[1], J Marvel[1], S Sikirica[1,2], J Xie[3], W Reichmann[4], C Zhao[3], R Sasane[1]
[1]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States, [2]Thomas Jefferson University, Jefferson School of Population Health, Philadelphia, PA, United States, [3]Analysis Group, Inc., New York, NY, United States, [4]Analysis Group, Inc., Boston, MA, United States

Background: Disease modifying therapies (DMTs) are the mainstay treatment in relapsing-remitting multiple sclerosis (RRMS). Certain DMTs, such as dimethyl fumarate (DMF), interferon beta-1a (IFN-β1a), and interferon beta-1b (IFN-β1b), require titration to reduce the risk of side effects associated with treatment initiation before reaching the maintenance dose recommended in the product labels.

Objectives: To assess neurologist-reported real-world titration periods and effectiveness of titration doses of DMF, IFN-β1a (intramuscular [IM] and subcutaneous [SC]), and IFN-β1b.

Methods: Forty US neurologists participated in this study. Respondents were blinded to the identity of the study sponsor. Neurologists practicing for at least 3 years and treating at least 10 patients with RRMS with an oral DMT in the past year were eligible for the study. Neurologists were provided a list of all DMTs requiring titration, and asked to provide the average duration for which their patients receive each pre-specified titration dose as well as their perceived effectiveness of each titration dose relative to the maintenance dose. Means and standard deviations were estimated for duration and perceived relative effectiveness of each titration dose for each DMT.

Results: On average, neurologists practiced for 15 years and treated 59 patients with an oral DMT in the past year. For DMF, neurologists reported a mean time of 20 (±24) days on the 120mg titration dose, 13 days longer than the label-recommended titration period. The perceived effectiveness of 120mg was reported to be 66% (±24%) of the maintenance dose (240mg). On average, IFN-β1a IM was titrated 15 to 17 days longer than recommended, with perceived effectiveness ranging between 46% and 63% of the maintenance dose. IFN-β1a SC was titrated 9 to 15 days longer with perceived effectiveness ranging between 44% and 69% of the maintenance dose. IFN-β1b was titrated 2 to 7 days longer than recommended with perceived effectiveness ranging between 43% and 57% of the maintenance dose.

Conclusions: Neurologists reported DMTs requiring titration need longer titration periods in practice than indicated in prescribing labels, and that titration doses are sub-therapeutic compared with maintenance doses. Study limitations include sample size and potential recall and selection bias. Additional studies with patient-level data are recommended to assess the impact of extended titration periods on clinical outcomes among patients with RRMS.

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Estimates of disease-modifying-drug effectiveness in slowing disability progression in relapsing-onset multiple sclerosis, adjusted for censoring-bias

MG Brown[1], M Asbridge[2], V Hicks[1], S Kirby[3], TJ Murray[4], P Andreou[1], D Lin[5], R McKelvey[3]
[1]Dalhousie University, Community Health and Epidemiology, Halifax, NS, Canada, [2]Dalhousie University, Community Health and Epidemiology, Emergency Medicine, Halifax, NS, Canada, [3]Dalhousie University, Neurology, Halifax, NS, Canada, [4]Dalhousie, Neurology, Community Health and Epidemilology, Halifax, NS, Canada, [5]Dalhousie University, Mathematics and Statistics, Halifax, NS, Canada

Background: Whether 1st line disease-modifying-drugs (DMDs) as a class (IFN-β1a, IFN-β1b, glatiramer acetate) slow irreversible disability progression in relapsing-onset multiple sclerosis (R-MS) is uncertain. Since events of interest - actual dates of irreversible disability progression - are unknown, analysts must assume minimum or maximum survival time at irreversible end-points, or somewhere in between. Previous studies accepted clinical observations at face value, implicitly assuming maximum survival time. Censoring-bias-adjustment methods which assume midpoint survival time give more representative estimates.

Objectives: First, to measure censoring-bias-size, variance, trends and shifts in 1979-2010 R-MS clinical observations. Second, to test if censoring-bias-adjusted estimates of disability

progression speed are faster -- and estimates of DMD effectiveness are larger -- than unadjusted estimates.

Methods: Our 1979-2010 Nova Scotia study population includes 2,346 definite R-MS patients with Expanded Disability Status Scale (EDSS) observations; 1,381 entered DMD treatment in 1998-2010; natural history comparators include 1,275 eventually-DMD-treated self-comparators and 965 never-DMD-treated other-comparators. Censoring-bias-reduction methods create expected midpoint measures for observed and censored EDSS endpoints. Estimates of natural history (NH) and new natural history (NNH) progression speed (given exposure to DMDs) are from annual change and survival models, populated with unadjusted or adjusted observations.

Results: Censoring-bias-size, variance, downward trends and shifts in 1979-2010 clinical observations are large. Adjusted estimates of disability progression speed are significantly faster. Adjusted estimates of DMD effectiveness -- measured by ratio NNH/NH annual EDSS change in range EDSS 0-6 - are: 0.85 for all 1,381 NNH patients relative to 1,275 self-comparators and 965 other-comparators; 0.73 for self-comparators only, and 1.02 for contemporary other-comparators only. Comparable unadjusted estimates are 1.04, 0.95 and 1.21. DMD effectiveness declines as EDSS increases.

Conclusions: Censoring-bias-adjusted estimates of disability progression speed in R-MS are faster, more representative and more comparable than unadjusted estimates, and adjusted estimates of DMD effectiveness are larger, more representative, and more comparable. Effectiveness estimates using self-comparators are larger and more credible than estimates using other-comparators.

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Gastrointestinal tolerability of delayed-release dimethyl fumarate in a multicenter, open-label study of patients with relapsing multiple sclerosis

EJ Fox[1], A Vasquez[2], W Grainger[3], TS Ma[4], C von Hehn[5], J Walsh[5], J Li[5], J Zambrano[5]

[1]University of Texas Medical Branch, Central Texas Neurology Consultants, Round Rock, TX, United States, [2]Suncoast Neuroscience Associates, St. Petersburg, FL, United States, [3]Neurological Physicians of Arizona, Gilbert, AZ, United States, [4]PharmStats, Ltd., Escondido, CA, United States, [5]Biogen Idec, Inc., Cambridge, MA, United States

Background: Delayed-release dimethyl fumarate (DMF) demonstrated efficacy and safety in relapsing-remitting multiple sclerosis (MS) in Phase 3 studies. Gastrointestinal (GI) events were common adverse events (AEs) associated with delayed-release DMF.

Objectives: Evaluate the prevalence of, effect of symptomatic therapy on, and putative risk factors for GI events in adult patients with relapsing MS initiating delayed-release DMF in clinical practice in the US, in the 12-week, open-label MANAGE study.

Methods: Patients were instructed to take delayed-release DMF with or within 1 hour after a meal (120 mg twice daily [BID] for 7 days; 240 mg BID thereafter). Use of symptomatic therapy for GI events was permitted, but no specific therapies were recommended or evaluated for differential efficacy. Patients were prompted to record information about GI events daily using an eDiary device and two numerical rating scales, and returned to the study site at Weeks 4, 8, and 12 for safety assessments.

Results: 237 patients were enrolled; 233 were included in the safety population (78% female; mean age 47 ± 12 years). The prevalence of eDiary-reported GI AEs in users of symptomatic therapy was highest during Weeks 1−4 (45.5%) and declined thereafter (Weeks 5−8, 27.9%; Weeks 9−12, 18.0%). In general, a decrease in the average worst severity of GI-related events was seen in patients who received treatment with one or more medications in the following categories: bismuth subsalicylate, acid-secretion blockers (proton pump inhibitors, histamine type 2 receptor blockers), antidiarrheals (antiperistaltic agents), centrally acting antiemetics, and anti-bloating/anti-constipation agents. Fewer patients who regularly took delayed-release DMF with food experienced GI AEs rated as "severe" or "extreme" (10%) compared with patients who did not regularly take delayed-release DMF with food (19%). Among patients who experienced overall GI events, 17% had a history of GI abnormalities, 61.2% had used alcohol prior to enrollment, and 35.9% had used tobacco prior to enrollment, compared with 18.5%, 55.6%, and 40.7% of patients who did not experience overall GI events.

Conclusions: Potential mitigation strategies for GI events associated with delayed-release DMF include symptomatic treatment usage and taking delayed-release DMF with food. There was no difference in terms of history of GI abnormalities or alcohol or tobacco usage between patients who experienced or did not experience GI events.

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A novel MIF inhibitor as therapy for multiple sclerosis and stroke

AA Vandenbark[1,2], R Meza-Romero[1], G Benedek[1,2], H Offner[1,2]

[1]Portland Veterans' Affairs Medical Center, Neuroimmunology Research, R&D-31, Portland, OR, United States, [2]Oregon Health & Science University, Portland, OR, United States

Background: CD74, the cell surface form of the MHC class II invariant chain, is a key inflammatory factor that is involved in various immune mediated diseases as part of the Macrophage Migration Inhibitory Factor (MIF) binding complex. We sought to identify a natural regulator of CD74 that could block MIF effects and treat multiple sclerosis (MS) and other CNS diseases.

Objectives:

1) Identify the CD74-binding region within DR-α1 and develop an optimal CD74-binding DR-α1 construct;
2) Evaluate inhibitory effects of DR-α1 constructs on monocyte and T-cell activation; and
3) Determine efficacy of DR-α1 constructs for treatment of experimental autoimmune encephalomyelitis (EAE) and experimental stroke.

Methods: DRa1-peptide constructs were produced, characterized for secondary structure and tested for competitive inhibition of MIF binding to immunopurified CD74, modulation of CD74 expression on CD11b+ monocytes and therapeutic effects on ongoing EAE and middle cerbral artery occlusion (MCAO) in mice.

Results: We found that DRa1 directly inhibited binding of MIF to CD74 and blocked its downstream inflammatory effects in the spinal cord of mice with EAE. Potency of the DRa1 domain could be destroyed by trypsin digestion but enhanced by addition of an

N-terminal peptide extension (MOG-35-55 peptide) that provided secondary structure not present in DRa1. The DRa1-MOG-35-55 construct reversed clinical and histological signs of EAE when administered after onset of disease signs and reduced infarct volumes when given 4 hours after MCAO.

Conclusions: These data suggest a conformationally-sensitive determinant on DRa1-MOG that is responsible for optimal binding to CD74 and antagonism of MIF effects, resulting in reduced axonal damage and reversal of ongoing clinical and histological signs of EAE and reduced infarct volume in MCAO. These results demonstrate natural antagonist activity of DRa1 for MIF that was strongly potentiated by the MOG peptide extension, resulting in a novel therapeutic, DRa1-MOG-35-55, that within the limitations of the EAE and MCAO models may have the potential to treat subjects with MS and stroke without need for HLA screening.

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Strategies to reduce adverse events related to oral dimethyl fumarate

C Sammarco[1], L Laing[1], J Herbert[1]
[1]*NYU Langone Multiple Sclerosis Care Center, Neurology, New York, NY, United States*

Background: Oral dimethyl fumarate (DMF) is approved in the United States for the treatment of relapsing forms of multiple sclerosis (MS). In the Phase 3 DEFINE and CONFIRM studies, the most common adverse events associated with DMF included flushing and gastrointestinal (GI) events. For most patients, these events were mild or moderate in severity and decreased in incidence after the first month of treatment. In clinical practice, DMF-associated adverse events have been largely related to medication tolerability rather than serious safety concerns. Tolerability of a medication may affect adherence, which in turn may affect efficacy of the drug. However, tolerability-related adverse events of DMF can often be overcome with time. If adverse events due to tolerability are not managed early, appropriate patients may discontinue therapy prematurely.

Objectives: To investigate the impact of a structured nursing initiation protocol (IP) on DMF adverse effects and adherence.

Methods: Immediately following introduction of DMF to the U.S. market, we initiated patients on DMF utilizing the standard pharmaceutical recommendations (PR-IP). Thereafter we developed a DMF Initiation Protocol (NYU-IP) that includes a modified titration schedule, pre-medication recommendations, specific dietary instructions, regular follow-up encounters and a variety of other educational measures to help patients manage DMF adverse effects. We conducted a retrospective review comparing DMF adherence following drug initiation utilizing NYU-IP and PR-IP.

Results: A total of 329 patients were initiated on DMF from March 2013 to January 2014, 124 patients using PR-IP (group 1) and 205 patients using the NYU-IP (group 2). Total discontinuations were 14 (12%) and 5 (2.5%) for groups 1 and 2, respectively (p = 0.0029). Discontinuations attributed to GI side effects were 10 (8%) and 4 (1.9%; p = 0.0215) respectively, and discontinuations due to flushing were 4 (3.2%) and 1 (0.5%; p=0.0733) respectively

Conclusions: A structured nursing protocol for initiation of DMF was highly effective in reducing adverse effects and maintaining adherence to DMF treatment. The specific components of the Initiation Protocol will be presented and discussed. Effective nursing strategies are key to optimizing treatment adherence and outcomes with DMF.

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Monthly pulse methylprednisolone as an add-on therapy is effective in long-term treatment of multiple sclerosis

S Ozakbas[1], B Piri Cinar[2], D Oz[3], T Kahraman[3], G Kosehasanogullari[4], B Bircan Kursun[3]
[1]*Dokuz Eylul University, Dept. of Neurology, Izmir, Turkey,*
[2]*Giresun State Hospital, Giresun, Turkey,* [3]*Dokuz Eylul University, Izmir, Turkey,* [4]*Usak State Hospital, Usak, Turkey*

Background: Although some conflicting results, there are some evidences for beneficial treatment effects of long-term pulsed intravenous methylprednisolone (IVMP) and combination of interferon beta (IFNB) and pulsed methylprednisolone in multiple sclerosis (MS), but more evidence are needed to establish clinical practice for such a treatment strategy.

Objectives: To evaluated the efficacy of monthly pulse methylprednisolone treatment added to IFNBs or Glatiramer acetate (GA) in breakthrough MS.

Methods: MS patients receiving ongoing IFNBs (IFNB 1b, IFNB 1a SC) treatment were eligible if they had Expanded Disability Status Scale (EDSS) scores of 5.5 or less. Patients with at least two relapses or at least one relapse and new T2 or gadolinium-enhanced lesion within the previous year. Patients received 1 g pulse IVMP once a month at least one year. Each participant was evaluated within a 1-month window of scheduled 12-month visits. Outcomes included relapse rate (primary), EDSS and Multiple Sclerosis International Quality of Life (MUSIQoL) scores.

Results: A total of 91 RRMS patients were included in the study. Two patients did not finish one year of study period, because they moved to another city and excluded. 89 (58 female) patients finished the one year study period. 63 patients were receiving IFNBs (32 with interferon beta 1b and 31 with interferon beta 1a SC), and 26 patients were receiving GA. Relapse rate was decreased from 1.6/ year to 0.3/year (p=0.000). 64 patients (65.3%) became relapse-free. Mean EDSS score was decreased significantly from 3.01±2.3 to 2.89±1.82 (p=0.012). 63 out of 89 (70.7%) patients had the same EDSS score at the end of one year. 15 (16.8%) patients were less disabled. 11 patients had sustained disability progression. There was no difference between treatment arms on the basis of efficacy of monthly IVMP treatment. Female patients responded better than male patients based on both relapse and disability. Health related quality of life (HRQoL) measured by MUSIQoL was significantly improved in the study population (p=0.005).

Conclusions: Our data suggested that methylprednisolone given in pulses every 4 weeks as an add-on therapy to subcutaneous interferon beta-1b, interferon beta 1a and glatiramer asetate in patients with relapsing-remitting multiple sclerosis leads to a significant reduction in relapse rate and disease progression. Significant improvement in HRQoL was also found in the study group. However, these findings need to be corroborated in larger cohorts

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Patient demographics and disease-modifying therapy use in relapsing-remitting and secondary progressive multiple sclerosis in the United States

HJ Gross[1], C Watson[2]

[1]*Kantar Health, Princeton, NJ, United States,* [2]*Biogen Idec Inc., Cambridge, MA, United States*

Background: Some patients with relapsing-remitting multiple sclerosis (RRMS) subsequently develop secondary progressive multiple sclerosis (SPMS). While the number of effective treatment options indicated for relapsing forms of multiple sclerosis (MS) in the United States (US) has increased over the years, the utilization of disease-modifying therapy (DMT) for patients with SPMS versus RRMS is unknown.

Objectives: To evaluate demographics and self-reported use of DMTs in a representative population of patients with RRMS and SPMS in the US.

Methods: Patient-reported data were derived from the Internet-based National Health and Wellness Survey (NHWS), a nationally representative annual survey of the healthcare attitudes and behaviors of adults ≥18 years of age in the US. The study population included NHWS respondents who reported a diagnosis of RRMS or SPMS in 2012 (survey conducted March- August) or 2013 (survey conducted April- August). Only the more recent survey was counted for patients responding to both annual surveys. Demographic characteristics and DMT use were compared between patients with RRMS and SPMS using chi-square (categorical variables) and independent sample t (continuous variables) tests.

Results: Across the 2012 and 2013 surveys, a total of 810 (0.6%) respondents reported a diagnosis of MS; 58.0% (n=458) had RRMS and 13.3% (n=105) had SPMS. Patients with RRMS compared with SPMS were younger (mean age 48.9 vs 55.7 years; $P<0.001$) and a higher percentage were female (71.6% vs 56.2%; $P=0.002$). A lower percentage of patients with RRMS versus SPMS were Caucasian (79.3% vs 87.6%; $P=0.05$). DMTs used by patients with SPMS included glatiramer acetate (13.5%); intramuscular interferon beta-1a (10.6%); interferon beta-1b (8.7%); fingolimod (8.7%); natalizumab (6.7%); subcutaneous interferon beta-1a (1.0%); and teriflunomide (1.0%). A lower proportion of patients with RRMS versus SPMS reported not using a DMT (26.5% vs 50.0%; $P<0.001$).

Conclusions: In this cross-sectional survey, patients with SPMS and RRMS had different characteristics, including age, gender, and ethnicity. A significantly lower proportion of patients with SPMS reported using DMTs compared with patients with RRMS, with approximately half of SPMS patients reporting no DMT use. These differences between RRMS and SPMS patients highlight the unmet need for therapies specifically indicated for the treatment of patients with SPMS.

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Comparative analysis of drop-out rates during the first year of fingolimod versus natalizumab treatment in the Swedish IMSE registry

T Frisell[1], L Jonsson[2], N Nordin[2], C Holmén[2], J Askling[1], J Hillert[2], F Piehl[2], T Olsson[2]
[1]*Karolinska Institutet, Department of Medicine, Stockholm, Sweden,* [2]*Karolinska Institutet, Department of Clinical Neuroscience, Stockholm, Sweden*

Background: Natalizumab (NTZ) and fingolimod (FGL) are mainly used as second line therapies for patients with relapsing-remitting multiple sclerosis and insufficient response on first line therapies. No formal randomized head-to-head studies have been conducted. In clinical practice many patients switch from NTZ to FGL due to anti-JC virus antibody positivity (JCV+).

Objectives: To compare reasons for discontinued treatment with NTZ and FGL.

Methods: We used data from the IMSE registry, started 2006 for NTZ and 2011 for FGL as a post-marketing surveillance study using nationwide data from the Swedish MS registry. The cohort included patients initiating treatment 2011-2013: n=609 with NTZ and n=514 with FGL, of which 242 (47%) had switched from NTZ to FGL (NTZtoFGL), of them, 97% were JCV+. Reasons to discontinue therapy was analyzed with multinomial logistic regression.

Results: The mean age was higher and the proportion of males was greater in the two FGL groups (39/39 years, 36%/34%) than in the NTZ group (36 years, 25%). Extended disability status scale (EDSS) scores at treatment start were similar in all groups, but Multiple Sclerosis Severity Score (MSSS) were higher and Symbol Digit Modalities test (SDMT) lower in NTZ patients, suggesting higher disease activity. The proportions of patients remaining on therapy at 1 year were 87%, 87% and 81% for NTZ, FGL and NTZtoFGL, respectively. The proportions of patients that discontinued therapy due to side effects were 2.4%, 7.4% and 10.7% for NTZ, FGL and NTZtoFGL, respectively, with similar results after adjustment for gender and age. The drop-out rates for lack of effect were similar between groups; 4.6%, 3.3% and 5.4% for NTZ, FGL and NTZtoFGL, respectively. However, there was a trend for more patients displaying lack of effect in both FGL groups in the last quarter of the follow-up period. In contrast, discontinuation of treatment due to lack of effect in NTZ patients occurred earlier and was mainly due to neutralizing antibodies.

Conclusions: The IMSE registry, with simultaneous follow-up of different drugs in the same registry platform, facilitates comparative studies and enables registration of long-term efficacy and adverse effects. The results of this study suggest that both FGL and NTZ are generally well tolerated, but that tolerability for FGL is somewhat lower than for NTZ, especially in patients switching from NTZ to FGL. We also noticed a trend for increased drop-out rates due to lack of effect in this group warranting further long-term follow-up.

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Clinical experience with rituximab in the treatment of refractory multiple sclerosis

F Gascón[1], A Navarré[1], C Alcalá[2], L Lacruz[3], F Pérez-Miralles[2], I Boscá[2], B Casanova[2], F Coret[1]
[1]*Hospital Clínico Universitario, Unit of Neuroimmunology - Neurology Department, Valencia, Spain,* [2]*Hospital Universitari i Politècnic La Fe, MS Unit - Neurology Department, Valencia, Spain,* [3]*Hospital Francesc De Borja De Gandia, Neurology Department, Gandia, Spain*

Background: Rituximab (RTX) is an anti-CD20 monoclonal antibody approved for rheumatoid arthritis and non-Hodgkin lymphoma that lyses B-cells. Off-label RTX has been used in autoimmune neurological diseases where B lymphocytes are involved, such as neuromyelitis optica, myasthenia gravis and multiple sclerosis (MS). RTX use in MS has been reported to be safe for up to 2 years of therapy, to reduce inflammatory activity in

relapsing-remitting MS (RRMS) and to control progression in a subset of primary progressive MS (PPMS) patients with gadolinum enhanced lesions (GEL) in MRI.

Objectives: To evaluate the efficacy and safety of compassionate use of rituximab in refractory MS patients.

Methods: We reviewed retrospectively 33 MS patients treated with RTX. Compassionate off-label RTX was used as monotherapy in MS patients unresponsive to all other approved MS therapies and/or with contraindication to all other approved MS therapies, after signing informed consent. A first course of 1000mg of RTX (on day 1 and day 15) was administered followed by a second or third course when CD19 B-cells were greater than 2%. Clinical response (relapses and progression) and MRI activity was analyzed 6-12 months after first dose.

Results: Thirty-three patients were treated with RTX (21 women, 63.6%); 18 SPMS (54.4%), 11 RRMS (33.3%) and 4 PPMS (12.1%). Baseline variables were as follows: mean age was 40.82 (SD 11.05), median EDSS 5.5 (range 2-7.5), 27 (84.4%) had oligoclonal bands in CSF, 17 patients (51.5%) had relapses, 20 (62.5%) had GEL and 16 (48.5%) sustained progression the year before RTX treatment. The median number of previous treatments was 2.73 (SD 1.57). After RTX treatment there was a reduction of 82.4% of relapses (p=0.001), 88.2% of GEL (p< 0.001) and of 62.5% of progression (p=0.012). 16 patients (57.1%) were free from further relapses, progression and GEL. Eleven patients (33.3%) experienced adverse events (AE): 10 mild AE; 7 related to infusion (21.2%) and 5 mild infections (15.2%). One patient experienced moderate neutropenia which required RTX withdrawal.

Conclusions: In our series RTX use appears overall safe with a major effect on MS inflammatory activity (clinical and radiological) and some effect on progression.

P316

Tolerability, safety and efficacy of fingolimod in clinical practice, experience of multiple sclerosis health network in Alsace region

C Berthe[1], J-C Ongagna[1], N Collongues[1], C Zaenker[2], A Benoilid[1], J De Seze[1], MS Network AlSacEP
[1]Hôpital de Hautepierre, Strasbourg, France, [2]alSacEP, Colmar, France

Background: Fingolimod is the first oral therapy for patient with very active relapsing-remitting multiple sclerosis.

Objectives: This study gives the first results about Fingolimod safety and tolerability of patients in Alsace.

Methods: In this retrospective study, 290 patients receiving Fingolimod were identified in EDMUS (European Database for Multiple Sclerosis). Clinical evaluations, adverse events and drug discontinuations were collected from may 2011 to february 2014.

Results: In the group of 199 patients who received Fingolimod during 12 months, 35 patients (17.6%) totalised 48 relapses. The average time between the beginning of treatment and the first relapse was 4.1 (3.3) months. The annualized relapse was significantly reduced (70.5%) and the EDSS score (Expanded Disability Status Scale) increased from 3.6 (±1.7) to 3.7 (±1.8). Thirty patients among the 290 stopped Fingolimod for different reasons: inefficacy (23.3%), any adverse events (60.0%) including 3 serious adverse events of macular edema. In term of efficiency,

FREEDOMS study announced a reduction in the annualized relapse rate by 54% against 70.5% in our patients. The initial EDSS score of our patients was higher (3.6±1.7) than the FREEDOMS study (2.4). All adverse events were recorded as described in the phase III studies with one exception: a case of kidney stones.

Conclusions: The disease activity seems well controlled under Fingolimod. Tolerance is good and discontinuations were mainly due to expected adverse events.

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Fingolimod effect on clinical and MRI disease activity in young adult patients with relapsing multiple sclerosis

T Chitnis[1], G Karlsson[2], DA Häring[2], A Ghezzi[3], D Pohl[4], N Putzki[2]
[1]Partners Pediatric Multiple Sclerosis Centre, Massachusetts General Hospital, Boston, MA, United States, [2]Novartis Pharma AG, Basel, Switzerland, [3]Centro Studi Sclerosi Multipla, Gallarate, Italy, [4]Children's Hospital of Eastern Ontario, Ottawa, ON, Canada

Background: Relapse and MRI activity have been reported to be higher in younger multiple sclerosis (MS) patients. To date, no controlled study has been completed to evaluate a disease modifying therapy in pediatric MS.

Objectives: To evaluate the effect of fingolimod 0.5mg on disease activity in young adults with MS from three Phase 3 trials.

Methods: Post-hoc analysis of annualized relapse rate (ARR), number of new/newly enlarging T2 lesions (neT2), freedom of disease activity (DAF: absence of: gadolinium enhancing and neT2 lesions, relapse, disability progression). Negative binomial regression (ARR, neT2) and logistic regression (DAF) models (adjustments: treatment, age at baseline, treatment-by-age interaction) were used in intent-to-treat populations of FREEDOMS, FREEDOMS II (2-year [yr] studies versus [vs] placebo [Pb]) and TRANSFORMS (1-yr study vs intramuscular interferon-β1a [IFN]); efficacy parameters were estimated at age 20yrs. Results in overall populations for neT2 and DAF are from negative binomial or logistic regression models with treatment as factor.

Results: ARR in 20yr/overall fingolimod groups was: FREEDOMS 0.16/0.18; FREEDOMS II 0.27/0.21; TRANSFORMS 0.14/0.16; while in control groups ARR was: FREEDOMS 0.73/0.40; FREEDOMS II 0.67/0.40; TRANSFORMS 0.60/0.33. Relative reduction in fingolimod vs control groups was (20yr/overall): FREEDOMS 79%/54%; FREEDOMS II 59%/48%; TRANSFORMS 77%/52% (all p< 0.001). Estimated number of neT2 lesions for fingolimod was (20yr/overall): FREEDOMS 6.0/2.5 (Pb:17.0/9.8); FREEDOMS II 7.5/2.3 (Pb:35.2/8.9); TRANSFORMS: 4.4/1.7 (IFN:4.9/2.6). Relative reduction of neT2 in favour of fingolimod was (20yr/overall): FREEDOMS 65%/77%; FREEDOMS II 79%/71% (all p< 0.001); TRANSFORMS 11%/30% (all p< 0.01). For fingolimod groups, estimated Odds Ratio (OR) of being free of disease activity vs control groups was (20yr/overall, OR): FREEDOMS 13.8/5.9; FREEDOMS II 17.8/3.9 (all p< 0.001); TRANSFORMS 2.16/1.9 (all p< 0.03).

Conclusions: Benefits of fingolimod in young adults with MS was consistently seen vs Pb and IFN on clinical and MRI measures of disease activity. Young patients had higher ARR in control

groups vs overall populations; ARR on fingolimod was low irrespective of age. Young adults had more neT2 lesions in all groups. The probability to be disease free was higher on fingolimod than on Pb or IFN, and was highest in young patients. A study of fingolimod vs IFN in pediatric MS (PARADIGMS) is currently recruiting worldwide.

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Systematic literature review and network meta-analysis of peginterferon beta-1a and injectable therapies for relapsing-remitting multiple sclerosis

K Tolley[1], M Hutchinson[2], A Pachner[3], ET Kinter[4], B Sperling[4], X You[4], P Wang[4], A Taneja[5], MK Siddiqui[5]
[1]*Tolley Health Economics Ltd, Buxton, United Kingdom, [2]St. Vincent's University Hospital, Dublin, Ireland, [3]Geisel School of Medicine at Dartmouth, Hanover, NH, United States, [4]Biogen Idec Inc., Cambridge, MA, United States, [5]HERON™ Commercialization - A Parexel® Company, Chandigarh, India*

Background: Peginterferon beta-1a (PEG-IFN; 125 µg every 2 weeks [Q2W] or every 4 weeks [Q4W]) has been studied in relapsing-remitting multiple sclerosis (RRMS) patients in the 2-year Phase 3 ADVANCE trial (placebo-controlled during Year 1). In the absence of direct evidence against an active comparator, network meta-analysis (NMA) provides an indirect assessment of PEG-IFN versus other therapies.
Objectives: To compare the efficacy, safety, and tolerability of subcutaneous PEG-IFN administered Q2W with other approved injectable therapies for RRMS.
Methods: For the NMA, systematic searches were conducted in MEDLINE®, Embase®, and the Cochrane Library, and conference proceedings from relevant annual symposia were hand searched. Included studies were randomized controlled trials evaluating first-line treatments including interferon (IFN) beta-1a 30, 44, and 22 µg, IFN beta-1b, and glatiramer acetate, in RRMS patients. Studies were included based on a pre-specified protocol and extracted by a team of independent reviewers and information scientists. The quality of included trials was assessed according to criteria recommended by Health Technology Assessment bodies in the UK (NICE) and Germany (IQWiG). The NMA was conducted using WinBUGS (v1.4.3) with data from the placebo-controlled phase (Year 1) of the ADVANCE trial. Safety and tolerability was assessed by annualized risk of event, combining multiple trials using a weighted average of the risk in a particular time period.
Results: In line with ADVANCE study findings, versus placebo, the NMA showed that PEG-IFN Q2W significantly reduced annualized relapse rate (ARR; rate ratio 0.654 [95% CI: 0.484-0.897]) and 6 month-confirmed disability progression (CDP6M; hazard ratio [HR] 0.421 [95% CI: 0.236-0.711]). CDP6M was also significantly reduced for PEG-IFN Q2W versus IFN beta-1a 30 µg (HR 0.46 [95% CI: 0.226-0.943]), with a numerical trend favoring PEG-IFN Q2W versus other IFNs assessed for ARR, and versus all other injectables for CDP6M. Patients on PEG-IFN Q2W did not have a higher risk of experiencing any adverse events (first incidence) versus other injectables and may experience fewer events based on the up to 93% lower injection frequency.
Conclusions: With similar efficacy compared to other injectables for RRMS in terms of ARR and CDP6M, a promising safety profile, and the lowest dosing frequency, PEG-IFN Q2W represents a valuable alternative treatment option for RRMS patients.

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Monitoring interferon beta treatment response with magnetic resonance spectroscopy in relapsing remitting multiple sclerosis

MF Yetkin[1], M Mirza[1], H Dönmez[2]
[1]*Erciyes University, Neurology, Kayseri, Turkey, [2]Erciyes University, Radiology, Kayseri, Turkey*

Background: MR imaging is the most sensitive and important paraclinical tool in the diagnosis and monitoring of multiple sclerosis.MR spectroscopy studies in MS patients have shown a significant decrease of NAA/Cr ratio in the normal appearing white matter and white matter lesions which indicates axonal damage even in the early stages of MS.
Objectives: The aim of this study is to compare the white matter of Multiple Sclerosis patients with those of healthy controls and to monitor the interferon beta treatment response with MRS.
Methods: Fifteen healthy controls and thirty-six recently diagnosed MS patients never treated with interferon beta were included in this study. In patients group MRS was performed before treatment, at sixth and twentieth month after initiation of treatment and once in control group. Patients group was divided into three interferon groups randomly. Physical examination findings were recorded as EDSS scores before treatment, at sixth and twentieth month of interferon treatment.
Results: At the end of one year follow up, twenty six of thirty-six patients completed the study. In patients' white matter lesions, NAA/Cr ratios were lower than control group's white matters. NAA/Cr ratios were higher in control group's white matter than patient's normal appearing white matter but this difference was not statistically meaningful. There was no difference in Cho/Cr ratios between two groups. In follow up period NAA/Cr and Cho/Cr ratios obtained from patients' white matter lesions and normal appearing white matter did not change statistically.
Conclusions: This study showed that in MS patients´ white matters, especially in white matter lesions, neuron viability is reduced and in patients treated with interferon beta NAA/Cr ratios remain stable. This stable levels of metabolite ratios in the patients who get interferon beta therapy can be explained by; the follow-up period in a chronic diseases like MS is short, or interferon therapy has positive effects over the course of the disease.

P320

Can fingolimod reduce the occurrence of MRI proven black hole and cerebral atrophy burden in Hispanic population with multiple sclerosis?

AR Chinea[1], YG Hernandez[1], ER Estades[1]
[1]*San Juan MS Center, Caribbean Center for Clinical Research, San Juan, Puerto Rico*

Background: Fingolimod (FG) is a sphingosine-1-phosphate (S1P) receptor modulator that is FDA approved for the treatment of Multiple Sclerosis (MS). FG ability to reduce black hole burden and cerebral atrophy in Hispanic MS patients is currently unknown. Magnetic Resonance Imaging (MRI) is the

gold standard in determining inflammation and permanent axonal damage. T1 hypointensity lesions (or black holes) represent areas of axonal damage. FG treated patient had reported a decrease in T1 hypointense lesion volume in clinical trials.

Objectives: To determine if FG can reduce black hole and brain atrophy burden in Hispanic population with MS.

Methods: Retrospective analysis of black hole burden was assessed by reviewing 50 patient MRI reports at baseline and 1 year post treatment with FG. MRI machines used were either 1.5 or 3.0 Tesla. Reports were submitted by board certified Neuroradiologist. Patients were instructed to go to the same MRI center for comparison with prior studies. The Hispanic patients are from a single independent specialized MS center. Another finding observed from the reports was cerebral atrophy.

Results: At baseline 50% of patients had black holes. At 1 year post treatment, 5 patients developed black holes and 9 patients worsened. From this data, 72% did not developed black holes. Approximately, 10% at 1 year follow up had evidence of cerebral atrophy. Only 2% of patients had developed black holes and cerebral atrophy.

Conclusions: We can conclude that FG can reduce the development of black holes and brain atrophy in Hispanic population with MS. The assessment of T1 hypointensity lesion burden should become a standard outcome in future clinical trials. This study will be continued and long-term resulted will be reported.

P321

Challenges experienced by neurologists in the individualization of multiple sclerosis treatment: findings from an international study

SM Hayes[1], S Mohammad[2], P Ng[1]
[1]AXDEV Group, Brossard, QC, Canada, [2]Colchester University Hospital, Colchester, United Kingdom

Background: The unpredictable nature of multiple sclerosis (MS) creates several challenges for healthcare providers in the optimal treatment and management of patients. With the movement towards patient-centered care, ensuring that treatment is suited to a patient's profile and preferences requires that providers demonstrate shared decision-making skills. An international needs assessment was conducted in 6 countries to obtain a better understanding of the knowledge, skill and confidence of providers, including nurses, neurologists, radiologists and pharmacists, involved in the treatment and management of patients with MS.

Objectives: To highlight the challenges experienced specifically by neurologists in the individualization of MS treatment.

Methods: This mixed-method International Review Board-approved study combined qualitative (semi-structured interviews) and quantitative (online surveys) data. Qualitative data were analyzed using thematic coding analysis and quantitative data were analyzed using frequencies and analyses of variance. Tamhane's T2 post-hoc tests were used to identify differences by country. Qualitative and quantitative findings were triangulated to strengthen the trustworthiness of the findings.

Results: The total sample included 148 actively practicing neurologists from Germany (n=22), Spain (n=22), France (n=23), the United Kingdom (n=23), Italy (n=22) and the United States (n=36). Eighty percent of neurologists had a caseload of more than 50 MS patients/year. Issues with knowledge, skill and confidence were identified. Almost half of neurologists (45%) reported that their knowledge of new and emerging treatments for MS was unacceptable or could be improved. Two-thirds of neurologists (66%) reported that individualizing the treatment plan according to disease activity in each patient was an essential skill; of those who reported this skill as essential, 47% reported their knowledge of this skill needed improvement. The individualization of treatment based on patient goals was also a challenge reported by neurologists, with more than half (58%) reporting the need for improvement in this skill.

Conclusions: Given the emergence of several new MS therapies, the individualization of treatment will become increasingly important in the provision of optimal patient care. As a result, greater emphasis should be placed on the development of shared decision-making and patient-provider communication skills, at both the graduate and post-graduate levels.

P322

Fingolimod (Gilenya) confers cognitive stability in active relapsing-remitting multiple sclerosis patients

Y Barak[1,2], D Magalashvili[3], T Paz[3], A Achiron[2,3]
[1]Abarbanel Mental Health Center, Psychogeriatrics, Bat-Yam, Israel, [2]Sackler School of Medicine, Tel-Aviv, Israel, [3]Sheba Medical Center, Multiple Sclerosis Center, Ramat Gan, Israel

Background: Fingolimod (Gilenya) has shown efficacy in reducing relapses and delaying disability progression in relapsing-remitting multiple sclerosis (RRMS) RRMS patients acting as a superagonist to sphingosine-1-phosphate receptors on the surface of thymocytes and lymphocytes. The effect of Gilenya on cognitive functions has not been thoroughly studied.

Objectives: To investigate the effects of Fingolimod (Gilenya) treatment on global cognitive performance in RRMS patients.

Methods: An observational, single-center, open-label, 1-year prospective study. Thirty RRMS patients were enrolled and 29 completed the one-year follow-up assessment, mean±SD age 40.0±8.7 years, disease duration 12.8±6.9 years and EDSS 3.2±1.5. Patients were clinically active in the year prior to enrollment as evidenced by progression in the EDSS of 0.4 and a mean number of 1.2 relapses. Participants underwent comprehensive cognitive assessment using the Mindstream Computerized Global Assessment Battery measuring verbal and non-verbal memory, executive function, visual spatial perception, verbal function, attention, information processing speed and motor skills at baseline (prior to initiation of Gilenya treatment) and at 1-year. Cognitive impairment was defined as below one SD for age and education matched healthy population norms.

Results: After 1-year of treatment patients were cognitively stable. No statistically significant changes were recorded in the GCS nor in any of the sub-scales. The baseline GCS was 89.4± 14.5 and following one year of treatment GCS was 93.6±10.5, p=0.322. Compared to published MS patients GCS (N=1,500; Achiron et al, PLoS One. 2013 PubMed PMID: 23936485) with similar disease duration, Gilenya's effect on cognitive stability held true.

Conclusions: We provide novel evidence of stable cognitive performance during 1-year treatment with Gilenya in clinically active RRMS patients. Studies of longer duration are called for to support these findings.

P323
Efficacy and safety of Fingolimod in clinical practice

AR Regal[1], L Midaglia[2], E Costa Arpín[3], M Rodríguez Rodríguez[4], A Pato Pato[5], AM López Real[6], MA Llaneza González[7], DA García Estévez[8], MJ Moreno Muñoz[2], D Escriche Jaime[2], ML Aguado Valcárcel[2], D Muñoz García[2], JM Prieto González[3], JR Lorenzo González[5], MC Amigo Jorrín[1]
[1]CHOP-Complejo Hospitalario Pontevedra, Pontevedra, Spain, [2]CHUVI-Complejo Hospitalario Universitario Vigo, Vigo, Spain, [3]CHUS- Complejo Hospitalario Santiago, Santiago de Compostela, Spain, [4]HULA- Hospital Universitario Lucus Augusti, Lugo, Spain, [5]POVISA, Vigo, Spain, [6]CHUAC-Complejo Hospitalario Universitario A Coruña, Coruña, Spain, [7]Complejo Hospitalario Arquitecto Marcide, Ferrol, Spain, [8]Hospital de Monforte, Monforte de Lemos, Spain

Background: Fingolimod is a treatment for relapsing-remitting multiple sclerosis (RRMS). The clinical trials that led to the approval of fingolimod demonstrated benefit on relapses, disability progression, magnetic resonance imaging (MRI) activity and brain volume loss. The safety and tolerability of fingolimod in general MS patient population are of interest. We present our initial experience prescribing fingolimod to 101 patients with RRMS
Objectives: To evaluate the efficacy and side effects of fingolimod in clinical practice.
Methods: We conducted a multicentric retrospective study. A total of one hundred and one Remitent-Recurrent Multiple Sclerosis (RR-MS) patients treated with fingolimod at eight Galician Hospitals (Spain) were included. Demographics, MS disease history (EDSS, relapses, treatments) and side effects were analized.
Results: 101 RR-MS patients (84% women, 16% men) were included. The mean of age was 40.30 years, the mean disease duration was 9.54 years and the mean treatment time was 9.49. ARR during the year before to fingolimod was 2.04, ARR plus fingolimod was 0.1 .The EDSS remained stabilized in 70% of patients, improved in 24% and deteriorated in 6% of them.

Fingolimod was prescribed as first-line agent in 7 patients, as second-line drug in 51 patients, as third-line in 29 patients and as a fourth/fifth-line agent in 14 patients. Natalizumab was the previous treatment in 30% of patients. Fingolimod demonstrated efficacy in the 94% of patients; only six of them (5,9%) had more relapses and/or disability progression.

Fingolimod was discontinuated in 4% of patients, due to inefficacy (n=2) and to side effects (n=2); symptomatic bradycardia during the first-dose observation time in one, and an abnormal liver function test at another one (x5 normal value). Another side effects were: macular edema (n=1), self-limited leukopenia (n=7); arterial hypertension (n=2); self-limited liver enzyme elevation (n=2) and urinary infection (n=2).
Conclusions: Fingolimod is safe (2% of discontinuation due to side effects) **and effective** (94% of patients improved or stabilized).

P324
Efficacy of second-line treatments in multiple sclerosis patients: a multicenter experience in clinical practice

R Totaro[1], G Costantino[2], R Fantozzi[3], P Bellantonio[3], C Di Carmine[1], A Fuiani[2], C Mundi[2], S Ruggieri[3], C Marini[1]
[1]University of L'Aquila, Department of Neurology, L'Aquila, Italy, [2]Ospedali Riuniti Foggia, Department of Neurology, Foggia, Italy, [3]IRCCS Meuromed, Department of Neurology, Pozzilli, Italy

Background: To evaluate efficacy of second-line treatments (natalizumab and fingolimod) in a cohort of relapsing-remitting multiple sclerosis (MS) patients completing a treatment period of 12 months in a real clinical practice setting.
Objectives: In Italy, natalizumab and fingolimod are registered as second-line therapy and reserved to patients with inadequate response to other disease-modifying drugs or with a rapidly evolving disease. However, there are no clinical studies available comparing the two drugs.
Methods: We report data of the first consecutive 200 patients receiving natalizumab or fingolimod at 3 Italian MS centers. Patients have been chosen in accord to AIFA Eligibility Criteria. Patients who started with fingolimod previously treated with natalizumab were excluded. Main efficacy endpoints were the proportion of patients free from relapses, from EDSS progression, from MRI activity, and from any disease activity.
Results: Out of 200 patients included, 71 were women and 29 men in natalizumab group, 63 were women and 37 men in fingolimod group. Mean age was 34.5±6.2 years in natalizumab group and 39.8±8.1 years in fingolimod group.

The ARR in the year preceding the start of treatment was 1.9±0.4 in the natalizumab group and 1.2±0.5 in the fingolimod group.

Proportion of patients with new T2 or Gd+ lesions at MRI prior treatment starting was 90% in natalizumab group and 78% in fingolimod group.

Mean EDSS score at the start of treatment was 2.9±0.9 in natalizumab group and 2.6±0.8 in fingolimod group.

At 1-year treatment follow-up, the proportion of patients free from relapse was 87% in natalizumab and 93% in fingolimod group.

The proportion of patients free from EDSS progression was 98% in natalizumab group and 99% in fingolimod group. The proportion of patients free from MRI activity was 93% in patients treated with natalizumab and 75% in those treated with fingolimod. The proportion of patients free from any disease activity was 79% in natalizumab group and 70% in fingolimod group.
Conclusions: Our data showed natalizumab and fingolimod positively influence the course of the disease in the first year the treatment. Both drugs achieved freedom of any measured disease activity in over two-third of the patients. Natalizumab seems to be more incisive in reducing MRI disease activity.

P325
Multiple sclerosis treatment practices in women of child-bearing age in Switzerland: results of the women with MS online survey

H Sorribas[1], S Muehl[1], PH Lalive[2]
[1]Merck (Schweiz) AG, Merck Serono, Zug, Switzerland, [2]Hôpitaux Universitaires et Faculté de Médecine, Médecin Adjoint Agrégé Service de Neurologie/Unité de Neuroimmunologie et SEP - HUG, Service de Médecine de Laboratoire - HUG, Département de Pathologie et Immunologie - CMU, Geneva, Switzerland

Background: Multiple sclerosis (MS) is more common among women, the majority of whom are of childbearing age. Evidence suggests positive effects of pregnancy on MS risk of relapse. For patients with relapsing-remitting MS (RRMS), treatment with an appropriate drug is recommended in early disease course. For women with MS, the treatment approach may be influenced by whether they wish to have children or not.

Objectives: The aim of the Women with MS survey was to analyze MS therapy practices for women of childbearing age (15-45 years) in Switzerland, according to their wish for a child.

Methods: Online 24-question survey in German and French to assess treatment management in women with MS; neurologists from hospital and private clinics in all regions were invited. Non-parametric tests were used (5% significance level, 2-sided), with no correction for multiple testing.

Results: The survey was completed by 56/223 invited neurologists at 48 centers treating 6034 patients with clinically isolated syndrome (CIS), RRMS or primary or secondary progressive (SPMS). A total of 67.8% patients with CIS/RRMS/SPMS were female, 52.2% of childbearing age. Of these, women were classed as having no wish for children (49.9%), or a short- (≤2 years; 18.9%) or medium-term (>2 years; 33.9%) wish for children. Disease-modifying drug (DMD) treatment was received by fewer women with a short- (51.1%) vs medium-term (69.2%) or no (78.9%) wish for children (p< 0.001). Their wish for children was given as the reason for not receiving a DMD for more women in the short- (42.8%) vs medium-term (17.8%; p< 0.001) wish group. Among women with a short-term wish for children, 79.7% were treated with immunomodulators (interferon β or glatiramer acetate), 9.8% with natalizumab, 3.7% with fingolimod and 9.7% with other DMDs. Among those with no wish for children, 66.1% were treated with immunomodulators, 17.7% with natalizumab, 16.6% with fingolimod and 2.8% with other DMDs. These 2 groups (short-term/no wish) had significantly different proportions of patients in the first 3 DMD categories (p≤0.001). The greatest proportion of neurologists (46.4%; n=26) gave an estimate of 7-12 months between stopping MS therapy and conception.

Conclusions: The data demonstrate that among women with MS in Switzerland, an intention to have children within 2 years was the primary reason for declining a DMD, and influenced the choice of therapy towards immunomodulatory over immunosuppressive drugs.

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Spanish Registry of patients with multiple sclerosis treated with fingolimod (GILENYA Registry): safety and effectiveness after one year on treatment

A Rodriguez-Antigüedad[1], C Oreja-Guevara[2], X Montalban[3], J Meca[4], D Muñoz[5], JC Álvarez-Cermeño[6], J Olascoaga[7], L Ramió[8], V Meca[9], A Saiz[10], JM Prieto[11], MÁ Hernández[12], B Casanova[13], ME Marzo[14], N Téllez[15], R Villaverde[16], RC Ginestal[17], J Gracia[18], A Escartín[19], S Martínez-Yélamos[20], L Landete[21], J Mallada[22], J Benito-León[23], L Brieva[24], M Garcia-Garcia[25], Ó Fernández[26]

[1]Hospital de Basurto, Neurology Department, Bilbao, Spain, [2]Hospital Clínico San Carlos, Neurology Department, Madrid, Spain, [3]Hospital Universitari Vall d'Hebron, Neurology Department, Barcelona, Spain, [4]Hospital Universitario Virgen de la Arrixaca, Neurology Department, Murcia, Spain,

[5]Hospital Xeral de Vigo, Neurology Department, Vigo, Spain, [6]Hospital Universitario Ramón y Cajal, Neurology Department, Madrid, Spain, [7]Hospital Universitario Donostia, Neurology Department, Donostia, Spain, [8]Dr. Josep Trueta University Hospital, Multiple Sclerosis and Neuroimmunology Unit, Girona Biomedical Research Institut (IDIBGI), Girona, Spain, [9]Hospital Universitario de la Princesa, Neurology Department, Madrid, Spain, [10]Hospital Clínic de Barcelona, Neurology Department, Barcelona, Spain, [11]Complejo Hospitalario Universitario de Santiago de Compostela, Neurology Department, Santiago, Spain, [12]Hospital Universitario Nuestra Señora de Candelaria, Neurology Department, Sta. Cruz Tenerife, Spain, [13]Hospital Universitari i Politècnic La Fe, Neurology Department, Valencia, Spain, [14]Hospital San Pedro, Neurology Department, La Rioja, Spain, [15]Hospital Clínico Universitario de Valladolid, Neurology Department, Valladolid, Spain, [16]Hospital General Universitario Morales Meseguer, Neurology Department, Murcia, Spain, [17]Hospital Universitario Fundación Jiménez Díaz, Neurology Department, Madrid, Spain, [18]Complejo Hospitalario Universitario de Albacete, Neurology Department, Albacete, Spain, [19]Hospital de la Santa Creu i San Pau, Neurology Department, Barcelona, Spain, [20]Hospital Universitari de Bellvitge, Neurology Department, Barcelona, Spain, [21]Hospital Universitario Doctor Peset, Neurology Department, Valencia, Spain, [22]Hospital General de Elda, Neurology Department, Elda, Spain, [23]Hospital Universitario 12 de Octubre, Neurology Department, Madrid, Spain, [24]Hospital Universitari Arnau de Vilanova, Neurology Department, Lleida, Spain, [25]Adknoma Health Research, Project Management, Barcelona, Spain, [26]Hospital Regional Universitario de Málaga, Neurology Department, Málaga, Spain

Background: The aim of the Spanish Gilenya Registry is to study the evolution of patients being treated with fingolimod in Spain.

Objectives: The aim of this preliminary analysis is to assess the safety and effectiveness of fingolimod during the first year after starting treatment.

Methods: Observational, retrospective/prospective and multi-center registry of cases, including all patients with relapsing remitting MS starting treatment with fingolimod in Spain.

Results: Data of the first 267 patients included in the registry by 24 specialized neurologists were analyzed, being available results for 105 patients 1 year after starting treatment. Mean age was 39.0 years (± 8.8), 70.0% women. Mean time since onset of symptoms of MS was 11.5 years (± 6.6) and mean time since diagnosis of MS was 9.3 years (± 6.1). The test for JC virus antibodies was performed in 184 patients (68.9%), being 157 seropositive (85.3%) and 27 seronegative (14.7%). Patients switched from natalizumab (27.0%), glatiramer acetate (24.7%), interferon beta-1a (Rebif®) (20.2%), interferon beta-1b (8.2%), interferon beta-1a (Avonex®) (6.4%), mitoxantrone (1.1%), and other (2.2%), respectively, to fingolimod. Main reason for switching to fingolimod was efficacy (50.6%), followed by safety (31.3%) and other (18.2%). Mean time under treatment with fingolimod was 13.1 months (± 6.7). 11.6% of patients were monitored more than 6 hours after the first dose of fingolimod and mean monitoring time was 7.3 hours (± 6.5). 9 patients (3.4%) withdrew from the study, being 3 (0.7%) due to adverse reactions. 21 patients (7.9%) showed 23 adverse reactions during the follow up period, being only 1 of them serious, second-degree atrioventricular block

(0.4%). 1 year after starting treatment with fingolimod, 80.0% of patients were relapse-free, 69.8% were free of disability progression [improvement or non-change of Expanded Disability Status Scale (EDSS) scores] and 56.3% were free of clinical activity (relapse-free and free of disability progression).

Conclusions: The results obtained in this preliminary analysis support the safety and effectiveness of fingolimod during the first year after starting treatment, although longer follow-up is required.

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Neurocognitive changes in patients with relapsing-remitting multiple sclerosis treated with natalizumab

N Doehler[1], S Mueller[1], J Vehoff[1], M Galovic[1], B Tettenborn[1]
[1]Cantonal Hospital of St. Gallen, Department of Neurology, St. Gallen, Switzerland

Background: Cognitive impairment (CI) affects up to 65% of Multiple Sclerosis (MS) patients and is a leading cause of disability. Natalizumab (NTZ) treatment may improve CI in MS patients. However, it is unknown which patients are likely to benefit from NTZ treatment with regard to CI.

Objectives: To observe CI under NTZ treatment over a 2-year period and to assess possible predictors of cognitive improvement in NTZ treated patients.

Methods: We included relapsing-remitting MS patients treated with NTZ in a single-center, observational, prospective study. We excluded patients with other possible causes of CI. Standardized assessments were performed at baseline and thereafter in 6 monthly intervals for 2 years with the Symbol Digit Modalities Test (SDMT), Fatigue Severity Scale (FSS) and Beck Depression Inventory (BDI). CI was defined as a written SDMT score ≤ 49 (age group < 30 years), ≤ 44 (age group 30-55 years) and ≤ 26 (age group >55 years). Repeated measurement analysis was performed using a Mixed Model approach.

Results: We enrolled 46 patients (age 37.3 ± 10.2 years, median EDSS 2.5). CI was found in 23 patients (50%, median SDMT score 44). 16 patients (34.8%) had relevant fatigue symptoms (FSS score 4.4 ± 1.9). 8 patients (17.4%) had relevant depressive symptoms (median BDI score 9). Prior NTZ treatment duration was 27.8 ± 14.3 months. At baseline, cognitive performance was significantly associated with fatigue (p=< 0.001) but not with depressive symptoms or NTZ treatment duration. Cognitive performance during 2 years of NTZ treatment significantly improved in all groups (median SDMT score improved from 44 to 50, p=< 0.001). There was a significant correlation between improvement of CI over time and baseline FSS score (p=0.042) but no significant correlations with baseline SDMT score, BDI score or NTZ treatment duration.

Conclusions: CI is likely to improve over a 2-year period in NTZ treated patients. Baseline fatigue symptoms but not baseline cognitive performance, depressive symptoms or NTZ treatment duration were significantly associated with improvement in CI over time.

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A monocentric, prospective, observational study to assess the satisfaction of patients treated with monthly natalizumab

M Vokaer[1], S Leemans[2], C Deladriere[1]
[1]Edith Cavell Hospital/Multiple Sclerosis Clinic/ULB, Neurology, Uccle, Belgium, [2]ULB/Erasmus Hospital, Neurology, Brussels, Belgium

Background: Patient satisfaction with a chronic treatment may affect treatment adherence and efficacy. The Treatment Satisfaction Questionnaire for Medication (TSQM) is a widely used, validated psychometric measure of patient satisfaction with 4 domains: effectiveness, side effects, convenience and overall satisfaction.

Objectives: To assess the satisfaction of patients treated with natalizumab (NTZ) in real life settings.

Methods: Open label, monocentric, prospective, observational Belgian study. After ethics committee approval and written informed consent, 74 relapsing-remitting MS (RRMS) patients were included in this analysis. All patients had been treated with NTZ for at least 3 months. All patients were evaluated with the Fatigue Severity Scale (FSS), the MS Walking Scale 12 items (MSWS-12) and TSQM. At the time of assessment, the mean treatment duration ($\pm$SD) was 28,3 ($\pm$15,5) months.

Results: The mean age was 40.3 ($\pm$10.8) years with mean disease duration of 8.1 ($\pm$5.8) years and mean therapy duration of 28.3 ($\pm$15.5) months. The annualized relapse rate in the year before the initiation of treatment with NTZ was 1.77. The mean Expanded Disability Status Scale (EDSS) at baseline (i.e. at the start of NTZ therapy) was 3.9 ($\pm$1.5). Under NTZ treatment, at the time of evaluation, the relapse rate dropped to 0.25. When compared to baseline, we observed a mean EDSS improvement of 0.47 ($\pm$1.04) points. The mean TSQM subscores were 80.2 ($\pm$15.5) for efficacy, 88.3 ($\pm$19.9) for side effects, 69.5 ($\pm$18.9) for convenience and 78.2 ($\pm$17.8) for overall satisfaction. The mean FSS score was 4.8 ($\pm$1.6) and the mean MSWS-12 score was 33.2 ($\pm$15.4). The overall satisfaction of patients with NTZ correlated with their EDSS (r=-0.25, p=0.03) and FSS (r=-0.32, p=0.006) scores. The satisfaction of patients with the efficacy of NTZ correlated with EDSS (r=-0.4, p=0.0005), FSS (r=-0.54, p< 0.00001) and MSWS-12 (r=-0.44, p=0.00009) scores. Patients who were free from measurable disease activity (i.e. no relapse, no EDSS progression, no new lesion and no active lesion on MRI) had significantly higher efficacy subscores than patients who had measurable disease activity (83.6 vs 73.9, p=0.01997).

Conclusions: Satisfaction was generally high in our population of NTZ-treated RRMS patients. Our findings suggest that NTZ treatment outcomes in terms of control of disease activity, EDSS, fatigue or mobility are well perceived by the patients in a subjective satisfaction assessment.

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Effectiveness of natalizumab in extended dosing interval

C Ramo-Tello[1], L Grau-Lopez[1], L Vilaró[2], C Seguí[2], S Delicado[2], X Bonafont[2]
[1]Hospital Universitari Germans Trias i Pujol, Neurosciences, Barcelona, Spain, [2]Hospital Universitari Germans Trias i Pujol, Pharmacy, Barcelona, Spain

Background: Natalizumab is an effective treatment for multiple sclerosis (MS) patients when administered in 300 mg every 4 weeks. However, the incidence of treatment-associated progressive multifocal leukoencephalopathy (PML) caused by JC virus, compromises this efficacious treatment. The administration of natalizumab every 6 weeks can maintain the same effectiveness providing a better quality of life for patients. Long-term studies are needed to fully assess the impact that extended-interval dosing (EID) might have on extending the PML risk period.

Objectives: To analyze the clinical and radiological evolution of patients with relapsing remitting MS treated with natalizumab at EID of 300 mg every 6 weeks.

Methods: A descriptive, retrospective study of data collected prospectively was performed. Patients who had received at least 13 doses of natalizumab every 4 weeks were asked to receive treatment every 6 weeks instead and they all signed consent forms. The protocol was approved by the Hospital Pharmaceutical Committee. The clinical course was analyzed by the annual relapse rate and the Expanded Disability Status Scale (EDSS). Radiological activity was studied by measuring Gadolinium enhancing (Gd+) lesions on brain MRI performed every 6 months. Pharmaceutical costs were also analyzed.

Results: Thirteen patients who received natalizumab every 6 weeks were included. Mean age 42±12 years; women 69% (9/13). Mean duration of natalizumab treatment 55±11.3 months. Mean duration of natalizumab every 6 weeks 9.1±2.3 months. 62% (8/13) of patients were JC seropositive and received natalizumab for more than 4 years. No patient treated at the 6 weeks dose range had a relapse. The mean EDSS with natalizumab every 4 weeks was 4.1 [1-6.5] and with natalizumab every 6 weeks 3.8 [0-6.5]. 46% of patients had Gd+ lesions before natalizumab treatment. No patient had Gd+ lesions after 6 weeks dose range. Each year of treatment with this regimen saves € 6,548 per patient, regardeless of the costs of nursing and pharmacy preparation time, commuting expenses and hours of work lost

Conclusions: In this sample, no clinical or radiological worsening disease under EID of natalizumab has been observed. The 6 weeks dose range provides greater patient comfort and significantly lower cost without compromising the effectiveness of treatment.

Epidemiology

P330

***In utero* 25-hydroxyvitamin D and risk of multiple sclerosis among offspring in the Finnish Maternity Cohort**

K Munger[1], M Soilu-Hänninen[2], J Åivo[2], K Hongell[2], H-M Surcel[3], A Ascherio[1]
[1]Harvard School of Public Health, Boston, MA, United States, [2]University Hospital of Turku, Turku, Finland, [3]National Institute for Health and Welfare, Oulu, Finland

Background: Adequate vitamin D nutrition is associated with a reduced risk of multiple sclerosis (MS), but whether vitamin D exposure *in utero* is associated with MS risk later in life is not clear.

Objectives: To measure 25-hydroxyvitamin D (25(OH)D) during pregnancy and determine whether these levels are associated with MS risk in the offspring later in life.

Methods: The Finnish Maternity Cohort (FMC) is comprised of over 800,000 women who have provided a blood sample from at least one pregnancy since 1983 for various pre-natal tests. Children of women in the FMC who were diagnosed with MS before December 31, 2009 were identified by searching the Finnish Hospital Discharge Register for diagnostic codes for MS, and the Social Insurance Register for reimbursements of MS disease modifying drugs. Cases were confirmed by review of the

medical records when available and matched to up to 7 controls (n=400) on county of birth, date of sample collection (+/- 60 days), and date of mother's birth (+/- 6 months). 25(OH)D was measured using an enzyme linked immunosorbent assay. Conditional logistic regression was used to estimate the relative risk (RR) and 95% confidence intervals.

Results: We identified a total of 197 individuals diagnosed with MS. Serum 25(OH)D levels could be determined in 193 cases, which were included in the analyses. Among these, 138 were confirmed by review of the medical record, whereas 55 were confirmed based on prescription of MS drugs. Over 70% of serum samples were collected at or before 12 weeks of gestation and 99% of samples were collected prior to 28 weeks gestation. Mean 25(OH)D levels did not differ based on trimester of collection (36.6 nmol/L in first vs. 36.2nmol/L in second, p=0.80). *In utero* 25(OH)D level was associated with a 41% decreased risk of MS among the offspring (top [median=56.8 nmol/L] vs. bottom [median=21.1 nmol/L] quintile of 25(OH)D, RR=0.59 (95%CI: 0.30-1.19), p for trend=0.01). Further adjusting for sex of the offspring attenuated the association though the overall trend remained statistically significant (RR=0.69 (95%CI: 0.33-1.43), p for trend=0.04).

Conclusions: These results support that *in utero* (early life) exposure to adequate vitamin D levels may be protective against the development of MS later in life.

P331

Timing of cod liver oil use as a vitamin D source and multiple sclerosis risk in Norway: the EnvIMS study

M Cortese[1,2,3], T Riise[2,4], K Bjørnevik[2,3,4], T Holmøy[5,6], MT Kampman[7,8], S Magalhaes[9], M Pugliatti[2,10], C Wolfson[11], K-M Myhr[1,4]
[1]KG Jebsen Centre for MS-Research, University of Bergen, Department of Clinical Medicine, Bergen, Norway, [2]University of Bergen, Department of Global Public Health and Primary Care, Bergen, Norway, [3]Harvard School of Public Health, Department of Nutrition, Boston, MA, United States, [4]Haukeland University Hospital, The Norwegian Multiple Sclerosis Competence Centre, Department of Neurology, Bergen, Norway, [5]University of Oslo, Institute of Clinical Medicine, Faculty of Medicine, Oslo, Norway, [6]Akershus University Hospital, Department of Neurology, Lørenskog, Norway, [7]University of Tromsø, Department of Clinical Neurology, Tromsø, Norway, [8]University Hospital of North Norway, Department of Neurology, Tromsø, Norway, [9]McGill University, Department of Epidemiology, Biostatistics and Occupational Health, Montréal, QC, Canada, [10]University of Sassari, Department of Clinical and Experimental Medicine, Sassari, Italy, [11]Research Institute of the McGill University Health Centre, Montréal, QC, Canada

Background: A low vitamin D level has been associated with an increased risk of multiple sclerosis.
It is still unclear whether this suggested effect is related to specific age periods prior to disease.

Objectives: To investigate the association between vitamin D_3 supplementation through cod liver oil during different age periods and the risk of MS.

Methods: For the Norwegian component of the multicenter multinational case-control study EnvIMS, cases with maximum disease

duration of 10 years were randomly selected from the Norwegian MS-registry. Controls, frequency-matched on sex and age, were randomly selected from a population-based registry in Statistics Norway.

Based on a self-administered questionnaire previously assessed for acceptability, feasibility and reliability a total of 953 MS patients and 1717 healthy controls reported whether they had used cod liver oil during childhood, adolescence and adulthood. Additionally, frequency and quantity of cod liver oil consumption during age 13-19 was explored. The associations between exposure and disease were estimated using logistic regression. All estimates were adjusted for age and sex. Further, the estimates were adjusted for possible confounders such as sun exposure, infectious mononucleosis and smoking.

Results: An inverse association was observed for supplementation of cod liver oil at ages 13-18, regardless of prior and subsequent use (OR 0.60, 95% CI 0.46-0.78), whereas supplementation in the first 12 years of life only appeared insufficient to reduce MS risk (OR 1.10, 95% CI 0.76-1.60). Those who never took cod liver oil at any age served as reference group. A statistically significant inverse association was found between the level of intake of cod liver oil during adolescence and MS risk suggesting a dose-response relationship (p-trend=0.001) with the strongest effect for an estimated vitamin D_3 intake of 600-800 IU/d (OR 0.46, 95% CI 0.31-0.70). Adjusting for possible confounders did not change the estimates in any meaningful way.

Conclusions: These findings suggest that the adolescence is the period in life most susceptible to the protective effect of commonly used doses of supplementary vitamin D contained in cod liver oil on the development of MS.

P332

Potential impact of air pollutants on multiple sclerosis incidence in Tehran, Iran: role of vitamin D

P Heydarpour[1], H Amini[2], S Khoshkish[1], H Seidkhani[3], M Yunesian[4], MA Sahraian[1]
[1]*Tehran University of Medical Sciences, Department of Neurology, Tehran, Iran, Islamic Republic of,* [2]*Kurdistan University of Medical Sciences, Kurdistan Environmental Health Research Center, Sanandaj, Iran, Islamic Republic of,* [3]*Tehran University, Lab of Systems Biology and Bioinformatics (LBB), Institute of Biochemistry and Biophysics (IBB), Tehran, Iran, Islamic Republic of,* [4]*Tehran University of Medical Sciences, Center for Air Pollution Research (CAPR), Institute for Environmental Research (IER), Tehran, Iran, Islamic Republic of*

Background: Multiple Sclerosis (MS) incidence has dramatically increased in Tehran, Iran. Although few studies have considered the potential role of air pollutants on MS incidence, the magnitude of health impact of air pollution in Tehran as measured by excess mortality underscores the need for attention to a possible association to this environmental risk factor.

Objectives: In this study, authors aimed to analyze spatial distribution of MS incidence to investigate the effect of long-term exposure to air pollutants via integrating health system data with various resources and finally explore the potential role of vitamin D.

Methods: Patient records meeting McDonald's criteria for definite MS diagnosis with disease onset during 2003-13 were obtained from Iranian Multiple Sclerosis Society. We then proceeded with records of patients who approved participation for research purposes. Next, location of 2188 patients was successfully geo-coded within Tehran metropolis by geographic information system (GIS) bureau of Iran's post office based on their phone number. Cluster analysis was performed using average nearest neighbor index (ANNI) and Quadrat analysis. The long-term exposure of MS patients to particulate matter (PM10), sulfur dioxide (SO2), nitrogen oxide (NO), nitrogen dioxide (NO2), and nitrogen oxides (NOx) were estimated using previously developed land use regression models. Lastly, we evaluated the correlation of serum 25(OH) Vit D levels with various air pollutants in an independent group of 580 patients after controlling for vitamin D supplementation and disease onset year.

Results: ANNI and Quadrat analysis showed a clustered pattern of MS patients in Tehran (nearest neighbor ratio = 0.56; Z score = -39.4; p < 0.001). Various air pollutants had an exponential distribution and were significantly inter-correlated (p< 0.001) except for NO & SO2. Principal component analysis revealed the main effect of air pollutants could be attributed to PM10 and SO2. Independent samples t-test showed a significant difference (P< 0.001) in exposure to PM10, SO2, NO2, and NOx but not for NO in MS cases compared with 8752 random cases (fourfold of MS cases). Serum Vitamin D levels in our group of patients were not correlated with various air pollutants.

Conclusions: This study revealed the potential role of long term exposure to air pollutants as an environmental risk factor in MS.

P333

Temporal effects on the presentation and evolution of multiple sclerosis

KE Harding[1], MD Willis[1], S Loveless[1], TP Pickersgill[2], NP Robertson[1,2]
[1]*Cardiff University, Institute for Psychological Medicine and Clinical Neuroscience, Cardiff, United Kingdom,* [2]*University Hospital of Wales, Neurology, Cardiff, United Kingdom*

Background: There is evidence that presentation of multiple sclerosis (MS) is changing, with increasing sex ratios reported in recent years. Natural history studies have also suggested that accumulation of disability may be decelerating, with time to disability milestones reported to be longer in more recently recruited cohorts.

Objectives: In order to understand this in more detail, we have investigated a large population-based cohort of MS patients with prospectively collected demographic and longitudinal disability data, comparing them by decade of birth from the 1940s through to the 1970s.

Methods: 1778 MS patients from a database containing a total of 2131 patients, born between 1st January 1940 and 31st December 1979 were recruited. Chi-squared test and ANOVA were used to compare demographic characteristics. Kaplan-Meier survival analysis and Cox proportional hazards regression were used to analyse time to expanded disability status scale (EDSS) 6.0, corrected for age at onset and disease duration.

Results: Female:male ratio was 1.88 for patients born in the 1940s, 2.02 for patients born in the 1950s, 2.51 for patients born in the 1960s, and 2.85 for patients born in the 1970s (p=0.03). After correction for age at onset and sex, there were fewer patients born in the 1960s who had primary progressive MS (PPMS)

(p=0.01) but there was no difference in proportion with PPMS for those born in the 1950s (p=0.22) or 1970s (p=0.25) as compared to those born in the 1940s. Proportion treated with disease-modifying therapies was 7% (1940s), 13% (1950s), 32% (1960s) and 45% (1970s). Although median time to EDSS 6.0 was shorter for patients born more recently (1940s median: 23.2 years, 1950s: 20.1y, 1960s: 18.6y, 1970s: 14.2y, p< 0.0001), this effect did not remain significant after correction for other variables (1950s: hazard ratio (HR) 1.17 (95% CI 0.92-1.49), p=0.20; 1960s: HR 1.40 (95% CI 0.97-2.03), p=0.08; 1970s: HR 1.46 (0.86-2.47), p=0.16).

Conclusions: Changes in sex ratio over time may be due to a sex-specific environmental influence on risk of MS. However, we have not found evidence that long-term prognosis has altered over the same period, suggesting that different factors may play a role in determining outcome of disease from those determining susceptibility. These findings have implications for design of clinical trials, ensuring suitable power of such trials, and directing avenues for future investigation of mechanisms underlying pathogenesis in MS.

P334
The association of multiple sclerosis prevalence and the soil heavy metal in Isfahan, Iran: one step closer to understanding etiology

M Etemadifar[1], R Kiani[2], B Mehrabi[3], M Fereidan-Esfahani[1]
[1]*Isfahan University of Medical Science, Isfahan, Iran, Islamic Republic of,* [2]*Isfahan Research Commitee of Multiple Sclerosis, Isfahan, Iran, Islamic Republic of,* [3]*Tarbiat Modares University, Tehran, Iran, Islamic Republic of*

Background: The steep rising in the number of multiple sclerosis (MS) patients in Isfahan province, makes this province a highly interesting region for MS research. Few studies have focused on the prevalence of MS with the soil heavy metal concentrations.

Objectives: We aimed to show the MS prevalence and incidence in the entire cities and villages of Isfahan province and to explore association between soil heavy metal factors in a very high risk region with the prevalence of 100 per 100,000 inhabitants or more.

Methods: Patients with definite MS according to McDonald criteria were initially recruited through clinical records at two MS referral centers, as the only referral centers in Isfahan province (with 101 cities and 1831 villages). Soil heavy metal factors sampling included cadmium (Cd), Cobalt (Co), Copper (Cu), lead (Pb) and zinc (Zn) were performed in very high risk region. Moreover, the absorbable form of Pb, Cd and Co in the soil sample were measured after sample treatment using 0.005 molar DTPA containing 0.01 molar $CaCl_2$. To assess the effects of soil pollution on the prevalence of MS, multivariate analysis were employed.

Results: There were 5,195 MS cases (1111 males, 4084 Females) from two MS referral centers. The total crude prevalence range from 5 to 156.65 in different cities of Isfahan province. The MS distribution were 168(3.24 %) in rural and 5,028(96.76%) in urban areas. There was a significant relationship between the high level of absorbable Pb (*p*< 0.0001) and the low level of absorbable Cd (p=0.007) with MS prevalence. However, we found no similar association between other non-absorbable soil heavy metals and absorbable type of Co concentration.

Conclusions: Although, there is several controversial data on the effect of lead in MS, our findings suggest that exposure to lead positively associated with MS prevalence. This is valuable clue to the etiology of MS in Isfahan province- which has the highest MS rate in Middle East- and should be addressed in the future research.

P335
Exploring early life sun exposure and MS risk using alternative life course epidemiology hypotheses: the EnvIMS study

S Magalhaes[1], K Bjornevik[2], K-M Myhr[3,4], M Pugliatti[5], T Riise[2,3], C Wolfson[1,6]
[1]*McGill Univeristy, Epidemiology, Biostatistics and Occupational Health, Montreal, QC, Canada,* [2]*University of Bergen, Department of Global Public Health and Primary Care, Bergen, Norway,* [3]*Norwegian Multiple Sclerosis Competence Centre, Haukeland University Hospital, Department of Neurology, Bergen, Norway,* [4]*University of Bergen, The KG Jebsen Centre for MS-Research, Department of Clinical Medicine, Bergen, Norway,* [5]*University of Sassari, Sassari, Italy,* [6]*McGill University Health Centre Research Institute, Montreal, QC, Canada*

Background: Early life sun exposure has been shown to be associated with risk of MS. Previous analyses have applied a critical time period hypothesis (CTPH) to estimate risk. Life Course Epidemiology offers alternative hypotheses to assess the relationship between exposure and disease, including the accumulation hypothesis (AH) and effect modification hypothesis (EMH).

Objectives: We assessed the likelihood of these three hypotheses on MS risk, using data on early life sun exposure.

Methods: Information on early life sun exposure (0-15 years) was collected through the multi-national Environmental Risk Factor in MS Study (EnvIMS). EnvIMS is a case-control study that enrolled MS cases and population-based controls in Canada, Italy and Norway. 564 cases and 939 controls enrolled in Canada, 650 cases and 1232 controls enrolled in Italy and 911 cases and 1628 controls enrolled in Norway, are included in the analyses. We used logistic regression models to assess the likelihood of each of the three hypotheses. Likelihood ratio tests were used to compare each model to a saturated model. Odds ratios (OR) and accompanying 95% confidence intervals are presented.

Results: Likelihood ratio tests indicated that all models fit the data as well as the saturated model (p>0.05). While not formally tested, upon visual inspection effect sizes obtained were quite similar and had overlapping confidence intervals in all models tested. Increased risk of MS was associated with lower levels of early life sun exposure using all models tested in all three countries. In Canada, ORs ranged from 1.21 (1.07-1.37) for the AH to 1.51 (1.15-1.99) for the CTPH between ages 0 and 5 years. In Norway, ORs ranged from 1.12 (1.04-1.22) for the AH to 1.34 (1.12-1.61) for the CTPH between ages 12 and 15 years. In Italy, ORs ranged from 1.11 (1.00-1.22) for the AH and 1.26 (1.03-1.55) for the CTPH between ages 0 and 5 years.

Conclusions: The data suggest that the association observed between early life sun exposure and MS is consistent with each of the three hypotheses tested, implying that this association may be more complex than has been previously reported using the CTPH.

Interestingly, findings are consistent across three countries that have different sun exposure profiles and MS risks.

P336
Neonatal vitamin D status and risk of multiple sclerosis

P Ueda[1], F Rafatnia[2], M Bäärnhielm[3], R Fröbom[3], G Korzunowicz[3], R Lönnerbro[3], D Eyles[4], T Olsson[1], L Alfredsson[3]

[1]Karolinska Institutet, Department of Clinical Neuroscience and Center for Molecular Medicine, Stockholm, Sweden, [2]Karolinska Institutet, Internal Medicine Department, Karolinska University Hospital, Stockholm, Sweden, [3]Karolinska Institutet, Institute of Environmental Medicine, Stockholm, Sweden, [4]The University of Queensland, Queensland Centre for Mental Health Research, Queensland Brain Institute, Brisbane, Australia

Background: Vitamin D status at birth may be associated with risk of adult onset multiple sclerosis but this link has not been studied directly.

Objectives: To assess the relation between 25-hydroxyvitamin D concentration at birth and risk of multiple sclerosis.

Methods: This was a population-based case-control study in Sweden including 459 incident cases of multiple sclerosis and 663 controls, randomly drawn from a national population registry and frequency matched on sex, age and residential area. Neonatal 25-hydroxyvitamin D concentrations were measured in dried blood spots from a nationwide biobank, using a highly sensitive liquid chromatography-tandem mass spectroscopy method. Using logistic regression, odds ratios for developing multiple sclerosis were compared between quintiles of neonatal 25-hydroxyvitamin D.

Results: There was no association between neonatal 25-hydroxyvitamin D quintile and risk of multiple sclerosis. The crude odds ratios for the quintiles, in increasing order, were 1.0 (reference), 1.0 (95% CI 0.68 - 1.43), 0.9 (0.65 - 1.37), 1.0 (0.67-1.42), and 1.0 (0.68-1.44). Adjusting for a number of potential confounding factors in early life (month of birth, latitude of birth, breastfeeding) and in adult life (serum 25-hydroxyvitamin D status, sun exposure, vitamin D intake from dairy products, fat fish consumption, smoking, body mass index at 20 years of age) as well as ancestry, multiple sclerosis heredity, and socioeconomic group, did not considerably affect the result.

Conclusions: By observing that vitamin D status at birth is not associated with risk of multiple sclerosis at a broad population level, this study provides no support for the widely discussed and hitherto only indirectly assessed hypothesis regarding the role of vitamin D in the etiology of MS.

P337
Multiple sclerosis in Møre and Romsdal, Western Norway 1960-2013. Time trends of incidence and prevalence through more than five decades

J Willumsen[1], R Midgard[1,2]

[1]Molde Hospital, Helse Møre and Romsdal Health Trust, Department of Neurology, Molde, Norway, [2]Norwegian University of Science and Technology (NTNU), Unit for Applied Clinical Research, Department of Cancer Research and Molecular Medicine, Trondheim, Norway

Background: A recent Norwegian study shows an increasing prevalence of multiple sclerosis (MS) in Norway. The nationwide crude prevalence on 1 January 2012 was 203/100,000. According to this study, Møre and Romsdal, a northwestern coastal county (approx. 260,000 population), has one of the highest prevalence rates of MS. Several previously published studies on the frequency of MS in Møre and Romsdal County, the first in 1952, have paved the ground for longitudinal, population-based epidemiological studies.

Objectives: The study has analyzed the time trends of incidence and prevalence in a stable population throughout a period of more than five decades.

Methods: We applied the McAlpine criteria prior to the introduction of ancillary investigations, e.g. cerebrospinal fluid analyses (1972), evoked potentials (1975) and magnetic resonance imaging (1984), thus clinical criteria formed the basis for the diagnoses. With the implementation of refined laboratory, neurophysiologic and radiologic diagnostic tools in combination with the development of new diagnostic criteria, diagnostic accuracy and case ascertainment increased.

We have traced every patient diagnosed with MS in the county and all MS patients living in Møre and Romsdal on Prevalence day 1 January 2013. The primary source for MS patients was the case files at the Department of Neurology and Clinical Neurophysiology at Molde Hospital. However, we have searched all available local, regional and national sources for incident and prevalent cases. Only patients diagnosed before prevalence day are included. An experienced neurologist has examined all patients, the majority several times, during the course of illness.

Results: The annual incidence of MS in 1935-48 was 1.7/100,000, increasing to 7.5/ 100,000 in 1985-89 and finally to 10.2/100,000 in 2000-04. The prevalence of definite/probable MS on 1 January 1961 was 24.3/100,000. By 1 January 1985, the prevalence, based on the same diagnostic criteria, increased to 75.4/100,000. On 1 January 2008, the prevalence was 246/100,000. We are currently updating the incidence until 2013 and the prevalence of MS on 1 January 2013. We present the reappraised data.

Conclusions: A change in diagnostic criteria, better case ascertainment and an increasing access to disease modifying therapy and possibly a better survival are factors of importance for the incline, but changing biologic relevant risk factors during more than fifty years might also play a role.

P338
High incidence and increasing prevalence of multiple sclerosis in British Columbia, Canada: findings from over two decades (1991-2010)

E Kingwell[1], F Zhu[1], RA Marrie[2], J Fisk[3], C Wolfson[4], S Warren[5], J Profetto-McGrath[5], L Svenson[5], N Jette[6], V Bhan[3], N Yu[2], L Elliot[2], H Tremlett[1]

[1]University of British Columbia, Vancouver, BC, Canada, [2]University of Manitoba, Winnipeg, MB, Canada, [3]Dalhousie University, Halifax, NS, Canada, [4]McGill University, Montreal, QC, Canada, [5]University of Alberta, Edmonton, AB, Canada, [6]University of Calgary, Calgary, AB, Canada

Background: British Columbia (BC) is the most western province of Canada, with a population of approximately 4.5 million in 2010.

Objectives: We used population-based administrative health databases and a previously validated case definition to estimate the incidence and prevalence of multiple sclerosis (MS) in BC over a 15 and 20 year period respectively.

Methods: We accessed the BC Hospital Separations, Medical Services Plan (physician visits), Vital Statistics (deaths), and Health Registration files to identify all BC residents meeting the case definition of ≥3 International Classification of Disease codes for MS. Point prevalence was estimated annually on July 1, 1991-2010. Incidence and prevalence were calculated per 100,000 people using the BC mid-year population, and were age-standardized to the 2001 Canadian population. Incidence estimates were generated based on the year of the first demyelinating disease claim for 1996-2010; a previous 5 year demyelinating disease claim-free period was required. We investigated changes in incidence, prevalence and sex ratios over the observation periods using regression analyses.

Results: On July 1, 2010, an estimated 11,963 people with MS were living in BC, giving a standardized point prevalence of 240.7 per 100,000 persons (95% CI: 236.3-245.1). The prevalence in 1991 was 90.4 (95% CI: 87.1-93.8), and increased by approximately 5% per year on average over the 20 year observation period (p< 0.001). The women:men prevalence ratio increased gradually from 2.27 in 1991 to 2.72 in 2010 (p< 0.001) and the peak prevalence age increased from 45-49 years in 1991 to 55-59 years in 2010. From 1996 to 2010 there were 6,250 incident MS cases in BC, with an average annual age-standardized incidence rate of 9.9 (95% CI: 9.0-10.9). The annual incidence of MS remained stable over the 15 year period while the incidence sex ratio decreased somewhat over time (p=0.02), but remained above 2 for all years (averaging 2.71:1).

Conclusions: The incidence and prevalence of MS in British Columbia are among the highest in the world, although they are comparable to estimates from other eastern and central Canadian provinces. Neither the incidence of MS nor the incidence sex ratio showed an increase over the study period, however MS prevalence, and the prevalence sex ratio appear to have increased significantly. These findings could be explained by the observed increase in the peak prevalence age of MS, possible immigration of non-incident MS cases to BC, and the greater life expectancy of women.

P339
35 years of mortality due to multiple sclerosis in Canada, 1975-2009: no decrease in mortality rates despite shift to older age at death

S Warren[1], W Janzen[1], K Warren[1], L Svenson[1], D Schopflocher[1]
[1]University of Alberta, Edmonton, AB, Canada

Background: In the past persons with multiple sclerosis (MS) died at notably younger ages than the general population. Since the 1990s important new treatments, such as disease modifying drugs, have been introduced. Their effects might be reflected in a shift to older age at death and decreasing mortality due to MS because patients are living longer to die from other causes.

Objectives: This study's goal was to describe mortality due to MS in Canada from 1975 to 2009 by age and gender and to determine whether there has been a change in age at death relative to the general population.

Methods: Data on deaths due to MS, coded according to the International Classification of Diseases, and populations at risk was derived from Statistics Canada. Rates and 95% confidence intervals (CIs) were calculated for the entire 35 year time span and for 5-year periods, age-standardized to the 2006 Canadian population. Trend analysis for the years 1975-2009 was performed using JoinPoint Regression. Data on deaths due to all causes in the general population was also derived from Statistics Canada.

Results: The average annual age-standardized MS mortality rate for 1975-2009 was 1.23 (1.03-1.43). 5-year rates for 1975-79, 1980-84, 1985-89, 1990-94, 1995-99, 2000-04, 2005-09 were 1.16, 0.94, 1.01, 1.16, 1.30, 1.43, 1.33. Trend analysis showed that mortality rates over the 35 years remained essentially stable, with an average annual percent change (AAPC) of < 1. The average annual 1975-2009 age-standardized rates for females and males were 1.45 (1.24-1.66) and 0.99 (0.80-1.17). 5-year rates for females were always significantly higher than for males but there was no change in rate ratios over time. Rates remained essentially stable over the 35 years within both genders, AAPCs < 1 each. Regardless of gender, trend analysis showed a significant decrease in MS mortality rates in the 0-39 age group and significant increases in the 60-69, 70-79, and 80+ age groups (all AAPCs < 1), whereas there were significant decreases in all-cause mortality rates across each age group (AAPCs < 1). The highest MS mortality rates were consistently in the 50-59 age group for both genders from 1975 to 2009, while the highest all-cause mortality rates were in the 80+ age group.

Conclusions: New treatment effects are not yet reflected in decreasing Canadian MS mortality rates. Changes in the age distribution of mortality rates indicate a shift to older age at death; however MS patients remain disadvantaged relative to the general population.

P340
Seasonal variation of relapse rate in MS is latitude-dependent

T Spelman[1], O Gray[2], M Trojano[3], T Petersen[4], G Izquierdo[5], A Lugaresi[6], R Hupperts[7], R Bergamaschi[8], P Duquette[9], P Grammond[10], G Giuliani[11], C Boz[12], F Verheul[13], C Oreja-Guevara[14], M Barnett[15], F Grand'Maison[16], H Butzkueven[1], on behalf of the MSBase Investigators
[1]University of Melbourne, Melbourne Brain Centre, Parkville, Australia, [2]Craigavon Area Hospital, Portadown, United Kingdom, [3]University of Bari, Department of Basic Medical Sciences, Neuroscience and Sense Organs, Bari, Italy, [4]Kommunehospitalet, Arhus C, Denmark, [5]Hospital Universitario Virgen Macarena, Sevilla, Spain, [6]University 'G. d'Annunzio', MS Center, Department of Neuroscience and Imaging, Chieti, Italy, [7]Orbis Medical Centre, Sittard-Geleen, Netherlands, [8]Neurological Institute IRCCS Mondino, Pavia, Italy, [9]Hôpital Notre Dame, Montreal, QC, Canada, [10]Center de Réadaptation Déficience Physique Chaudière-Appalache, Levis, QC, Canada, [11]Ospedale di Macerata, Macerata, Italy, [12]Karadeniz Technical University, Trabzon, Turkey, [13]Groene Hart Ziekenhuis, Gouda, Netherlands, [14]University Hospital San Carlos, Madrid, Spain, [15]Brain and Mind Research Institute, Sydney, Australia, [16]Neuro Rive-Sud, Hôpital Charles LeMoyne, Greenfield Park, QC, Canada

Background: Previous studies into seasonal variation of relapses in multiple sclerosis have had conflicting results. Small relapse numbers, differing diagnostic criteria, differing relapse definitions and single region studies limit the generalizability of results. However, a large meta-analysis found that relapse onset probability varies seasonally.

Objectives: The aim of this study was to determine if there is a temporal variation in onset of relapses in both the northern and southern hemispheres and to investigate whether the lag between location-specific seasonal ultra-violet radiation (UVR) trough and subsequent relapse peak varied with latitude.

Methods: Relapses were analyzed by hemisphere and latitudinal location. All analyses were weighted for the number of patients contributed by each center. A sine regression model consisting of one sine and one cosine function, describing a single annual cycle with one peak and one trough separated by six months, was used to model relapse onset and UVR seasonality. Linear regression was used to investigate associations between latitude and lag between UVR trough and subsequent relapse peak.

Results: 32,762 relapses from 9811 patients in across 30 countries were analysed. Relapse onset followed an annual cyclical sinusoidal pattern with peaks in spring and troughs in autumn in both hemispheres. This seasonal variation was statistically significant, with an estimated relapse peak of the 7th March (95% CI 10th February, 28th March) in the northern hemisphere and 5th September (95% CI 10th August, 26th September) in the southern hemisphere. There was no difference in this pattern by hemisphere (p=0.254). Every 10 degrees of latitude away from the equator was associated with a mean decrease in ultra-violet radiation trough to subsequent relapse peak lag of 28.5 days (95% CI 3.29, 53.71, p=0.028), weighting for the number of patients per location and controlling for absolute UVR at each location (Figure 1). There was no difference in this association by hemisphere (p=0.811).

Conclusions: In our large, multinational study of MS outcomes, we confirm prior meta-analyses showing a strongly seasonal relapse probability in the northern hemisphere, and extend this observation to the southern hemisphere. We demonstrate for the first time that there is a statistical relationship between seasonal UVR trough and relapse onset peak that is latitude-dependent, with increasing latitudes associated with shorter gaps.

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Risk of multiple sclerosis related to month of birth changes over time

EG Celius[1], SH Haug[2]
[1]Oslo University Hospital, Ullevål, Dep. of Neurology, Oslo, Norway, [2]University Of Oslo, Faculty of Medicine, Oslo, Norway

Background: Several studies have shown an increased risk of MS in spring births in the northern hemisphere, while the risk is increased in autumn births in the southern hemisphere. Decreased sun exposure in winter pregnancies, with a concomitant reduction in vitamin D levels, has been suggested as the environmental factor explaining this pattern.

Objectives: To determine if the risk of MS associated with season of birth is influenced by time period, gender and disease course.

Methods: Patients born between 1901 and 1990 registered in the Oslo City MS registry (n=1658) were compared to the total Norwegian population born in the same period (n=5105367,

Statistics Norway). The patients and controls were subdivided in 30-year cohorts, and gender and disease course (relapsing-remitting, RRMS and primary progressive, PPMS) were analysed separately.

Results: An increased risk of MS for patients born in spring was only found for patients born in the period 1961-90 (p=0.00096) and only for patients with RRMS. There was no difference between females and males.

Conclusions: This study confirms an increased risk of MS in patients born in spring, but shows also that this risk is restricted to patients born after 1960 and to RRMS coinciding with the period of increasing prevalence of MS. This indicates that the risk of MS may be related to a change in environmental factors occurring after 1960 and thus further studies of changes in lifestyle habits triggering MS is warranted.

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The changing face of MS: does ARR vary by epoch?

BC Healy[1], T Chitnis[1], F Dangond[2], HL Weiner[1]
[1]Brigham and Women's Hospital, Neurology, Partners MS Center, Brookline, MA, United States, [2]EMD Serono, Inc., Rockland, MA, United States

Background: Several recent studies have described a decreasing relapse rate over time in the placebo arms of clinical trials. One potential explanation for this observation is that the face of MS is changing due to the ability to diagnose the disease earlier and in milder forms.

Objectives: The goal of this study is to assess whether the relapse rate before and after initiation of an MS treatment is changing over time.

Methods: We tabulated the number of relapses in the year prior to and the year after initiation of subcutaneous beta-interferon-1a (Rebif) in subjects enrolled in the CLIMB at the Partners MS Center who started treatment in three time periods (2001-2005, 2005-2009, 2009-2013). An intent-to treat principle was followed such that patients who stopped treatment before the end of the first year contributed an entire year to the analysis. The number of relapses in the year prior to treatment and the year after treatment was compared across the three time periods using a Kruskal-Wallis test. The change in pre- and post-treatment difference in ARR over the periods was assessed using a repeated measures Poisson regression model.

Results: The mean (SD) number of relapses in the year prior to treatment initiation was 0.65 (0.75) for subjects who started treatment between 1/1/2001-1/1/2005, 0.72 (0.79) for 1/1/2005-1/1/2009, and 0.71 (0.80) for 1/1/2009-1/1/2013. No significant difference between the time intervals was observed in the patients prior to Rebif treatment (p=0.71 for three group comparison). The mean (SD) number of relapses in the year post-treatment initiation was 0.31 (0.60) for subjects who started treatment between 1/1/2001-1/1/2005, 0.34 (0.78) for 1/1/2005-1/1/2009, and 0.28 (0.56) for 1/1/2009-1/1/2013. No significant difference between the time intervals was observed (p=0.82 for three group comparison). The percent change in pre versus post-treatment ARR numerically increased over time (decrease in ARR was 52%, 53% and 61% for 1/1/2001-1/1/2005, 1/1/2005-1/1/2009, and 1/1/2009-1/1/2013, respectively, when compared to ARR prior to starting Rebif), but the change in the pre- and post-treatment difference in ARR was not statistically significant (p=0.66).

Conclusions: Despite some numerical changes in pre-treatment/ post treatment ARR over time in subjects starting treatment with Rebif, there was no statistically significant difference between epochs. Further studies are required to investigate the changing face of MS hypothesis.

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The incidence of multiple sclerosis in New Zealand, 2013: a population- based study
S Alla[1,2], J Pearson[3], A Richardson[4], D Mason[2,5]
[1]University of Otago, School of Medicine, Christchurch, New Zealand, [2]New Zealand Brain Research Institute, Christchurch, New Zealand, [3]University of Otago, Deans Department, Christchurch, New Zealand, [4]University of Canterbury, Public Health, Christchurch, New Zealand, [5]Christchurch Public Hospital, Department of Neurology, Christchurch, New Zealand

Background: Worldwide, the incidence of multiple sclerosis (MS) appears to be increasing. Currently there are no national estimates of the incidence of MS in New Zealand (NZ).
Objectives: The aim of this study is to survey the national incidence of MS in 2013 and examine its relationship with the latitudinal gradient in New Zealand (35- 48⁰S).
Methods: The data were obtained from the NZ National MS Incidence Study (NZNMSI), a population-based longitudinal study designed to survey the incidence and natural history of definite MS (McDonald criteria 2005) of people resident in NZ over a period of 2 years. The study used multiple sources of case ascertainment and included all patients notified and diagnosed with MS by neurologists. The interim data from 1 January - 31 December 2013 is reported here with full results available in June 2014. The population demographics were obtained from 2013 NZ census and incidence was age standardised to the European standard population. The latitude gradient was estimated using a simple linear regression model on the population weighted centroid latitudes south of Auckland.
Results: We identified 113 people newly-diagnosed with MS who met the inclusion criteria. The male to female sex ratio was 1:3.3. The onset was relapsing-remitting type in 87% of the cases. The mean age at the onset of symptoms was 39.1±12.5 years and the mean age at diagnosis was 43.8 ± 13.5 years. The age-standardized incidence (ASI) for 2013 was 2.7 per 100,000 population. A latitudinal gradient was seen with ASI increasing from the North (35⁰S) to the South (48⁰ S) at a rate of 0.7± 0.05 cases per degree of latitude south of 37.9°S.
Conclusions: The results of the first ever population-based MS incidence study to include an entire country confirm a high incidence of MS in NZ. The latitude gradient of incidence is consistent with the ongoing impact of environmental factors responsible for the previously reported prevalence gradient with latitude.

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Genes and environment in multiple sclerosis (GEMS) study: enabling the prospective study of individuals at risk of multiple sclerosis
Z Xia[1,2], L Chibnik[1], A von Korff[1], DS Reich[3], PL De Jager[1,2]
[1]Brigham and Women's Hospital, Program in Translational NeuroPsychiatric Genomics, Department of Neurology, Boston, MA, United States, [2]Harvard Medical School, Boston, MA,

United States, [3]National Institute of Neurological Disorders and Stroke, Translational Neuroradiology Unit, Neuroimmunology Branch, Bethesda, MD, United States

Background: There is currently no reliable tool to guide individualized risk assessment for multiple sclerosis (MS).
Objectives: To test the efficacy of an algorithm that integrates validated genetic and environmental risk factors into a single aggregate estimate of an individual's risk of developing MS. We hypothesize that such risk estimate can help identify individuals at increased risk for MS.
Methods: We created a weighted genetic and environmental risk score (GERS) that includes 63 genetic variants, sex, infectious mononucleosis (IM), and smoking. We tested the efficacy of GERS in the initial 1,355 subjects with at least one first-degree relative (FDR) with MS from the Genes and Environment in Multiple Sclerosis (GEMS) cohort, a prospective study that has recruited over 2,500 subjects from across the United States since 2011. Subjects with FDR and self-diagnosis of MS (6% of total) are included as embedded positive controls. Each subject submits saliva for targeted genotyping and completes a detailed web-based questionnaire that captures demographics and risk factors. MS diagnosis is confirmed by review of medical records.
Results: In a cross-sectional analysis of 1,265 asymptomatic and 90 MS subjects the GEMS cohort, MS subjects have a higher mean GERS than asymptomatic subjects (p=1.8e-5, after adjusting for age). In a receiver-operator curve analysis, GERS (area under the curve, AUC=0.628) performs better than the genetic risk score (GRS, AUC=0.614) or environmental risk score (sex, IM, smoking; AUC=0.565) alone in predicting MS within these FDR. Further, GRS without HLA variants (AUC=0.547) and GERS without HLA variants (AUC=0.579) are still informative of MS risk, supporting the contribution of non-HLA variants to GRS and GERS. When ranking subjects into seven quantiles based on their GERS, the proportion of MS subjects in the highest GERS quantile (13%) is significantly greater than in the lowest quantile (3%), such that an increasing GERS is associated with a greater likelihood of MS in first-degree relatives of MS patients (p-trend=8.8e-5).
Conclusions: Our study suggests that, within MS family members, an aggregate risk estimate that includes genetic burden and environmental exposure is informative of MS risk beyond family history. Although this risk score is not yet clinically deployable, it enables the design of an adequately powered, prospective study of the higher-risk subset of MS family members to understand an individual's transition from health to disease.

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Prevalence and incidence of multiple sclerosis estimated in European Register for Multiple Sclerosis (EUReMS): study protocol of the Epi-1d study
M Pugliatti[1], K Buckow[2], D Ellenberger[2], S Otero[3], J Sastre-Garriga[3], K-M Myhr[4,5], P Flachenecker[6], IR Zarbo[7,8], C Marcoci[7,9], G Arru[7], L Ramió-Torrentà[10], I Pericot[11], O Carmona[12], T Friede[2], E Kasilingam[13], T Schyns-Liharska[13], C Thalheim[13], for the EUReMS Consortium
[1]University of Sassari, Sassari, Italy, [2]University Medical Center, Georg-August Universität, Göttingen, Germany, [3]Multiple Sclerosis Centre of Catalonia (Cemcat), Valld'Hebron University Hospital, Barcelona, Spain, [4]Norwegian Multiple

Sclerosis Competence Centre, Haukeland University Hospital, Dept. of Neurology, Bergen, Norway, [5]KG Jebsen Centre for MS Research, University of Bergen, Dept. of Clinical Medicine, Bergen, Norway, [6]Neurological Rehabilitation Center Quellenhof, Bad Wildbad, Germany, [7]University of Sassari, Dept. of Clinical and Experimental Medicine, Sassari, Italy, [8]University of Sassari, Dept. of Biomedical Sciences, Sassari, Italy, [9]State University of Medicine and Pharmacy 'Nicolae Testemitanu', Chisinau, Moldova, Republic of, [10]Hospital Universitari Josep Trueta, Neurologia, Girona, Spain, [11]Hospital Santa Caterina, Neurologia, Girona, Spain, [12]Fundació Salut Empordà, Neurology Dept., Figueres, Spain, [13]European Multiple Sclerosis Platform, EMSP, Brussels, Belgium

Background: The attempt to define the burden of MS in Europe is hampered by the variability of the surveyed populations and the different ascertainment across studies. To overcome this, epidemiological indices should be derived based on standardized procedures for data collection.This requires a consolidated collaborative network, harmonizing data structure and capturing, designing a registry system for both existing and prospective longitudinally collected data as well as shared analytical plans and interpretation of results.

Objectives: To fulfill one of EUReMS missions: MS epidemiological and clinical surveillance across European countries, including the assessment of the MS burden in Europe; to test the ultimate research hypothesis that MS in Europe is changing over time and space.

Methods: A survey was conducted between July 2013 and February 2014 by administering an ad hoc questionnaire (EPI-Q) to the leaders of eligible existing European databases, to collect data on database management and governance, contents (demographics, MS course, year of onset/diagnosis, diagnostic validation through lab and instrumental tests, EDSS), format and quality of data. Specific focus was given to detect the possibility for generating population-based estimates on better-ascertained sub-areas.

Results: Out of 18 databases contacted, EPI-Q was successfully administered to Croatia, Czech Republic, Denmark, Finland, Germany, Italy (Liguria, Tuscany, iMED), Norway, Poland, Serbia, Spain, Sweden and United Kingdom. Population-based epidemiological data collected since 2003 can be integrated into a database of ca. 17,000 MS patients over a total population of 18,000,000 for sub-areas in Catalunya/Spain, Italy, Sweden, UK, Norway, Finland and Serbia, despite some heterogeneity across regions.

Conclusions: Benefitting from EUReMS architectural infrastructure, and from previous work on purposes and constructs of existing MS databases in Europe, population-based sex- and age-specific incidence and prevalence from well-defined geographic sub-areas and over time, temporal trends of gender-ratio, age at onset and diagnostic delay will be computed, likely ensuring the 'best estimate' of the MS burden in Europe available to date.

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Vitamin D in multiple sclerosis; clinical and immunological implications

J Hejgaard Laursen[1], H Bach Søndergaard[1], P Soelberg Sørensen[1], F Sellebjerg[1], A Oturai[1]

[1]Copenhagen University Hospital Rigshospitalet, Danish Multiple Sclerosis Center, Copenhagen, Denmark

Background: Vitamin D insufficiency is common among multiple sclerosis (MS) patients, and hypovitaminosis D has been associated with MS risk and disease activity. This finding has been supported by *in vitro* studies, which have demonstrated anti-inflammatory effects of vitamin D. Moreover synergistic effects of vitamin D and interferon-beta (IFN-β) have been suggested. However, the overall evidence for a beneficial effect of vitamin D in MS is inconclusive.

Objectives: To investigate how screening for vitamin D insufficiency and recommendation on vitamin D3 supplies affect 25(OH)D levels in MS patients and to examine the clinical and immunological implications of this action.

Methods: A cohort of 210 natalizumab-treated relapsing-remitting MS (RRMS) patients was enrolled in the study. In winter 2009/2010 (period 1) patients had a blood sample collected and the procedure was repeated the following winter (period 2). Patients with serum 25(OH)D < 50nmol/l in period 1 were recommended treatment with vitamin D3 (50 to 100μg per day). Information on disease duration, annualized relapse-rate (ARR) and status for neutralizing antibodies (NAbs) to IFN-β was obtained retrospectively from the Danish MS Treatment Register. To asses how changes in 25(OH)D affect the immune system, quantitative real-time PCR analysis of MX1, USP18, PD-1, PD-L1, IFIT1, IFIT2, IL10, IL10RA, FOXP3 and IDO1 was performed on whole blood samples from period 1 and 2 in patients with the highest change in vitamin D level between period 1 and 2, n=30.

Results: Mean 25(OH)D increased significantly from 63 nmol/l (95% CI 58.8-67.7) to 76 nmol/l (95% CI 71.8-80.7) from period 1 to period 2 (p=5.1×10^{-8}). At the same time mean ARR decreased from 0.61 to 0.54. We found a trend between increasing levels of 25(OH)D and decreasing ARR (p=0.07). None of the ten genes examined were associated with changes in serum 25(OH)D levels.

Conclusions: Recommendation of vitamin D supplies to MS patients with 25(OH)D < 50nmol/l resulted in a significant increase in mean 25(OH)D but was not associated with a statistically significant decrease in ARR. Whether this relates to an insufficient increase in 25(OH)D or lack of efficacy of 25(OH)D supplementation remains to be established. Changes in 25(OH)D levels did not affect gene expression of genes previously associated with either endogenous IFN-response, vitamin D or both, which underlines the complexity of vitamin D research in MS.

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Impact of wGRS on familial aggregation and clinical phenotypes in Italian multiple sclerosis patients

F Esposito[1,2], C Guaschino[1,2], L Ferrè[1,2], M Sorosina[2], L Moiola[1], M Rodegher[1], B Colombo[1], V Martinelli[1], G Comi[1,2], F Martinelli Boneschi[1,2]

[1]Scientific Institute San Raffaele, Department of Neurology, Milan, Italy, [2]Scientific Institute San Raffaele, Laboratory of Genetics of Neurological Complex Disorders, Milan, Italy

Background: Multiple sclerosis (MS) is a multifactorial neurologic disease characterized by modest but tractable heritability. In

the last years the knowledge about the genetic variants associated with MS is improved, validating the role of 110 MS risk variants outside the human leukocyte antigen (HLA) region.

Objectives: To investigate the impact of the established MS genetic risk variants on both familial aggregation and clinical phenotypes in an Italian monocentric MS cohort.

Methods: 1476 Italian MS patients were screened for familial history of MS using a specific questionnaire administered during an outpatient visit at San Raffaele MS center. Among them, 461 sporadic probands and 93 familial probands were genotyped for 107 MS-associated single nucleotide polymorphisms (SNPs). The weighted genetic risk score (wGRS) was calculated combining the odds ratio of 106 non-HLA variants and one SNP tagging the HLA-DRB1*1501 allele.

Results: Familial and sporadic MS probands are indistinguishable in terms of gender, age at onset (AAO), disease course, disability and oligoclonal bands (OCB) status. In our cohort there were no statistical differences in the total wGRS score between MS cases reporting any family history of the disease and those reporting no family history, even after stratification by gender. We observed that an earlier AAO correlates with a higher wGRS score (p-value=0.03). Disease severity measured by MS severity score (MSSS), clinical course (bout onset vs progressive onset MS) and OCB status failed to show significant association with wGRS.

Conclusions: This is the first Italian study aimed to evaluate the aggregation of susceptibility variants in MS patients. In our cohort, no major differences were observed between sporadic and familial MS cases in terms of wGRS, suggesting that other variants outside the known MS associated loci, probably rare variants and/or environmental factors, can explain the aggregation of the disease within families. In agreement with previous studies, we confirmed the association between a higher wGRS and a lower AAO. We speculate that the accumulation of known genetic risk factors may reduce the threshold for the clinical manifestation of the disease, without influencing the disease severity. We also observed a lack of association between wGRS and disability nor clinical course.

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A prospective case-control study of dietary salt intake and risk of pediatric MS

J McDonald[1], J Graves[1], S Lulu[1], A Waldman[2], A Belman[3], B Greenberg[4], B Weinstock-Guttman[5], G Aaen[6], J Mendelt-Tillema[7], J Hart[1], J Ness[8], J Rubin[9], L Krupp[3], M Gorman[10], L Benson[10], M Rodriguez[7], T Chitnis[10], T Simmons[11], TC Casper[11], J Rose[12], E Waubant[1]

[1]UCSF Regional Pediatric MS Center, San Francisco, CA, United States, [2]University of Pennsylvania, Department of Neurology, Philadelphia, PA, United States, [3]SUNY Stony Brook, Department of Neurology, Stony Brook, NY, United States, [4]UT Southwestern, Department of Neurology, Dallas, TX, United States, [5]SUNY Buffalo, The Pediatric MS Center at the Jacobs Neurological Institute, Buffalo, NY, United States, [6]Loma Linda University, Department of Child Neurology, Loma Linda, CA, United States, [7]Mayo Clinic, Department of Neurology, Rochester, MN, United States, [8]Alabama Pediatric MS Center, Birmingham, AL, United States, [9]Northwestern Feinberg School of Medicine, Department of Neurology, Chicago, IL, United States, [10]Massachusetts General Hospital, Partners Pediatric MS Center, Boston, MA, United States, [11]University of Utah, Department of Pediatrics, Salt Lake City, UT, United States, [12]University of Utah, Department of Neurology, Salt Lake City, UT, United States

Background: Environmental and dietary factors have become increasingly recognized in the past decades as potential risk factors for developing multiple sclerosis (MS). Pediatric MS offers a unique opportunity to study such factors, due to temporal proximity at the time of diagnosis to the exposure, thereby minimizing recall bias. High salt intake has been shown to increase disease onset and progression in recent animal studies. Whether these results are applicable to human disease is currently unknown.

Objectives: To determine if dietary salt intake is a risk factor for pediatric MS in a multi-center cohort of pediatric cases and controls.

Methods: A prospective case-control study was performed with pediatric-onset MS patients (first clinical attack before 18 years) with disease onset less than 2 years duration who were seen at one of 13 pediatric MS centers. Controls, less than 20 years old, were recruited at the same centers.

Dietary sodium intake was assessed using the Block Kids Food Screener (NutritionQuest), a validated, self-report questionnaire that evaluates the frequency and portion of beverages/foods consumed. Sodium intake was compared between cases and controls and adjusted for age, gender, race and ethnicity in logistic regression models.

Results: Among 138 cases (mean age =15 years) and 285 controls (mean age = 14 years), baseline characteristics were similar for mean energy intake (kcal/d), total fat (g/d) and race. There were significantly more females (60.14 vs. 48.07%) and Hispanic/Latino (31.88% vs. 17.89%) cases compared to controls.

There was no significant difference in unadjusted mean sodium intake between cases (1965 mg/d) and controls (2072 mg/d) and the proportion of subjects exceeding the adequate intake was similar between cases and controls (62% vs. 68%). Among male subjects, both cases (2349 mg/d) and controls (2435 mg/d) exceeded the Tolerable Upper Limit (2300 mg/d) for sodium intake.

A non-significant trend towards increased odds of MS (1.015) for each 100 mg increase in sodium (95% CI 0.992, 1.038; p=0.19) was observed in the analyses adjusted for age, gender, race and ethnicity. Adjusted analyses including socioeconomic status and body mass index are pending.

Conclusions: No difference in dietary salt intake was found between cases and controls in the preliminary analyses. Further analyses that include variables associated with MS risk are needed to explore whether increased salt contributes to the development of pediatric MS.

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Increasing prevalence and stable incidence of multiple sclerosis in Western Norway, 1953-2013

N Grytten[1], JH Aarseth[2], HMB Lunde[1], K-M Myhr[2]
[1]National Multiple Sclerosis Competence Centre, Department of Neurology, Bergen, Norway, [2]Norwegian MS Registry & Biobank, Department of Neurology, Bergen, Norway

Background: Hordaland County, Western Norway is a high risk area for multiple sclerosis (MS). Follow-up studies have suggested a rising prevalence although a stable incidence since the 1980`ies. Increase in prevalence followed by a change in

age distribution in MS has been reported elsewhere. The rising prevalence may be attributed to longer disease duration due to earlier age at symptom onset and diagnosis and/or later age at death. We performed a 60 years follow up of incidence and prevalence of MS to describe the occurrence of MS in Western Norway.

Objectives: To compare the prevalence of MS in 2003 and 2013, and to explore the long-term incidence and age distribution of MS in Hordaland County, Western Norway.

Methods: All patients in Hordaland County diagnosed with MS at the Department of Neurology, Haukeland University Hospital, Bergen, Norway, were identified. The patients were diagnosed with MS according to Poser criteria (definite and probable MS) and McDonald`s criteria (during 2003-2012). The study comprised 1558 MS; of whom 897 living in Hordaland County per January 1st 2003, and 1035 per January 1st 2013.

Results: The prevalence increased 10- fold from 20 per 100,000 in 1963, to 203 per 100,000 (95% CI: 190.1-216.8) in 2003 and 211.0 (95% CI: 198.3-224.2) per 100,000 in 2013. Prevalence in 2003 increased from 150 at follow-up 1.1.2003, to 203 per 100,000 at follow-up 1.1.2013 with the inclusion of additional 220 patients with onset prior to 2003. The annual mean incidence rate of MS was stable at 8-9 per 100,000 since 1982. The peak age specific prevalence shifted from 45-59 years in 2003 to 65-69 years in 2013 and there was also a trend towards increased age specific prevalence rates in younger age groups. The sex ratio was stable at 1.8:1 during the whole period. Time delay from symptom onset to diagnosis declined from a mean of 10 years since 1958 to 0.7 in 2008-2012.

Conclusions: We detected a rising prevalence throughout the study period, but a stable incidence since 1982 indicating possible longer disease duration due to earlier diagnosis and improved survival. Prevalence studies based on year of onset needs an extended period of sampling during several years in order to collect all valid patients.

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The spectrum of idiopathic inflammatory demyelinating diseases in South America: a multicenter study

R Papais-Alvarenga[1,2], C Ferreira Vasconcelos[1], L Campanella[1], M Papais-Alvarenga[1], S Camargo[2], A Carra[3], FH Dias de Bedoya[4], V Fleitas[5], S Florentin[5], IS Castillo[6], H Cabeças[7], A Pereira Gomes Netto[8], P Marinho[9], MCDN Barroso[9], AK Grzesiuk[10], HH Siqueira[11], SC Machado[12], ML Brito Ferreira[13], YD Fragoso[14], J Brooks[15], MSG Rocha[16], AB Calmon[17], F Costa Pereira[18], MLV Pimentel[19], MP Alvarenga[2], M Gonçalves[20], MK Parolin[21], LC Thuller[22]
[1]UNIRIO, Neurology, Rio de Janeiro, Brazil, [2]Hospital da Lagoa, Rio de Janeiro, Brazil, [3]Hospital Britânico, Buenos Ayres, Argentina, [4]Hospital de Paraguay, Assuncion, Paraguay, [5]Instituto de Previzion Social, Assuncion, Paraguay, [6]Hospital Univesítário de Maracaibo, Maracaibo, Venezuela, [7]Hospital Ofir Loyola, Belem, Brazil, [8]Santa Casa, Belo Horizonte, Brazil, [9]Rede Sarah, Brasilia, Brazil, [10]Centro de Reabilitação, Cuiabá, Brazil, [11]Universidade Federal de Mato Grosso, Cuiabá, Brazil, [12]H C Cetom, Florianópolis, Brazil, [13]Hospital da Restauração, Recife, Brazil, [14]Centro Neurológico do Litoral Paulista, Santos, Brazil, [15]Centro Neurológico do Litoral Paulista, Santoss, Brazil, [16]Hospital Santa Marcelina, São Paulo, Brazil, [17]Universidade Sul Fluminense, Vassouras, Brazil, [18]Centro Neurologico de Volta Redonda, Volta Redonda, Brazil,

[19]Santa Casa, Rio de Janeiro, Brazil, [20]Universidade de Joinville, Joinville, Brazil, [21]Clinica de Curitiba, Curitiba, Brazil, [22]INCA, Rio de Janeiro, Brazil

Background: Although population-based studies have estimated that the NMO prevalence rates are similar in Caucasians and non-Caucasians populations the review of cohorts, previously diagnosed as MS, in the light of current criteria reported a high variability of relative frequency of NMO among MS patients, according to the ethnic background.

Objectives: To analyze the spectrum of Idiopathic Inflammatory Demyelinating Diseases in South America, accounting for the ethnic heterogeneity of its population.

Methods: descriptive, multicenter, cross-sectional study. Were included individuals with IIDD followed regularly in MS centers in 2011. Only cases with a confirmed diagnosis based on the current criteria were considered eligible. Data collected: type of unit, town and country; demographic and clinical data, ethnicity/skin color [white, mestizo, Afrodescendant, Asian] and score on the EDSS at last assessment; diagnosis; diagnostic tests including anti-AQP4 antibody. The data entered in an ad hoc Excel spreadsheet; analysis in the SPSS software 14.

Results: The data from 1,777 individuals with IIDD who were followed in 19 reference centers distributed across latitudes [+ 10 from - 34] were included for analysis. Five cities were located in Hispanic America and 12 cities, in five Brazilian regions. The frequencies of the six main categories of IIDD were: MS (75%), NMO (12%), NMOSD (6%), CIS (3%), ADEM (1%) and rare forms (0.3%). In all categories, females predominated (61 to 83%), with a mean age corresponding to the third and fourth decades of life . White ethnicity also predominated, except for NMO, for which 51% of the affected individuals were non-white. Four cases in Asians and no cases in Indians. The relative frequency of NMO varied from 43% in Venezuela, 14% in Brazil, 8% in Paraguay and 2% in Argentina and the frequency of NonWhites in NMO was respectively 82%, 50%, 33% and 0% in Argentina. Anti-AQP4 antibodies were measured in 261 cases, with positive results in 56% of patients with NMO and in 28% of the patients with NMOSD and negative results in the remainder of the investigated IIDD categories.

Conclusions: Despite the lower prevalence of MS in South America, the disease follow the same clinical pattern of high prevalence areas. The MS frequency increase in a north south gradient differing from NMO, suggesting an genetic influence. The identification of the 14.5% of NMO among MS cases has many implications for healthcare services.

P351

Sodium intake in multiple sclerosis patients

MF Farez[1], MP Fiol[1], MI Gaitán[1], FJ Quintana[2], J Correale[1]
[1]Raúl Carrea Institute for Neurological Research (FLENI), Neurology, Buenos Aires, Argentina, [2]Center for Neurologic Diseases - Brigham and Women's Hospital, Boston, MA, United States

Background: Sodium has been recently reported to promote the differentiation of pathogenic T cells and worsen disease in an experimental model of MS. However, the relevance of these observations for MS is unknown. Here, we investigated the

relationship between salt consumption and MS disease clinical and radiological activity.

Objectives: To asses the reliability of sodium intake measurement using spot urine and to investigate the relationship between salt consumption and clinical and radiological disease activity in MS.

Methods: Sodium intake was calculated in spot urine samples from a cohort of 70 relapsing-remitting multiple sclerosis patients using Tanaka's equation. The effect of sodium intake in MS disease activity was estimated by regression analysis. Because large fluctuations on sodium intake could have an impact on our study results, we retested all 70 patients for sodium intake every 3 months during a year and repeated the analyses. Finally, we then replicated our findings in a separate group of 52 MS patients.

Results: There were no significant changes in sodium intake across all measurements (P=0.2), suggesting that sodium intake remained relatively stable. We found an exacerbation rate that was 2.75- (95% CI 1.3-5.8) or 3.95-fold (95% CI 1.4-11.2) higher in patients with medium or high sodium intakes compared with the low-intake group. Additionally, individuals with high sodium intake had a 3.4-fold greater chance of developing a new lesion on the MRI. To evaluate the possible impact of sodium intake fluctuations in our findings we repeated the analyses using the other 3 timepoints. As with our main analysis, we found a positive correlation between exacerbation rate and sodium intake at months 3, 6 and 9 in a multivariate model. We then tested the robustness of our results by repeating the main analyses with a different equation to estimate sodium intake with spot urine: compared with the baseline group, the average and above average intake groups presented an exacerbation rate of 2.75 (95% CI 0.6-12.6) and 3.54-fold higher (95% CI 1.13-11.3) than the baseline group. Finally, a similar relationship was found in the independent replication group of 52 MS patients.

Conclusions: Our results suggest that sodium intake estimation using spot urine is a stable and valid test and that a higher sodium intake is associated with increased clinical and radiological disease activity in MS patients.

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Body mass index and baseline vitamin D status modify the response to vitamin D supplementation in multiple sclerosis patients and healthy controls

P Bhargava[1], SU Steele[1], JF Marcus[2], NR Revirajan[2], E Waubant[3], EM Mowry[1]

[1]Johns Hopkins University School of Medicine, Neurology, Baltimore, MD, United States, [2]University of California San Francisco, San Francisco, CA, United States, [3]University of California San Francisco, Neurology, San Francisco, CA, United States

Background: While vitamin D insufficiency is a risk factor for multiple sclerosis (MS), it is common in the general population. Since genes associated with vitamin D metabolism have been linked to MS risk, we hypothesized that vitamin D metabolism may differ in MS patients compared to healthy individuals.

Objectives: To determine if vitamin D supplementation leads to a similar increase in serum 25-hydroxyvitamin D levels in MS patients and healthy controls (HCs), and to determine the factors affecting response to vitamin D supplementation.

Methods: Participants in this open-label study were female, white, aged 18-60 years, had 25-hydroxyvitamin D levels ≤ 30 ng/mL at screening, and had relapsing-remitting MS or were HCs. Subjects received 5,000 IU (125 µg)/day of oral cholecalciferol (vitamin D_3) for 90 days. The primary outcome variable was the change in mean serum 25-hydroxyvitamin D level. The primary predictor was disease status (MS versus HC). Serum 25-hydroxyvitamin D levels were measured as a single batch using liquid chromatography-mass spectrometry. Multiple linear regression models were used to examine the relationship between the primary outcome variable and the primary as well as secondary predictors.

Results: 27 subjects with MS and 30 HCs were enrolled. There was no significant difference in baseline demographics except for higher BMI in the MS group (25.3 kg/m² vs 23.6 kg/m², p=0.035). Baseline serum 25-hydroxyvitamin D levels were similar in both groups (22.1± 7.9 vs 22.3±8.0 ng/ml, p=0.94). 24 subjects with MS and 29 HCs completed the study. In univariate models, there was a larger increase in serum vitamin D levels in HCs compared to MS patients (33.1±11.4 vs 26.4±11.6 ng/ml, p=0.039). In multivariate models accounting for age, BMI, medication adherence, and baseline vitamin D and albumin levels, there was still some evidence that MS patients may have a reduced response to vitamin D supplementation, although the 95% confidence intervals included zero. Higher BMI (p=0.006), worse medication adherence (p=0.002), lower baseline vitamin D levels (p=0.003), and higher baseline serum albumin levels (p=0.003) were independently associated with a less robust change in serum vitamin D levels.

Conclusions: While subjects with MS appear to have a lower rise in vitamin D levels with supplementation, this may be explained in part by BMI and baseline vitamin D levels. Modification of vitamin D dosing may be required based on these variables.

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Epidemiology of multiple sclerosis in the Republic of Moldova: an incidence and prevalence study in the northern and central regions

C Marcoci[1,2,3], V Lisnic[1,2], M Sangheli[1,2], A Belenciuc[1,2], G Rosu[4], M Leone[5], M Pugliatti[6]

[1]State University of Medicine and Pharmacy 'N.Testemiţanu', Chisinau, Moldova, Republic of, [2]Institute of Neurology and Neurosurgery, Dept. of Neurology, Chisinau, Moldova, Republic of, [3]Dept. of Clinical and Experimental Medicine, University of Sassari, Sassari, Italy, [4]District Hospital of Riscani, Riscani, Moldova, Republic of, [5]Ospedale Maggiore della Carità, Novara, Italy, [6]University of Sassari, Dept. of Clinical and Experimental Medicine, Sassari, Italy

Background: In Europe the total prevalence of MS is about 83 per 100,000 and the estimated mean annual incidence rate is about 4 per 100,000. The literature on MS epidemiology in Eastern Europe is scarce and out of date. Data from Bulgaria, Czech Republic, Hungary, Poland, Romania, Russia, Russia, Slovakia, and Ukraine show a prevalence of 21 to 83, and an annual incidence of 0.7 to 6.0 per 100,000 pop. No studies are reported for Moldovans, an ethnicity sharing features with Romanians, Russians and Ukrainians.

Objectives: This study aims to estimate age and sex-specific incidence and prevalence of MS in Moldovans.

Methods: The study area is represented by the Municipality of Chisinau (800,601 pop. on 2013 National Statistics), and by the Regions of Central and Northern Moldova (348,649 and 379,592 pop., respectively). Patients with MS with 2010 McDonald Criteria were included, and the following epidemiological sources sought: records from Chisinau Hospitals, District Hospitals of Ungheni, Nisporeni, Criuleni, Straseni, Riscani, Briceni, Edinet, Glodeni, and Singerei, and the Moldovan MS Association. The mean crude annual incidence for the period 2006-12, the crude prevalence for December 31st 2012, and the distribution of relapsing remitting (RR), or progressive initial course were computed.

Results: Between 2006 and 2012, 112 patients (43 men, 69 women) had MS onset in the study area, yielding a crude mean annual incidence rate of 1.0 (95% confidence intervals, CIs, -1.7, 3.8), with a woman:man (W:M) ratio of 1.5. Mean (SD) age at onset was 31.8 (10.8) years, 28.7 (9.8) in men and 33.8 (11.0) in women (p=0.014); 106 (94.6%) had a RR course at onset, and 6 (5.4%) a progressive course. On prevalence day, 244 individuals (84 men, 160 women) with MS were living in the study area, for a crude onset-adjusted prevalence of 16.0 per 100,000 (95%CIs: 12.2, 19.8) and a W:M ratio of 1.7. Mean (SD) age on prevalence day was 40.4 (11.4) years, 37.3 (11.9) in men and 42.0 (10.9) in women (p=0.002).

Conclusions: This is the first MS epidemiological study in the Republic of Moldova, covering 43% of the country population. MS was found to be rarer than on average in Europe. Although, ascertainment difficulties cannot be ruled out, this evidence is rather consistent with what reported for neighboring countries Romania and Ukraine.

P354

Increasing incidence of multiple sclerosis among women in Buenos Aires: a 21-year health maintenance organization based study

JI Rojas[1], J Miguez[1], L Patrucco[1], D Giunta[2], H Peroni[2], E Cristiano[1]
[1]Centro de Esclerosis Múltiple de Buenos Aires, Buenos Aires, Argentina, [2]Hospital Italiano, Buenos Aires, Argentina

Background: Epidemiological studies in multiple sclerosis (MS) suggest a trend of increasing disease prevalence and incidence in susceptible populations and mainly a disproportional increase in the incidence of multiple sclerosis in women. The reasons for this are unclear and might be related to environmental factors. No studies were done in Latin-America to explore the previous findings.

Objectives: The objective of this study was to determine the secular trend on incidence of MS between women and men in a health maintenance organization from Buenos Aires, the largest populated area in Argentina.

Methods: Population was all members of a Hospital based HMO who were affiliated since January 1992 up to December 2013. Each person was followed contributing time at risk since January 1992 or enrollment date to the final date. Cases with definite diagnosis according to Poser's or McDonald criteria were included. Incidence density was calculated with 95% confidence intervals and compared between woman and men.

Results: 230,642 subjects were followed for a total of 1,488,575 person-years, of whom 42 developed MS. Incidence density was 2.8 /100,000 person-years (95 % CI: 2.1 - 3.5/100,000 person-years). During this period (1992-2013), the incidence rate in women increased from 1/100,000 (95%CI 0.8-1.6) to 4.9/100,000 (95%CI 4.1-5.4) (p< 0.001) while in men the incidence ranged from 1.4/100,000 (95%CI 1-1.7) to 1.8 (1.3-2.1) (p=0.16).

Conclusions: The incidence density increased during the study period in women signicantly but not in men. This is the first report of this phenomenon in Latin America region.

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eQTL discovery in MS patients elucidates functional mechanisms associated with disease susceptibility and treatment

JM Replogle[1,2,3], L Ottoboni[1,2,4], T Raj[1,2,3], NA Patsopoulos[1,2,3], PL De Jager[1,2,3]
[1]Brigham and Women's Hospital, Department of Neurology, Boston, MA, United States, [2]Broad Institute, Program in Medical and Population Genetics, Cambridge, MA, United States, [3]Harvard Medical School, Boston, MA, United States, [4]San Raffaele Scientific Institute, Milan, Italy

Background: Multiple sclerosis (MS) is a demyelinating autoimmune disease influenced by a combination of genetic and environmental factors. Genome-wide association studies (GWAS) have uncovered >100 genetic variants associated with MS susceptibility. Although their molecular functions remain to be fully characterized, many of these variants modulate gene expression levels as expression quantitative trait loci (eQTLs), and we recently showed that MS-associated eQTLs tend to be T-cell specific (Raj et al. 2014, *Science*).

Objectives: Here we perform an eQTL analysis in peripheral blood mononuclear cells isolated from MS patients in order to: (i) functionally characterize variants previously associated with MS and (ii) describe drug-specific eQTLs.

Methods: We isolated peripheral blood mononuclear cells from 206 patients with relapsing remitting MS and 26 patients with clinically isolated syndrome and measured mRNA expression using the Affymetrix GeneChip Human Genome U133 Plus 2.0 Array. Of the patients, 79 were untreated, 90 were treated with interferon beta, and 63 were treated with glatiramer acetate at the time of sampling. For our *cis*-eQTL analysis, we computed the correlation between gene expression and genotypes within 1 Mb of the gene transcription start site in the entire cohort and in the cohort stratified by treatment. Using these *cis*-eQTLs, we examined the overlap of regulatory SNPs with MS-associated SNPs using Relative Trait Concordance. Finally, we used a robust statistical method (π_1) to quantify the proportion of sharing between treatments as estimated from the enrichment of low p-values.

Results: We show that 52 MS susceptibility variants are *cis*-eQTLs at $p < 10^{-5}$. For the majority of these loci, the MS and *cis*-eQTL effects are likely driven by the same marker variant suggesting that this colocalization is not coincidental. Next, we demonstrate the utility of *cis*-eQTL data in fine-mapping the *SLC15A2* locus. Finally, we illustrate that a significant proportion of regulatory effects are treatment specific and that interferon beta has a stronger effect on the PBMC regulatory landscape than glatiramer acetate.

Conclusions: Our systematic analyses provide evidence for a primary role of MS susceptibility alleles in altering mRNA expression. We highlight the power of intermediate traits in fine-mapping and the importance of context-specific eQTL analyses in the functional characterization of MS-associated variants.

P356
The use of valproic acid and multiple sclerosis

NM Nielsen[1], H Svanström[1], E Stenager[2,3,4], M Magyari[5], N Koch-Henriksen[6,7], B Pasternak[1], A Hviid[1]
[1]Statens Serum Institut, Department of Epidemiology Research, Copenhagen, Denmark, [2]University of Southern Denmark, Institut of Regional Health Research, Odense, Denmark, [3]Rigshospitalet, Danish Multiple Sclerosis Registry, Copenhagen, Denmark, [4]Multiple Sclerosis Clinic of Southern Jutland, Department of Neurology, Sønderborg, Denmark, [5]Danish Multiple Sclerosis Research Centre, Department of Neurology, Neuroscience Center, Rigshospitalet, Copenhagen, Denmark, [6]University of Aarhus, Department of Clinical Epidemiology, Clinical Institute, Aarhus, Denmark, [7]Rigshospitalet, The Danish Multiple Sclerosis Registry, Copenhagen, Denmark

Background: Animal studies have suggested that drugs that inhibit the enzyme histone deacetylase (HDAC) might have a beneficial effect on experimental allergic encephalomyelitis (a murine model of multiple sclerosis). Valproic acid (VPA), an anti-epileptic drug, is the only widely used human drug with a HDAC inhibitory effect. No one has examined, however, whether use of VPA among humans reduces the risk of Multiple Sclerosis (MS).
Objectives: To examine if VPA use is associated with a reduced risk of MS.
Methods: Using information on filled VPA prescriptions from the nation-wide Danish Prescription Drug Registry established in 1996, we identified a cohort of all new users of VPA and a cohort of non-users of VPA in the period 1997-2011. Incident MS cases were identified in the Danish Multiple Sclerosis Registry. To adjust for baseline differences in the probability of receiving anti-epileptic treatment, we estimated propensity scores as the probability of VPA use among the cohort of VPA users and among the cohort of non-users of VPA given variables potentially associated with use of VPA such as age, sex, place of birth, region of residence, calendar year, migraine, epilepsy, depression and other psychiatric affective disorders. Information on these covariates was obtained from the Danish Civil Registration System or the Danish National Patient Registry. VPA users were subsequently matched on propensity scores with non-users of VPA in a 1:4 ratio and incidence rates of MS were compared among VPA users and non-users of VPA using Cox regression to estimate hazard ratios (HRs).
Results: Among 16,028 ever-users of VPA and 54,172 non-users we identified 19 and 31 cases of MS, respectively. Compared to non-users of VPA, current-users of VPA were not at a reduced risk of MS (HR=1.09 (95% confidence interval; 0.38-3.16), n=4) neither were recent-users of VPA who had ceased VPA treatment within the last year (HR=1.11 (0.26-4.81), n=2), respectively. Similarly in an intention-to-treat analysis ever-users of VPA were not at reduced risk of MS (HR=2.15 (1.20-3.81), n=19).
Conclusions: : In the first human study addressing a possible beneficial effect of VPA use on the risk of MS we found no support

for a protective effect. However, the few numbers of MS in the present study does limit the conclusion that can be drawn. Future studies have to be carried out to support or decline a possible therapeutic role of VPA in MS.

P357
Vitamin D levels and antibody titers against Epstein-Barr virus and human herpesvirus 6 in multiple sclerosis patients: a one-year follow-up study

I Ortega-Madueño[1], L Lopez-Lozano[1], M Garcia-Montojo[1], MI Dominguez-Mozo[1], AM Arias-Leal[1], MA Garcia-Martinez[1], I Casanova[1], MJ Torrejon[1], R Arroyo[1], R Alvarez-Lafuente[1]
[1]Hospital Clinico San Carlos, Madrid, Spain

Background: Systemic or locally produced 1,25(OH)(2) Vitamin D3 exerts its effects on several immune-cell types, including macrophages, dendritic cells, T and B cells; it has been described that 1,25(OH)2VD3 is able to block B-cell proliferation, plasma-cell differentiation and immunoglobulin production. In recent years, altered levels of vitamin D have been associated with multiple sclerosis (MS).
Objectives: To evaluate the possible association between the levels of 25-OH Vitamin D with the levels of IgG and IgM antibodies against Epstein-Barr Virus (EBV) and human herpesvirus 6 (HHV-6) in MS patients in a one-year follow-up study.
Methods: Serum samples from 304 MS patients were analyzed in a prospective study of one-year of duration. Two serum samples were collected for each one of the MS patients: at the recruitment and 12 months later (mean 11.8 ±1.2 months). For each one of the samples we analyzed: the levels of 25-OH Vitamin D (Abbott), IgG antibodies against Epstein-Barr nuclear antigen (EBNA) (Trinity), IgG antibodies against EBV viral capsid antigen (VCA) (Trinity), and IgG and IgM anti-HHV-6 (Panbio). Samples were analyzed in duplicate for each test.
Results: For the 50.5% of MS patients the levels of 25-OH Vitamin D were >20 ng/ml; only for the 13.2% of MS patients the levels of 25-OH Vitamin D were >30 ng/ml. When we analyzed the correlation of the variation of 25-OH Vitamin D levels between the basal visit and the 12 month visit with the variation in the anti-EBNA IgG levels, anti-VCA IgG levels, anti-HHV-6 IgG and IgM levels after one-year of follow-up, we did not find any statistical significant difference. However, when we only considered those MS patients with basal levels of 25-OH Vitamin D >20 ng/ml, we found that the 80% and the 75% of MS patients with a decrease in the levels of the 25-OH Vitamin D>25% between the basal visit and the 12 month visit experienced an increase of the anti-EBNA IgG levels (p=0.037) and the anti-HHV-6 IgG levels (p=0.044), respectively.
Conclusions: Variations of the 25-OH Vitamin D levels in MS patients with low 25-OH Vitamin D levels did not correlate with possible variations in the antibody titers against EBV and HHV-6. However, significant decreases in the 25-OH Vitamin D levels in MS patients with higher levels of 25-OH Vitamin D could be correlated with significant increases of the anti-EBNA IgG and the anti-HHV-6 IgG levels, two of the main candidates associated with MS etiology. Further studies will be needed to confirm these results.

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Early-onset multiple sclerosis in Isfahan, Iran: a report of the demographic and clinical features of 221 patients

M Fereidan-Esfahani[1], M Etemadifar[1]
[1]*Isfahan University of Medical Science, Isfahan, Iran, Islamic Republic of*

Background: It is estimated that early onset MS (EOMS) approximately incorporates 3-5% of the MS population.

Objectives: There has been about 4-fold increase in MS population in Isfahan to date; hence, we aim to give an update and compare the demographic features, clinical and imaging findings at onset of EOMS in true childhood MS versus juvenile MS, and to discuss them in the light of earlier studies on pediatric MS.

Methods: This prospective study concerned MS patients in whom the disease started before the age of 16 years and who were referred to Isfahan MS Society from October 1997 to February 2014. Clinical and demographic data of children with less than 16 years of age were reviewed retrospectively. According to the first acute demyelinating event, the EOMS patients were divided into two following groups:

(1) True childhood-onset MS (onset age ≤ 10) and
(2) Juvenile MS (10 < onset age ≤ 16).

Results: Out of 4,536 MS patients referred to our center, 221 patients (4.8%) had MS starting at the age of 16 or less (11 True childhood-onset Vs. 210 Juvenile MS), the Female to male ratio was 4.81:1. In the mean follow-up period of 6.2 years, 22 patients (10.5%) had positive family history of MS, 196 (88.6%) patients were classified as relapsing-remitting MS, 20 (9%);the mean (± SD EDSS) was 1.5 ± 1.1 at the last evaluation. The mean ± SD age at onset of the neurological symptoms was 14.7 ± 1.8. The most common initial presentation was optic nerve involvement (36.1%) and cerebellar sign and symptoms (14.6%). 13 patients (5.8%) had experienced seizure in the course of MS. According to Barkhof`s criteria, the characteristic MRI findings for MS, were found in 212 patients (97%).

Regarding our True childhood-onset MS group, the mean age at MS onset was 9.1 ± 1.2. All 11 patients had experienced the RRMS pattern. The most common presentation was cerebellar sign and symptom in this group.

Conclusions: Our recent updates showed that EOMS is not rare and does not differ significantly from our previous report in 2007,however there was a wide range of difference in clinical features between pre and post pubertal group. To optimize early diagnosis, it is important to gather worldwide data on the clinical course of EOMS to narrow the multiplicity of differential diagnosis of MS during childhood.

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Using patient-derived multiple sclerosis severity score to demonstrate differences in MS severity across racial groups in an urban MS center

T Bacon[1], I Kister[1], E Chamot[2], G Cutter[2], A Salter[2], AO Antezana[1], J Herbert[1]
[1]*NYU School of Medicine, Neurology, New York, NY, United States,* [2]*University of Alabama at Birmingham, Epidemiology, Birmingham, AL, United States*

Background: Patient-Derived Multiple Sclerosis Severity Score (P-MSSS) represents disease duration-adjusted mean ranks of Patient-Determined Disease Steps (PDDS), a validated, patient-rated disability scale that correlates closely with clinician-derived Expanded Disability Status Scale.

Objectives: To investigate inter-racial differences in MS severity among NYU MS Care Center patients using P-MSSS.

Methods: We administered PDDS to consecutive patients in our clinic over a three-month period. Age, disease duration, race, treatment status were obtained from chart review. P-MSSS were calculated using published reference table (Kister et al., Neurology 2013;80:1018). Linear regression analysis of P-MSSS by race and gender adjusted for age was carried out.

Results: 465 MS outpatients completed PDDS (completion rate >90%). 257 (55%) were Caucasian, 96 (21%) African-American (AA), 85 (18%) Hispanic and 6% 'other'. AA were similar in age to Caucasians, 46.2 (12.0) vs. 45.5 (11.7) (p=0.599), and disease duration, 12.6 (8.3) vs. 13.6 (10.4) years (p=0.45). Hispanics were younger than Caucasians, 41.1 (10.7) years (p< 0.0002) and had shorter disease duration, 11.0 (7.3) years (p= 0.036). There were more women among AA (80.2%) and Hispanics (79.9%) than among Caucasians (67.7%), (p< 0.0001 for both). Disease-modifying therapy use was similarly high across all groups: 83.3% Caucasians, 80.2% AA and 84.7% Hispanics. Mean P-MSSS differed significantly (p< 0.001) among the three races: they were the highest in AA (4.48 +/- 3.02), intermediate in Hispanics (4.14 +/- 2.81) and lowest in Caucasians (3.42 +/- 2.5). Linear regression analysis of P-MSSS by race and gender after adjustment for age revealed that, compared to reference Caucasian women group, AA men had the highest increase in disease severity (P-MSSS increase of +2.20, p=0.002), followed by Hispanic women (+1.10, p=0.004) and AA women (+1.01, p=0.005). There was a trend toward increased severity in Hispanic men (+1.53, p=0.02), but not in Caucasian men (+0.32, p=0.36).

Conclusions: P-MSSS affords a uniquely quick and easy way to compare disease severity among patient subpopulations in a busy clinic setting. Our P-MSSS-based analysis confirms earlier reports of the more rapid disease course in AA as compared to Caucasians and suggests that in Hispanics disease course may also be more rapid than in Caucasians. Gender was an effect modifier of the relation between disease severity and race; the most severe disease course was observed in AA men.

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Disease progression in multiple sclerosis after age 65

E Leray[1,2], M Genevray[3], S Mrejen[4], C Papeix[4], C Lubetzki[4], G Edan[2,3], M Rosenheim[5]
[1]*EHESP School of Public Health, Epidemiology, Rennes, France,* [2]*INSERM CIC-P 1414, Rennes, France,* [3]*Pontchaillou Hospital, Neurology Department, Rennes, France,* [4]*AP-HP - Salpetriere Hospital, Neurology Department, Paris, France,* [5]*AP-HP - Salpetriere Hospital, Infectious Diseases Department, Paris, France*

Background: Age at onset of multiple sclerosis (MS) is known to be associated with both disease phenotype and later disability progression. But little is known about disease progression after age 60-65, as only small numbers of old patients have been included in natural history studies. Neuropathology studies (Frischer, 2009)

reported that in older patients with long-term disease duration, inflammatory infiltrates decline to levels similar to those found in age-matched controls and the extent of axonal injury is not different from that in age-matched controls. This suggests that disease activity and progression may die out in aged patients with long MS duration.

Objectives: To compare MS disability progression before and after age 65.

Methods: Data from the Rennes and Paris-Salpêtrière MS databases were used. Inclusion criteria were: definite diagnosis of MS, disease duration of more than 5 years, and at least two EDSS measurements (1-year interval). In a first analysis, two EDSS scores were randomly selected among MS patients after age 65. For each case older than 65, we selected 4 less than 60-year-old MS patients matched for the first EDSS score and the follow-up period between the two EDSS measurements. Percentages of patients with increased EDSS score (1 point if initial EDSS score was < 5, and 0.5 point if ≥5.5) were compared between the two groups. In a second analysis, times remaining at each EDSS step before reaching the next EDSS scores (sustained only) will be compared between the two groups.

Results: In the first analysis, 48 patients aged more than 65 were matched to 142 patients less than 60. Age at MS onset was significantly higher (40 years (y) vs 26 y, p< .0001) and total follow-up duration was longer (31 y vs 21 y, p< .0001) in old patients compared to patients below 60 years. The median first randomly selected score was 6 (range: 0-9) in both groups. During the follow-up period to the second randomly selected score (mean 3 y), 35.4% of old patients and 44.1% of younger patients had an EDSS increase (p=0.313).

For the second analysis, 101 old patients were compared to 951 patients younger than 60 years. The follow-up duration from MS onset was longer in the old patients group than in the younger patients' group (27 y vs 14 y, p< .0001). Comparisons of times remaining at each EDSS step have not been analyzed yet.

Conclusions: Preliminary results suggest that disease progression may slow down in MS patients after age 65.

P361
Age at disease onset in familial and sporadic multiple sclerosis in Argentina

JI Rojas[1], L Patrucco[1], J Miguez[1], F Cáceres[2], N Fernandez Liguori[3], ML Saladino[2], M Parada Marcilla[4], MI Arrigoni[5], J Correale[6], M Fiol[6], MC Ysrraelit[6], A Carrá[7], MC Curbelo[7], A Martinez[7], J Steinbeg[7], JP Hryb[8], JL Di Pace[8], MB Perassolo[8], E Carnero[9], A Caride[9], PA Lopez[9], C Martinez[4], E Cristiano[1]
[1]Centro de Esclerosis Múltiple de Buenos Aires, Buenos Aires, Argentina, [2]Neurosciences Institute of Buenos Aires, Buenos Aires, Argentina, [3]Multiple Sclerosis Section Hospital E.Tornú, Buenos Aires, Argentina, [4]Private Office, Buenos Aires, Argentina, [5]Private Office, Cordoba, Argentina, [6]Department of Neurology, Institute for Neurological Research Dr. Raúl Carrea, FLENI, Buenos Aires, Argentina, [7]Hospital Británico, Buenos Aires, Argentina, [8]Hospital General de Agudos Carlos G Durand, Buenos Aires, Argentina, [9]Hospital Aleman, Buenos Aires, Argentina

Background: Anticipation of age at onset in younger generations is characteristic of neurological diseases in which genetic inheritance has a role. In multiple sclerosis (MS), some population studies found an anticipation of age at onset in younger generations, however, this was not evaluated in Latin America.

Objectives: This study was performed to assess if there is an anticipation of age at onset in younger generations of familial multiple sclerosis (FMS) vs. sporadic MS (SMS) in Argentina.

Methods: this was a multicenter study from 10 MS Centers of Buenos Aires, Argentina. Patients with MS diagnosis (Poser or McDonald criteria) were included and considered as FMS if they had in their family at least one relative of first or second degree diagnosed with MS, otherwise patients were considered to have SMS. We compared the age at onset between familial and sporadic cases as well as the age at onset between relatives from different generations in FMS vs. sporadic MS. Age at onset was defined as a single event of acute onset in the CNS suggestive of demyelination.

Results: a total of 891 patients were included, 83 were familial MS (9.3%). No differences in gender and MS subtype were found between SMS and FMS. A lower age at onset in the younger generations of FMS was found versus older generations of FMS (mean 23.6± 4.6 years vs 31.9±8.7 years; p < 0.001) as well versus SMS (mean 32.7 ± 8.9; p< 0.001). No differences were observed between older generations of FMS versus SMS (p=0.56).

Conclusions: we observed an anticipation of the age at onset of MS in the younger generations of patients with FMS versus older generations of FMS and SMS. No differences were observed between first generations of FMS versus SMS. Our findings are in line with previous studies in other regions.

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Vitamin D, latitude and sunshine hours in Scotland

EM Weiss[1], L Zgaga[1], R McQuillan[1], H Campbell[1], JF Wilson[1]
[1]University of Edinburgh, Center for Population Health Sciences, Edinburgh, United Kingdom

Background: Vitamin D deficiency has been associated with several autoimmune conditions including multiple sclerosis (MS), and occurs more frequently in regions of high and low latitude where ultraviolet (UV) radiation is both weaker and scarcer. Scotland, sitting at a relatively high latitude, has a high prevalence of MS (188/100,000) (MS Atlas, 2013), and Orkney, at an even higher latitude (59°N), has the highest prevalence in the world (402/100,000) (Visser et al., 2012). Vitamin D deficiency has been hypothesised as a possible environmental risk factor for MS.

Objectives: We aimed to better understand plasma vitamin D levels in mainland Scotland and Orkney, by both latitude (Orkney vs. mainland Scotland) and climate (sunny vs. cloudy halves of the country).

Methods: We obtained plasma vitamin D measurements for 4155 residents of Orkney and mainland Scotland, and adjusted them to the month of May to remove the seasonal effect. We further categorised May-adjusted vitamin D into good (>50 nmol/L), low risk (40-50 nmol/L), high risk (25-40 nmol/L), deficient (12.5-25 nmol/L) and severely deficient (< 12.5 nmol/L).

Results: In an age- and sex-adjusted linear model, seasonally-adjusted vitamin D concentration was significantly higher in Orkney compared to mainland Scotland (p < 0.001). Severe deficiency was significantly higher in mainland Scotland (p < 0.001).

In an age- and sex-adjusted linear model seasonally-adjusted vitamin D concentration was also associated with climate; vitamin D concentration was significantly higher in the sunnier half of the country (p=0.04).

Conclusions: The higher prevalence of severely deficient individuals in mainland Scotland compared to Orkney may be due to the "outdoors lifestyle" in Orkney compared to mainland Scotland. Furthermore, the significantly higher vitamin D associated with greater sunshine hours suggests that longitude is more important than latitude, reflecting the different climates in the east and west of Scotland. Future work will investigate how occupation and time spent outdoors are associated with vitamin D in Scotland.

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Prevalence, demographics and clinical characteristics of multiple sclerosis in the city of Tlemcen, Algeria

Z Barka Bedrane[1], L Henaoui[2], M Senoussaoui[2], D Regagaba[2], R Manaa[2], S Benabadji[1], D Bouchenak Khelladi[1], M Arezki[3]
[1]CHU Dr T. Damerdji, Service de Neurologie, Tlemcen, Algeria, [2]CHU Dr T. Damerdji, Service d'Epidemiologie, Tlemcen, Algeria, [3]CHU Frantz Fanon, Service de Neurologie, Blida, Algeria

Background: Previous epidemiological studies have indicated that Algeria is a low-risk zone for multiple sclerosis (MS).

Objectives: Our objective were to determine the prevalence, demographics and clinical characteristics of MS in Tlemcen city.

Methods: Tlemcen is located in the northwest of Algeria at 520 km from the capital Algiers and 64 km at the border of morrocco. Our study was descriptive transversal. The study population was all residents of Tlemcen city during the period from february 2008 to November 2012.

Results, a total of 202 patients fulfilled the McDonald diagnostic criteria(2005- 2010).

Results: On 30 November 2012, the prevalence of MS in Tlemcen city was 26,3/100 000 inhabitants (95%CI: 21,2-31,4). The female to male ratio was 1.84. The mean age of onset was 29.23±7.5 ans. A positive family history was found in 9,6 %. 70,8% have relapsing-remitting MS 18,8 %were secondary progressive MS, 7,4% were primary progressive MS.

Conclusions: We conclude that Tlemcen city is now a medium risk area for MS. Our study is the first in Tlemcen city, with some important differences in clinical characteristics as compared to other algerian cities and other countries in the region.

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Large scale epidemiological survey of disability progression in Japanese multiple sclerosis patients

I Nakashima[1], N Harada[2], F Nakaya[2], K Iwamoto[2]
[1]Tohoku University School of Medicine, Department of Neurology, Sendai, Japan, [2]Biogen Idec Japan Ltd, Tokyo, Japan

Background: Epidemiological data on the disability status and progression in Japanese patients with multiple sclerosis (MS) has not been well established. Kumar et al. reported that MS in Japan was associated with less disability than UK based on a limited sample size (ECTRIMS 2013, P764).

Objectives: This survey was undertaken to evaluate the status and progression of disability and to assess the degree of severity based on Patient Determined Disease Step (PDDS) scale.

Methods: This survey was conducted by collecting questionnaire forms from patients via postal mail. The questionnaire including demographic/clinical information was sent to the patients through three Japanese MS patients' associations. The patients were asked to evaluate their own disability using two standards -- PDDS and the SF-8 Quality of Life (QoL).

Results: MS patients (n=2,823) were asked to complete the questionnaires and 1,089(38.6%) responses were received, of which 74% were MS patients and 24% were Neuromyelitis Optica (NMO) patients. Age range was very similar to that of the recipients of Certificates of Specified Disease Treatment in Japan. According to the PDDS result of the patients, about 45 % of patients have gait disability (PDDS=3) or higher. It is demonstrated that the older at onset of MS, the shorter the duration from "mild/moderate disability" to "bilateral support/wheelchair/bedridden". The mean duration from first symptom to initiation of treatment was 4.5 years. The duration was longer (7.8 years) for young onset group (less than 29 years of age) than that (2.2 years) of the old onset group (more than 40). The patients whose current disabilities were reported as "early or late cane/bilateral support/wheelchair/bedridden" tended to start treatment after gait disability. Regarding QoL, the PDDS scores correlated with the physical component (PCS) but not with the mental component (MCS), although the MCS tends to be lower than that of the Japanese healthy population.

Conclusions: This survey revealed that the prevalence of Japanese MS patients with gait disability (PDDS=3 or more) was 45%. In addition, the duration from first symptom to the initiation of treatment in MS patients with severe impairment tends to be longer than that of patients with mild impairment, which suggests that earlier treatment may slow the progression of MS.

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Highly active multiple sclerosis and Epstein-Barr virus reactivation

MM Paz Soldan[1], EP Flanagan[1], OH Kantarci[1]
[1]Mayo Clinic, Neurology, Rochester, MN, United States

Background: Risk of developing multiple sclerosis (MS) has been associated with an expanding number of factors, including infections. Of all infectious agents studied, Epstein-Barr Virus (EBV) has shown the strongest association with MS. EBV has also been suspected to influence disease activity, but studies have been contradictory. Investigations of EBV reactivation in highly active MS have not been reported.

Objectives: To report patients with EBV reactivation coincident with highly active MS.

Methods: Patients were identified from our clinical practice. MS disease activity was assessed by neurologic evaluation and MRI. Serologic testing for EBV nuclear antigen (EBNA)-1 IgG, viral capsid antigen (VCA) IgG, and VCA IgM was performed by multiplex fluoromagnetic bead assay.

Results:

Patient 1 - A 29-year-old man was admitted to hospital for subacutely worsening gait ataxia, blurred vision and headache. MRI revealed extensive gadolinium-enhancing lesions within the

cerebral, posterior fossa and spinal cord white matter. Serologies returned positive for EBNA-1 IgG, VCA IgG and VCA IgM. Evaluation was consistent with MS, he improved following IV methylprednisolone, and interferon beta-1a was initiated. He remained without clinical relapse at follow up the next year and VCA IgM had become negative. MRI showed a few enhancing lesions and he transitioned to fingolimod. A few months later he returned with multifocal neurologic symptoms and examination findings. MRI showed extensive MS activity and VCA IgM was again positive. He improved with acute therapy and was transitioned to dimethyl fumarate. MS activity was quiet and VCA IgM negative at last follow up.

Patient 2 - A 45-year-old man was admitted to hospital for subacutely worsening myelopathy. MRI showed numerous gadolinium-enhancing lesions within the cerebral and spinal cord white matter. Serologies returned positive for EBNA-1 IgG, VCA IgG and VCA IgM. Evaluation was consistent with MS and he improved with acute therapy.

Conclusions: We present patients with highly active MS coincident with serologic evidence for EBV reactivation. Longer follow up for patient-1 also established a concurrent relapsing pattern. The temporal association with fingolimod, which is known to increase risk for herpes virus reactivation, may be informative. We propose that, in some patients, highly active MS may be precipitated by EBV reactivation. However, causality cannot be established from these reports.

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Residential distance from main roads, air pollution, and multiple sclerosis disability in Southern California

L Amezcua[1], V Chat[2], T Islam[3]
[1]*University of Southern California, Neurology, Los Angeles, CA, United States,* [2]*UAW, Public Health, Dhaka, Bangladesh,* [3]*University of Southern California, Preventive Medicine, Los Angeles, CA, United States*

Background: CNS inflammation and axonal degeneration contribute to multiple sclerosis (MS)-related disability. Air pollution has been reported to be an important trigger for CNS inflammation and axonal injury, yet little is known about the impact of traffic-induced pollution on disability among MS patients.

Objectives: To investigate the association between exposures to traffic related air pollution and MS disability.

Methods: Clinical characteristics and residential information from medical charts and in-person interviews were compared in a cross-sectional sample of Hispanics (n = 68) with relapsing remitting MS who reside in Southern California and receive treatment at the University of Southern California. Residential proximity from main roads measured in meters (m) and by ArcGIS software was used as a surrogate for exposure to traffic-related air pollution. MS disability was captured by Expanded Disability Status Scale (EDSS). Impaired ambulation was defined as EDSS ≤4. We used linear and logistic regression to investigate the association between air pollution and EDSS.

Results: The majority of the participants were female (64.7%, n=44), with MS first symptom between 20-40 years, and an EDSS between 0-7 (Mean 3.6 SD 2.3). Individuals who lived closer to the main roads had EDSS scores of 5.1(±2.1), while those who lived further had 3.4(±2.3). After adjusting for sex, age at first

symptom and disease duration, MS patients living at < 150 m from main roads experienced a 1.82 increment in EDSS (95%CIs 0.21-3.42, p=0.03) and were found to 6 times (OR 5.7 95%CIs 1.01-32.12, p=0.05) more likely to experience impaired ambulation compared to individuals living at a longer distance from main roads (≥150 m).

Conclusions: MS individuals residing near main roads were found to be at an increased risk of disability. Air pollution exposure may influence disease progression. Further studies with larger samples and other racial/ethnic backgrounds should be done to explore the association of more specific air pollutants to MS disability.

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Comparison of factors impacting vitamin D status in childhood & adult-onset demyelinating disease

JN Brenton[1], MD Goldman[2]
[1]*University of Virginia, Pediatric Neurology, Galloway, OH, United States,* [2]*University of Virginia, Charlottesville, VA, United States*

Background: Identification of modifiable risk factors for multiple sclerosis is ongoing. Exposure to some of these risk factors has been found to be important in childhood and potentially even in utero. No study has directly compared serum 25-hydroxyvitamin D levels in geographically-similar adults and children with demyelinating disease; nor has any study directly compared the demographic factors impacting these levels in these two distinct populations.

Objectives: Evaluate the prevalence and associated factors impacting vitamin D insufficiency and deficiency in childhood versus adult-onset demyelinating disease.

Methods: We conducted a retrospective, chart-review cohort study on geographically-similar pediatric, young adult, and adult patients with a diagnosis of demyelinating disease spectrum disorders identified at the University of Virginia from 2008 to 2013. The prevalence of vitamin D insufficiency and deficiency was evaluated between the three groups. The effect of variables potentially impacting vitamin D status was analyzed.

Results: We identified 24 childhood-onset (CO), 33 young adult-onset (Y-AO), and 59 adult-onset (AO) cases diagnosed with demyelinating disease. There was no difference in the prevalence of vitamin D insufficiency or deficiency between the cohorts. Non-Caucasian race and elevated body mass index were significantly associated with low vitamin D levels, regardless of age of onset. In regression models, race and obesity were independent predictors of vitamin D status. The prevalence of obesity was significantly higher in the childhood-onset cohort (CO=58.5%; Y-AO=31%; AO=34%; p=0.02).

Conclusions: Our findings demonstrate no difference in the prevalence of vitamin D insufficiency/deficiency between childhood and adult-onset demyelinating disease, suggesting age at disease onset is irrelevant to vitamin D status in demyelinating disease. Both race and obesity are independent factors impacting vitamin D insufficiency/deficiency, regardless of age of disease onset. Childhood obesity, regardless of gender, is significantly higher and may have a role in the development of childhood-onset multiple sclerosis.

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Vitamin D level and its clinical correlation in Thai patients with central nervous system demyelinating diseases

J Jitprapaikulsan[1,2], S Siritho[3], N Prayoonwiwat[1]
[1]Faculty of Medicine Siriraj Hospital, Mahidol University, Department of Medicine, Bangkok, Thailand, [2]Buddachinaraj Hospital, Department of Medicine, Phitsanulok, Thailand, [3]Bumrungrad International Hospital, Bangkok, Thailand

Background: There had several studies demonstrated that low level of vitamin D was one of the risk factor for multiple sclerosis (MS). Moreover, some reported found that replacement vitamin D in patients with MS who had vitamin D deficiency reduced relapse rate. However there has no report about vitamin D status in other demyelinating diseases such as Clinical Isolated Syndrome (CIS) or neuromyelitis optica (NMO)/NMO spectrum disorders (NMOSDs).

Objectives: To evaluate vitamin D status in Thai patients with idiopathic inflammatory demyelinating Central Nervous System Disorders (IIDCDs).

Methods: Serum 25-hydroxyvitamin D [25(OH)D] was determined in this cross-sectional study among Thai patients with IIDCDs attending the MS Clinic, Siriraj Hospital, Thailand during April 2012 and January 2014. Correlations between Expanded Disability Status Score (EDSS), annualized relapse rate (ARR) and 25(OH)D levels were analysed.

Results: There were 20 CIS, 34 MS and 76 NMO/NMOSDs patients. Mean vitamin D level was 22.17 ± 8.29 ng/ml in CIS, 23.41 ± 11.99 ng/ml in MS and 23.55 ± 9.33 ng/ml in NMO/NMOSDs patients while the average level of vitamin D in healthy Thai was 31.77 ± 0.32 ng/ml. Vitamin D insufficiency (level 21-30 ng/ml) were found in 8 CIS (40%), 9 MS (27%) and 32 (42%) NMO/NMOSDs patients, while vitamin D deficiency (level < 20 ng/mL) was found in 8 CIS (40%), 15 MS (45%) and 29 (38%) NMO/NMOSDs patients, respectively. Regarding the disability of disease determined by EDSS >3, 4/6 CIS (66%), 10/12 MS (83%) and 23/30 NMO/NMOSDs (76%) patients had vitamin D insufficiency (less than 30 ng/mL) while 2 CIS, 2 MS, 7 NMO/NMOSDs patients had normal vitamin D level; p=0.34, p=0.57, p=0.38 respectively. For patients who had ARR>1, 2/2 CIS (100%), 7/9 (77%) MS and 29/37 (78%) NMO/NMOSDs had vitamin D level < 30 ng/mL whereas none of the CIS, 2 (23%) MS, 8 (22%) NMO/NMOSDs patients had normal vitamin D level; p=0.18, p=0.85, p=0.85 respectively.

Conclusions: Our study demonstrated that vitamin D insufficiency was commonly found in Thai patients with CIS, MS and NMO/NMOSDs. We found a trend of vitamin D insufficiency in patients who had more disability (EDSS>3) but no statistically significant difference. No association was found between annualized relapse rate and vitamin D level.

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Clinical characteristics and outcome measures associated with disease progression in a prospective cohort of early diagnosed MS patients

BE Teter[1,2,3], KS Kavak[1,2], K Zakalik[1,2], K Edwards[2,4], C Patricia[2,5], L Krupp[2,5], J Herbert[2,6], I Kister[2,6], B Jubelt[2,7], A Goodman[2,8], M Gottesman[2,9], A Perel[2,10], A Gerber[2,11], R Zivadinov[2,3,12], M Ramanathan[13], R Benedict[3], B Weinstock-Guttman[1,2,3]
[1]Jacobs Comprehensive MS Treatment and Research Center, Buffalo, NY, United States, [2]New York State MS Consortium, Buffalo, NY, United States, [3]SUNY University of Buffalo School of Medicine and Biomedical Sciences, Department of Neurology, Buffalo, NY, United States, [4]MS Center of Northeastern New York, Latham, NY, United States, [5]SUNY-Stony Brook MS Comprehensive Care Center, Neurology, Stony Brook, NY, United States, [6]New York University Langone Medical Center, MS Comprehensive Care Center, New York, NY, United States, [7]University of Rochester Medical Center, Department Neurology, Rochester, NY, United States, [8]SUNY Upstate Medical University, Neurology, Rochester, NY, United States, [9]Winthrop University Hospital, Winthrop Comprehensive MS Care Center, Mineola, NY, United States, [10]Alpha Neurology, Staten Island University Hospital, Staten Island, NY, United States, [11]Albany Medical College, Neurology, Albany, NY, United States, [12]Buffalo Neuroimaging Analysis Center, Buffalo, NY, United States, [13]SUNY - Buffalo Pharmaceutical Sciences, Neuroscience, Buffalo, OK, United States

Background: Multiple sclerosis (MS) patients progress at varying rates related to different underlying pathological processes. Currently, there are no established early sensitive measures that can predict long-term progression.

Objectives: To identify clinical characteristics associated with rapid progression and validate the most sensitive and clinically relevant outcome measures that can be used to predict long term progression.

Methods: The Progression Risk (PR) study is a prospective study aiming to enroll an early (≤5 years from symptom onset) MS cohort of relapsing remitting (RR) and primary progressive (PP) MS patients. Collected data includes clinical, MRI, neurocognitive and gene-environment measures from 10 MS centers part of the New York State Multiple Sclerosis Consortium (NYSMSC). The present analysis is based on a preliminary sample of 243 patients evaluated at baseline, 163 with 6-months, and 126 with 12-months follow-up. EDSS worsening was defined as a sustained (for 6 m) increase of ≥1 or ≥0.5 based on baseline EDSS (i.e. < 6 or≥6 respectively), while Timed 25 Foot Walk (T25FW) as sustained ≥ 20% worsening.

Results: Of the 243 patients with EDSS scores available at baseline, 205 (84.4%) had an EDSS score of ≤3.5 while 38 (15.6%) had baseline scores of >3.5. Those with higher baseline EDSS scores were older at study enrollment (48.1 ± 11.0 vs 40.2 ± 12.0, p< .001), more likely to be African-American (28.9% vs 12.7%, p=.011), less likely to have a college education or greater (61.5% vs 80.7%, p=.031), more often diagnosed with PPMS (23.7% vs 2.4%, p< .001) and more likely to smoke (53.8% vs 30.3%, p=.019) compared to patients with an EDSS ≤3.5. Of the126 patients with one-year follow-up data available 14 (13.7%) showed EDSS worsening at 6 months of which 4 (28.6%) had sustained worsening measured at 12-month. Eight patients had a 20% increase in T25FW at 6 months compared to baseline, of which 75% showed sustained worsening at 12 months. In the EDSS worsening group 78.5% were RRMS.

Conclusions: Preliminary results suggest that T25FW change may be more sensitive to measure sustained worsening than EDSS scores in RR patients. Our prospective study can advance the

understanding and improve identification of clinical, MRI, genetic and environmental interactions that are associated with increased risk of disease progression. Additional follow-up data including MRI, visual, cognitive and patient reported data will be available at the time of presentation.

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Vitamin D is associated with degree of disability in patients with fully ambulatory relapsing-remitting multiple sclerosis

E Thouvenot[1,2], M Orsini[3], J-P Daures[3], W Camu[4,5]
[1]CHU Carémeau, Neurology Department, Nimes, France, [2]Institut de Génomique Fonctionnelle, UMR 5203, Université Montpellier 1 et 2, Montpellier, France, [3]University Institute of Clinical Research, Université Montpellier 1, Laboratory of Biostatistics, Epidemiology and Public Health, Montpellier, France, [4]CHU Gui de Chauliac, Neurology Department, Montpellier, France, [5]INSERM U 1051, Université Montpellier 1, Montpellier, France

Background: Vitamin D deficiency is a recognized risk factor for multiple sclerosis (MS) and is associated with increased disease activity. It has also been proposed that the lower the vitamin D levels the higher was the handicap.

Objectives: To refine the links between vitamin D insufficiency and disability in MS patients and investigate the potential prognostic role of vitamin D in MS.

Methods: We performed a retrospective cohort analysis of 181 patients: data included age, gender, age at MS onset, MS type, MS activity, Expanded Disability Status Scale (EDSS) and plasma vitamin-D levels.

Results: Vitamin D levels were significantly higher in relapsing-remitting MS than in progressive forms of MS in multivariate analyses adjusted for age, ethnicity, gender, disease duration and season ($p = 0.0487$). Overall, there was a negative correlation between vitamin D level and EDSS score ($p = 0.0001$, r = -0.33). In relapsing-remitting MS, vitamin D levels were only correlated with disability scores for EDSS< 4 ($p = 0.0012$). Patients with >20ng/mL of vitamin D were 2.78 times more likely to have an EDSS < 4 ($p = 0.0011$, 95% CI:1.49-5.00).

Conclusions: Data support previous works suggesting that vitamin D deficiency is associated with higher risk of disability in MS. Vitamin D levels also correlated with the degree of disability in fully ambulatory patients with relapsing-remitting MS. These additional results support the pertinence of future studies analysing the interest of an early vitamin D supplementation in MS patients to influence evolution of disability.

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Vitamin D and multiple sclerosis: a comparison of serum 25-hydroxyvitamin D with demographic findings and paraclinical outcomes

V Nykvist[1], JL Frederiksen[1]
[1]Glostrup Hospital, University of Copenhagen, Neurology, Glostrup, Denmark

Background: The aetiology of multiple sclerosis (MS) is complex, both genetic traits and environmental factors contribute to MS susceptibility. With improved knowledge about vitamin D´s immune modulating effects has the hypothesis of vitamin D as a protective environmental factor in MS emerged.

Objectives: The study is retrospective with the objective to determine serum 25-hydroxyvitamin D (25-(OH)D) status of MS patients from a geographically well defined area and investigate correlations to demographic and paraclinical findings.

Methods: Data used is from the Main Sclerosis Database at Glostrup Hospital, including 554 consecutive patients from the uptake area with a registered serum 25-(OH)D level. Serum 25-(OH)D was compared to demographic findings and paraclinical outcomes, sample groups ranged between 28-554 patients. Analyses where additionally performed on date-adjusted paraclinical data (+/- 30 days) to the date of serum 25-(OH)D measure, sample groups ranged between 9-50 patients. Categorical data was analyzed using Qui-square test and quantitative data was analyzed using Spearman´s correlation. Significance was defined as a p-value < 0.05.

Results: Our study showed a seasonal (P=0.014) and monthly (Speraman´s rho (SR)=0.127; P=0.003) variation in distribution of serum 25-(OH)D. Age was positively correlated to increasing serum 25-(OH)D (SR=0.155; P< 0.001), vitamin D supplementation could possible explain this. Likewise was age at time of onset and increasing serum 25-(OH)D correlated (SR=0.090; P=0.035). There was no significant relation with sex, month of birth, course of disease or Kurtzke Score. A negative correlation was found with immunoglobulin G (IgG) index in cerebrospinal fluids (CSF) and serum 25-(OH)D (SR=-0.302; P=0.035). In contrary, a higher number of demyelinising medullar MRI lesions were correlated to increased serum 25-(OH)D (SR=0.479; P=0.033). Both correlations were found in the date-adjusted material, which was weakened by smaller sample sizes. The number of cerebral MRI lesions were not significantly related to serum 25-(OH)D, although a trend was seen (SR=0.318; P=0.087). No significant differences were found with CSF oligoclonal bands, CSF leucocytes, evoked potentials or body mineral density.

Conclusions: Decreasing IgG index was correlated to increasing serum 25-(OH)D, which implies a protective role of vitamin D. Although, further investigations, preferentially longitudinal prospective studies, are required to approach vitamin D´s future role in treatment and prevention of MS.

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Is relapsing-remitting MS a benign disease?

LA Rolak[1], S Anderson[1]
[1]Marshfield Clinic, Marshfield, WI, United States

Background: The extent to which disability in MS arises from relapses (as opposed to secondary progression) remains uncertain, due in part to conflicting data from existing studies.

Objectives: To clarify the nature of disability produced by MS relapses.

Methods: We prospectively recorded every relapse in every MS patient seen at the Marshfield Multiple Sclerosis Center for 3 years (2011-2013). Relapses were defined as an abrupt symptom producing a change of 1 step or more in at least one Functional System, lasting at least 24 hours. Expanded Disability Status Scale (EDSS) scores were also recorded for each patient.

Results: The 754 relapsing-remitting MS patients had 186 relapses, for an anuual relapse rate of 0.25. 483 patients (64%) were being treated with a disease-modifying therapy (DMT). 74% of all relapses were treated with steroids. Prior to their relapse, the mean EDSS of all patients was 0.6 and 82% of patients had an EDSS of zero. The average EDSS score during a relapse worsened to 3.4. Then 83% of relapses recovered back to baseline, which took 6 weeks (range 1-20). 17% of relapses left permanent disability but with an average EDSS worsening of only 2.5. Only one patient became disabled (EDSS=6). The most common symptom was numbness (58%) followed by optic neuritis (16%). Patients treated with a DMT were only half as likely to have a relapse, but paradoxically the most disabling relapses occured in treated patients. 92% of all patients continued to work without missing any days of employment.The average cost of a relapse, including lost wages and non-medical expenses was $4,505. The average yearly cost of a DMT was $57,540.

Conclusions: The majority of patients with relapsing-remitting MS are normal (EDSS=0) before and after their relapse. Most relapses are mild, sensory, and transient. Over 3 years of observation only 31 (4%) of 754 patients had sustained worsening due to a relapse and only one became disabled. Thus, MS relapses can be distressing and occasionally disabling but they are ultimately benign in most patients.

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Specific clinical phenotypes of relapsing multiple sclerosis based on disease activity

EJ Gettings[1], CT Hackett[1,2], CJ Schramke[1,3], TF Scott[1,3]
[1]Allegheny General Hospital, Neurology, Pittsburgh, PA, United States, [2]University of South Carolina, Columbia, SC, United States, [3]Drexel University College of Medicine, Pittsburgh, PA, United States

Background: Progression occurring with or without clinical relapses creates complex patterns of disease course in individual patients which nonetheless may be stratified according to such patterns.

Objectives: To identify and characterize clinical phenotypes of relapsing multiple sclerosis (MS) in a longitudinally designed retrospective study. We aimed to examine progression of disability over a number of years with particular attention to the possible contribution of relapse activity and severity to this progression.

Methods: We recorded the clinical course of MS in groups of patients followed soon after initial diagnosis under the following clinical phenotypes: relapse-associated progression; progression without relapses (pure progression); relapse-associated progression and progression without relapses (mixed); relapse without progression (non-sustained progression); and no relapses or progression (disease free). The patients were further categorized as above according to five-year epochs of disease duration.

Results: Of 176 patients followed longitudinally for 12.6±4.2 years, 92.6% (163/176) experienced some type of progression in their first 5 years of MS. Significantly less patients, 47.7% (84/176), suffered progression in the following five years of disease duration. Patients primarily progressed via relapse-associated progression in the first epoch, 65.6% (107/163), with equal amounts of pure and mixed progression, 17.2% (28/163), in each group. Eleven patients (6.3%) were disease free in the first

epoch. In the second epoch, the majority of progressing patients, 61.9% (52/84), did so by pure progression with 29.8% (25/84) relapse-associated progression and 8.3% (7/84) mixed progression. A large portion of patients, 28.4% (50/176), were disease free in the second epoch. The mixed group was the most severe phenotype, with the highest relapse rate in epoch 1 (p < 0.001) and epoch 2 (p< 0.001). The mixed group also remained more disabled at final sustained visit in epoch 1 (p=0.04) and epoch 2 (p=0.03). Patients with no disease progression in the first epoch had a significantly lower final sustained MS Severity Score (MSSS), p< 0.001, compared to the progressive group.

Conclusions: We were able to identify multiple specific phenotypes of MS according to relapse type and progression. Identification of phenotypic patterns of disease course may be especially important in the treatment era of MS, as treatment response to all or some immune-modulating agents may vary according to clinical phenotypes.

Experimental models

P374

The CNS barriers differentially regulate the migration of B-cells

L Michel[1], JI Alvarez[1], H Kebir[1], L Bourbonnière[1], J Poirier[2], P Duquette[2], A Bar-Or[3], J Gommerman[4], A Prat[1,2]
[1]CRCHUM, Neurosciences, Montréal, QC, Canada, [2]Notre Dame Hospital, Neurology, Montréal, QC, Canada, [3]Mc Gill University, Neurology and Neurosurgery, Montréal, QC, Canada, [4]Toronto University, Immunology, Toronto, ON, Canada

Background: Multiple Sclerosis (MS) is classically considered as a T lymphocyte- mediated autoimmune disease. However, the efficacy of therapies targeting B cells and the presence of lymphoid follicles within the meninges of some SPMS patients, plead for an important role of B lymphocytes in MS physiopathology.

Objectives: To analyze the interactions of B cells with endothelial cells (ECs) derived from distinct central nervous system (CNS) barriers.

Methods: 15 healthy volunteers (HVs) were included. The expression of cell adhesion molecules (CAMs) and chemokines receptors by *ex vivo* B cells was first analyzed by flow cytometry. Then, transmigration of B lymphocytes was assessed in primary cultures of parenchymal and meningeal ECs that replicate *in vitro* the Blood Brain Barrier (BBB) and Blood Meningeal Barrier (BMB).

Results: The majority of *ex vivo* human B lymphocytes express the chemokine receptors CCR6, CCR7, CXCR3, CXCR4, CXCR5, and CD62L. Ex vivo human B lymphocytes also express VLA-4 (96%), LFA-1 (96.5%) and ALCAM (30%). These ALCAM^{+} B lymphocytes contain significantly more CD19^{+}CD27^{+}/CD24^{hi}CD38^{-} memory B lymphocytes. They were also significantly enriched in markers of activation, such as CD95, CD80 and CD86, as compared to ALCAM^{neg} B cells. ALCAM was not associated with expression of CD5 or with the transitional B lymphocyte phenotype (CD24^{hi}CD38^{hi} B cells).

Trans-endothelial migration assays revealed that BBB tend to be less permissive to B cell migration when compare to the BMB

(10.8% (BMB) vs. 7.1% (BBB)) (n=6 HVs). Interestingly, the use of anti-ALCAM blocking antibodies induced a 25% reduction in the number of migrated B lymphocytes across the BMB (n=3 HVs).
Conclusions: The BMB is more permissive to B cell transmigration as compared to the BBB and ALCAM is likely playing an important role in this process. Our future work aims to study the phenotype of the migrated B lymphocytes to identify additional pathways implicated in their transmigration across distinct CNS vascular beds.

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B7-H1 limits T-cell-mediated brain endothelial cell dysfunction and endothelial barrier disruption in a spontaneous model of CNS autoimmunity

I Kuzmanov[1], V Posevitz[1], S Hucke[1], D Chudyka[1], L Klotz[1], H Wiendl[1]
[1]University Hospital Münster, Department of Neurology, Münster, Germany

Background: Transmigration of activated encephalitogenic T cells across the blood-brain-barrier (BBB) is a crucial step in the disease pathogenesis of central nervous system (CNS) autoimmunity. However, the consequences on brain endothelial cell function upon interaction with such T cells are largely unknown.
Objectives: The aim of our study was to investigate the role of the co-inhibitory molecule B7-H1 on T cells for modulation of brain endothelial cell dysfunction and barrier disruption in the context of CNS autoimmunity.
Methods: To this end, we developed an assay that allowed continuous evaluation of endothelial cell function and barrier integrity upon immune cell interaction over time by measuring transendothelial cell resistance and capacitance correlated with permeability for soluble molecules as well as immune cell transmigration. Moreover, we made use of a genetically determined model of experimental autoimmune encephalomyelitis in transgenic mice harboring MOG specific T and B cells (so-called Devic mice) to elucidate the relevance of B7-H1 in spontaneous CNS autoimmunity.
Results: Activated but not naïve MOG-reactive T cells caused endothelial cell dysfunction characterized by reduced transendothelial electrical resistance (TEER) and increased permeability for soluble molecules. Importantly, lack of the co-inhibitory molecule B7-homologue 1 (B7-H1) on T cells strongly augmented endothelial barrier dysfunction and enhanced T cell transmigration, thus pointing to an unexpected role of B7-H1 for modulation of T cell / endothelial cell interactions.

In our spontaneous model of CNS autoimmunity, lack of B7-H1 resulted in earlier disease onset and significantly increased disease severity, although cytokine responses were not altered. Intriguingly, we observed that Devic mice lacking B7-H1 not only exhibited characteristic spinal cord infiltrates but frequently displayed meningeal and parenchymal T cell infiltrations in the brain and cerebellum - CNS areas typically spared in this model, thus indicating that the propensity of encephalitogenic T cells to break through the BBB is enhanced in these mice.
Conclusions: Together, our data point to a novel and important role of B7-H1 on T cells in the context of CNS autoimmunity by limiting T cell-mediated endothelial cell dysfunction and BBB disruption. Treatment strategies limiting such T cell-mediated endothelial cell dysfunction thus represent a novel promising approach for control of CNS autoimmunity.

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Serpine1 is a negative regulator of experimental autoimmune encephalomyelitis

M Rangachari[1], N Boivin[1], A Chen[2], C Zhu[3], VK Kuchroo[3]
[1]Centre de Recherche du CHU de Québec, Quebec, QC, Canada,
[2]Stony Brook School of Medicine, Stony Brook, NY, United States,
[3]Brigham & Women's Hospital, Boston, MA, United States

Background: Serine protease inhibitor clade E member 1 (Serpine1) is a serine protease inhibitor that inhibits the conversion of plasminogen to mature plasmin by negatively regulating the activity of the proteases urokinase and tissue plasminogen activator (tPA). *Serpine1^{-/-}* T cells display exacerbated production of IFNγ and a polymorphism in the Serpine1 promoter, which correlates with reduced Serpine1 serum expression, has been linked genetically to the increased incidence of multiple sclerosis (MS). These findings suggest that Serpine1 can repress central nervous system (CNS) autoimmunity. However, its function in modulating the severity of EAE has not been studied.
Objectives: Our goal was to assess the role of Serpine1 in Th1 cell-mediated adoptive transfer models of EAE, as well as a model of active immunization.
Methods: We used retrovirally (RV)-mediated gene delivery to overexpress Serpine1 in 2D2 CD4+ T cells, which express a transgenic T cell receptor that bears specificity to myelin oligodendrocyte glycoprotein epitopes 35-55 (MOG$_{[35-55]}$). We transferred the RV-infected cells to *Rag1^{-/-}* mice to assess their ability to transfer EAE. To assess the role of Serpine1 in the context of actively induced EAE, we immunized *Serpine1^{-/-}* mice with MOG$_{[35-55]}$ in complete Freund's adjuvant. T cell function was analyzed by [^{3}H]-thymidine incorporation, flow cytometry for surface or intracellular antigens, and ELISA.
Results: We find that RV-mediated overexpression of Serpine1 in Th1 cells substantially reduces IFNγ and TNFα production, while increasing their generation of immunoregulatory IL-10. Serpine1-overexpressing 2D2 Th1 cells induced EAE of delayed onset and reduced severity relative to controls. MOG$_{[35-55]}$-immunized *Serpine1^{-/-}* mice are impaired in their ability to recover from EAE. Further, 5 of 19 *Serpine1^{-/-}* x 2D2 mice developed spontaneous EAE characterized by numerous leukocytic foci in the spinal cord, as well as optic nerve inflammation.
Conclusions: Our data indicate that Serpine1 negatively regulates Th1 responses and inhibits T-cell mediated EAE.

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MR molecular Imaging of VCAM-1 in EAE mice treated by statin: a new perspective for diagnosis and therapeutic management

M Gauberti[1], A Montagne[2], D Vivien[1], G Defer[1,3], F Docagne[1], R Macrez[1]
[1]Inserm U 919, University of Caen, Caen, France, [2]University of Southern California, Los Angeles, CA, United States, [3]University Hospital of Caen, Neurology, Caen, France

Background: Today MR diagnosis and therapeutic assessment of multiple sclerosis (MS) is only based on quantification of contrast-enhancing lesions and change of lesion load.
Objectives: Developing new tools for improving sensitivity of imaging in MS could provide valuable information for disease physiopathology and therapeutic assessment. Leukocytes

recruitment is mediated by adhesion molecule expressed on endothelial-cells. Especially VCAM-1 because its concentration is correlated to disease activity and overexpression (one of the most early event in the disease course). Therefore imaging VCAM-1 expression may represent a new approach of MS disease.

Methods: We validated the use of IV anti-VCAM-1 antibodies conjugated to 1μm sized MPIO to detect in vivo VCAM-1 expression in a EAE-mice MOG model at different stages of the disease. VCAM-1 expression was quantified using 3D T2*-weighted gradient echo imaging with flow compensation to visualize MPIOs carrying antibodies for brain, cerebellum and spinal cord and correlated to clinical scores. To evaluate the usefulness of the technique to assess drug effect on VCAM-1 expression, we test the impact of atorvastatin on the model at three different time (+10, 15 and 21D post-EAE induction, n=5/ group/ time). Atorvastatin has been described to decrease the expression of VCAM-1.

Results: We demonstrated that T2* weighted imaging with VCAM1 targeted MPIOs detects disease onset before any appearance of clinical symptoms. Subsequently, we observed increasing density and spatial extend of MPIOs binding together with aggravation of clinical symptoms: at disease onset, VCAM-1 detection spares the cerebellum and brain. When clinical symptoms appear, MPIOs binding extends already from the brain and cerebellum to the spinal cord. MPIO-VCAM-1-induced contrast reaches its maximum when mice were graded 4 to the EAE CS. During remitting phase, MPIOs binding decreases gradually but remains higher than in control mice even one month after disease activity peak. Atorvastatin induced a significant reduction of VCAM-1 expression on the whole central nervous system especially at the spinal cord level.

Conclusions: We demonstrated that molecular MRI of VCAM-1 allows non-invasive assessment of early step of disease activity. This new tool provides additional information inaccessible to conventional used MRI techniques. A successful translation from bench to bedside could raise new avenue in trial design, treatment and MS patients' management.

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ATX-MS-1467 reduces MRI lesions and prevents disease progression in a humanized mouse model of multiple sclerosis

D Graham[1], S Huang[1], J-K Choi[2], S Rudin[1], D Yu[1], B Jenkins[2], J Mandeville[2], G Dai[2], R Chang[1], B Tomkinson[1], T Dellovade[1]
[1]EMD Serono Research and Development Institute, Inc., Neurology eTIP, Translational & Biomarker Research Group, Billerica, MA, United States, [2]Massachusetts General Hospital, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, United States

Background: ATX-MS-1467 (ATX), a mixture of 4 antigen-processing independent epitopes of human myelin basic protein (MBP), selected based on immunodominant epitopes in multiple sclerosis (MS) patients with human leukocyte antigen (HLA) haplotypes DRB1*1501 and DQB1*0602. ATX is a new therapeutic under investigation in clinical trials. Experimental autoimmune encephalomyelitis (EAE) induced in humanized mice engineered to express the above HLA haplotypes is a suitable model to evaluate the therapeutic potential of ATX. MRI can provide real-time assessment of ATX effects on lesion development and blood-brain barrier (BBB) leakage.

Objectives: Evaluate the treatment effects of ATX on BBB leakage using MRI in the humanized mouse EAE model of MS.

Methods: EAE was induced with spinal cord homogenate in double-transgenic (human HLA-DR15/MBP-specific T-cell receptor) mice. In non-treated EAE mice (N=21), MRI was performed at 7, 10, 14 or 22 days post-injection (dpi) to determine optimal time point for subsequent studies with ATX. In a separate group of mice (N=18), treatment with ATX (100 μg/mouse, subcutaneously) or vehicle (phosphate-buffered saline [PBS]) began at induction and was administered 3x/week until 14 days dpi. Disease severity was monitored daily (subjective 0-5 point scale); MRI was performed during the peak of disease (12, 13 or 14 dpi). T1-weighted (T1W) gadolinium-enhancing (Gd+) and T2-weighted (T2W) MRI was used to examine the effects of ATX on BBB leakage and lesion development, respectively.

Results: In non-treated EAE animals, clinical disability first appeared in 20% of animals at ~7 dpi and 100% of animals by 10 dpi. BBB leakage was detected in 15% of animals at 7 dpi, but in 100% of animals by 10 dpi. T2W MRI confirmed the presence of spinal cord lesions in non-treated EAE mice. Treatment with ATX initiated at the time of induction reduced clinical disability compared with PBS-treated animals (p< 0.05) and prevented T1W Gd leakage in the cerebellum. ATX-treated mice had a significant reduction in Gd leakage volume (90.2% reduction) and in percent signal change (80.4% reduction) vs PBS-treated animals (p< 0.01). Linear regression analysis revealed a significant correlation between clinical disability and leakage volume (p< 0.01).

Conclusions: Prophylactic treatment with ATX prevents BBB leakage as measured by T1W Gd+ MRI. Data from this preclinical study are consistent with human Phase Ib data, suggesting that such preclinical endpoints may provide predictive information for clinical studies.

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Astrocyte CCL2 sustains immune cell infiltration in chronic experimental autoimmune encephalomyelitis

R Kim[1], N Itoh[1], A Hoffman[1], R Spence[1], Y Ao[1], M Sofroniew[1], R Voskuhl[1]
[1]University of California, Los Angeles, CA, United States

Background: Chemokine (C-C motif) ligand 2 (CCL2), initially identified as monocyte chemoattractant protein-1 (MCP-1), is known to be important in recruiting immune cells to the central nervous system (CNS) during autoimmune inflammation. Since CCL2 can be expressed by multiple cell types, which cell is responsible for CCL2 function *in vivo* during disease in the most widely used multiple sclerosis model, experimental autoimmune encephalomyelitis (EAE), is not known.

Objectives: Determine the role of CCL2 in astrocytes *in vivo* during EAE using *Cre-loxP* gene deletion.

Methods: CCL2 conditional gene deletion knockouts (CCL2-CKO) from astrocytes (astro-CCL2-CKO) were generated by crossing mice of GFAP-cre line 73.12 with mice carrying a CCL2 gene flanked by loxP sites (CCL2flox/flox). Astro-CCL2-CKO and littermate control (WT) mice were induced with active EAE using myelin oligodendrocyte glycoprotein (MOG) peptide 35-55. Immunohistochemistry was first done to demonstrate that CCL2

had been selectively deleted only from astrocytes, then effects of this cell specific gene deletion on levels of inflammation, glial activation, axonal loss and demyelination were determined in spinal cords during EAE.

Results: Mice with a conditional gene deletion of CCL2 from astrocytes had less severe EAE late in disease while having a similar incidence and severity of disease at onset as compared to wild type (WT) control littermates. EAE mice devoid of CCL2 in astrocytes had less macrophage and T cell inflammation in the white matter of the spinal cord and less diffuse activation of astrocytes and microglia in both white and gray matter as well as less axonal loss and demyelination, as compared to WT littermates.

Conclusions: These findings demonstrate that CCL2 in astrocytes plays an important role in the continued recruitment and activation of immune cells in the CNS during chronic EAE, thereby suggesting a novel cell specific target for neuroprotective treatments of chronic neuroinflammatory diseases such as EAE and potentially MS.

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Beneficial effects of short chain fatty acids on the course of experimental autoimmune encephalomyelitis

A Haghikia[1], A Duscha[1], J Berg[1], L Hinz[1], J Thöne[1], S Demir[1], R Gold[1]
[1]Ruhr-University Bochum, Department of Neurology, Bochum, Germany

Background: Despite new insights into the genetics and epigenetics of multiple sclerosis (MS) its etiology, in particular the role that the environment plays is still widely unknown. Lately, the role of the environment within the human organism, the gut microbiome as a potential cause for complex disorders has gained attention. The microbiomic theory has, however, raised new questions, i.e. which factors fundamentally influence the composition of the gut microbiome in individuals and whether nutrition may beneficially influence the microbiome and course of disase.

Objectives: Recent findings suggest that fatty acids may the immune response, and hence, alter the natural course of immune related disorders. We investigated the role of short chain fatty acids (SCFA), in particular propionic acid (PA) on the course of experimental autoimmune encephalomyelitis (EAE).

Methods: MOG-immunized C57/Bl6-mice were either treated with PA from the day of immunization (prophylactic group; n=15), or the solvent (water control group; n=29), or with PA after onset of first EAE symptoms (therapeutic group; n=25) via oral gavage. We then quantified the extent of spinal cord demyelination and neuronal damage and assessed possible changes in immune cell subsets in the peripheral and gut compartment.

Results: We observed a significantly ameliorated course of EAE in the prophylactic group as compared to the water control group. However, the therapeutic group did not reveal any significant differences to the water control group. Within the spinal cord we observed considerably less demyelination and axonal damage in the prophylactic group. So far, our results point to shift towards increased regulatory elements (Foxp3+ CD25+) within the gut compartment.

Conclusions: Our findings suggest that SCFA as shown for PA may influence the course of EAE. First data point to a direct effect of SCFA on regulatory immune cells within the lamina propria of the gut. However, since SCFA are produced by resident gut bacteria from indigestible carbohydrates, e.g. vegetables, the question remains whether the effect seen in our setup may be partially due to the induction/proliferation of a certain phylum or class of bacteria that preferably produce SCFA. If so, change in diet may become an integral part of MS therapy in addition to immunomodulatory drugs.

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Laquinimod prevents disability progression in a model of spontaneous chronic EAE and interferes with the development of follicular helper T-cells

M Varrin-Doyer[1], U Schulze Topphoff[1], K Pekarek[1], RA Sobel[2], SS Zamvil[1]
[1]University of California, Neurology, San Francsico, CA, United States, [2]Stanford University, Pathology, Stanford, CA, United States

Background: Laquinimod is a novel oral agent with immunomodulatory properties that is being developed for the treatment of relapsing-remitting multiple sclerosis (RRMS) and other inflammatory and neurodegenerative diseases. In two Phase 3 RRMS clinical trials, laquinimod has shown to be efficacious in reducing disease activity and progression. Previously, we demonstrated that laquinimod modulates adaptive T cell immune responses via its effects on antigen presenting cells (APC), including CD11c+CD4+ dendritic cells (DC) that are known to participate in the generation of T follicular helper (Tfh) cells. Tfh cells are critical in B cell differentiation, germinal center formation and IgG class switching.

Objectives: Here, we investigated the effect of laquinimod on the generation of Tfh cells and the associated B cell differentiation in active EAE and in spontaneous opticospinal EAE (OSE).

Methods: Acute EAE was examined in C57BL/6 mice by immunization with recombinant MOG. Spontaneous EAE was evaluated in MOG-specific TCR transgenic (2D2) x MOG-specific BCR knock-in (Th) mice, which develop chronic OSE.

Results: In acute EAE, laquinimod treatment was associated with decreased frequency of Tfh cells and reduced expression of BCL6, a transcriptional repressor that directs Tfh differentiation. Inhibition of Tfh differentiation by laquinimod was dependent upon its effects on APC. Production of interleukin (IL)-21,a Tfh cytokine that contributes to the formation and function of GC, was reduced upon treatment. Laquinimod also induced a decreased frequency of germinal center (GC) B cells that paralleled a reduction in anti-MOG IgG antibodies and clinical EAE. Oral laquinimod treatment reduced the incidence and severity of spontaneous OSE and was associated with reduction in Tfh cells, anti-MOG IgG antibodies and formation of meningeal follicle-like structures. When administered after onset, laquinimod inhibited progression of spontaneous OSE. This effect was also associated with decreased frequency of Tfh and GC B cells.

Conclusions: Laquinimod treatment of active EAE or spontaneous OSE interfered with the generation of Tfh cells, maturation of germinal center B cells and production of anti-MOG IgG. These findings indicate that laquinimod may be beneficial in modulating T-B interaction associated with MS progression.

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Oxysterols regulate T lymphocytes trafficking during experimental autoimmune encephalomyelitis

F Chalmin[1], V Rochemont[1], C Lippens[1], D Merkler[1], S Hugues[1], C Pot[1,2]

[1]Geneva University, Department of Pathology and Immunology, Geneva, Switzerland, [2]Geneva University Hospitals, Division of Neurology, Geneva, Switzerland

Background: Serum oxysterols levels have been proposed as candidate biomarkers for neurological diseases such as Multiple sclerosis (MS). Oxysterols, oxidised forms of cholesterol, have recently been shown to modulate immune response. The enzyme cholesterol 25 hydroxylase (Ch25h) is the rate limiting step to synthetize 7α,25-dihydroxycholesterol (7α,25-OHC) from cholesterol. In addition to its basic metabolic properties in bile synthesis and sterol transportation, 7α,25-OHC guides macrophages, dendritic cells and B cells within germinal centers. However how oxysterols modulate adaptive immunity is largely unknown and their role in autoimmunity has not been evaluated.

Objectives: We proposed to assess the role of oxysterols and of Ch25h in the pathogenesis of experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis and to investigate the underlying mechanisms.

Methods: EAE model with MOG_{35-55} peptide was performed in wild-type and Ch25h^{-/-} mice on C57Bl6 background. Migration assays were further conducted both *in vitro* with transwell assays and *in vivo* using chimeric mouse models .

Results: We report that deletion of Ch25h attenuated EAE disease course by limiting pathogenic T lymphocytes trafficking to the central nervous system (CNS). Mechanistically, we show a critical involvement for oxysterols in recruiting leukocytes into inflamed tissues and show that 7α,25-OHC preferentially promotes the migration of subset of inflammatory T lymphocytes both *in vitro* and *in vivo*.

Conclusions: Collectively, our results revealed a critical involvement for oxysterols in the development of EAE and for T lymphocytes trafficking. Overall, not only these findings highlight a pro-inflammatory role of oxysterols during EAE, but identify oxysterols as potential therapeutic targets to inhibit development of autoimmunity.

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Development of a cortical lesion in a new rat model of focal inflammatory demyelination in serial MRI

S Hochmeister[1], T Birngruber[2], MZ Adzemovic[3], M Haindl[1], F Fazekas[1], S Ropele[1], F Sinner[2]

[1]Medical University Graz, Department of Neurology, Graz, Austria, [2]Joanneum Research, Graz, Austria, [3]Karolinska Institute, Center for Molecular Medicine, Stockholm, Sweden

Background: While cortical demyelinating lesions significantly contribute to disease severity and cognitive impairment especially in later stages of multiple sclerosis (MS), they can be hardly detected by conventional MRI. Moreover, in the common model of MS in the rodent, the Experimental Autoimmune Encephalomyelitis (EAE), cortical lesions occur only occasionally, further complicating investigation.

Objectives: The aim of our explorative study was to follow up the development of cortical lesions in the neocortex of the rat using serial MRI and subsequent confirmation through histological analysis.

Methods: Using the cerebral open microperfusion (cOFM) catheter, a novel minimal invasive MRI compatible device implanted in the neocortex of the rat, we were able to predictably produce an inflammatory demyelinating cortical lesion in direct vicinity of the catheter implantation site. After implantation of the cOFM probe and a healing period of two weeks, rats were subclinically immunized with Myelin Oligodendrocyte Glycoprotein (MOG) in incomplete Freund's adjuvant. After establishing a stable IgG-antibody titre against MOG, the blood brain barrier was selectively opened by insertion of 250ng recombinant TNF-alpha and 150U IFN-g in phosphate buffered saline via the cOFM. This resulted in a selective opening of the blood brain barrier (BBB), influx of the anti-MOG antibodies and the formation of an inflammatory demyelinating lesion in direct vicinity of the cOFM catheter. MRI was performed before and 3, 6 and 10 days after opening of the BBB with the catheter in place to depict the development of the lesion. Proton density and T2 weighted MRI (in-plane resolution 150x150 mm) was performed at 3 Tesla using dedicated planar surface coils. Following MRI, animals were sacrificed and the brains underwent extensive histological analysis.

Results: Histology revealed that first minimal inflammatory changes are detectable on day 3 after opening of the BBB and are fully established after day 6. At day 10, a fully demyelinating lesion was established which could also be detected by T2 weighted MRI.

Conclusions: Our approach allows to predictably induce a single inflammatory demyelinating lesion in the neocortex of the rat which can be monitored non-invasively with high resolution MRI. Together, this setting opens new avenues to better understand MR contrast of cortical lesions in MS and to monitor also cOFM administered therapy.

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Effects of isoxazolo-pyridinone 7e, a potent activator of the Nurr1 signaling pathway, on experimental autoimmune encephalomyelitis in mouse

F Montarolo[1], C Raffaele[2], S Perga[1], S Martire[1], A Finardi[2], R Furlan[2], S Hintermann[3], A Bertolotto[1]

[1]Neuroscience Institute Cavalieri Ottolenghi (NICO), University Hospital S. Luigi Gonzaga (CReSM), Orbassano, Italy, [2]Experimental Neurology Institute (INSPE), Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy, [3]Novartis Institutes for BioMedical Research, Global Discovery Chemistry, Basel, Switzerland

Background: Multiple sclerosis (MS) is an autoimmune disease affecting central nervous system, in which Th1/Th17 cells are involved. Gene expression profiling showed that Nurr1, an orphan nuclear receptor involved in Th17 differentiation, is down-regulated in peripheral blood mononuclear cells of MS patients. Furthermore, Nurr1 exerts anti-inflammatory effects resulting in clearance of NF-kB and transcriptional repression. Nevertheless, its role in MS has not yet been clarified.

Objectives: To better characterized the role of Nurr1 in MS, in this study we show the effect of a potent activator of the Nurr1

signaling pathway, isoxazolo-pyridinone 7e (IP7e), in a chronic murine model of MS (experimental autoimmune encephalomyelitis, EAE).

Methods: Chronic progressive EAE was induced in 6-8 weeks old female C57BL/6J mice using myelin oligodentrocyte glycoprotein (MOG_{35-55}). Two kind of IP7e gavage twice daily treatment were performed: preventive administration (before disease onset) from 7 to 23 days post immunization (dpi) and therapeutic (after disease onset) from 21 to 36 dpi. Control animals received the Tween 80 dissolved saline solution (0.9 % NaCl) twice daily. During treatments, body weight and clinical score were recorded daily. At the end of treatments, spinal cords were analyzed.

Results: Here, for the first time we report the preventive and the therapeutic effects of IP7e in EAE. We demonstrate that the preventive administration of IP7e delays the onset and reduces the incidence and the severity of EAE, improving neuroinflammatory and -pathological signs in EAE spinal cord of treated mice, whereas EAE course is not influenced by the therapeutic administration. Finally, the preventive administration of IP7e induces a down-regulation of NF-kB downstream genes in spinal cord supporting an inhibiting action on the NF-kB signaling due to a strong activation of Nurr1 pathway when administered before EAE onset.

Conclusions: Our data and the evidences concerning the role of Nurr1 in T cells development and in its anti-inflammatory functions suggest a possible role of this activation pathway in the early phase of EAE, controlling the inflammation and the invasion of immunity component into the parenchyma.

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Neuroanatomical organization and global transcriptome analyses of c-Fos activated astrocytes in EAE lesions, altered by administration of fingolimod

A Groves[1,2], Y Kihara[1], M Mayford[1], J Chun[1]
[1]Scripps Research Institute, La Jolla, CA, United States,
[2]University of California San Diego, Neuroscience, La Jolla, CA, United States

Background: Sphingosine 1-phosphate (S1P), a lysophospholipid, was shown to be relevant to multiple sclerosis (MS) therapeutics through oral fingolimod (FTY720), an S1P analog that upon phosphorylation can interact with four of five S1P receptors (S1PRs), $S1P_{1,3-5}$. In addition to effects of lymphocyte retention in secondary lymphoid organs, fingolimod can enter the CNS to access S1PRs, notably $S1P_1$ on astrocytes, to produce internalization and functional receptor loss associated with fingolimod efficacy. Removal of $S1P_1$ on astrocytes ameliorates EAE severity and eliminates fingolimod efficacy, illustrating a key role of astrocytic S1P signaling in EAE and likely MS. A transgenic mouse that reports neural cell activation *in vivo* was developed whereby activated cells expressing the intermediate early gene (IEG) c-Fos are semi-permanently marked by green fluorescent cells (GFCs), and after EAE, astrocytes were labeled.

Objectives: To interrogate EAE-activated astrocytes for neuroanatomical 3-D organization and global transcriptome changes when altering astrocytic $S1P_1$ signaling by of fingolimod or genetics.

Methods: c-Fos GFCs were analyzed after monophasic EAE, and studied by advanced 2-photon microscopy, while fluorescence-activated cell sorting was used to isolate cell types for transcriptional analysis using RNA-seq.

Results: During acute EAE, astrocytes were activated in discrete areas of the spinal cord, consistent with EAE lesion sites having spheroid dimensions. Activated astrocytes in the spinal cord were linearly correlated with EAE clinical score. Administration of fingolimod reduced the number of activated astrocytes while tracking with reduced clinical score. Astrocytic transcriptional changes occurred upon development of EAE signs, administration of fingolimod, and the selective removal of $S1P_1$ on astrocytes.

Conclusions: The c-Fos reporter mouse identified activated cell lineages during EAE that were predominantly astrocytes. This activity was responsive to S1P signaling disruption by fingolimod exposure or genetic removal of $S1P_1$ on astrocytes. Lesion sites were visualized. Transcriptome changes during EAE and in response to fingolimod were also determined. These data implicate specifically activated astrocytes in geometrically defined lesion sites that show distinct transcriptome changes in EAE and during fingolimod exposure, implicating direct, cell autonomous molecular changes occurring in astrocytes that are activated by S1P signaling and ameliorated by exposure to fingolimod.

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The lesion localization of passive transfer NMO-IgG model in Lewis rats

K Kurosawa[1], T Misu[2], Y Takahashi[1], D Sato[1], S Nishiyama[1], H Kuroda[1], I Nakashima[1], K Fujihara[1], M Aoki[2]
[1]Tohoku University Graduate School of Medicine, Department of Multiple Sclerosis Therapeutics, Sendai, Japan, [2]Tohoku University Graduate School of Medicine, Department of Neurology, Sendai, Japan

Background: Neuromyelitis optica (NMO) is an autoimmune disease associated with NMO-IgG, which targets aquaporin 4 (AQP4) mainly localized at astrocyte endfeet in the central nervous system. In NMO patients, hypothalamic and brain stem lesions in addition to optic nerves and spinal cords are well observed. In contrast, it´s well known that loss of AQP4 compatible with human NMO pathology could be mainly observed in spinal cords or cerebrum by passive transfer model or direct injection model, and the systemic study of lesion localization in vivo model has never been studied sufficiently.

Objectives: To study the lesion localization of passive transfer NMO-IgG model in Lewis rats.

Methods: Human-IgG was purified from NMO patients and control serum, using protein A beads. Purified IgG with complement inactivated by 56℃ 30 minutes were used for this study. 13 female Lewis rats (8～10 weeks of age) were immunized with an encephalitogenic mixture containing guinea pig brain myelin basic protein in complete Freund's adjuvant supplemented with of H37 Ra *Mycobacterium Tuberculosis* for the purpose of breaking down blood brain barrier. Then the rats were infused 20mg of purified NMO-IgG (n=8) and control IgG (n=5) intraperitoneally at the onset of tail paresis or body weight loss more than 10mg/day. We dissected the animals within 3days from the infusion and studied systematically the whole brain and spinal cord.

Results: In NMO-IgG infused rats, vasculocentric AQP4 loss were found in cerebral white matter near ventricles (6/7), hypothalamus (3/7), brain stem (8/8), optic chiasma (3/6), optic tract

(2/6) and spinal cord (8/8), but never observed in cerebral and cerebellar gray matter. AQP4 loss was outstandingly observed around gray matter adjacent to border between gray matter and white matter in spinal cord lesions as well as hypothalamic or chiasma lesions. Spinal cord lesions were severe especially in lumbar cords, - but there is no marked demyelination as previously reported. In control-IgG infused rats, there was no marked loss of AQP4 as above mentioned.

Conclusions: We revealed that AQP4 loss was observed at cerebral white matter, hypothalamus, brain stem, optic tract, chiasma and spinal cord by passive transfer NMO-IgG model in Lewis rat, which is compatible with the lesion distribution in NMO patients.

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Laquinimod prevents NMOIg-induced disease exacerbation in a model of neuromyelitis optica

AT Argaw[1,2,3], L Asp[1,2,3], J Zhang[1,2,3], VJ Cogliani[1,2,3], P Waters[4], P Hayardeny[5], M Levy[6], GR John[1,2,3]
[1]Icahn School of Medicine at Mount Sinai, Corinne Goldsmith Dickinson Center for MS, New York, NY, United States, [2]Icahn School of Medicine at Mount Sinai, Friedman Brain Institute, New York, NY, United States, [3]Icahn School of Medicine at Mount Sinai, Neurology, New York, NY, United States, [4]John Radcliffe Hospital, Neuroimmunology Group, Oxford, United Kingdom, [5]Teva Pharmaceuticals, Netanya, Israel, [6]Johns Hopkins Hospital, Neurology, Baltimore, MD, United States

Background: Neuromyelitis optica (NMO) is an autoimmune neurologic disease characterized by a serum autoantibody, NMOIg, which targets the astrocytic water channel aquaporin-4 (AQP4) and causes significant tissue damage upon CNS entry through a disrupted blood-brain barrier (BBB). Current therapies target autoantibody production, but agents that restrict BBB breakdown could provide additional, perhaps synergistic benefits. Recently, we demonstrated that inflammatory BBB disruption is driven in part by reactive astroglial responses, via mechanisms including VEGF-A production and consequent eNOS-dependent downregulation of endothelial BBB tight junctions.

Objectives: Here, we now show that inhibition of innate immune responses, including astrocytic responses, using the immunomodulator laquinimod, currently in a Phase 3 trial for multiple sclerosis, restricts NMOIg CNS entry and exacerbation of neuropathology and neurologic deficit in a model of NMO.

Methods: C57BL/6 mice immunized with MOG_{35-55} received high-titer NMOIg or control Ig via passive transfer from 14-18dpi, and mice receiving NMOIg were also treated with laquinimod 25mg/kg or vehicle from immunization.

Results: NMOIg severely exacerbated paralysis in MOG_{35-55}-immunized controls, resulting in 50% mortality. In contrast, in laquinimod-treated immunized mice, NMOIg had no exacerbatory effect, and all mice survived. Spinal cords of mice receiving NMOIg displayed severe subpial and perivascular BBB breakdown and endothelial BBB tight junction disruption associated with complement fixation, loss of astrocytic AQP4, oligodendrocyte damage and demyelination. In contrast, in laquinimod-treated mice, neuropathology was greatly reduced. This effect correlated with restriction of BBB disruption in laquinimod-treated animals, and with laquinimod modulation of astrocytic production of inflammatory factors including VEGF-A in human cultures.

Conclusions: Collectively, our data demonstrate that laquinimod treatment prevents disease exacerbation in a model of NMO, and suggest rescue of BBB disruption as one mechanism of action. Use of laquinimod in combination therapy may protect NMO patients from autoantibody entry into the CNS, thus restricting neuropathology and neurologic deficit.

P388

Anti-murine CD52 therapy provides anti-inflammatory and neuroprotective effects in EAE

MJ Turner[1], N Chretien[1], E Havari[1], J Huang[1], P Pang[1], MJ LaMorte[1], C Garron[1], BL Roberts[1], JM Kaplan[1], WM Siders[1]
[1]Neuroimmunology Research, Genzyme, a Sanofi Company, Framingham, MA, United States

Background: Alemtuzumab is a humanized monoclonal antibody that selectively targets CD52, causing depletion of circulating T and B lymphocytes. Depletion is followed by a distinctive pattern of T- and B-cell repopulation, potentially leading to a rebalancing of the immune system. Testing of an anti-mouse CD52 antibody (anti-muCD52) in an experimental autoimmune encephalomyelitis (EAE) mouse model has allowed for further characterization of the impact of anti-CD52 treatment, particularly in the central nervous system (CNS).

Objectives: To investigate the effects of anti-muCD52 treatment in an EAE mouse model of multiple sclerosis (MS) to provide a better understanding of the mechanism of action of alemtuzumab.

Methods: Mice were immunized with myelin-derived peptide to induce EAE and were treated with anti-muCD52 at onset of disease symptoms. Cohorts were evaluated for disease severity as well as for several immunological and neurological readouts including flow cytometry and immunohistochemistry. Axonal damage was assessed by staining for unphosphorylated neurofilament. Electrophysiology studies were performed to functionally assess axonal integrity in the spinal cord.

Results: Administration of anti-muCD52 significantly reduced the severity and progression of disease. Treatment benefit was associated with a reduction in the total numbers of lymphocytes and myelin oligodendrocyte glycoprotein $(MOG)_{35-55}$ autoreactive T cells, as well as reduced levels of inflammatory cytokine production. Neuroprotective effects were also observed as evidenced by a reduction in demyelination and axonal damage in the CNS. Furthermore, axonal conductance, as assessed by measurement of spinal motor evoked potentials, demonstrated a higher peak amplitude as well as reduced peak latency in anti-muCD52-treated mice compared with that in vehicle controls.

Conclusions: Collectively, these results indicate that the therapeutic benefit of anti-muCD52 treatment in EAE can be attributed to a combination of reduced number of autoreactive T cells, decreased CNS inflammation, and protection of CNS integrity.

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Therapeutic testosterone administration ameliorates clinical disability and cortical atrophy in EAE

RD Spence[1], N Itoh[1], CRL Mongerson[1], SH Wailes[1], AJ Wisdom[1], RR Voskuhl[1], A MacKenzie-Graham[1]
[1]University of California, Department of Neurology, Los Angeles, CA, United States

Background: Gray matter atrophy is an important correlate to clinical disability and disease duration in multiple sclerosis (MS). Gray matter atrophy in the cerebral cortex has been shown by MRI in experimental autoimmune encephalomyelitis (EAE), the most widely used model of MS. The clinical severity of EAE is reduced in mice pretreated with testosterone, but it is unknown if testosterone treatment given after disease onset can ameliorate clinical disease or slow cerebral cortical atrophy in EAE.

Objectives: To determine if testosterone treatment given after disease onset can reduce clinical disease and/or slow gray matter atrophy.

Methods: EAE was induced in gonadally intact, male C57BL/6J mice, then, after disease onset, the mice received subcutaneous pellets containing either testosterone or vehicle. 45 days after disease induction, testosterone-treated and vehicle-treated EAE mice and age-matched healthy controls were sacrificed and high-resolution MR images were collected. Volumetry was used to evaluate cortical atrophy. Immunohistochemistry was used to evaluate inflammation, myelination, axonal integrity, and synapses.

Results: Clinical disease scores were significantly improved in testosterone-treated compared to vehicle-treated EAE mice. Volumetry demonstrated a significant 8% decrease in cortical volume in vehicle-treated EAE mice as compared to matched healthy controls, whereas no significant cortical atrophy was observed in testosterone-treated EAE mice. Immunohistochemistry demonstrated significantly reduced inflammation, demyelination, axonal disruption and synaptic loss in testosterone-treated compared to vehicle-treated EAE mice.

Conclusions: These results indicate that testosterone treatment reduces clinical disability and inhibits cortical gray matter atrophy even when administered after disease onset.

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Chondroitin 6-O-sulfate ameliorates experimental autoimmune encephalomyelitis

K Miyamoto[1], R Ueno[1], K Kadomatsu[2], H Kitagawa[3], S Kusunoki[1]
[1]Kinki University School of Medicine, Neurology, Osaka-Sayama, Japan, [2]Nagoya University School of Medicine, Biochemistry, Nagoya, Japan, [3]Kobe Pharmaceutical University, Biochemistry, Kobe, Japan

Background: Chondroitin sulfate proteoglycans (CSPGs) are the main component of the extracellular matrix in the central nervous system (CNS) and influences neuroplasticity. Although CSPG is considered an inhibitory factor for nerve repair in spinal cord injury, it is unclear whether CSPG influences the pathogenetic mechanisms of neuroimmunological diseases.

Objectives: To analyze the role of CSPG in EAE using C6ST1-deficient mice.

Methods: Chondroitin 6-O-sulfate transferase 1-deficient (C6st1$^{-/-}$) mice were induced experimental autoimmune encephalomyelitis (EAE) . C6ST1 is the enzyme that transfers sulfate residues to position 6 of N-acetylgalactosamine in the sugar chain of CSPG.

Results: The phenotypes of EAE in C6st1$^{-/-}$ mice were more severe than those in wild-type mice were. In adoptive-transfer EAE, in which antigen-reactive T cells from wild-type mice were transferred to C6st1$^{-/-}$ and wild-type mice, phenotypes were significantly more severe in C6st1$^{-/-}$ than in wild-type

mice. The recall response of antigen-reactive T cells was not significantly different among the groups. Furthermore, the number of pathogenic T cells within the CNS was also not considerably different. When EAE was induced in C6ST1 transgenic mice with C6ST1 overexpression, the mice showed considerably milder symptoms compared with those in wild-type mice.

Conclusions: The presence of sulfate at position 6 of N-acetylgalactosamine of CSPG may influence the effecter phase of EAE to prevent the progression of pathogenesis. Thus, modification of the carbohydrate residue of CSPG may be a novel therapeutic strategy for neuroimmunological diseases such as multiple sclerosis.

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Adaptive angioplasticity promotes recovery in experimental autoimmune encephalomyelitis

N Esen[1], P Dore-Duffy[1]
[1]Wayne State University, Detroit, MI, United States

Background: Infiltration of immune cells into the CNS in MS may lead to oxygen and glucose deprivation that promotes metabolic stress and tissue injury. Thus protective mechanisms that restore tissue homeostasis and cell plasticity have been shown to promote recovery in models of ischemic injury. One such mechanism is the induction of adaptive angioplasticity induced by exposure to mild stress signals (stress conditioning). We hypothesize that adaptive angioplasticity will ameliorate experimental autoimmune encephalomyelitis (EAE) in mice through a Hypoxia Inducible Factor-1alpha (HIF-1a)/HIF-2a-dependent manner. While the exact mechanisms responsible for HIF-1a-induced protection are unclear it has been shown that the interaction between HIF-1a and reactive oxygen species (ROS) is important for restoring homeostasis. Thus angioplasticity may promote cell survival as a result of restoration of cell and mitochondrial stability and bioenergetic homeostasis.

Objectives: Evaluate the effect of adaptive angioplasty in a neurodegenerative disease model of multiple sclerosis (MS).

Methods: C57BL/6 mice were immunized with MOG35-55 peptide. Following development of clinical symptoms mice were placed in normobaric hypoxia chambers calibrated to 10% oxygen for up to 3 weeks. Clinical scores weight and hematocrit were evaluated daily. Hypoxia level in spinal cords was determined using a hypoxyprobe kit, and immunohistochemical and flowcytometric stainings were done to determine disease pathology, vascular density, and mitochondrial damage in the CNS. ROS levels were assayed through mitochondrial superoxide indicator MitoSOX.

Results: Induction of adaptive angioplasticity in immunized and sham immunized control mice ameliorated the signs and symptoms of chronic EAE during the treatment period. Recovery in the EAE model was HIF-1a-mediated and was associated with evidence of decreased inflammatory activity in the spinal cord and improved tissue oxygen. MitoSox staining as an indicator of ROS production and mitochondrial damage was found decreased in hypoxia exposed animals.

Conclusions: Adaptive angioplasticity promotes recovery of EAE in a HIF-1 dependent manner. Our data suggest that the interaction between HIF-1a and ROS is important for

maintenance of homeostasis and energy balance. Thus angioplasticity may promote cell survival as a result of restoration of cell and mitochondrial stability. Further mechanistic insight may lead to the identification of novel new therapeutic targets for the treatment of MS.

P392
Bringing CLARITY to EAE

RD Spence[1], F Kurth[1], N Itoh[1], CRL Mongerson[1], SH Wailes[1], MS Peng[1], A MacKenzie-Graham[1]
[1]University of California, Department of Neurology, Los Angeles, CA, United States

Background: Gray matter atrophy in cerebral cortex by magnetic resonance imaging (MRI) correlates strongly with disease duration and clinical disability in multiple sclerosis (MS). However, the mechanisms underlying gray matter atrophy remain elusive. Gray matter atrophy in the cerebral cortex has been shown by MRI in experimental autoimmune encephalomyelitis (EAE), the most widely used model of MS.
Objectives: In this study we investigated EAE mice using combined magnetic resonance imaging (MRI) with clear lipid-exchanged acrylamide-hybridized rigid imaging-compatible tissue-hydrogel (CLARITY), a recently developed optical clearing technology that permits microscopic imaging of the entire brain, to better understand these mechanisms.
Methods: EAE was induced in female C57BL/6J mice which were then scanned using in vivo MRI. The mice were sacrificed, their brains and spinal cords optically cleared using CLARITY, and imaged intact using confocal microscopy.
Results: Volumetry demonstrated decreased cerebral cortex volumes compared to healthy controls. Axons were followed longitudinally in intact spinal cords revealing that 61% axons exhibited ovoids in mice with EAE with a mean of 22 ovoids per axon over a 5 mm length. 8% of axons in mice with EAE exhibited end bulbs. Healthy control mice exhibited almost no axonal abnormalities. Layer V cortical neurons were decreased in intact cerebral hemispheres in mice with EAE compared to healthy controls. Cross-modality correlations revealed a direct relationship between cortical volume loss and spinal cord end bulb number, but not ovoid number.
Conclusions: There is a strong direct correlation between cortical atrophy and the number of axonal end bulbs in the spinal cord. Interestingly, there was no correlation between cortical atrophy and axonal ovoid number, suggesting that there is a critical window wherein axons may be damaged, but not yet transected. This is the first report of the use of CLARITY in an animal model of disease and the first report of the combined application of CLARITY with MRI.

P393
The role of glatiramer acetate in mitochondrial dynamics and biogenesis in EAE

CT Bever Jr[1,2], VKC Nimmagadda[1], R Jain[1], SIV Judge[1,2], D Trisler[1,2], TK Makar[1,2]
[1]University of Maryland Baltimore, Neurology, Baltimore, MD, United States, [2]MS Center of Excellence-EAST, VA Maryland Health Care System, Baltimore, MD, United States

Background: Glatiramer acetate (GA) is one of the disease modifying therapies (DMTs) approved for Multiple Sclerosis(MS). Besides being a potent anti-inflammatory drug, it may reduce neurodegeneration, but the mechanism for that effect is not fully understood. Recent evidences suggest the potential role of mitochondria in MS-associated neuronal degeneration. Mitochondria undergo frequent fusion and fission, and the balance of these opposing processes plays a critical role in maintaining functional mitochondria when cells experience metabolic or environmental stresses. Mitochondrial fission facilitates apoptosis, whereas mitochondrial fusion plays a protective role. However, the tendency and molecular basis of mitochondrial dynamic change in the CNS after MS and after GA treatment have not been elucidated.
Objectives: Determine the effect of GA treatment on mitochondrial dynamics and biogenesis in experimental allergic encephalomyelitis (EAE), an animal model for MS.
Methods: EAE was induced in C57Bl/6 female mice by immunization with myelin oligodendroglial glycoprotein peptide 35-55. GA (150 μg/mouse/day) was administered intraperitoneally starting at disease onset. Mice were euthanized on day 20 of GA treatment and lumbar spinal cords were examined histologically.
Results: GA treatment significantly reduced inflammation and demyelination in EAE. More Myelin Basic Protein expression was seen in GA treated EAE spinal cords compared to untreated. GA treated EAE mice showed decreased Mitochondrial Fis1 and DNM1-L (markers of mitochondrial fission) and increased Mito fusion-2 and OPA-1(markers of fusion) compared with untreated EAE mice . GA treatment increased the levels of sirtuin 1 (SIRT1), peroxisome proliferator-activated receptor gamma co-activator 1 alpha (PGC-1α) and nuclear respiratory factor 2 (NRF-2), indicators of mitochondrial biogenesis.
Conclusions: Herein, we show that GA treatment upregulates mitochondrial biogenesis, increases fusion and decreases fission; which correlates with the functional outcome of the disease. These results not only demonstrate a mechanism of action of GA but also provide a good target to prevent neurodegeneration in EAE and MS.

P394
Superior efficacy of glucocorticoid treatment of experimental autoimmune encephalomyelitis in macrophage migration inhibitory factor deficient mice

N Ji[1], TG Forsthuber[2]
[1]University of Texas at San Antonio, San Antonio, TX, United States, [2]University of Texas at San Antonio, Biology, San Antonio, TX, United States

Background: Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine with the unique property of being induced by glucocorticoids (GCs) and the ability to counter-regulate their anti-inflammatory effects. GCs are the standard treatment for acute attacks of multiple sclerosis (MS), however, they eventually lose efficacy and overall do not prevent long-term progression of the disease. Additionally, GC treatment has numerous side effects and some patients develop GC resistance.
Objectives: We wanted to determine whether MIF plays a role in resistance to GC treatment using experimental autoimmune encephalomyelitis (EAE), a common animal model of MS.

Methods: We induced EAE in both Wt and MIF knockout (MIF-/-) C57BL/6 mice followed by the treatment of dexamethasone (Dex) before or upon the onset of disease. Splenocytes and brain mononuclear cells were harvested for cytokine ELISPOT assay, flow cytometry analysis and immunofluorescence staining.

Results: Treatment of EAE with Dex in MIF-/- mice was substantially more efficacious as compared with Wt mice in delaying EAE onset and decreasing disease severity. Dex treatment suppressed inflammatory infiltration in both the brains of Wt and MIF-/- mice; however, the suppression lasted longer in MIF-/- mice once the treatment was stopped. In contrast, antigen-specific cytokine production by T cells was partially suppressed by Dex and slightly affected by MIF deficiency. Importantly, Dex profoundly inhibited the upregulation of transcription factor T-bet in CD4^{+} T cells from the brains of MIF-/- mice as compared with Wt mice. Furthermore, adoptive transfer studies showed that Dex inhibited EAE in MIF-/- mice mainly by downregulating pathogenicity of MOG$_{35-55}$-specific CD4^{+} T cells rather than effects on central nervous system.

Conclusions: Our data suggest that MIF promotes EAE and possibly MS by antagonizing GC effects on the pathogenicity of autoreactive T cell in EAE. MIF may serve as a potential therapeutic target to improve GC treatment for MS, for example using MIF inhibitors.

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Modulation of ARNT2 expression as an indicator of neuronal responses in models of MS

T Rahim[1], A Leung[1], A Yu[1], J Quandt[1]
[1]University of British Columbia, Pathology and Laboratory Medicine, Vancouver, BC, Canada

Background: Multiple sclerosis (MS) is a complex inflammatory neurodegenerative disease, with both demyelination and axonal degeneration contributing to its pathophysiology. Our lab has become interested in ARNT2 (aryl-hydrocarbon receptor nuclear translocator 2), a transcription factor that influences neuronal survival and protection in response to environmental and physiological stimuli.

Objectives: Our objective was to examine the functional relevance of ARNT2 regulation in MS; specifically, to characterize the ability of inflammatory cells or other physiological stimuli to influence ARNT2 expression and associated changes in neuronal viability and function.

Methods: Primary cultures of rat or mouse cortical neurons were enriched from E16-18 rat or mouse embryos. DIV14-17 cultures were treated with excitatory (potassium chloride, 4-aminopryridine), inflammatory or oxidative stimuli and ARNT2 expression was examined by western blotting and immunocytochemistry. Cell viability was examined by analysis of cell/nuclear morphology and release of lactate dehydrogenase (LDH). Mouse neuronal cultures were coincubated with resting or anti-CD3 activated spleen cells to test the influence of soluble inflammatory mediators on ARNT2 expression and cell viability.

Results: Potassium chloride had no effect on ARNT2 expression, whereas 4-aminopyridine enhanced ARNT2 expression by 50% at 3hrs and dropped thereafter. Oxidative stress mimicked by exposure of cells to 30 or 300uM H_2O_2 for increasing periods of time had differential effects on ARNT2 expression. A "stressing" exposure of 30uM briefly increased ARNT2 expression at 1-2 hrs but thereafter had no effect on ARNT2 or LDH levels. 300uM H_2O_2 raised ARNT2 expression very shortly after exposure in a neuroprotective manner, and extended exposure led to a 50% reduction in ARNT2 expression by 4 hours and complete loss of ARNT2 by 8 hrs. This correlated with decreasing nuclear size, retraction of dendrites stained with MAP2, increased levels of LDH release into the media and ultimately cell death. Coincubation of neuronal cells with anti-CD3 activated spleen cells increased ARNT2 expression at about 3 hrs but dropped thereafter as death became apparent.

Conclusions: These studies identify a correlation between ARNT2 expression and inflammatory stimuli which alter neuronal viability and function. Further investigation of this relationship may enable the use of ARNT2 as an indicator of neuronal function and viability during early and late stages of MS pathogenesis.

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The novel Bach1 inhibitor HPP971 uniquely activates Nrf2 and reduces disease severity in a mouse model of experimental autoimmune encephalomyelitis

S-K Kim[1], J Kassis[1], O Attucks[1], J Freeman[1], Z Zhong[1], S Gupta[2], S Victory[2], D Polisetti[2], A Mjalli[2], R Andrews[2], M Kostura[1], M Guzel[2], B Gaddam[2], S Weaver[1], K Sakmann[1], ST Davis[1]
[1]High Point Pharmaceuticals, LLC, Biology, High Point, NC, United States, [2]High Point Pharmaceuticals, LLC, Chemistry, High Point, NC, United States

Background: Pharmacological activation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is an attractive mechanism for the treatment of Multiple Sclerosis (MS) since Nrf2 promotes both neuroprotection and anti-inflammation. Bach1 is the transcriptional repressor of heme oxygenase-1 (HMOX1), an Nrf2-driven cytoprotective gene. Bach1 deficiency in mice confers cytoprotection against spinal cord injury and experimental autoimmune encephalomyelitis (EAE). We therefore designed potent and specific inhibitors of Bach1 to evaluate as a treatment for MS.

Objectives: Determine the pharmacodynamic and therapeutic effects of Bach1 inhibitor HPP971 after oral administration in naïve and EAE mice.

Methods: Recombinant human MBP-Bach1 protein was overexpressed in E.coli and purified using a protein fusion tag. Direct binding of HPP971 was measured using microscale thermophoresis. HMOX1, NQO1, and GCLC gene expression were measured in human astrocytes *in vitro* and in mouse tissues using the Quantigene Reagent 2.0 system (Affymetrix). Human primary astrocytes were treated with HPP971 for 6 hr for reduced glutathione (GSH) measurement and 24 hr for assessment of cytoprotection against H2O2 by propidium iodide staining. In an EAE model, C57Bl/6 female mice were immunized with MOG peptide 35-55/CFA on day 1. HPP971 dosing was on day 2 through day 20. Clinical scores were assessed on days 11-20 (0=no disease, 1=limp tail, 2=affected gait, 3=hind limp paresis, 4=hind limb paralysis).

Results: HPP971 binds human Bach1 protein (K_d=120 nM) and activates HMOX1 expression in an Nrf2-dependent manner. HPP971 acutely elevates GSH levels and protects human

astrocytes from H2O2-induced cell death *in vitro*. HPP971 inhibits IFN-γ-induced MHC class II expression in bone marrow derived macrophages. Oral HPP971 (PO, 20 mg/kg) induces HMOX1 expression in tissues, and attenuated loss of motor functions in a murine EAE model of MS.

Conclusions: Bach1 inhibitor HPP971 exhibits a unique combination of anti-oxidant, cytoprotective and anti-inflammatory properties. HPP971 attenuates pro-inflammatory cytokine production and MHC class II expression. Oral HPP971 was efficacious in the EAE model with activity comparable to Tecfidera™. Bach1 inhibition offers an innovative approach to Nrf2 activation as this mechanism is electrophile-independent and is not predicated on glutathione depletion.

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Characterization of GALT derived lymphocyte with regulatory properties from mice treated with murine antiCD52 antibody

S Begum-Haque[1], AB Pant[1], Y Wang[1], A Haque[1], LH Kasper[1]
[1]*Geisel School of Medicine at Dartmouth, Department of Microbiology/Immunology, Hanover, NH, United States*

Background: The gut associated lymphoid tissue comprises 80% of the immune cells and is the single largest component of the immune system. The GALT serves as an important reservoir for both T and B regulatory cell populations. The interaction between the commensal microflora and the gut associated lymphoid tissue (GALT) or gut microbiome is of critical importance in a range of experimental conditions including obesity and autoimmunity. The functional properties of GALT derived regulatory populations and the phenotypic characteristics of APCs in EAE and human MS are not appreciated. Alemtuzumab, a humanized monoclonal antibody targeting the co-stimulatory molecule CD52, significantly reduces the risk of relapse and accumulation of disability. Preliminary reports from our lab demonstrate a rise in IL-10 producing CD39+ regulatory cells following treatment with alemtuzumab. Recent studies by Turner et al have demonstrated that murine anti-CD52 (m-anti CD52) mAb treatment reduces autoreactive MOG specific T cells and diminished lymphocyte infiltration into the CNS. Although the peripheral lymphocyte count drops substantially following anti-CD52 infusion the extent to which CD52 expressing cells are eliminated in the GALT is unknown. Thus GALT may represent the reservoir for the regulatory phase in EAE mice that have been treated with m-anti-CD52.

Objectives: To assess the impact of recently developed m-anti-CD52 mAb on GALT mediated immune regulatory cell populations in EAE.

Methods: C57BL/6 mice were immunized with MOG 35-55 peptide to induce EAE and treated therapeutically with m-anti-CD52 antibody. A flow cytometric analysis was used to determine the impact of m-anti-CD52 therapy on GALT derived lymphocyte populations and in the CNS. The GALT derived cells were phenotyped by FACS, and for the expression of various activation and anti-inflammatory markers was determined by RT-PCR.

Results: The association between the GALT immune reservoir and the effect of current therapies for treating MS has not been investigated. We have observed potent IL-10 responses elicited by

regulatory CD4+ T cells that express enhanced levels of Foxp3+CD39 cells in treated EAE mice. These *in vivo* studies predict the capacity of m-anti-CD52 antibody to modulate the phenotype and functional regulation of specific immune cell compartments of the GALT in EAE mice.

Conclusions: These findings would suggest a possible relationship between gut microbiota and mucosal immune system.

P398

Plovamer acetate causes a more pronounced increase in eosinophils and CCL22 in naïve and EAE mice compared with glatiramer acetate

A Savinainen[1], T Crandall[1], K Crook[1], U Boschert[1], T Dellovade[1]
[1]*EMD Serono Research & Development Institute, Inc., Billerica, MA, United States*

Background: Plovamer acetate (PA) is a copolymer mixture of 4 amino acids of defined ratio, rationally designed to have improved efficacy over glatiramer acetate (GA). Due to the complex nature of both molecules, direct pharmacokinetic measurements are challenging. In addition, the mode of action (MoA) of PA and GA is complex and incompletely understood. Therefore, testing pharmacodynamic (PD) markers is of interest, as they may inform about MoA and correlate with dose and exposure.

Objectives: To compare the effect of PA versus GA following injection into naïve mice by measuring the following PD markers: CCL22, CXCL13, eosinophil counts.

Methods: Naïve SJL/J mice were injected subcutaneously with PA or GA and blood samples were taken at various time points up to 4 hours post injection. Samples were assayed for levels of cytokines and chemokines, including CCL22 and CXCL13. In separate experiments, e*xperimental autoimmune encephalomyelitis* (EAE) was induced in SJL/J mice with proteolipid protein peptide (PLP$_{(139-151)}$); blood samples were taken at different time points throughout the disease course and after administration of PA or GA. Levels of cytokines, chemokines and eosinophils were measured.

Results: In naïve mice, PA consistently induced a dose-dependent increase in serum levels of CXCL13 and CCL22, which peaked 15-30 minutes after injection. A less pronounced increase was induced by GA. In EAE mice, PA administration increased serum levels of CCL22 at 15 minutes following injection, while GA had no effect. CXCL13 was also raised in EAE mice compared with healthy control mice. However, the levels of this cytokine were not altered by treatment with PA or GA. In EAE mice, treatment with PA or GA caused a delayed increase in eosinophil counts. The increase was more robust and sustained with PA than with GA treatment.

Conclusions: These studies in naïve and EAE mice indicate that while both molecules induce eosinophils and CCL22, each associated with a Th2 response, this induction is more pronounced with PA than with GA.

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Therapeutic effect and mechanisms of antigen-specific tolerogenic dendritic cells in experimental autoimmune encephalomyelitis

MJ Mansilla[1], S Fabregas[1], J Navarro[1], A Teniente[1], L Grau-López[2], C Ramo-Tello[2], EM Martínez-Cáceres[1]

[1]*Hospital Universitari Germans Trias i Pujol, Immunology, Barcelona, Spain,* [2]*Hospital Universitari Germans Trias i Pujol, Neurosciences, Barcelona, Spain*

Background: Treatment with tolerogenic dendritic cells (TolDCs) loaded with autoantigens is a promising specific cell therapy for the attenuation of pathogenic T cells in autoimmune diseases such as multiple sclerosis (MS).

Objectives: To compare the therapeutic effect of antigen-specific TolDCs and unloaded TolDCs in the animal model of MS, experimental autoimmune encephalomyelitis (EAE).

Methods: Bone marrow (BM) cells from C57BL/6 mice donors were cultured in presence of GM-CSF, LPS and vitamin D3 (VitD3) as tolerogenic agent. Cells were pulsed or not with myelin oligodendrocyte glycoprotein $(MOG)_{40-55}$ peptide.

A total of $1 \cdot 10^6$ generated TolDC-MOG cells, unpulsed TolDC or PBS (sham control) were administrated pre-clinically (on days 5 and 9 pi) or therapeutically (on days 15, 19, 23 and 33pi) on C57BL/6 mice immunized with MOG_{40-55}. Clinical and immunological parameters were evaluated.

Results: Splenocytes from mice receiving unpulsed TolDC or TolDC-MOG therapeutically showed reduced antigen-specific proliferative reactivity *in vitro* (vehicle *vs* TolDC, p=0.022 and vehicle *vs* TolDC-MOG, p=0.004). In addition, following MOG-stimulation, IL-10 overproduction was found in splenocytes from mice treated with TolDC-MOG (either pre-clinically or therapeutically, p=0.008 and p=0.036, respectively) or TolDC (therapeutically, p=0.017). However, increased % of regulatory T cells (Treg) (pre-clinically, p=0.032 and therapeutically, p=0.036) and reduced EAE severity (less cumulative and maximum score, p=0.037 and p=0.038, respectively) were only found in mice treated with TolDC-MOG.

Conclusions: Tolerogenic mechanisms triggered by unpulsed TolDC were not sufficient to ameliorate EAE clinical signs and consequently, antigen-specific tolerogenic DC-based therapies are required to treat EAE. These results provide relevant information for the design of specific tolerogenic therapies for MS.

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Diffusion tensor imaging (DTI) reveals cortical structure and axon circuit alterations in a chronic demyelinating mouse model of multiple sclerosis

N Harris[1], A Khalaj[2], R Mofrad-Babapour[2], L Martinez-Torres[2], Z Winchester[2], SK Tiwari-Woodruff[2,3]
[1]*School of Medicine at University of California, Neurosurgery, Los Angeles, CA, United States,* [2]*School of Medicine at University of California, Los Angeles, CA, United States,* [3]*School of Medicine at University of California at Riverside, Riverside, CA, United States*

Background: Unlike autoimmune demyelinating pathology in multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE) mice, cuprizone (CPZ) diet-induced demyelination and normal diet-induced remyelination is independent of blood brain barrier compromise and infiltration by peripheral immune cells. This model provides a predictable course of chronic demyelination (closely reminiscent of progressive MS) and remyelination, and examination of direct effects on axon damage and remyelination. Moreover, functional correlates for longitudinal analysis by diffusion tensor imaging (DTI) allow for translational, detailed evaluation and comparison of myelin and axon changes under various experimental conditions.

Objectives: DTI was used to examine the effects of chronic demyelination on brain fiber tract diffusivity and tractography in mice *in vivo*, and these data were correlated with pathological assessments of corpus callosum (CC), cingulum, dorsal hippocampus, and cortical layers.

Methods: DTI images obtained from mice having undergone nine weeks of CPZ or normal diet were registered to an anatomical template. Group data were analyzed by voxel-based statistical analysis for diffusion-direction parameters and by fiber-tractography based on fractional anisotropy. DTI-imaged brains were subsequently assessed via immunohistochemistry and electron microscopy.

Results: Pathological assessments revealed substantial demyelination in the CC, dorsal hippocampus, and cortical layers of chronically demyelinated mice. Reductions in axial and radial diffusivity within the CC indicated reduced myelination and altered axonal integrity. Region-of-interest tractography revealed reductions in number and mean length of fiber tracts within the cingulum, and CC indicating further alterations in structural integrity and axonal circuits. These findings correlated with decreased myelin proteins and oligodendrocytes (OLs), and increased axon damage and astrocyte and microglia activation.

Conclusions: Current data support DTI as a high translational *in vivo* biomarker of myelin and axon integrity in a chronically demyelinating mouse model; thus, it may be used to assess longitudinal efficacy of currently-lacking progressive MS therapeutics. Next, we will assess therapeutic estrogen receptor β ligand treatment-induced increases in OL progenitor cells, acceleration of remyelination, preservation of myelin integrity, and improvements in CC axon conduction.

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Visual evoked potentials and MRI reveal optic nerve involvement in a relapsing remitting model of multiple sclerosis

R Santangelo[1], V Castoldi[1], L Camaleonti[1], M Cursi[1], G Dina[1], G Comi[1], L Chaabane[1], A Quattrini[1], L Leocani[1]
[1]*Scientific Institute and University Hospital San Raffaele, Neurology and INSPE-Institute of Experimental Neurology, Milan, Italy*

Background: Experimental Autoimmune Encephalomyelitis (EAE) is a pre-clinical disease model of Multiple Sclerosis (MS), traditionally induced by injecting Myelin Oligodendrocyte Glycoprotein(MOG). Optic nerve involvement and VEP diagnostic reliability was already shown in MOG EAE rats. In the present study we monitored a model of MS induced in Dark-Agouti (DA) rats with another compound, i.e. spinal cord homogenate (SCH).

Objectives: To show optic nerve involvement and assess VEP usefulness as neurophysiological biomarker in a relapsing remitting model of MS induced with spinal cord homogenate (SCH).

Methods: Nineteen DA rats were used in the experiment: 7 immunized by SCH (EAE) and 12 healthy (H) controls. Flash VEPs from both eyes were recorded with epidural electrodes under sevoflurane volatile anesthesia once a week for 6 weeks (one day before immunization, days 6, 13, 20, 27, 34 post) with

measurement P1 latency from N1-P1-N2 complex. Values exceeding 2.5 SD from control mean were considered abnormal. MRI analyses on both Optic Nerves were also performed using a 7 Tesla technology. After the last VEP session, 7 EAE and 3 H animals underwent histological analysis on a transverse section of both optic nerves.

Results: P1 latency in EAE group was significantly increased at days 13-20-27 post immunization and was abnormal in 10/14 eyes in EAE rats (p< 0.05). Neither histology nor VEPs showed pathologic findings in any H control. MRI analysis showed Fractional Anistropy (FA) and Diffusion Tensor Imaging (DTI) pathological values in EAE rats, too. Histological optic nerve damage was found in 6/14 eyes in EAE, with a 57% agreement between VEPs and histologic data. Considering histology data as the gold standard, in our EAE model VEPs showed a sensitivity of 83% and a specificity of 37%.

Conclusions: Our data show optic nerve involvement in SCH EAE in DA rats. VEPs latencies are significantly delayed in EAE and show a good sensitivity in identifying affected eyes such as MRI analysis. Suboptimal agreement between histology and VEPs and lowest VEP specificity are probably due to single optic nerve sections that may underestimate actual optic nerve involvement, because of patchy disease pattern. On the other hand, VEPs abnormalities may also derive from lesions affecting the visual pathways behind the optic chiasm. In any case, these findings suggest that VEPs could be a useful tool in monitoring the disease course in SCH-EAE and prompt further studies specifically addressing their value in testing novel treatments.

P402

Spectroscopic determination of chelating properties and uptake in the cuprizone multiple sclerosis model

AA Taraboletti[1], JA Caporoso[1], H Huang[1], MJ Taschner[1], TL Walker[2], CJ Ziegler[1], LP Shriver[1,3]
[1]University of Akron, Chemistry, Akron, OH, United States,
[2]Indiana University Northwest, Chemistry, Gary, IN, United States, [3]University of Akron, Biology, Akron, OH, United States

Background: The copper chelator, cuprizone, has been used for almost 50 years as a model to study pathways involved in white matter damage that occurs in multiple sclerosis (MS). Administration of cuprizone to mice results in reproducible and selective damage to the oligodendrocyte, while withdrawal from mouse feed induces spontaneous remyelination. Despite the extensive use of this model to test neuroprotective therapies, little is known of its structure or its mechanism of action.

Objectives: To determine cuprizone's structural properties and chelating ability using copper-containing active site mimics as well as quantifying cuprizone uptake in cells and tissues.

Methods: Cuprizone's structure in solution was analyzed using both quadrupole time of flight mass spectrometry (QToF-MS), and proton nuclear magnetic resonance (H-NMR) spectroscopy. The ability of this compound to bind copper-bound protein active site mimics was also monitored using H-NMR and absorption spectroscopy.

Quantification of cellular uptake was determined in MO3.13 cells, a human oligodendrocyte cell line using a copper-dependent colorimetric assay based on the strong absorbance at 600 nm for the copper-cuprizone complex. These levels were confirmed by

selected reaction monitoring (SRM) with liquid chromatography mass spectrometry (LC-MS).

Results: QToF-MS revealed the copper-cuprizone complex to exist as multiple hydrolyzed forms in solution at pH 7.5-8. Cuprizone is able to lose one or both of its cyclohexane rings when bound to copper. When cuprizone is added to synthetic protein active sites that contain copper, a structural change occurs which is observable using both absorption spectroscopy and H-NMR. Cuprizone does not seem able to remove copper from the site, but instead forms a complex, coordinating to the metal.

The colorimetric assay displayed a loss of cuprizone in the cell media indicating that is compound can cross the cell membrane. This uptake was associated with loss of viability. Selected reaction monitoring quantified the cellular level of cuprizone to be approximately 30 nM.

Conclusions: Our chemical investigation determined that cuprizone is taken up by cells; however, it cannot chelate away copper from enzyme active sites and instead forms a complex. These results indicate a more complicated mechanism of action than simple metal chelation.

P403

Well-defined functional deficits and protracted course of EAE in rats with intraspinal injection of VEGF after low-dose immunization with MOG

S Kapitza[1], B Zörner[2], C Bleul[3], B Ineichen[3], ME Schwab[3], M Linnebank[1]
[1]University Hospital Zurich, Neurology, Zurich, Switzerland,
[2]University Zurich, Balgrist Hospital, Zurich, Switzerland,
[3]University Zurich, Brain Research Institute, Zurich, Switzerland

Background: The targeted experimental autoimmune encephalomyelitis (EAE) model in rats is a variant of EAE, which reflects the pathological hallmarks of EAE but allows defining the localization and onset of the lesion. However, accidental incidence of disseminated EAE symptoms on the one hand or exiguous clinical manifestation on the other hand may impact the reproducibility of this model.

Objectives: Here we analyzed several rat strains, antigen dosages and environmental factors, which might influence the incidence of targeted EAE symptoms. Finally, an adapted variant of the targeted EAE model is presented, which leads to accentuated pathophysiological characteristics and protracted functional deficits.

Methods: Sprague Dawley (SD), Long Evans (LE), Dark Agouti (DA) and Lewis (LEW) rats received intracutaneous injections of low-dose myelin oligodendrocyte glycoprotein (MOG), followed by intraspinal injections of the proinflammatory cytokines interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) into the cervical corticospinal tract (CST) with or without combination of vascular endothelial growth factor (VEGF).

Results: Immunization with MOG >12.5µg resulted in a high rate of disseminated EAE (50-100%), whereas a dosage of 6µg resulted in a dissemination rate of < 25%. Susceptibility to disseminated EAE was strikingly higher in other rat strains (SD, LE, DA) than in LEW rats. Apart from rat strain and antigen dosage, the targeted EAE model was prone to several factors including animal supplier, housing conditions and stress levels (e.g. behavior testing). Intraspinal injections of VEGF in combination with IFN-γ and TNF-α led to accentuated pathophysiological

characteristics of the targeted EAE lesion and protracted the lesion outcome without increasing the dissemination rate, whereas injections of cytokines-only led to little demyelination and rapid spontaneous functional recovery. The amount of spared CST fibers which were identified by anterograde tracing was strikingly reduced. These histological alterations were closely related to marked functional forelimb deficits reflected by a success rate of only 1.8% on the horizontal ladder at day 2 post operation followed by a rapid and progressive spontaneous recovery with back to 70.4% and 79.9% correct steps on the horizontal ladder on day 14 and 28 post operation respectively.

Conclusions: Once shielded from environmental variables, the targeted EAE model is highly reproducible and helpful to mimic a predictable onset and phenotype of an experimental MS.

P404

Clinical outcome of experimental autoimmune encephalomyelitis in semaphorin 7A-deficient mice

A Gutiérrez-Franco[1], H Eixarch[1], C Costa[1], M Casillo[1], X Montalban[1], C Espejo[1]
[1]Vall Hebron University Hospital, Multiple Sclerosis Centre of Catalonia, Neuroimmunology Department, Barcelona, Spain

Background: Semaphorin 7A (sema7A) is an immune semaphorin that is also involved in glial scar formation after a central nervous system (CNS) injury. Its role in the pathogenesis of experimental autoimmune encephalomyelitis (EAE) is controversial.

Objectives: We aimed to study the role of sema7A in the clinical outcome of MOG-induced EAE.

Methods: EAE was induced in C57BL/6J sema7A-deficient (sema7AKO) (n=18) and wild-type (WT) littermate mice (n=20) using our current protocol: 50μg of MOG_{35-55}, 300μg of *Mycobacterium tuberculosis* (McT) and 150ng of *pertussis toxin* (Pt) per mouse. Additionally, different doses of antigen and adjuvants were used to determine the relevance of the immunization protocol in the establishment and development of EAE (as it is described in the literature): 1, 10, 50 and 100μg of MOG_{35-55}, 100μg of McT and 100ng of Pt. On day 12 post-immunization, spleens from 4-6 mice were removed to evaluate their proliferative capacity upon MOG- and PHA-stimulation by measuring ^{3}H-thymidine incorporation. Cytokine release was assessed by flow cytometry in the supernatants of MOG-stimulated splenocytes and CNS histophatological studies were performed at the end of the experiment.

Results: Sema7AKO and WT mice immunized with our current protocol exhibited a similar clinical outcome. The use of other doses of antigen and adjuvants reported no differences between sema7AKO and WT mice when the incidence, the onset day, the accumulated score, the maximum score and the mortality were compared. Sema7AKO or WT mice immunized with 1ug did not develop EAE. Proliferation of splenocytes from sema7AKO mice upon both MOG- and PHA-stimulation was reduced compared with WT, being statistically significant in mice immunized with 50μg of MOG-peptide, 100μg McT and 100ng of Pt (MOG: p=0.017; PHA: p=0.022). Similarly, the levels of IFN-g and TNF-a proinflammatory cytokines were decreased in all groups of sema7AKO mice, although the differences did not reach statistical significance respect to those observed in WT mice. No differences were found in the histopathological studies between sema7AKO and WT mice.

Conclusions: Our results show that sema7A modulates the immune response during EAE favoring T-cell responses as determined by T-cell proliferation assay and cytokine release determination. Moreover, the absence of sema7A does not ameliorate nor abrogate EAE symptoms, suggesting that this molecule is not crucial for EAE outcome.

P405

Gender-specific neuregulin1 modulation of experimental autoimmune encephalomyelitis

F Song[1], H Deol[1], J Liu[1], EH Simpson[2], JA Loeb[1]
[1]University of Illinois at Chicago, Neurology and Rehabilitation, Chicago, IL, United States, [2]Columbia University, Psychiatry, New York, NY, United States

Background: The mechanisms that modulate disease severity and progression in multiple sclerosis (MS) are poorly understood and MS is more common in women than men. One potential mediator is neuregulin1 (NRG1) which is a membrane bound and secreted growth and differentiation factor that regulates glial development, survival, synaptogenesis, axoglial interactions, and microglial activation. We developed a targeted NRG1 antagonist called HBD-S-H4 that given intrathecally reduces microglial activation in a rat spinal cord pain model, suggesting that it may have similar effects in other diseases. Here we test the hypothesis that blocking NRG1 in the central nervous system (CNS) could be a therapeutic approach to reduce neuroinflammation and demyelination in MS. Since sex steroids can also modulate microglial activation, it will be important to examine any sex differences.

Objectives: To determine the gender-specific effects of a NRG1 antagonist (HBD-S-H4) on myelin oligodendrocyte glycoprotein (MOG)-induced experimental autoimmune encephalomyelitis (EAE).

Methods: HBD-S-H4 is a novel humanized fusion protein consisting of a decoy Her4 receptor fused to NRG1's heparin-binding, targeting domain. MOG-induced EAE was induced in transgenic mice that were developed to express this fusion protein in the CNS, and compared to control mice. More and less potent EAE disease induction models were compared as well as gender-specific differences.

Results: Transgenic expression of HBD-S-H4 in the CNS did not result in any significant neurological or other overt phenotypes. With induction of less potent EAE disease, female HBD-S-H4 mice were less severely affected compared to their male HBD-S-H4 littermates. However, with more potent disease induction, female HBD-S-H4 mice were affected more than the males of the same genotype, suggesting complex interaction between NRG1 signaling and gender.

Conclusions: Blocking NRG1 is protective in female mice in mild disease, but this effect was not seen in more severe disease, suggesting a complex interplay between NRG1 and sex hormones in EAE that is dependent on disease severity. One possible explanation for this may be from combined effects of NRG1 and estrogens on microglia. Future studies of gender and hormonal influences on NRG1 signaling in microglia will be important to understand the heterogeneity of disease pathology and the therapeutic potential of targeting microglial activation in human MS in men and women.

P406

Oleanolic acid controls oxidative stress to protect against optic nerve degeneration in an experimental model of multiple sclerosis

C Cordova[1], B Gutierrez[2], R Martin[3], M Hernandez[2], N Tellez[4], ML Nieto[2]
[1]IBGM-CSIC/Uva, I3U, Valladolid, Spain, [2]IBGM-CSIC/UVa, I3U, Valladolid, Spain, [3]Hospital Clinico Universitario, Valladolid, Spain, [4]Hospital Clinico Universitario, Neurologia, Valladolid, Spain

Background: Optic neuritis (ON) is a frequent and early symptom of multiple sclerosis (MS). ON is a condition involving inflammation, oxidative stress, demyelination, and axonal injury in the optic nerve and leads to apoptotic retinal ganglion cell (RGC) death, which contributes to the persistence of visual loss. Currently, ON has no effective treatment. Experimental autoimmune encephalomyelitis (EAE) is the animal model used to study MS and ON. The triterpene, oleanolic acid (OA), has proven effective in EAE via an immunomodulatory and antiinflammatory mechanism.

Objectives: Our goal was to determine the usefulness of OA in preventing ON with a focus on neuroprotection.

Methods: OA (50 mg/kg/day) was intraperitoneally administered to MOG_{35-55} immunized-C57/BL6 mice from immunization to day 21. Clinical score, as well as cell infiltration (hematoxylin/eosin, H&E), myelin lost (Luxol fast blue, LFB) and oxidative stress (dichlorofluorescein diacetate, DCFDA, and dihydroethidium, DHE) were analyzed in the optic nerve from untreated and OA-treated EAE mice. A RGC cell line was used to measure effectiveness of OA in vitro.

Results: High levels of ROS were detected in optic nerve sections from EAE mice, compared to healthy mice, and were strongly attenuated in samples from OA-treated EAE mice. Histopathological analysis of optic nerves showed presence of cell infiltration (H&E) and myelin loss (LFB stain) in EAE mice, whereas these effects were not detectable in tissue sections from healthy or OA-treated EAE mice. In addition, OA intervention suppressed lymphocyte proliferation (1.2 ± 0.1, 2.6 ± 0.4 and 1.4 ± 0.2, in control, EAE and OA-treated EAE mice, respectively, $p < 0.001$). At the same time, studies in vitro showed ROS accumulation in the RGC-5 cell line by addition of 500 μM hydrogen peroxide for 24 h ($23 \pm 2\%$ of cells were positives for DCF fluorescence and $53 \pm 4\%$ for DHE), which resulted in significant apoptotic cell loss ($65 \pm 7\%$ were stained with annexin-V). The presence of 10 μM of OA or 5 mM of NAC reduced ROS levels at resting situation (0.2% of cells positives for DCF and DHE fluorescence) and promoted cell survival (only $8 \pm 0.5\%$ and $7.5 \pm 0.3\%$ stained with annexin-V, respectively) in RGC-5 cells ($p < 0.001$).

Conclusions: OA suppressed clinical and histopathologic signs of ON preventing recruitment of inflammatory cells to the optic nerve, ameliorating production/accumulation of ROS, and restraining myelin fiber injury. Therefore OA may be a therapeutic strategy for suppressing neurodegeneration in optic neuritis.

P407

Relative protection of *H. pylori* sonicate administration against experimental autoimmune encephalomyelitis, irrespective of its antigenic properties

M Boziki[1], E Kofidou[1], E Kesidou[1], R Lagoudaki[1], O Touloumi[1], E Nousiopoulou[1], N Delivanoglou[1],

K-N Poulatsidou[1], K Papadakos[2], D Sgouras[2], E Panagiotopoulou[2], A Mentis[2], G Deretzi[3], N Taskos[4], D Karacostas[4], J Kountouras[5], N Grigoriadis[1]
[1]Aristotle University of Thessaloniki, Laboratory of Experimental Neurology and Neuroimmunology, B' Neurological Department, AHEPA General Hospital, Thessaloniki, Greece, [2]Hellenic Pasteur Institute, Laboratory of Medical Microbiology, Athens, Greece, [3]'G. Papageorgiou' General Hospital, Neurology Clinic, Thessaloniki, Greece, [4]Aristotle University of Thessaloniki, B' Department of Neurology, Thessaloniki, Greece, [5]Aristotle University of Thessaloniki, B' Pathology Clinic, Thessaloniki, Greece

Background: We recently describe evidence of epidemiological correlation between *Helicobacter Pylori* (*Hp*) infection and multiple sclerosis (MS). However, experimental evidence on the field is lacking.

Objectives: To investigate immunomodulatory properties of *Hp* sonicate administration in Experimental Autoimmune Encephalomyelitis (EAE), with respect to antigen presentation mechanisms, and its antigenic properties.

Methods: 6-8 week-old female C57Bl/6 mice (6-7 mice per group) were intra-peritoneally administered either with 5 μg/mouse Hp sonicate, or with PBS, in three weekly injections. *Escherichia coli (e.coli)* sonicate served as control.

Results: We report a relative protective effect of *Hp* sonicate administration, compared to the PBS-treated group, upon induction of experimental autoimmune encephalomyelitis (EAE), through immunization with MOG_{35-55} peptide (mean EAE score±SE: $0.7 \pm .45$ vs. 2.45 ± 1.5 respectively, $p=.045$). *Hp*-treated mice B-cells and macrophages showed down-regulation of Major Histocompatibility Complex class II (MHC-II) molecule expression (for B-cells: 268.6 ± 59.72 vs. 725.6 ± 127.6 respectively, $p=.012$, and for macrophages: 551.6 ± 134 vs. 1372 ± 291.4 respectively, $p=.042$), compared to the PBS-treated group. We do not provide evidence of difference in terms of cytokine production. At the end of the pre-conditioning period, a stronger relative upregulation in the expression levels of CCL2 and CXCL13 proinflammatory chemokines in the peripheral lymph nodes of mice administered with e.coli sonicate, relative to the PBS-treated group (for CCL2: 11.78 ± 2.08 vs. 3.53 ± 1.44, $p=0.008$ respectively, and for CXCL13: 5.37 ± 1.3 vs. 0.76 ± 0.2, $p=0.006$ respectively), was noticed, whereas relative upregulation was weak for Hp-treated, compared to the PBS-treated mice (for CCL2: 6.9 ± 3.14 vs. 3.54 ± 1.14, respectively, $p=0.305$ and for CXCL13: 3.32 ± 0.99 vs. 0.765 ± 0.20, respectively, $p=0.036$).

Conclusions: *Hp* sonicate administration exerts relative protective effect in EAE, possibly by directly interfering to the antigen-presentation, in the absence of strong antigenic properties.

P408

B cell antigen presentation is sufficient to drive neuro-inflammation in an animal model of multiple sclerosis

CR Parker[1], AS Archambault[1], J Sim[2], JH Russell[2], GF Wu[1]
[1]Washington University in St. Louis, Neurology, St. Louis, MO, United States, [2]Washington University in St. Louis, Developmental Biology, St. Louis, MO, United States

Background: B cells are increasingly regarded as integral to the pathogenesis of multiple sclerosis (MS). The mechanisms by which B cells participate in neuro-inflammatory responses in MS

remain unclear. While several functions of B cells, including cytokine secretion, immunologlobulin production and antigen presentation have been suggested to play a role in MS, the capacity for B cells to independently drive CD4 T cell autoreactivity to myelin targets during in neuroinflammation has not been determined. We initially reported that B cell antigen presentation is not sufficient to support disease in the animal model of MS, experimental autoimmune encephalomyelitis (EAE). However, due to the indirect clinical evidence for B cell antigen presentation during EAE and MS, we chose to explore the role of antigen presentation by myelin antigen-specific B cells.

Objectives: We sought to determine the sufficiency of B cells for APC function during the initiation and propagation of experimental autoimmune encephalomyelitis (EAE). In particular, we aimed to examine the role for antigen presentation by cognate antigen-specific B cells during EAE.

Methods: Active EAE was induced using MOG protein or peptide, while passive EAE was induced using encephalitogenic CD4 T cell lines. Mice were subjected to active and passive EAE included those expressing MHCII by DCs alone and those in which B cells are deficient in MHCII expression. Further, we examined mice expressing MHCII by B cells alone with or without an increase in precursor frequency for MOG-specific B cell receptors. Additional experiments involved the transfer of MOG-specific antibody.

Results: We found that maximal disease in protein-induced active EAE models is dependent upon B cell antigen presentation. Further, increasing the precursor frequency of MOG-specific B cells, but not addition of soluble MOG-specific antibody, is sufficient to facilitate passive EAE in mice expressing MHCII by B cells alone.

Conclusions: This is the first direct demonstration *in vivo* that B cells can serve as the sole APC and coordinate CD4 T cell autoreactivity to myelin antigens during EAE. These data support a model in which expansion of antigen-specific B cells during CNS autoimmunity amplifies cognate interactions between B and CD4 T cells and independently drive neuro-inflammation at later stages of disease.

P409

Antigen-specific myeloid-derived suppressor cells ameliorate experimental autoimmune encaphalomyelitis

S Casacuberta-Serra[1], C Costa[2], S López-Estévez[1], H Eixarch[2], L Martorell[1], X Montalban[2], C Espejo[2], J Barquinero[1]

[1]Vall d'Hebron Institut de Recerca, Gene and Cell Therapy Lab, Barcelona, Spain, [2]Vall Hebron University Hospital, Multiple Sclerosis Centre of Catalonia, Neuroimmunology Department, Barcelona, Spain

Background: Previously we described that transferring bone marrow cells (BMCs) transduced with MOG_{40-55} peptide into experimental autoimmune encephalomyelitis (EAE) mice improved the disease. We also reported that the majority of cells generated in standard retroviral transduction cultures of BMCs consisted of myeloid-derived suppressor cells (MDSCs).

Objectives: To better characterize the MDSCs generated during the transduction cultures and to investigate their contribution to the therapeutic effect observed in the EAE model.

Methods: BMCs were transduced with either the retroviral vector pSF91-Ii-IRES-EGFP (Ii) or the pSF91-IiMOG-IRES-EGFP (IiMOG). EAE was induced by immunizing C57BL6/J mice with MOG_{45-55}. A single infusion of 1×10^6 unfractioned BMCs or 0.5-1×10^6 MDSCs was administrated 7 days before (preventive arm) or 13 days after (therapeutic arm) EAE induction. Mice were daily assessed for neurological signs using a 6-point scale. Histo- and immunohistopathological and immunological studies are currently being performed.

Results: In a preventive approach infusion of BM-IiMOG ameliorated the clinical course of EAE compared to BM-Ii group (accumulated score±standard deviation: 22.86±23.96 vs 58.31±28.39, p=0.021) to a similar extent as MDSCs-IiMOG cells (35.25±31.83 vs 61.67±16.72, p=0.087), although it did not reach statistical significance, indicating that MDSCs are most likely contributing to the therapeutic effect. Both IiMOG-groups had significantly lower maximum score compared to Ii-groups (BM: 2.14±2.04 vs 4.19±1.87, p=0.023; MDSCs: 2.75±2.14 vs 4.33±0.26, p=0.04). Furthermore, MDSCs-IiMOG mice presented reduced percentage of activated T cells (CD3$^+$CD4$^+$CD25$^+$FoxP3$^-$) (2.03%±0.95 vs 3.22%±0.9, p=0.035) and increased B regulatory cells (CD45$^+$B220$^+$CD5$^+$CD1d$^+$) (3.03%±0.60 vs 2.19%±0.58, p=0.023) than their counterparts. In a therapeutic approach, BM-IiMOG cells significantly improved accumulated (51.57±34.80 vs 94.44±8.40, p=0.003), maximum (3.14±1.57 vs 4.31±0.26, p=0.01) clinical score and reduced the percentage of activated T cells (1.90%±0.41 vs 2.76%±0.73, p=0.017) compared to controls. Mice treated with BMCs or MDSCs expressing IiMOG showed milder inflammatory infiltration and demyelination in the spinal cord white matter compared to Ii-treated mice.

Conclusions: Retroviral transduction of murine hematopoietic cells generates transgene-expressing MDSCs that contribute to the amelioration of the EAE clinical course in an antigen-specific manner.

P410

TGM6 is highly expressed by reactive astrocytes in the murine spinal cord during EAE and its levels correlate with the disease course

M Cristofanilli[1], D Gratch[1], B Pagano[1], SA Sadiq[1]
[1]Tisch MS Research Center of New York, New York, NY, United States

Background: Transglutaminases (TGM) are a family of enzymes involved primarily in protein crosslinking. Their altered expression induced by pathologic stimuli is thought to play a major role in cell injury and death in a number of chronic neurodegenerative conditions. Notably, TGM6, which is expressed predominately by neuronal cells under physiological conditions, has been implicated in cerebellar ataxia and schizophrenia. Although its relative TGM2 has been found to exacerbate MOG-induced EAE in mice through positive regulation of T cell differentiation and inflammation, the involvement of TGM6 in EAE and multiple sclerosis is still unknown.

Objectives: To investigate TGM6 in murine EAE.

Methods: EAE was induced in C57BL6 mice by MOG 35-55/CFA immunization followed by pertussis toxin injections (at 0 and 48h post immunization). Animals were sacrificed at 0,7,14,21,28, and 35 days post immunization and TG6 expression in their brains

and spinal cords was analyzed by q-RT-PCR, ELISA, Western Blot, IF, and IHC.

Results: TGM6 RNA and protein levels were increased at disease onset and correlated with its course. Furthermore, immunostaining of spinal cord at disease peak revealed strong expression of TGM6 in reactive astrocytes that infiltrated demyelinated areas, which was not found in control animals.

Conclusions: Based on these findings, we hypothesize that the expression of TGM6 by reactive astrocytes during EAE might contribute to disease pathogenesis.

Genetics and epigenetics

P411
Genetic modification of 25(OH)D levels in MS

K Munger[1], K Kochert[2], K Fitzgerald[1], B Arnason[3], F Barkhof[4], G Comi[5], S Cook[6], G Edan[7], M Filippi[8], M Freedman[9], D Goodin[10], H-P Hartung[11], D Jeffery[12], L Kappos[13], D Miller[14], X Montalban[15], P O'Connor[16], B Hemmer[17], B Mueller-Myhsok[18], M Muhlau[17], G Suarez[19], R Sandbrink[2,11], A Ascherio[1], C Pohl[2,20], The BENEFIT and BEYOND Study Groups

[1]Harvard School of Public Health, Boston, MA, United States, [2]Bayer Pharma AG, Berlin, Germany, [3]University of Chicago Surgery Brain Research Institutes, Department of Neurology, Chicago, IL, United States, [4]VU University Medical Center, Amsterdam, Netherlands, [5]Università Vita-Salute San Raffaele, Department of Neurology and Institute of Experimental Neurology, Milan, Italy, [6]Rutgers, The State University of New Jersey, Deptartment of Neurology and Neurosciences, Newark, NJ, United States, [7]CHU-Hopital Pontchaillou, Rennes, France, [8]Neuroimaging Research Unit, Division of Neuroscience, Scientific Institute and University Hospital San Raffaele, Milan, Italy, [9]University of Ottawa and the Ottawa Hospital Research Institute, Ottawa, ON, Canada, [10]University of California, Department of Neurology, San Francisco, CA, United States, [11]Heinrich-Heine University, Department of Neurology, Düsseldorf, Germany, [12]Wake Forest University School of Medicine, Winston-Salem, NC, United States, [13]University Hospital Basel, Basel, Switzerland, [14]UCL Institute of Neurology, London, United Kingdom, [15]Hospital Universitari Vall d'Hebron, Barcelona, Spain, [16]Division of Neurology, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada, [17]Technische Universität München, Munich, Germany, [18]Max Planck Institute of Psychiatry, Munich, Germany, [19]Bayer HealthCare Pharmaceuticals, Whippany, NJ, United States, [20]University Hospital of Bonn, Department of Neurology, Bonn, Germany

Background: Genome wide association studies provide robust evidence that in the general population, single nucleotide polymorphisms located within genomic regions of the genes DHCR7, GC and CYP2R1 are associated with 25-hydroxyvitamin D (25[OH]D) serum levels. It is not known, whether these results are also applicable to MS patients.

Objectives: Using interferon beta-1b-treated RRMS and CIS subjects from the BEYOND and BENEFIT trials, we analyzed candidate SNPs to assess their impact on 25(OH)D levels. Also, a 25(OH)D genetic risk score was implemented for patient stratification.

Methods: 25(OH)D levels were measured at two to three time points during the trials using an enzyme-linked immunosorbent assay or a chemiluminescence-based immunoassay and seasonally adjusted to derive an averaged 25(OH)D levels for each patient. Eligible data were combined and resulted in 819 unique patients for whom data was available. 25(OH)D values were $\log_e$-transformed and modeled as a function of candidate SNPs using Gaussian linear models. The first two ancestry components were included as covariates to correct for population stratification (resulting $\lambda_{GC} \sim 1.03$), as were gender, age, treatment and maximum NAb titer under treatment within the period of time 25(OH)D was measured in.

Results: All assessed candidate SNPs were significantly associated with 25(OH)D levels with $p \leq 0.05$. The most significant SNPs were located within the genomic region incorporating gene GC (coding for vitamin D binding protein) with $p = 1.05 \times 10^{-6}$ for SNP rs17467825. 25(OH)D levels were reduced by 10% comparing one to zero risk allele copies. In the genomic region of gene DHCR7, rs4945008 was the most significantly associated SNP with $p = 6.1 \times 10^{-4}$ and a reduction of 25(OH)D by 7%. With respect to the genomic risk region incorporating gene CYP2R1, the most significant SNP was rs1993116 with $p = 4.7 \times 10^{-3}$ and a reduction of 25(OH)D levels by 6%. The cumulative count of risk alleles per patient was used to derive a 25(OH)D risk score and indicate the odds ratio of being 25(OH)D deficient. For example, the odds ratio for a risk score of 4 relative to risk score 0 is OR=5.29 ($p = 1.05 \times 10^{-5}$).

Conclusions: All candidate SNPs were significantly associated with 25(OH)D levels at the nominal level. The genetic background and derived 25(OH)D risk score of patients and their first degree relatives could help to assess individual risk of 25(OH)D deficiency.

P412
Multiple quantitative trait loci for anti-EBNA-1 IgG titres are associated with risk of multiple sclerosis

Y Zhou[1], G Zhu[2], DR Nyholt[2], J Charlesworth[1], S Simpson Jr[1], I van der Mei[1], NA Patsopoulos[3], C Laverty[4], A Henders[2], J Ellis[2], GW Montgomery[2], R Rubicz[5], J Blangero[6], HHH Göring[6], NG Martin[2], BV Taylor[1]

[1]Menzies Research Institute Tasmania, Hobart, Australia, [2]Queensland Institute of Medical Research, Genetic Epidemiology, Molecular Epidemiology and Neurogenetics Laboratories, Queensland, Australia, [3]Brigham & Women's Hospital, Program in Translational NeuroPsychiatric Genomics, Institute for the Neuroscience, Department of Neurology, Boston, MA, United States, [4]Monash University, Monash Antibody Technologies Facility, Melbourne, Australia, [5]Fred Hutchinson Cancer Research Center, Seattle, WA, United States, [6]Texas Biomedical Research Institute, Department of Genetics, San Antonio, TX, United States

Background: Epstein-Barr virus (EBV) is a ubiquitous double-stranded DNA virus and infection with EBV is associated with an increased risk of multiple sclerosis (MS).

Objectives: To identify genetic susceptibility loci for EBV nuclear antigen-1 IgG antibody titres (EBNA-1) and hypothesised that these loci may play an important role in MS risk.

Methods: Approximately 2.4 million SNPs were tested for their association with ELISA measured anti-EBNA-1 IgG titres in 3,760 individuals from a large unselected twin family cohort. We then conducted a meta-analysis combining our results with a large Mexican American familial GWAS cohort (N=1956). Thirdly, *cis*-eQTL analyses using two microarray expression datasets and one RNA-seq dataset were carried out to ascertain the function of the top significant SNPs. Finally, we examined the shared polygenic risk utilising our EBNA-1 meta results (effective sample size=5,555) with the results of a large, well-validated MS meta-analysis (effective sample size=15,365) to determine the genetic architecture of anti-EBNA-1 immune responses, and whether these loci were over-represented in MS cases compared to healthy controls, thus representing novel MS susceptibility loci.

Results: We identified one locus of strong association within the human leukocyte antigen (HLA) region, of which the most significantly associated genotyped SNP was rs2516049 (P=4.11×10^{-9}), *cis*-eQTL analysis revealed that rs2516049 consistently changed the expression of the nearby gene, *HLA-DRB1*, using three different expression datasets. SNP effect concordant analysis (SECA) and genetic risk score analysis found that anti-EBNA-1 IgG titre status predicted the development of MS; however the reverse, MS status predicting anti-EBNA-1 IgG titre, was not observed. Finally, in the pooled meta-analysis using the MS meta results and EBNA-1 meta results we found several loci outside the HLA region reaching genome-wide significance. Interaction analysis revealed these SNPs and their related genes (*EVI5*, *EOMES* and *IL2RA*) interact with *HLA-DRB1* and this interaction is modulated by EBNA IgG titre.

Conclusions: Our results provide an explanation for the genetic susceptibility to MS via differential immune system reactivity to EBV infection, whereby the different SNP genotypes identified may result in an altered immune response to EBV infection and/or by modulating the efficiency of EBV infection, thus overcoming the burden and enhancing the immune response in that fashion.

P413

A *tumor necrosis factor beta Nco*I polymorphism is associated with inflammatory and metabolic markers in multiple sclerosis patients

AP Kallaur[1], SR Oliveira[1], PRVP Rodrigues[1], LJV Schiavão[1], WLCJ Pereira[1], DR Kaimen-Maciel[1], DF Alfieri[1], J Lopes[1], DF Rodrigues[1], F Delongui[1], ANC Simão[1], EMV Reiche[1]
[1]State University of Londrina, Londrina, Brazil

Background: Studies showed that *tumor necrosis factor beta* (*TNFB) Nco*I polymorphism is associated with increased tumor necrosis factor alpha (TNFA) levels, a pro-inflammatory cytokine that might induce the inflammatory process in multiple sclerosis (MS) patients and results in high disability levels and worse clinical progression of the disease. The increase in the inflammatory response may also affect the inflammatory and metabolic markers differently according to the gender, probably modulated by the gonadal hormones.

Objectives: The aims of this study were to evaluate the relationship between the *TNFB Nco*I polymorphism with inflammatory and metabolic markers according to the gender of MS patients, and to evaluate the association of these markers with the disease disability.

Methods: The study included 123 female and 43 male MS patients during 2013. The disability was evaluated using the Expanded Disability Status Scale (EDSS). The *TNFB Nco*I genotyping was evaluated PCR-RFLP. The serum levels of the cytokines Interleukin (IL)-1B, IL-12p70, IL-6, TNFA, interferon gamma (IFNG), IL-4, IL-10, and IL-17, as well as the lipid profile, plasma insulin levels, and homeostasis model assessment for insulin resistance (HOMA-IR) were evaluated.

Results: Females carrying the TNFB2/B2 genotype presented decreased IL-4 and IL-10 levels, increased TNFA, glucose, and insulin levels, and increased HOMA-IR, as well as a positive correlation between EDSS, glucose, and HOMA-IR (p< 0.05). Males carrying the TNFB2/B2 genotype presented increased levels of TNFA, IFNG, and IL-17, decreased levels of IL-4, IL-10, insulin, and decreased HOMA-IR. A positive correlation was found between EDSS and TNFA levels (r=0.5084, p=0.0157).

Conclusions: The TNFB2/B2 genotype of the *TNFB Nco*I polymorphism was associated with increased inflammatory and metabolic markers, and also decreased anti-inflammatory markers; however, the association between these markers and EDSS was dependent on the sex of MS patients. This may explain, in part, the sexual dimorphism in MS onset and course, as well as potential interactions between sex and other factors influencing MS pathogenesis, incidence and severity.

P414

Impact of genetic risk loci in multiple sclerosis on expression of proximal genes

T James[1], M Lindén[1], M Huss[2], M Brandi[3], M Khademi[1], J Tegnér[4], D Gomez-Cabrero[4], I Kockum[1], T Olsson[1]
[1]Karolinska Institutet, Clinical Neuroscience, Stockholm, Sweden, [2]Stockhom Univiersity, Science for Life Laboratory, Department of Biochemistry and Biophysics, Stockholm, Sweden, [3]Royal Institute of Technology, Science for Life Labratory, Stockholm, Sweden, [4]Karolinska Institutet, Department of Medicine, Stockholm, Sweden

Background: The major genetic susceptibility factors for multiple sclerosis (MS) are different alleles in the *HLA-DRB1* and *HLA-A* genes, but more than 100 non-*HLA* genetic loci have also been associated with MS. To be able to understand the impact of genetics on MS pathogenesis and disease biology, it is of great importance to investigate the relationship between MS risk loci and gene expression.

Objectives: The aim of this study was to study expression quantitative trait loci (eQTL) for genes mapping within 400 kb of established MS risk loci.

Methods: We sequenced the transcriptome in peripheral blood mononuclear cells (PBMCs) from a total of 183 individuals with MS and other neurological diseases using 100bp paired-end reads with an average sequencing depth of 36 Mreads. We estimated expression levels of genes in proximity of established MS risk loci using trimmed mean of M-values. These were correlated to genotypes from 109 MS susceptibility loci and four *HLA* variants (DRB1*15:01, 03:01, 13:02 and A*02:01). Genotyping was carried out using the Immunochip, HLA alleles were imputed using HLA*IMP:02. We used a generalized linear model, assuming negative binomial distribution of the expression data to correlate this to number of risk alleles assuming an additive genetic model.

Gender, experimental batch, disease state and treatment were included as covariates. We selected eQTL associations based on the significance of permutation-based p-values, strength of the correlation and false discovery rate.

We validated our findings in public RNA-seq data from lymphoblastic cell lines (LCLs) from 248 individuals with genotypes from the 1000 Genomes Project, and in sorted CD4^{+}, CD8^{+}, CD19^{+} and CD14^{+} cells from 57 individuals.

Results: We identified 28 non-*HLA* and 11 *HLA* eQTL signals in PBMC. Eleven of the non-*HLA* and many of the *HLA* eQTLs were replicated in the expression data from LCL.

We confirmed previously observed eQTL effects, such as rs1021156 affecting *FAM164A* expression. We also report several new eQTLs such as rs1920296 that affects *IQCB1* and rs4794058 that affects *TBKBP1* and *MRPL45P2*. We further show that rs12946510 affects *ORMDL3* transcription in CD19+ cells, and rs7595717 affects *PLEK* expression in CD4+ cells.

Conclusions: With this study we have gained further insight into which genes are affected by MS associated polymorphisms, confirming that these are not necessarily the genes that are located closest to the associated polymorphism.

P415

Multiple sclerosis susceptibility genes are associated with cervical cord atrophy and may explain disability status

DA Akkad[1], B Bellenberg[2], S Esser[1], JT Epplen[1], R Gold[3], C Lukas[2], A Haghikia[3]
[1]*Ruhr-University Bochum, Department of Human Genetics, Bochum, Germany,* [2]*Ruhr-University Bochum, Department of Radiology, Bochum, Germany,* [3]*Ruhr-University Bochum, Department of Neurology, Bochum, Germany*

Background: The genetic basis of multiple sclerosis (MS) as a multifactorial disease was underscored by the recent large multi-centre genome wide association study (GWAS) that prompted the discovery of >50 MS-associated common genetic variants.

Objectives: Hitherto, few of the newly reported variants have been replicated or correlated for clinical/paraclinical phenotypes such as brain or spinal cord atrophy in independent patient cohorts.

Methods: We genotyped a cohort of 141 patients with clinically definite MS and a consistent genetic background for all 58 variants reported to reach genome wide significance. Clinical disability according to expanded disability status scale (EDSS) and disease duration (DD) at the date of MR imaging were available from regular clinical examinations in our neurological university setting. MRI at 1.5 Tesla included sagittal high-resolution 3D-T1 weighted magnetization prepared rapid acquisition gradient echo of the cervical cord region used for volumetry. Due to significant association of cervical cord atrophy (CCA) with EDSS and DD, linear correction operations compensating the EDSS and disease duration dependencies were performed. We performed correlation analyses for each MS risk loci for possible association between corresponding genotypes and CCA.

Results: We identified eleven variations that significantly correlated with CCA located in or near the genes *BATF, CYP27B1, IL12B, NFKB1, IL7, PLEK, TYK2, CLEC16A, RGS1, EVI5, and TAGAP*. For eight of these loci patients homozygous for the MS risk allele revealed a considerably higher degree of atrophy - for

TYK2, CLEC16A and RGS1 we observed an inverse effect. Furthermore, the weighted genetic risk score that we calculated for our cohort according to the GWAS risk alleles, showed strong inverse correlation with CCA in the extended regression analysis.

Conclusions: Our data show a phenotypic correlation, *i.e.* spinal atrophy with MS risk genes, despite the relatively low numbers of patients investigated. Larger cohorts may reveal further risk genes associated with spinal atrophy with a less pronounced effect. Assessment of clinical/paraclinical correlations with risk genes may allow more reliable characterization of MS patients and serve as prognostic markers. Since CCA clearly impacts the EDSS, the risk genes identified in our study may be indicative for disability progression in the course of MS.

P416

A genome-wide copy number variation study identified *T-cell receptor* as a susceptibility gene for multiple sclerosis and neuromyelitis optica

S Sato[1], K Yamamoto[2], T Matsushita[1], N Isobe[1], Y Kawano[1], K Iinuma[1], T Yonekawa[1], K Masaki[1], S Yoshimura[1], R Yamasaki[3], J-I Kira[1], The Japan Multiple Sclerosis Genetics Consortium
[1]*Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Department of Neurology, Fukuoka, Japan,* [2]*Research Center for Transomics Medicine, Medical Institute of Bioregulation, Kyushu University, Division of Genomics, Fukuoka, Japan,* [3]*Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Department of Neurological Therapeutics, Fukuoka, Japan*

Background: Remarkable advances in genome technology, such as high-density DNA microarrays, have permitted effective screening for single nucleotide polymorphisms (SNPs) and copy number variations (CNVs). Genomic regions containing CNVs collectively span between 10 and -20% of the genome and contribute to human genetic and phenotypic diversity, including disease susceptibility. Although susceptibility CNVs have been reported in several diseases, the effect of CNVs on susceptibility to multiple sclerosis (MS) and neuromyelitis optica (NMO) is unknown.

Objectives: To identify CNVs associated with MS and NMO and to clarify the correlation between CNVs and clinical phenotypes.

Methods: We performed a genome-wide association study of CNVs among 277 MS patients, 135 NMO/NMO spectrum disorder (NMOSD) patients, and 288 healthy individuals as a discovery cohort, and then among 296 MS patients, 76 NMO/NMOSD patients, and 790 healthy individuals as a replication cohort in Japan using high-density microarrays, containing 700 K probes corresponding to known SNPs. Statistical significance was set at p < 0.01 to detect candidate CNVs.

Results: A series of discovery and replication studies identified approximately 30 disease-associated CNVs in MS patients and 20 in NMO/NMOSD patients. Most were deletions of 5-50 kb in size at particular regions of the T cell receptor (TCR) gamma and alpha genes. Among these CNVs, a deletion within the TCR gamma gene was found in 16.40% of all MS patients (combined p = 2.4E-40, combined odds ratio (OR) = 52.6, 95% confidence interval (CI) = 19.7-198.6). Deletion within the TCR alpha gene was found in 17.28% of all MS patients (combined p = 1.7E-31,

combined OR = 13.0, 95% CI = 7.6-23.5) and 13.27% of all NMO/NMOSD patients (combined p = 5.8E-20, combined OR = 54.6, 95% CI = 16.6-281.5). These findings were confirmed by quantitative PCR at the same genomic regions. In addition, NMO/NMOSD patients carrying the most significant CNVs were seronegative for anti-aquaporin 4 antibody or had lower titers than those without significant CNVs (mean ± SEM by enzyme-linked immunosorbent assay: 65.4 ± 22.7 U/mL vs. 565.4 ± 195.0 U/mL, respectively, p = 0.0146).

Conclusions: Deletion-type CNVs within specific regions of TCR genes may lead to skewed usage of the TCR repertoire, followed by emergence of T cells expressing autoreactive pathogenic TCRs in Japanese patients with MS and NMO.

P417

Genetic interaction analysis of multiple sclerosis risk loci

M Lindén[1], I Lima Bomfim[1], J Hillert[1], L Alfredsson[2], T Olsson[1], I Kockum[1]
[1]Karolinska Institutet, Clinical Neuroscience, Stockholm, Sweden, [2]Karolinska Institutet, Institute of Environmental Medicine, Stockholm, Sweden

Background: The sibling recurrence risk for multiple sclerosis (MS) is estimated to be 7.1. The major genetic susceptibility factors for MS are found to be different alleles in the *HLA-DRB1* and *HLA-A* genes. In addition more than 100 non-*HLA* genetic loci have been found to associate with MS. These genes together only explain a fraction (28%) of the familial clustering of MS. This missing heritability could be due to remaining unidentified genetic risk factors, epigenetics or interactions with other genes or environmental risk factors.

Objectives: The aim was to study the interaction between established genetic risk factors for MS in the Swedish population.

Methods: We used genotypes for 109 single nucleotide polymorphisms in established non-*HLA* MS risk loci and four *HLA* alleles (DRB1*15:01, 03:01, 13:02 and A*02:01) and assessed whether any of these variants interact in causing disease risk. Genotyping was carried out using the Immunochip in 2081 MS cases and 2166 healthy controls from Sweden. HLA alleles were imputed using HLA*IMP:02. We evaluated interaction as departure from multiplicativity (product term in a logistic model) as well as departure from additivity of effects (attributable proportion due to interaction (AP)). P values were corrected for multiple comparison by performing permutation analysis.

Results: We detected three variant pairs showing significant interaction on the additive scale: *HLA-DRB1*15:01* with absence of *HLA-A*02:01* (AP=0.55, p=0.011), *HLA-DRB1*1501* with rs6677306_A, mapping near *CD58,* (AP=0.44, p=0.013), and *HLA-DRB1*03:01* with rs7196953_A, mapping between *MAF* and *DYNLRB2,* (AP=0.71, p=0.018). We have previously reported the interaction between *HLA-DRB1*15:01* and absence of *HLA-A*02:01* and here we confirm it in an extended cohort. No significant interactions after correction for multiple comparisons were detected with the multiplicative model.

Conclusions: We report three significant gene-gene interactions among risk loci MS, where the effect departs from additivity of the separate effects of the variants. These findings need to be replicated in sparate cohorts and functional consequences of these potential interactions have to be investigated in order to elucidate their role in MS pathogenesis.

P418

Non-HLA risk genes in Dutch MS multiplex families

JY Mescheriakova[1], C Wijmenga[2], RQ Hintzen[1]
[1]Erasmus MC, Neurology, Rotterdam, Netherlands, [2]University Medical Centre Groningen, Groningen, Netherlands

Background: In the recent IMSGC collaborative study 110 multiple sclerosis (MS) risk loci have been established which, next to Human Leukocyte Antigen (HLA) class II genes, have concomittant although modest effects on MS susceptibility. These studies are often done in sporadic MS cases. There is some evidence for aggregation of MS non-HLA susceptibility genes in MS multiplex families.

Objectives: In this study we assessed 110 non-HLA MS risk loci in Dutch MS multiplex families and compared them to Dutch healthy controls and sporadic MS cases.

Methods: The study population comprising of 319 MS cases from Dutch multiplex families, was genotyped on the Immunochip. A control data set of 1146 healthy unrelated individuals from Dutch population was also genotyped on the Immunochip to perform a case-control analysis. The group of Dutch sporadic MS cases consisted of 355 unrelated individuals and was previously genotyped on the Illumina Human 610-Quad Bead Array. When a SNP was not present on the array, we used its best proxy according to the linkage disequilibrium (R²>0.9).

Results: After quality-control of the data, 88 out of 110 risk loci were available for the analysis in 316 MS patients from multiplex families and 1146 healthy individuals. The familial MS cases showed a significant overrepresentation of the risk alleles of SNPs associated with *MMEL1, FOXP1, IQCB1, ZNF767, IL2RA, CD6, CXCR5, TRAF3, CLEC16, RMI2, SCL2A4RG* (*p*< 0.05), *STAT4, TAGAP, CTSH, STAT3, VMP1, EPS15L1 (p< 0.01)* and *THFSF14, TYK2 (p< 0.001)* compared with healthy controls. We found a significant association in difference of risk-allele frequencies in half of these genetic loci (*STAT4, IQCB1, TAGAP, IL2RA, CD6, CLEC16A, VMP1, TYK2 and SCL2A4RG*) between sporadic and familial cases (*p< 0.05).* Although not statistically proven, the risk-allele frequencies and effect-sizes of these 19 loci appeared to be higher in the familial MS cases compared to sporadic cases in the original IMSGC paper.

Conclusions: The results from this study show that multiplex MS families have risk genes similar to the general MS population. However, the risk allele frequencies seem to be higher than in sporadic MS cases (and in some case can have a higher effect size), which results in increased susceptibility to the disease, at least in Dutch MS patients. These results support the previous studies.

P419

Susceptibility variants for multiple sclerosis in the Japanese population

T Matsushita[1], S Sato[1], K Yamamoto[2], L Madireddy[3], P Gourraud[3], S Baranzini[3], J Oksenberg[3], J-I Kira[1], the Japan Multiple Sclerosis Genetics Consortium
[1]Kyushu University, Neurology, Fukuoka, Japan, [2]Medical Institute of Bioregulation, Kyushu University, Research Center

for Transomics Medicine, Fukuoka, Japan, ³University of California, Neurology, San Francisco, CA, United States

Background: Multiple sclerosis (MS) is characterized by temporal and spatial dissemination of demyelination in central nervous system. Susceptibility to MS is thought to be influenced by both environmental and genetic factors. Ethnicity is one of such risk factors. MS is most prevalent among people of Northern European descent, and uncommon in people of Asian. While genetic risk variants for MS have been identified among people of European descent by genome-wide association study (GWAS), the variants are not elucidated among Asians.

Objectives: To clarify susceptibility variants for Japanese MS by GWAS and replication or difference of the risks between people of European descent and Japanese.

Methods: Genome-wide SNPs were genotyped in 275 MS cases and 974 controls for a discovery dataset and in 297 cases and 944 controls for a replication dataset in the Japanese population and the allelic effects for MS were calculated. Individual MS genetic burden (MSGB) was calculated based on reported 110 risk variants in people of European descent. Four-digit type of HLA-DRB1 was determined in 508 cases and 334 controls among these individuals.

Results: GWAS for 553 cases and 1,798 controls of Japanese identified 26 risk loci (FDR corrected $p < 0.05$). Two loci (CD58 and ZNF438) were reported in European study and the others were novel in the Japanese population. In SNP level, 13 SNPs out of reported 97 risk variants were replicated ($p < 0.05$). MSGB score based on 98 risk SNPs was significantly higher in cases than in controls ($p < 2.2e-16$, Nagelkerke´s $R^2 = 0.047$). HLA-DRB1*04:05 and 15:01 were risk alleles and DRB1*13:02, 01:01, and 09:01 were protective alleles for MS.

Conclusions: GWAS in the Japanese population identified novel genetic risks for MS. MSGB showed common genetic effect for MS between people of Japanese and European descent.

P420
Genetic predictors of multiple sclerosis

G Disanto[1], R Dobson[2], J Pakpoor[3], RI Elangovan[3], R Adiutori[2], C Gobbi[1], J Kuhle[2], G Giovannoni[2]
*¹Ospedale Regionale Civico Lugano, Lugano, Switzerland,
²Queen Mary University of London, London, United Kingdom,
³University of Oxford, Oxford, United Kingdom*

Background: Multiple sclerosis (MS) is a complex disorder with a strong genetic component. The main genetic locus for MS (the *HLA-DRB1* gene) was discovered in the 1970s within the major histocompatibility complex region. Two genome wide association studies (GWAS) published in 2011 provided evidence for approximately 60 single nucleotide polymorphisms (SNPs) influencing MS risk. An updated GWAS has recently increased the number of known MS associated variants to 110.

Objectives: We aimed to estimate what proportion of the general population can be considered at increased risk of MS and whether the predictive performance of MS associations has increased now that their number has exceeded 100.

Methods: We used summary statistics from GWAS in MS to estimate the distribution of risk within a large simulated general population. We profiled MS associated loci in 70 MS patients and 79 healthy controls (HC) and assessed their position within the distribution of risk in the simulated population. The predictive performance of a weighted genetic risk score (wGRS) on disease status was investigated using receiver operating characteristic statistics.

Results: When all known variants were considered, 40.8% of the general population was predicted to be at reduced risk, 49% at average, 6.9% at elevated and 3.3% at high risk of MS. Fifty percent of MS patients were at either reduced or average risk of disease. The median wGRS in MS was higher than in HC (13.47 vs 12.46, $p=4.08 \times 10^{-10}$). The area under the curve (AUC) discriminating MS and HC increased with the increasing number of considered MS associations (*HLA-DRB1* only, AUC=70.8%; *HLA-DRB1*+SNPs known in 2011, AUC=76.6%; *HLA-DRB1*+all currently known SNPs, AUC=79.7%). The best wGRS threshold was 13.0 (sensitivity=71.4%, specificity=78.5%). However, when the prevalence of MS in the general population was considered, the positive predictive value was below 1%.

Conclusions: We estimated that about 90% of the general population is at either average or reduced risk of MS. The predictive performance of the wGRS improved with the increasing number of discovered associations and the best threshold was 71.4% sensitive and 78.5% specific. However, given the low prevalence of MS, the positive predictive value was very low. Genetics is still unlikely to be useful for disease prediction in clinical settings and a more complete understanding of the complexity of MS is needed.

P421
The PhenoGenetic Project: a biobank with which to investigate the genetic and environmental architecture of immune variation in multiple sclerosis

PA Winn[1], M Cimpean[1], A Robbins[1], T Xue[1,2], P de Jager[1,2,3]
¹Brigham and Women's Hospital, Center for Neurologic Diseases, Boston, MA, United States, ²Harvard Medical School, Boston, MA, United States, ³Brigham and Women's Hospital, Program in Translational NeuroPsychiatric Genomics, Institute for the Neurosciences, Department of Neurology and Psychiatry, Boston, MA, United States

Background: Multiple genetic as well as environmental factors influence susceptibility to multiple sclerosis (MS). These genetic risk factors are common in the general population.

Objectives: The PhenoGenetic Project supports the ongoing systematic or targeted investigation of genetic variation to construct molecular networks contributing to the onset of MS.

Methods: All participants (n=1753) complete a health history questionnaire and provide a blood sample upon enrollment for DNA, serum, plasma and peripheral blood mononuclear cells that are kept in a frozen archive, which is available to investigators. The archive is supplemented by the availability of fresh blood, stool or urine from subjects recalled by genotype or demographic feature.

Results: Blood samples from this tissue bank have contributed to projects that illustrate different experimental paradigms, including (1) screening the phenotypic and functional profile of NK cells in 100 randomly selected subjects, (2) phenotyping a subset of subjects homozygous for a specific MS susceptibility allele such as the one found in the TNFRSF1A loci (Ottoboni *et al Neurology*, 2013), (3) supporting the large-scale RNA profiling of

over 681 healthy subjects to establish an atlas relating genetic and RNA variation in the immune system (ImmVar project, Raj *et al Science* 2014) (4) using control stool samples to discover elements of the gut flora that may be enriched in patients with MS.

Conclusions: The availability of a large population of healthy individuals in our biobank facilitates the dissection of functional consequences of genetic and environmental risk factors.

P422

SNPs within genes for cytokines and their receptors modulate IFN-γ and TNF-α associations with relapse in multiple sclerosis

Y Zhou[1], BV Taylor[1], N Stewart[1], J Charlesworth[1], I Van der Mei[1], S Simpson Jr[1]

[1]Menzies Research Institute Tasmania, Hobart, Australia

Background: Alterations in peripheral blood mononuclear cells (PBMC) production of cytokines have been found in multiple sclerosis (MS) compared to healthy controls. We have previously found that stimulated PBMC-produced IFN-γ and TNF-α significantly modulated MS relapse risk.

Objectives: To assess whether SNPs within genes for cytokines and their receptors could significantly modulate the associations of IFN-γ and TNF-α with relapse, thus providing information about these cytokine effects and the role of these genes in MS.

Methods: A prospective cohort study of 91 participants with relapsing-remitting MS and cytokine and genotype data were used. SNPs (N=361) within a window of 10kb around each cytokine and cytokine receptor gene (N=84) were selected for analysis. Predictors of PBMC cytokines were evaluated by multi-level mixed-effects linear regression. Predictors of relapse were evaluated by Cox proportional hazards regression for repeated events. Hypergeometric test was used for gene set enrichment analysis. Bonferroni correction was used to adjust multiple testing, thus $P < 1.39 \times 10^{-4}$ was defined as significant.

Results: The carriers of CC genotype of rs522807 and the AA genotype of rs25879 showed a strong association with IFN-γ levels and increased relapse risk ($P_{interaction} = 8.21 \times 10^{-5}$ and 1.70×10^{-5} respectively). Carriers of the A allele (CA+AA) of rs522807 and GG genotype of rs3218295 showed **a** significant protective effect of TNF-α on relapse ($P_{interaction} = 3.83 \times 10^{-4}$ and 5.04×10^{-5} respectively). Using the Kyoto Encyclopedia of Genes and Genomes (KEGG)pathways analysis, we found that *IFN-γ*, *TNF-α* and interactions-significant SNPs related genes were enriched in the Jak-STAT signlaing pathway($P = 4.53 \times 10^{-7}$), whose major role is signal transduction, and its dysregulation has pathological implicatons for autoimmune and neuroinflammatory diseases.

Conclusions: Our results provide novel detailed interaction of SNPs in some cytokine and cytokine receptor genes with major pro and anti-inflammatory cytokines in predicting MS relapse. These finding suggest the potential for the JaK-STAT signalling pathway as a therapeutic target in MS.

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Age at onset and disease severity in primary progressive multiple sclerosis: a genome-wide association study, pathway and network analysis

G Giacalone[1], F Clarelli[1], A Osiceanu[1], C Guaschino[1], M Sorosina[1], G Liberatore[1], N Barizzone[2], D Vecchio[3], V Martinelli[1], M Leone[3], G Comi[1], S D'Alfonso[2], F Martinelli Boneschi[1], PROGEMUS, PROGRESSO

[1]San Raffaele Scientific Institute, Institute of Experimental Neurology (INSPE), Milan, Italy, [2]University of Eastern Piedmont, Department of Health Sciences and Interdisciplinary Research Center of Autoimmune Diseases (IRCAD), Novara, Italy, [3]AOU Maggiore della Carità, MS Centre, SCDU Neurology, Novara, Italy

Background: The mechanisms underlying the accumulation of neurological disability during the progressive phase of Multiple Sclerosis (MS) are currently unresolved. In the present study, a model of progressive symptoms from onset, the primary progressive (PPMS) disease course, has been used to identify genes, pathways and networks involved in influencing the clinical manifestations and severity of the disease.

Objectives: To look for common genetic variants associated with age at onset (AAO) and severity of PPMS, measured as Multiple Sclerosis Severity Score (MSSS).

Methods: 451 PPMS patients of Italian origin were genotyped for 296,589 SNPs using Illumina® OmniExpress and Human660-Quad chips, and allelic association with AAO and MSSS was studied; a protein-interaction based pathway and network analysis was performed using the following tools/databases: VEGAS, GTEx eQTL-browser, STRINGv9.05, WebGestalt, GeneCodis, GO, KEGG, MetaCore™.

Results: No single association signal exceeded genome-wide significance in either AAO and MSSS analyses. We observed a replication at nominal level for the SNP rs758944$_A$ (p=1.15*10-3; beta=0.76), mapping in the locus of *LOC100289506-YWHAG*, which was previously identified as suggestively associated to disease severity in MS patients (IMSGC Genes and Imm 2011). Nominally associated loci at gene-level to AAO (n=950) were enriched for pathways related to chemokine signaling (adjusted-p=9*10-4) and oxidative phosphorylation (adjusted-p=9*10-4) among others, while for MSSS the 845 associated genes were mainly associated to leukocyte trans-endothelial migration (adjusted-p=2.4*10-3) and B-cell receptor activity (adjusted-p=2.2*10-3) among others. *P53* and *CREB1* genes were identified as central hubs in network analysis of AAO and MSSS trait respectively.

Conclusions: Despite no major-effect signals were detected in the present GWAS, our data suggest that common low-risk genetic variants acting in the context of pathways and networks related to both neurodegenerative and immune processes are associated with progression of neurological disability. In particular, according to our data, the role of immune processes seems to be of greater importance in the clinical expression of PPMS than what expected before. These observations could have interesting future therapeutic implications.

P424

Evaluation of interlukin 18 gene polymorphism and plasma concentration of IL-18 and IL-36 in relapsing remitting multiple sclerosis patients

F Khosravian[1], M Azadi[1], F Alsahebfosoul[2], M Etemadifar[3]
[1]Isfahan University of Medical Sciences, Molecular Biology Department, Isfahan, Iran, Islamic Republic of, [2]Isfahan University of Medical Sciences, Isfahan MS and Neuroimmunology Reseach Center, Immunology Department,

Isfahan, Iran, Islamic Republic of, [3]Isfahan University of Medical Sciences, Isfahan MS and Neuroimmunology Reseach Center, Neurology Department, Isfahan, Iran, Islamic Republic of

Background: Interleukin-1 (IL-1) family is a central mediator of innate immunity and inflammation. Interleukin-1R like receptors ligand family includes pro-inflammatory molecules such as IL-1α and IL-1β (IL-1F1), IL-18/IL-1F4, IL-36α/IL-1F6, IL-36β/IL-1F8, and IL-36γ/IL-1F9. Other members of the IL-1 family show anti-inflammatory activity. What is important is that all cells of the innate immune system express and/or are affected by IL-1 family members. Moreover, IL-1 family members play a key role in the differentiation and function of polarized innate and adaptive lymphoid cells. Also it has reported that cytokines play an important role in the pathogenesis of multiple sclerosis (MS). Here we will focus on two of the key members of this family are the IL-18 and IL-36 in Iranian Relapsing Remitting Multiple Sclerosis patients(RRMS).

Objectives: The purpose of the current study was to determine the serum levels IL-18, interleukin IL-36 and measure the frequency of rs360719 and rs1946518 SNPs on IL-18 gene in Iranian patients with RRMS compare to healthy control group.

Methods: 105 Iranian patients that clinically definite as multiple sclerosis (RRM) and 113 healthy controls were enrolled. IL-18 gene SNPs was assessed by HRM-PCR method. Also In a case-control study, venous blood was collected from healthy subjects as control group (n=45) and MS patients (n=45). All selected patients were clinically diagnosed as having relapsing remitting multiple sclerosis (RRMS) .The plasma levels of the cytokines IL-36 and IL-18 were measured using ELISA method.

Results: Elevated of IL-36 and IL-18 plasma level has been observed in patient with RRMS in comparison with control group. These findings also show that carriers of the (rs360719) and (rs1946518) display a slight protection against MS development. Patients homozygous for both SNPs showed a significantly higher proportion of MS patients.

Conclusions: We found a highly significant increase of IL-18 and IL-36 plasma levels in MS patients in comparison with the control group. also These protective effects might be related to functional outcomes of these IL-18 variations. This investigate confirms that IL-18 and the gene may be contribute in MS development and its progression particularly. The results indicate a pivotal role of IL-36 and IL-18 in immunopathogenesis of MS.

P425

Magnetic resonance imaging findings in healthy, genetically characterized, asymptomatic first-degree relatives of multiple sclerosis patients

SU Steele[1], AC Bakshi[1], Z Xia[2,3], A von Korff[2,3], EK Owen[2], ICM Cortese[4], PL De Jager[2,3], DS Reich[1]

[1]Translational Neuroradiology Unit, NINDS, NIH, Bethesda, MD, United States, [2]Program in Translational NeuroPsychiatric Genomics, Departments of Neurology, Brigham and Women's Hospital, Boston, MA, United States, [3]Harvard Medical School, Boston, MA, United States, [4]National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD, United States

Background: Subclinical demyelinating lesions precede the onset of clinical signs and symptoms in multiple sclerosis (MS).

Identification of a subset of first-degree relatives at the highest disease risk may enable studies of early stages of MS development and preventive trials.

Objectives: The "Genes and Environment in Multiple Sclerosis" (GEMS) study is a MS inception cohort with a prospective design that investigates factors that increase a person's risk of developing the disease. The specific aim of this substudy was to assess the prevalence of brain magnetic resonance imaging (MRI) abnormalities consistent with demyelination.

Methods: The GEMS study is a prospective natural-history study of individuals with at least one first-degree relative with MS. Subjects were assigned a genetic and environmental risk score (GERS) based on targeted genotyping of validated risk variants and questionnaires covering known environmental risk factors. Individuals in the top and bottom 5% of the GERS distribution underwent 3 tesla brain MRI with and without gadolinium contrast agent that included the following sequences: 3D-T1, 3D-FLAIR (1 mm isotropic), and 3D-EPI T2*-weighted (0.65 mm isotropic). The primary outcome was the presence of lesions on T2 images meeting the 2010 MRI criteria for dissemination in space, a precursor to clinical MS.

Results: The mean age of the 22 (15 females) subjects was $34\pm8y$, and the group comprised equal numbers of high and low GERS individuals. Five subjects (23%) reported a history of Epstein-Barr virus infection and eight (36%) were current or former smokers. In this interim analysis, three out of the eleven high-risk subjects (27%) and one out of the eleven low-risk subjects (9%) met the primary outcome (p=0.31). Further, four subjects (18%) had periventricular lesions, and seven (32%) had juxtacortical lesions. The mean total number of perivenular lesions in the low and high GERS cohort was 0.9 ± 1.3 ($14\pm20\%$) and 1.6 ± 1.7 ($33\pm37\%$), respectively.

Conclusions: Our interim results demonstrate the occurrence of subclinical demyelination in some neurologically asymptomatic family members and inform the power calculation of our study. MRI results of a larger cohort (>50 cases) will be presented. The detection of clinically meaningful MRI findings has important implications as early treatment and intervention is beneficial for reducing the accumulation of neurological disability.

P426

Target resequencing of regions associated with multiple sclerosis in the Italian population

N Barizzone[1], S Anand[2,3], M Sorosina[4], E Mangano[2], R Bordoni[2], F Clarelli[4], F Esposito[4], O Raymkulova[5], G Predebon[6], V Martinelli[4], G Comi[4], M Leone[4], G De Bellis[2], F Martinelli Boneschi[4], S D'Alfonso[1], (PROGEMUS, PROGRESSO)

[1]A. Avogadro University, IRCAD, Health Sciences, Novara, Italy, [2]Institute for Biomedical Technologies (ITB) National Research Council (CNR), Milan, Italy, [3]University of Sannio, Department of Science and Technology, Benevento, Italy, [4]San Raffaele Scientific Institute, Milan, Italy, [5]MS Centre, SCDU Neurology, AOU Maggiore della Carità, Novara, Italy, [6]A. Avogadro University, Health Sciences, Novara, Italy

Background: Several large international association studies identified over 100 genetic loci associated to Multiple Sclerosis (MS). However, for the majority of them the causal variant is not yet

identified and, generally, only common variants have been studied.

Objectives: The aim of this study was to follow-up the MS loci in the Italian population, searching for the primarily associated variants, focusing also on rare variants.

Methods: After an association study in 1750 Italian MS cases and 2272 matched controls (Illumina 660-Q,Immunochip), we selected for target resequencing 32 MS associated regions showing a significant association in the Italian population. The selected regions (1.9 Mb), either including the whole genomic segment (N=17 regions, 45 genes) or only the coding sequences (further 48 genes), were captured (Agilent SureSelect) and sequenced (GAIIx Illumina) in 576 Italian MS patients and 400 matched controls pooled in groups of 12 individuals. We used the variant caller CRISP to call the variants, ANNOVAR to annotate them, and custom R-scripts to calculate allele frequencies and compare them between patients and controls.

Results: We first determined the accuracy of our pipeline for the calculation of allele frequency from DNA pools, by comparing these results with those obtained by genotyping the single individuals with SNP array for a random subset of 144 variants. For each pool, a high concordance between the two methods was observed (mean correlation R2=0.989 ±0.0016 SE).Overall, we identified about 21000 variants present in patients and/or controls, 81% absent in databases and including about 1800 variants with a predicted functional consequence on the gene product (missense, nonsense, splice variants), thus potentially directly involved in MS susceptibility.A total of 7517 variants were present in both patients and controls, only 20% of them were present in genotyping chips previously utilized in MS association studies. A significantly (p< 0.05) different frequency between patients and controls was observed for 1503 variants, 8.5% of them absent in databases. For 33 of the analysed genes/regions, at least one variant identified from target resequencing showed a more significant p value than the marker present in the genotyping chips, possibly indicating a more associated signal for those regions

Conclusions: We developed an accurate pipeline that allowed to better define the association signal of MS loci. A replication in a larger population is ongoing .

P427

Human *Aquaporin 4* gene polymorphisms in Chinese patients with neuromyelitis optica spectrum disorders

W Qiu[1], Y Chang[1], R Li[1], C Li[2], Y Long[3], J Huang[1], W Mai[4], Y Dai[1], X Sun[1], W Xu[1], Y Chen[1], Z Lu[1], X Hu[1]
[1]*Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, [2]School of Mathmatics and Computational Science, Sun Yat-sen University, Guangzhou, China, [3]Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, China, [4]Fifth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*

Background: Aquaporin 4 (AQP4) and anti-AQP4 autoantibodies（NMO-IgG） are involved in the pathogenesis of neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorders (NMOSD). Conflicting results have been reported regarding the association between AQP4 gene polymorphisms and NMO.

Objectives: The study was designed to investigate the correlation between allele frequencies, genotype frequencies and haplotype frequencies in selected single nucleotide polymorphism(SNP) sites of *AQP4* gene and NMOSD in Chinese People.

Methods: 10 target SNPs were selected based on their minor allele frequency and positon in *AQP4* gene(2 in exon, 3 in intron, 1 in 5′-UTR and 4 in 3′-UTR). The SNPs were genotyped using multiplex polymerase chain reaction-ligase detection reaction in 208 NMO-IgG seropositive NMOSD patients and 204 healthy controls, their allele frequencies, genotype frequencies and haplotype frequencies in the target SNPs were calculated and a case-control association analysis was made.

Results: The heterozygous genotype at two 3′-untranslated region (UTR) SNPs was significantly higher in cases than controls: the A/T genotype of SNP rs1058424 (54.81% vs. 42.65%, padjusted = 0.024, odds ratio = 1.670, 95% confidence interval = 1.071-2.605) and the C/T genotype of SNP rs3763043 (53.85% vs. 42.65%, padjusted = 0.028, odds ratio = 1.638, 95% confidence interval = 1.054-2.545). Moreover, haplotype rs6508459A-rs1058424T-rs335929A-rs3763043T-rs3763040G- rs162007G-rs2075575A- rs151244T may be protective for NMO (7.67% vs. 12.18%, p = 0.042).

Conclusions: Polymorphisms in the coding region of *AQP4* are unlikely to confer NMOSD susceptibility. However, the 3′-UTR of this gene presents several polymorphic sites that may affect NMOSD risk in the Chinese. Functional studies are needed to support the statistical findings.

P428

Defining the functional role of a novel MS susceptibility gene, IL7R alpha chain

L Bergamaschi[1], G Galarza-Muñoz[2], F Briggs[3], S Arvai[1], L Barcellos[4], M Garcia-Blanco[5], S Gregory[1]
[1]*Duke Molecular Physiology Institute, Medicine, Durham, NC, United States, [2]Duke University, Molecular Gnetics and Microbiology, Durham, NC, United States, [3]Case Western Reserve University, Epidemiology and Biostatistics, Cleveland, OH, United States, [4]University of California, School of Public Health, Berkeley, CA, United States, [5]Duke University Medical Center, Molecular Gnetics and Microbiology, Durham, NC, United States*

Background: We previously established that rs6897932 in the interleukin 7 alpha chain receptor (IL-7Rα) gene is associated with MS. I*n vitro* and *in vivo* functional analysis show that the associated "C" risk allele increases alternative splicing of IL-7Rα which, in turn, alters the ratio of the receptor and soluble proteins.

Objectives: To build upon this data by identifying the mechanisms associated with IL-7Rα splicing and signaling with MS. Genes identified by these analyses represent MS candidates that can be tested for genetic association within MS case/control cohorts. To define the effects of allele specific expression of IL-7Rα on IL-7 signaling in CD4+ and CD8+ T cells within controls and RR-MS patients to define the role of IL7R in MS.

Methods: We used tobramycin affinity chromatography to identify *trans*-acting protein factors that interact with IL7R exon 6 and validated their splicing using siRNA-based screening in depleted HeLa cells. We screened for genetic association of the trans-acting

proteins in IMSGC case/control cohorts from the IMSGC. Finally, we investigated the levels of phosphorylated STAT5 by flow cytometry in primary T cell cultures after IL-7 stimulation in relapsing-remitting MS patients and concurrently in HEK293 cell lines.

Results: We identified several *trans*-acting protein factors that interact with IL-7R exon 6 and established the role of cleavage and CPSF1, MAP4, PTBP1, DDX39B in gene cleavage. We also identified significant genetic association of DDX39B independent of HLA-DRB1*15:01. Interestingly, DDX39B (BAT1) has also been associated with Myasthenia Gravis, rheumatoid arthritis and systemic lupus. Analyses of naïve CD4+ T cells in MS patients and controls show a trend in which MS 'C' allele carriers have higher IL-7 signaling. However, quantification of sIL7R in plasma shows higher level of soluble IL-7Rα in a genotype dependent manner. Finally, incubation of transiently transfected cell lines with IL-7 and soluble IL-7Rα-Fc protein significantly reduces phosphorylation of STAT5 (p< 0.01) independent of genotype.

Conclusions: We have identified and validated several proteins from the trans-acting complex that regulate IL-7Rα exon 6 splicing one of which is genetically associated with MS independent of the HLA. We have established that 'C' allele carriers have higher IL-7 signaling in CD4+ cells, contrasting with data that suggests that MS 'C' carriers produce more soluble IL-7Rα which we found significantly reduces IL-7 signaling.

P429

Progranulin gene variability influences recovery and residual disability after relapses in multiple sclerosis

M Vercellino[1], C Fenoglio[2], C Chiavazza[1], A Mattioda[1], S Masera[1], D Galimberti[2], E Scarpini[2], L Pinessi[1], P Cavalla[1]
[1]AOU Città della Salute e della Scienza di Torino, Torino, Italy, [2]IRCSS Ospedale Maggiore Policlinico di Milano, Milano, Italy

Background: Progranulin (PGRN) is a multifunctional protein involved in inflammation and wound healing, and also a neurotrophic factor that enhances neuronal survival and axonal outgrowth. PGRN is strongly expressed in MS brains by inflammatory cells (macrophages/microglia) in active demyelinating lesions, and PGRN CSF levels have been showed to be increased during MS relapses.

Objectives: To evaluate the influence of PRGN polimorfisms on relapse recovery in MS patients.

Methods: PGRN gene variability was analyzed in a sample of 100 patients with relapsing-remitting MS. Data on relapses was collected and clinical outcomes of relapses were recorded (complete/incomplete recovery and residual disability) Residual disability was defined as the difference between EDSS at follow-up evaluations and EDSS before the relapse.

Results: Incomplete recovery and persistence of residual disability after a relapse was correlated with an increased frequency of the rs9897526 AA genotype (37.2% incomplete recovery vs 3.6% complete recovery, OR 15.704, p < 0.0001); likewise a severe residual disability after a relapse (EDSS increase after a relapse >1) was also correlated with an increased frequency of the rs9897526 AA genotype (44.0% vs 20.0%, OR 3.2, p = 0.029).

Conclusions: PGRN haplotypes likely influence recovery and residual disability after relapses in Multiple Sclerosis.

Imaging-1

P430

White matter abnormalities and gray matter atrophy measurements in long disease duration multiple sclerosis: prediction of a benign course

A Ruet[1], MD Steenwijk[1,2], A Versteeg[1], M Daams[1,2,3], PJW Pouwels[2,4], LJ Balk[2,5], PK Tewarie[2,5], J Killestein[2,5], BMJ Uitdehaag[2,5,6], JJG Geurts[2,3], F Barkhof[1,2], H Vrenken[1,2,4]
[1]VU University Medical Center, Department of Radiology and Nuclear Medicine, Amsterdam, Netherlands, [2]Neuroscience Campus Amsterdam, Amsterdam, Netherlands, [3]VU University Medical Center, Department of Anatomy and Neurosciences, Amsterdam, Netherlands, [4]VU University Medical Center, Department of Physics and Medical Technology, Amsterdam, Netherlands, [5]VU University Medical Center, Department of Neurology, Amsterdam, Netherlands, [6]VU University Medical Center, Department of Epidemiology and Biostatistics, Amsterdam, Netherlands

Background: White matter (WM) abnormalities and gray matter (GM) atrophy are related to clinical disability in multiple sclerosis (MS), but their respective contribution is still debated.

Objectives: To investigate WM and GM damage in benign multiple sclerosis (BMS).

Methods: A prospective study included relapsing-remitting MS patients with long disease duration (DD) (≥15 years from disease onset) and healthy controls (HCs). Patients underwent clinical assessment using the Expanded Disability Status Scale (EDSS) and were classified as BMS if their EDSS score did not exceed 3, and non BMS (nBMS) otherwise. MRI scans were acquired at 3.0 T. Focal WM lesions were segmented using 3DFLAIR and kNN-TTP method. LEAP method was applied for lesion filling. FreeSurfer software (5.1) was used to measure global and regional cortical thickness (cTh) and deep GM (DGM) volumes from 3DT1. Fractional anisotropy (FA), mean, axial and radial diffusivity (MD, AD, RD) were obtained from diffusion tensor imaging and averaged across the WM skeleton obtained with FSL tract-based spatial statistics analysis.

Results: 60 HCs and 91 MS patients were recruited including 51 BMS and 40 nBMS. Mean age (50.3±7.1, 50.8±8.3, 54.1±8.1 years for HCs, BMS and nBMS), sex ratio, and mean DD (20.8±4.7, 23.6±4.8 years for BMS and nBMS) did not differ between groups. The median normalized WM lesion volume (NLV) was lower in BMS than in nBMS (p< 0.05). Mean whole-brain cTh was reduced in BMS (2.49±0.08 mm) and nBMS (2.44±0.10 mm) than HCs (2.56±0.09 mm) (p< 0.01 and p< 0.001). There was more cortical atrophy in nBMS than in BMS patients(p< 0.05) in particular in frontal (p< 0.05), precentral (p< 0.01) and postcentral (p< 0.05) areas. After adjustment for NLV, the mean whole-brain cTh did not differ between BMS and nBMS. Normalized DGM volume (NDGMV) was lower in BMS and nBMS than in HCs (p< 0.01 and p< 0.001). There was more subcortical atrophy in nBMS than in BMS (p< 0.05), even when controlling for WM lesions. Mean FA was significantly decreased and mean MD, AD and RD were significantly increased in nBMS compared to BMS and HCs, and in each MS group versus HCs. In stepwise logistic regression including age, sex, NLV, mean cTh,

NDGMV, and FA, BMS was predicted by NDGMV (64.8% of cases correctly classified). In a model including regional cTh, BMS was predicted by precentral cTh.

Conclusions: BMS patients had less WM damage and less cortical and DGM atrophy than nBMS patients. Low subcortical atrophy was the strongest predictor for a benign disease course.

P431

Regional distribution and evolution of grey matter changes in different MS phenotypes: a 5-year longitudinal study

M Calabrese[1], R Reynolds[2], R Magliozzi[3], M Castellaro[4], A Scalfari[5], OW Howell[6], A Morra[7], A Gajofatto[1], C Romualdi[8], MD Benedetti[1], S Monaco[1]

[1]University Hospital of Verona, Dept. of Neurological and Movement Sciences, Verona, Italy, [2]Imperial College, Division of Brain Sciences, Faculty of Medicine, London, United Kingdom, [3]Istituto Superiore di Sanità, Dept. of Cell Biology and Neuroscience, Rome, Italy, [4]University of Padova, Dept. of Information Engineering, Padova, Italy, [5]Imperial College, Neuroscience Dept., London, United Kingdom, [6]Swansea University, Institute of Life Science 'ILS', Swansea, United Kingdom, [7]Euganea Medica, Neuroradiology Unit, Padova, Italy, [8]University of Padova, Dept. of Biology, Padova, Italy

Background: Several studies suggested that grey matter (GM) atrophy occurs from the earliest stages of the Multiple Sclerosis (MS) and is a major determinant of long-term disability. Nevertheless, understanding mechanisms underlying the cortical atrophy is still challenging.

Objectives: The aim of this study was to elucidate the relationship between focal and diffuse GM damage, by assessing how the appearance of new cortical lesions (CLs) affects the regional distribution and the longitudinal evolution of the cortical thinning.

Methods: Ninety-six patients were included in this 5-year longitudinal study. At baseline (T0), 20 patients had clinical isolated syndrome (CIS), 27 had early Relapsing Remitting MS (early RRMS) (disease duration < 5 years), 29 had late RRMS (disease duration ≥ 5 years) and 20 had secondary progressive MS (SPMS). Cortical thinning and new CLs were evaluated in more than 40 cortical areas by using Freesurfer and 3D DIR sequence both at T0 and after 5 years (T5).

Results: New CLs mainly occurred in hippocampus (9.1%), insula (8.9%), cingulate cortex (8.3%), superior frontal gyrus (8.1%) and cerebellum (6.5%). Significant differences were observed among different disease subtypes (p< 0.001). Frontal regions were more involved in the early course of the disease, whereas during later stages the appearance of new CLs was more widespread. Similarly, the cortical thinning and volume loss distribution varied according to the disease duration. These were more severe in hippocampal gyrus, insula and cingulate cortex of CIS (7.7%, 6.2% and 7.0% respectively) and early RRMS (5.6%, 7.0% and 6.7% respectively), conversely they were significantly greater in precentral gyrus, postcentral gyrus, and cerebellum of late RRMS (-6.9%,-6.5% and -6.8%) and SPMS (-6.1%,-6.5% and -6.5 %). The total number of new CLs correlated with the global cortical thickness change in the whole group (r^2=26.2, p< 0.001). However, such a correlation was more marked in CIS (r^2=50.0, p< 0.001) and in early RRMS patients (r^2=52.3,

p< 0.001), moderate in late RRMS (r^2=25.5, p< 0.001) and absent in SPMS (r^2=6.3, p=0.133).

Conclusions: In line with previous neuropathological studies on lymphoid-like meningeal immune cell infiltrates and subpial demyelination, some cortical regions seem to be more susceptible to both diffuse and focal damage than others. New CLs correlated with the development of cortical atrophy, at least in the early disease course, thus suggesting a potential relationship between focal and diffuse GM damage.

P432

The association of thoracic spinal cord gray matter atrophy with disability and disease type in multiple sclerosis

R Schlaeger[1,2], ND Papinutto[1], C Bevan[1], E Caverzasi[1], J Gelfand[1], A Green[1,3], KM Jordan[1,4], W Stern[1], H-C von Büdingen[1], E Waubant[1], A Zhu[1], DS Goodin[1], BA Cree[1], SL Hauser[1], RG Henry[1,4,5]

[1]UCSF, Neurology, San Francisco, CA, United States, [2]University Hospital Basel, University of Basel, Neurology, Basel, Switzerland, [3]UCSF, Opthalmology, San Francisco, CA, United States, [4]Bioengineering Graduate Group, University of California San Francisco & Berkeley, San Francisco & Berkeley, CA, United States, [5]UCSF, Radiology and Biomedical Imaging, San Francisco, CA, United States

Background: In multiple sclerosis (MS) cerebral gray matter (GM) atrophy correlates more strongly with disability than white matter (WM) atrophy. The corresponding relationships in the thoracic spinal cord are unknown due to technical limitations in assessing spinal GM atrophy using standard acquisition and analysis protocols.

Objectives: To determine the association of the thoracic cord spinal GM and WM areas with MS disability and disease type using phase sensitive inversion recovery (PSIR) MRI.

Methods: 143 MS patients and 20 healthy controls were scanned on a Siemens 3T Skyra scanner with a 20-channel neck-head coil and a 32-channel spine coil. A PSIR sequence was acquired at the T8/9 and in a subset of 115 patients also at the T9/10 intervertebral disc levels (dependent on available scanning time). Moreover, each subject received a brain MPRAGE, 1mm cubic voxels. Total cord and cord GM areas were segmented at each level, and cord WM areas were calculated as the difference between them. Correlations between the spinal cord areas and the Expanded Disability Status Score (EDSS) were assessed by Spearman rank correlation. Differences in cord areas between groups were assessed using age and sex as covariates. The relationship between EDSS (as dependent variable) to MRI measures of brain GM and WM volumes and thoracic spinal GM and WM areas were assessed using multivariate regression analysis.

Results: At both thoracic levels, relapsing (R) MS patients showed smaller spinal GM areas compared to their age and sex matched controls (T8/9: p=0.0025, T9/10: p=0.0099) without significant differences in spinal WM or total cord areas. Progressive (P) MS patients showed smaller spinal GM (p=0.0002, p< 0.0001) and total cord areas (p=0.0004, p=0.0043) compared to RMS patients at both T8/9 and T9/10 levels, respectively. Spinal cord GM, WM, and whole cord areas inversely correlated with EDSS (at T8/9: rho: -0.48, -0.32, -0.40, respectively; at T9/10: rho:

-0.49, -0.36, -0.40, respectively; all p< 0.001). Brain and thoracic spinal GM independently contributed to EDSS.

Conclusions: Thoracic spinal cord GM atrophy is detectable in-vivo in the absence of WM atrophy in RMS. It is more pronounced in PMS than RMS and contributes to patient disability in MS independently from brain GM atrophy.

P433

Brain parenchymal fraction in the healthy - determined by MRI in an age stratified population and via a systematic review of the literature

M Vågberg[1], T Lindqvist[2], R Birgander[2], A Svenningsson[1]
[1]Umeå University, Dept. of Pharmacology and Clinical Neuroscience, Umeå, Sweden, [2]Umeå University, Dept. of Radiation Sciences, Diagnostic Radiology, Umeå, Sweden

Background: Brain atrophy is of great interest in many neuro-degenerative diseases, such as multiple sclerosis and Alzheimer's disease. It is further established that age-related brain atrophy occurs regardless of pathological neurodegeneration. Brain atrophy is commonly measured using magnetic resonance imaging (MRI) and often described in terms of the brain parenchymal fraction (BPF), which is most often defined as the ratio of total brain parenchyma to total intracranial space. The BPF is of interest both in the research setting and in clinical practice, but in order to be able to properly interpret this variable in the clinical setting, the normal range of the BPF in relation to age must be known.

Objectives: To present normal values for BPF, stratified by age.

Methods: The BPF of 78 healthy individuals aged 21 to 70 was determined using a semiautomated MRI-method. In addition, a systematic review of PubMed and Scopus was performed, identifying studies presenting the BPF of healthy individuals.

Results: The mean (± 1.96 SE) BPF of the whole study population was 0.863 (± 0.007). The BPF decreased with increasing age. In the literature search, 56 articles presenting BPF in a total of 6691 healthy individuals were found. Age-stratified values of the BPF of healthy individuals are presented, both from the new group of healthy volunteers examined in this study and compiled from available published studies found via the literature search.

Conclusions: There was a clear relationship between increasing age and decreasing BPF, representing age-related brain atrophy. Knowledge of the range of normal BPF in a specific age group will help in the interpretation of BPF data in individual patients, when no control subjects are available.

P434

The rate of GM lesion development is similar in all MS disease subtypes

R Abdel-Fahim[1], O Mougin[2], CM Allen[3], A Pitiot[4], P Gowland[2], N Evangelou[1]
[1]University of Nottingham, Division of Clinical Neurosciences, Nottingham, United Kingdom, [2]University of Nottingham, Sir Peter Mansfield MR Centre, Nottingham, United Kingdom, [3]Queen Elizabeth Hospital, London, United Kingdom, [4]University of Nottingham, School of Psychology, Nottingham, United Kingdom

Background: Focal cortical demyelination occurs in all MS phenotypes and is associated with physical and cognitive disability. Cortical lesions can be detected using different MRI sequences such as DIR, MPRAGE, PSIR, 7T T2* as well as 7T MTR. Previous studies using 1.5 T DIR found that the rate of cortical lesions accumulation in MS patients was associated with disability progression.

Objectives:

- Measure the rate of cortical lesions accumulation at 14 months using more sensitive ultra high field imaging (7T).
- Assess the association between the rate of cortical and white matter lesion (WML) accumulation with the disability progression.

Methods: Forty MS patients (8 CIS, 12 RRMS, 10 PPMS and 10 SPMS) were scanned at baseline and 22 of them were rescanned 14 months later so far. We used amongst others MTR and PSIR sequences at 7 Tesla MRI scans (voxel size 0.6 mm3 isotropic). Grey matter and white matter lesion segmentation was performed by two independent observers, blinded to the patient's disease status.

Results: At baseline SPMS patients had the highest median grey matter lesions (GML) volume (1797 mm³), while CIS patients had the lowest (218 mm³). There was no significant difference between PPMS and RRMS patients in terms of GML volumes (413 mm³ and 546 mm³ respectively). There was a significant correlation of disease duration with the baseline GML counts and volumes. At 14 months, the median new GML accumulation was the same 1 lesion/ per patient and that was not significantly different across disease subtypes. The rate of EDSS progression was the highest in PPMS patients at the 14 months visit. There was a significant correlation between the rate of change of EDSS and the rate of new GML development (but not WML) over 14 months (rho =0.74, p < 0.05). A significant correlation was also detected between the GML and WML accumulation over 14 months period (rho = 0.64, p = 0.001).

Conclusions: Our study suggests that focal grey matter pathology contributes to physical disability progression in MS patients. Our results also suggests that GML develop at the same rate throughout the course of the illness and is associated with the development of short term physical disability.

P435

Motor network global and local efficiency changes across the MS spectrum

M Pardini[1,2], Ö Yaldizli[1,3], V Sethi[1], N Muhlert[1,4], Z Liu[1,5], M Ron[1], C Wheeler-Kingshott[1], DH Miller[1], DT Chard[1,6]
[1]UCL Institute of Neurology, NMR Research Unit, Queen Square MS Center, London, United Kingdom, [2]University of Genoa, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Genoa, Italy, [3]University Hospital Basel, Department of Neurology, Basel, Switzerland, [4]Cardiff University, Department of Psychology, Cardiff, United Kingdom, [5]Xuanwu Hospital of Capital Medical University, Beijing, China, [6]National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre, London, United Kingdom

Background: While motor function depends on the integration of a widespread network, the impact of structural pathology on

information exchange inside this network is poorly understood. The potential of a network to exchange information between its components can be characterized using Network efficiency (NE), a graph theory-based measure that takes into account the integrity of network components as well as the topological properties of the network (i.e. the existence and distribution of the connections between elements).

Objectives: To evaluate the potential of NE to capture the impact of diffuse structural pathology in the motor network in subjects with multiple sclerosis (MS). To explore the impact of NE changes on motor disability across subtypes of MS.

Methods: 90 people with MS (18 subjects with primary progressive [PP] MS, 28 subjects with secondary progressive [SP] MS and 44 subjects with relapsing remitting [RR] MS) and 22 age-matched controls were included in this study. For each person we acquired diffusion imaging, magnetization transfer ratio (MTR) data and T1 volumetric sequences as well as metrics of upper limb disability (9 hole peg test), walking difficulties (timed walking test) and global disability (EDSS). Constrained spherical deconvolution tractography was used to create study-specific masks of motor system cortico-cortical, cortico-cerebellar and cortico-striatal fibres in controls. Fractional anisotropy, MTR and volume data were computed for each tract and combined to create a single, multi-modal metric of structural pathology. The combined metric thus obtained for each tract was then used to compute global and local NE for the motor network in each participant in the study.

Results: People with MS had a significantly lower global NE in the motor network compared to controls. The SPMS group presented with lower motor network global NE values compared to PPMS subjects, also when taking into account global disability, as well as lower global NE values compared to RRMS patients. Regression analysis identified local NE changes in the pre-frontal and basal ganglia nodes of the motor network as the more relevant anatomical substrata of motor disability.

Conclusions: The study findings indicate the potential of single-network global efficiency analysis to provide novel insights into the physiopathology of motor deficits in MS and to highlight phenotype-specific differences in discrete regions within a network.

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The link between subpial and diffuse white matter pathology in MS: a multimodal 7T and 3T MRI study using a surface-based and a tract-based analysis

C Louapre[1,2], ST Govindarajan[1], C Giannì[1,2], J Cohen-Adad[3], RP Kinkel[4], C Mainero[1,2]

[1]AA Martinos Center for Biomedical Imaging, Charlestown, MA, United States, [2]Harvard University, Boston, MA, United States, [3]Ecole Polytechnique de Montréal, Montreal, QC, Canada, [4]Beth Israel Deaconess Medical Center, Boston, MA, United States

Background: Subpial and diffuse white matter (WM) injury are the pathological substrate of clinical progression in multiple sclerosis (MS). The interdependence between these two processes, however, is still unclear.

Objectives: Using multimodal 7T and 3T MRI, we assessed:

1) the relationship between subpial pathology and juxta-cortical WM injury using a surface-based method,

2) the relationship between subpial pathology and "long distance" WM injury in tractographically connected tracts as a function of distance from the cortex,

3) the relative contribution of subpial and WM damage to clinical metrics.

Methods: Thirty-four patients underwent 7T MRI multi-echo T2* imaging (0.33×0.33×1 mm^3) for intracortical laminar quantification of T2* decay; 3T MRI for acquiring

1) T1-weighted images optimized for cortical surface reconstruction using FreeSurfer,

2) diffusion tensor images (DTI, 1.85 mm iso, 60 directions). T2* maps were registered to cortical surfaces, and sampled along the cortex at 25%, 50%, 75% depth from pial surface.

WM tracts of interest (cingulum, corticospinal tract, CST, thalamic radiation, longitudinal fasciculus) were reconstructed using probabilistic tractography. The relationship between DTI metrics at each voxel along the tracts and laminar T2* in the projection cortex was tested with a multi-linear regression model. The relationship between T2* at each cortical depth and juxta-cortical WM pathology (DTI metrics sampled at 2mm below the cortex) was tested vertex-wise using a General Linear Model (GLM).

Results: Increase in T2* at 25%, 50% and 75% depth from pial surface (suggestive of iron and myelin loss) was associated with juxta-cortical WM degeneration in widespread bilateral areas (p< 0.05, corrected); this association was maximal for T2* at 75% depth. Increase in subpial T2* also correlated with DTI abnormalities in long-distance WM tracts, mainly in the proximal portion of the tracts. In a multi-linear regression model testing the contribution of spatially associated subpial and long distance WM pathology to MS clinical metrics, pyramidal EDSS subscore was best predicted by axial diffusivity in the CST (p< 0.01); Symbol Digit Modalities Test scores were best predicted by increased T2* in the isthmus cingulate (p=0.007).

Conclusions: We found a spatial association between subpial pathology and both juxta-cortical and long distance WM injury. Despite the association, the two pathological processes contribute independently to clinical measures.

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Multiple sclerosis lesion fingerprint using quantitative MRI multicontrast analysis

G Bonnier[1,2], A Roche[2], D Romanasco[2,3], S Simioni[4], D Meskaldji[3], D Rotzinger[5], Y-C Lin[6], G Menegaz[6], M Schluep[4], R Du Pasquier[4], TJ Sumpf[7], J Frahm[7], J-P Thiran[3], G Krueger[2,8], C Granziera[2,4]

[1]University of Lausanne, Lausanne, Switzerland, [2]Advanced Clinical Imaging Technology Group, Siemens-EPFL, Lausanne, Switzerland, [3]Ecole Polytechnique Federale Lausanne, STI / IEL / LTS5, Lausanne, Switzerland, [4]Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Department of Clinical Neurosciences, Lausanne, Switzerland, [5]Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Department of Radiology, Lausanne, Switzerland, [6]University of Verona, Department of Computer Science, Verona, Italy, [7]Max Planck Institute for Biophysical Chemistry, Biomedizinische NMR Forschungs GmbH, Goettingen, Germany, [8]Siemens Schweiz AG, Healthcare Sector IM&WS S, Renens, Switzerland

Background: Multiple sclerosis (MS) is a disease with heterogeneous pathogenetic mechanisms. This heterogeneity reflects variable amount of inflammatory, degenerative and reparative processes. While conventional magnetic resonance imaging allows to count and localise MS lesions, new quantitative (q)MRI techniques provide measurements that reflect pathological processes underlying tissue alteration and could potentially provide new tool to differentiate brain lesions severity.

Objectives: In this study, we combined T1, T2, T2* relaxometry and Magnetisation Transfer Ratio (MTR) imaging in order to provide a multimodal MRI fingerprint of lesions pathology and severity. We assessed the correlation between the MRI fingerprint of local damage severity and clinical motor and cognitive performances in MS patients.

Methods: We enrolled 36 patients with early relapsing-remitting MS (34.8 years, 24 women/12 men, disease duration < 6 years) and 18 age-matched healthy controls who underwent advanced MRI examinations at 3T. Lesion count and segmentation were performed by certified neurologist and radiologist in 3D DIR, 3D FLAIR and 3D MP2RAGE images. Clinical examination were assessed using an extensive battery of cognitive, motor and disability tests. Lesions fingerprints were defined for both cortical and subcortical lesions by combining z-score measurements in 4 MRI modalities (z_{T1}, z_{T2}, z_{T2*}, z_{MTR}) between lesion and healthy tissue distribution in the corresponding ROI. Linear regression analysis was performed between lesions fingerprints and clinical scores for all patients. Correction for multiple comparison and cross-validation test were applied.

Results: Lesion fingerprint analysis showed 12 patterns including plaques with prevalent inflammation (isolated high z_{T2} and/or z_{T2*}), gliosis (moderate low z_{MTR} and high $z_{T2/T2*}$, z_{T1}), axonal/myelin damage (moderate high z_{T1}, $z_{T2/T2*}$ and low z_{MTR}), tissue loss (large z_{T1} and low z_{MTR}). The regression analysis revealed a highly significant association, confirmed by cross-validation results, between lesions fingerprints and general disability score (Adj-R^2 = 0.6, p < 0.0001), execution score (Adj-R^2 = 0.5, p < 0.001) and verbal memory score (Adj-R^2 = 0.4, p < 0.01).

Conclusions: Combination of qMRI parameters provides a new tool to identify the nature and severity of tissue alterations in MS lesions and proposes an "in vivo" histopathological characterisation of local damage that highly correlate with clinical performances in patients.

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Texture of deep gray matter areas relates to disability in multiple sclerosis

L Gaetano[1], S Magon[1], M Chakravarty[2,3], O Findling[1], M Amann[1,4,5], J Reinhardt[5], Y Naegelin[1], C Stippich[5], L Kappos[1], E-W Radue[4], T Sprenger[1,4,5]

[1]University Hospital Basel, Department of Neurology, Basel, Switzerland, [2]Centre for Addiction and Mental Health, Kimel Family Translational Imaging-Genetics Research Laboratory, Research Imaging Centre, Toronto, ON, Canada, [3]University of Toronto, Department of Psychiatry and Institute of Biomaterials and Biomedical Imaging, Toronto, ON, Canada, [4]University Hospital Basel, Medical Image Analysis Center, Basel, Switzerland, [5]University Hospital Basel, Department of Radiology, Division of Diagnostic and Interventional Neuroradiology, Basel, Switzerland

Background: Multiple Sclerosis (MS) is traditionally considered a white matter disease, but inflammatory and degenerative changes are also abundant in the neocortex and deep gray matter (dGM) nuclei. The detection and quantification of dGM abnormalities is challenging in vivo, because of the limited size of these structures and the low contrast to surrounding tissues in conventional MRI.

Objectives: The aim of this work was to investigate dGM abnormalities on MRI images using texture analysis (TA), a novel approach that describes and quantifies the spatial distribution of intensity values in regions-of-interest. We aimed at relating texture to MS-related disability as measured by EDSS (Expanded Disability Status Scale).

Methods: 118 patients with relapsing-remitting MS were studied (80 women; age 44.9±10.4 y; disease duration 15.3±8.6 y; EDSS 2.7±1.4). T1-weighted MPRAGE and PD/T2-weighted images were acquired at 1.5T. Lesions were segmented semi-automatically. Cortical GM and dGM (i.e., thalamus, globus pallidus and striatum) were segmented using automated approaches (SIENAX and MAGeT). For each dGM structure, 139 features describing the texture (based on the histogram, gray level co-occurrence matrix, gradient, and run-length matrix) were extracted from T1w, normalized and reduced with principal component (PC) analysis using Matlab. Multiple linear regression was conducted to explore the relation between EDSS and the TA of dGM structures: in the first model, the explanatory variables (EVs) were the first *k* PCs that explained 95% of the variance of the original dataset; in the second model, the EVs were age, gender, disease duration, the most significant PCs derived from the previous model (p< 0.05), lesion volume, and GM volume. All statistical analyses were performed using R.

Results: Using the most significant PCs of the thalamus, striatum and globus pallidus as EVs and EDSS as independent variable, R^2 values of 0.308, 0.161, 0.167, respectively, were found. R^2 reached 0.329 if a combination of all 3 dGM structures PCs was used. Adding age, gender, disease duration, lesion and GM volume to those PCs led to a R^2 of 0.352, 0.344, 0.321 and 0.371 for the thalamus, striatum, globus pallidus, and a combination of all 3.

Conclusions: Our results confirm the involvement of dGM in the pathophysiology of MS. Moreover, the data suggest that the texture of dGM reflects disease processes, which in turn relate to disability.

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Sustained low rate of brain volume loss under long-term fingolimod treatment in relapsing multiple sclerosis: results from the LONGTERMS study

EW Radue[1], F Barkhof[2], J Cohen[3], R Gottschalk[4], Y Zhang[5], L Cappiello[5], P von Rosenstiel[4], L Kappos[6]

[1]Medical Image Analysis Center (MIAC), Basel, Switzerland, [2]VU University Medical Center, Amsterdam, Netherlands, [3]Cleveland Clinic, Neurological Institute, Cleveland, OH, United States, [4]Novartis Pharma AG, Basel, Switzerland, [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States, [6]University Hospital, Department of Neurology, Basel, Switzerland

Background: Brain volume loss (BVL) in multiple sclerosis (MS) occurs at rates that exceed those reported in healthy controls

and is related to long-term disability. In the 2 year, phase 3, FREEDOMS and FREEDOMS 2 studies, fingolimod 0.5 mg once daily significantly reduced BVL versus placebo. LONGTERMS is an open-label, single-arm, long-term follow-up extension study of phase 2, 3 and 3b trials of fingolimod in relapsing MS. It commenced in June 2010 and will continue, with annual interim analyses, until June 2016, providing the opportunity to study long- term effects of fingolimod on BVL.

Objectives: To evaluate long-term BVL in patients who received fingolimod 0.5 mg or placebo in the FREEDOMS or FREEDOMS 2, core or extension studies, and later entered LONGTERMS.

Methods: We performed a pooled analysis of patients who completed the FREEDOMS and FREEDOMS 2 core studies (full analysis set) and received at least one fingolimod dose in LONGTERMS. We calculated the percent brain volume change (PBVC) and the mean annualized rate of brain atrophy (ARBA) at different time points from the core baseline using SIENA (Structural Image Evaluation using Normalization of Atrophy).

Results up to month (M) 72 are presented for those patients who received continuous fingolimod 0.5 mg throughout core and extension and those who switched from placebo to fingolimod (placebo-fingolimod).

Results: Data were available from 2355 patients (fingolimod 0.5 mg: 783, placebo-fingolimod: 773). The overall median (Q1-Q3) exposure to fingolimod was 915(271-1689) days (fingolimod 0.5 mg: 1271[699-2250]; placebo-fingolimod: 379[0-1486]); 18.8% of all patients had fingolimod exposure for ≥2160 days (6 years). At M 6, 12, 24, 36, and 48, mean PBVC was -0.22 vs. -0.36; -0.44 vs. -0.63; -0.83 vs. -1.28; -1.22 vs.-1.73 and -1.61 vs. -2.16 for fingolimod 0.5 mg vs. placebo-fingolimod. Mean ARBA was -0.43 vs.-0.70;-0.45 vs.-0.64;-0.43vs.-0.67;-0.41 vs.-0.59 and -0.43 vs. -0.58. A similar pattern was observed at M 60 and 72 for both PBVC (-1.49 vs.-2.41 and -1.58 vs.-2.99) and ARBA (-0.31 vs.-0.51 and -0.27 vs.-0.52), although patient numbers at these time points were small.

Conclusions: Long-term treatment with fingolimod 0.5 mg once daily is attended by sustained low rates of brain volume loss up to 6 years. Patients switching after the core studies from placebo to fingolimod did not catch up regarding overall brain volume loss.

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Iron in multiple sclerosis lesions can be detected by larger volumes on quantitative susceptibility mapping than on T2 weighted imaging

C Wisnieff[1,2], S Ramanan[3], Y Wang[1,2], D Pitt[4]
[1]Cornell University, Ithaca, NY, United States, [2]Weill Medical College, New York, NY, United States, [3]Yale University, New Haven, CT, United States, [4]Yale University, New Haven, NY, United States

Background: A key feature of inflamed multiple sclerosis lesions is the presence of activated microglia/macrophages (m/M), some of which contain high amounts of iron (Fe). Detecting Fe positive (Fe+) m/M could thus provide an *in vivo* imaging biomarker to distinguish actively inflamed lesions from Fe negative (Fe-) chronic silent lesions. Quantitative susceptibility mapping (QSM) from gradient echo MRI measures tissue magnetic susceptibility and is particularly sensitive to iron and myelin in white matter. Conventional T2 weighted (T2w) MRI is sensitive to the cellular

content in a voxel of water. The combination of QSM and T2w would enable detection of iron in MS lesion.

Objectives: To test the hypothesis that a Fe+ lesion can be detected by its volume increase from T2w to QSM using MRI and histological analysis (for Fe, myelin and m/M).

Methods: MRI: 7 formalin fixed MS brain specimens were imbedded in 1% agar. QSM (gradient echo) and T2w (fast spin echo) images were acquired on a 3T scanner using imaging parameters TR/TE spacing/#Echoes = 53.8ms/ 4.15ms/12 at a resolution of $0.7x0.7x0.7mm^3$ for QSM and TE/TR = 83-103ms/1-2.5s at resolution $0.75x0.75x1.2\ mm^3$ for T2w. The volume of 12 lesions on MRI data were assessed. Histological sections: 4 lesions were examined with immunohistochemical labeling for myelin (MBP), m/M (CD68), ferritin and Perls stain; 2 of these had iron measurements using laser ablation inductively coupled mass spectrometry (LAICPMS).

Results: Four lesions with histology showed that volumes on QSM (Fe ±): 6.9 (Fe-), 51.3 (Fe+), 138.0 (Fe+), and 303.5 (Fe+) mm^3 were larger than that on T2w: 6.6, 41.5, 100.3 and 245.4 mm^3 by 4.1%, 23.6%, 37.6% and 27.2% respectively. Fe± for lesions were determined by iron staining or LAICPMS measurements. While the Fe- lesion had no m/M on CD68, all Fe+ lesions had activated m/M at the lesion border on CD68. 0%, 76.9%, 23.1% and 91.2% of the QSM volumes of these lesions had paramagnetic susceptibilities, with their spatial extent from lesion periphery into interior consistent with that on histologic iron staining. All lesions showed near complete demyelination on MBP. Lesion spatial extents on T2w were consistent with that of demyelination on MBP. Twelve lesions were identified on T2w: 6 showed substantial volume increases (>10 mm^3) from QSM to T2w and 6 showing no substantial volume difference (< 5 mm^3).

Conclusions: Our preliminary data suggests that a volume increase from T2w toQSM indicates iron presence in an MS lesion.

P441
Grey matter abnormalities in mesial temporal lobe characterize patients with multiple sclerosis and epilepsy

M Calabrese[1], NS Orefice[2], M Castellaro[3], A Morra[4], F Bortolon[5], S Monaco[1], P Manganotti[1]
[1]University Hospital of Verona, Dept. of Neurological and Movement Sciences, Verona, Italy, [2]University of Naples Federico II, Department of Pharmacology, Napoli, Italy, [3]University of Padova, Department of Information Engineering, Padova, Italy, [4]Euganea Medica, Neuroradiology Unit, Padova, Italy, [5]Multiple Sclerosis Centre, ULSS 6, Vicenza, Italy

Background: Epilepsy occurs more frequently in Multiple Sclerosis (MS) than in the general population and sometimes seizures may constitute the first manifestation of MS. Nevertheless the pathophysiology of epileptic seizures in MS remains a matter of debate, although in previous cross-sectional and longitudinal studies we observed that MS patients with epilepsy had a significant increase in number and volume of cortical lesions (CLs) compared to age- and sex-matched MS patients.

Objectives: Aim of our study is now to evaluate the regional distribution of both focal a diffuse grey matter abnormalities in a group of patients affected by MS and epilepsy.

Methods: Twenty one MS patients (MS/E) who presented, during the course of the disease, epileptic seizures that could not be

explained by any other cause than MS, undergone a 1.5T MRI including a new 3D Double inversion recovery (DIR). Twenty-one MS patients age-, gender-,and disease duration-matched with MS/E were included as control group. Regional distribution of CLs and regional cortical thinning were evaluated.

Results: An accurate anamnesis revealed that 15 of 21 patients had simple partial seizures. Among these 15 patients, 9 reported symptoms that could be ascribed to temporal lobe epilepsy (such as deja vu, jamais vu or auditory, gustatory or olfactory abnormalities) and 8 patients had secondarily generalized tonic-clonic seizures. Two patients had complex partial seizures while the remaining 4 patients had primarily generalized tonic-clonic seizure (2 of which were nighttime). Imaging analysis revealed that MS/E had higher CL number and volume than MS (p< 0.001 for both comparisons). CLs were observed in the mesial temporal lobe (MTL) of 20/21 MS/E patients (95.2%) and in 5/21 MS (23.8%, p< 0.001). Among the 194 CLs identified in MS/E, 34 (17.5%) were located in the MTL whereas among the 98 CLs identified in MS, only 8 (8.2%, p=0.021) were located in the MTL. Beyond focal lesions, DIR also revealed some diffuse abnormalities in the MTL of these patients. Moreover significant reduction of the hippocampal and parahippocampal volume was observed together with a widespread cortical atrophy.

Conclusions: Our results indicate that focal and diffuse grey matter damage of the MTL plays a major role in development of epileptic seizures in MS. This would be in line with the high frequency of temporal lobe epilepsy observed in our patients.

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OASIS and SuBLIME software for MS lesion segmentation

E Sweeney[1], R Shinohara[2], A Gherman[3], D Reich[4], C Crainiceanu[1]

[1]Johns Hopkins, Department of Biostatistics, Baltimore, MD, United States, [2]University of Pennsylvania, Department of Biostatistics and Epidemiology, Philadelphia, PA, United States, [3]Johns Hopkins, Institute of Genetic Medicine, Baltimore, MD, United States, [4]National Institute of Neurological Disorders and Stroke, Translational Neuroradiology Unit, Bethesda, MD, United States

Background: Magnetic resonance imaging (MRI) can be used to detect lesions in the brains of multiple sclerosis (MS) patients and is essential for evaluating disease-modifying therapies and monitoring disease progression. In practice, lesion load is often quantified by expert manual segmentation of MRI, which is time-consuming, costly, and associated with large inter- and intra-observer variability. Therefore automated lesion segmentation methods with accessible software implementations are necessary.

Objectives: We recently proposed two lesion segmentation methods, Subtraction-Based Logistic Inference for Modeling and Estimation (SuBLIME) and OASIS is Automated Statistical Inference for Segmentation (OASIS). SuBLIME is an automated method for segmenting incident lesion voxels between baseline and follow-up MRI studies. OASIS is an automated method for segmenting lesion voxels from a single MRI study. Both methods use carefully intensity-normalized T1-weighted (T1-w), T2-weighted (T2-w), fluid-attenuated inversion recovery (FLAIR) and proton density (PD) MRI volumes and are logistic regression

models trained on manual lesion segmentations. Here we present software implementations of SuBLIME and OASIS, where users can upload MRI studies to a website to produce lesion segmentations within minutes. We also present validation results for OASIS lesion segmentations on a new data set.

Methods: We demonstrate the SuBLIME and OASIS software (https://smart-stats-tools.org). We also present new results from OASIS segmentations on a new validation dataset. The dataset consists of 49 MRI studies from patients with MS. Each study consists of a T1-w, T2-w, FLAIR, and PD volume on a 3T Phillips MRI scanner. For each study we have manual segmentations made by a technician with over 10 years experience in delineating white matter lesions. We use 5 subjects to adjust the tuning parameter for the OASIS model and report results from the remaining 44 subjects.

Results: On the remaining 44 subjects in the new validation dataset and using the manual segmentation as a gold standard, OASIS has a sensitivity of 0.998, a specificity of 0.673, and a Dice similarity coefficient of 0.597 for detecting lesion voxels.

Conclusions: Automated segmentation of MS lesion voxels is important for monitoring the disease progression of MS. There are currently few publicly available software implementations of MS lesion segmentation algorithms; therefore the OASIS and SuBLIME software are an important contribution.

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Myelin water MRI reveals long-term demyelination in normal appearing white matter from relapsing remitting multiple sclerosis

IM Vavasour[1], SC Huijskens[2], SM Meyers[2], AL Traboulsee[3], DKB Li[1], W Moore[4], AL Mackay[1,2], C Laule[1,4]

[1]University of British Columbia, Radiology, Vancouver, BC, Canada, [2]University of British Columbia, Physics and Astronomy, Vancouver, BC, Canada, [3]University of British Columbia, Medicine, Vancouver, BC, Canada, [4]University of British Columbia, Pathology and Laboratory Medicine, Vancouver, BC, Canada

Background: Focal lesions generally accumulate over time in the brains of people with multiple sclerosis (MS), but there is also evidence for on-going pathological changes within the white matter that appears normal on conventional MRI (normal-appearing white matter (NAWM)). MS NAWM demonstrates reduced myelin water fraction (MWF, an advanced MRI marker specific to myelin) compared to controls, however a prior study did not detect a change over 6 months.

Objectives: We performed a longer-term longitudinal assessment of MWF in NAWM and new lesions to determine the timescale of demyelination.

Methods: 10 subjects with relapsing-remitting MS (age=33-58y, disease duration=1-30y, EDSS=1-4.5) and 3 controls (age=38-62y) were scanned on a 3T MRI at baseline and long-term follow up (LTFU, range 3-6y). Myelin water MRI was performed using a 32-echo T_2 relaxation acquisition (7 slices, TR=1200ms, TE=10ms, FOV=24cm, voxel=0.94x1.88x5mm). T_2 distributions were obtained by fitting the data to a multi-exponential decay model. Voxel-wise MWF was defined as the portion of the T_2 distribution from 10-40ms. NAWM masks, which excluded focal MS lesions, and masks of new lesions at baseline and LTFU were

applied to MWF images. Mean, peak height and peak location were extracted from mask-based histograms of MWF.

Results: NAWM MWF histogram mean and peak height were significantly decreased at LTFU (mean = 0.095 vs 0.084, p=0.03; peak height = 0.104 vs 0.096, p=0.01). Control white matter showed no difference. MWF changes in new lesions were variable, with some increasing and some decreasing MWF at lesion first appearance and at LTFU.

Conclusions: This study is the first to investigate long-term changes in MWF in relapsing-remitting MS over a period as long as 5 years. The decrease in MWF at LTFU indicates ongoing demyelination within NAWM. In acute lesions, patterns of demyelination and remyelination are expected, leading to different patterns of MWF changes. For the first time, MWF was used to detect tissue myelination changes over several years, demonstrating utility for monitoring therapeutic efficacy in longitudinal studies.

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Extended cortical lesion determining acute relapses in multiple sclerosis

M Puthenparampil[1], D Poggiali[1], P Perini[1], F Rinaldi[1], G Rolma[1], F Causin[1], P Gallo[1]
[1]University of Padova, Department of Neuroscience SNPSRR, Padova, Italy

Background: Cortical lesions can be observed at multiple sclerosis onset, increase in number and volume over the course of the disease and are thought to play a significant role in determining the progressive physical and cognitive deterioration observed in MS. Up to date, however, no association between acute clinical relapses and cortical lesions has been described.

Objectives: To investigate whether MS patients may present with clinical relapses due to the acute development of cortical lesions.

Methods: MS patients who had acute relapses characterized by cortical symptoms were investigated for the presence of cortical lesions by double inversion recovery (DIR) and phase-sensitive inversion recovery (PSIR) magnetic resonance imaging sequences.

Results: Five multiple sclerosis patients had acute "cortical relapses" characterized by

1) Wernicke's aphasia,
2) agraphia with acalculia not associated to motor deficit or linguistic disturbance,
3) hyposthenia of the left arm followed by muscle twitching of the hand, spreading to arm and face,
4) acute onset of left lower limb paroxysmal hypertonia,
5) temporal lobe status epilepticus with psychotic symptoms mimicking encephalitis.

DIR and PSIR disclosed large, snake-like, inflammatory lesions in the corresponding cortex. The symptoms completely recovered after high-dose steroid therapy.

Conclusions: Grey matter pathology has been associated to the progressive phase of MS, characterized by the accumulation of physical and cognitive disability, while acute clinical relapses are classically considered the consequence of acute inflammatory white matter lesions involving functional systems. Our observations indicate that 'cortical relapses' may occur in MS. Indeed, the symptoms observed in our patients had the clinical features of MS

relapses: they had an acute presentation, lasted more than 24 ours, were explained by the magnetic resonance imaging findings and recovered after high-dose steroids. In all cases the vascular nature of the lesions was excluded. The routine magnetic resonance imaging investigation in MS should include sequences aimed at visualizing cortical lesions, such DIR or PSIR, especially in the presence of symptoms that suggest a cortical dysfunction. 'Cortical relapse' has to be considered a new clinical aspect of MS. The inclusion of cortical lesions in the MRI diagnostic criteria for MS has to be evaluated.

P445

Brain positron emission tomography scanning can be used to image pathological determinants of progressive multiple sclerosis

L Airas[1], E Rissanen[2], M Gardberg[1], M Sucksdorff[1], J Tuisku[2], J Rinne[2]
[1]Turku University Hospital, Turku, Finland, [2]Turku PET Centre, Turku, Finland

Background: In secondary progressive multiple sclerosis (SPMS),there is diffuse smoldering inflammation compartmentalized within the central nervous system (CNS), and immune cell trafficking from the periphery into the CNS is likely less significant in the pathogenesis. This makes development of therapies for SPMS challenging. The conventional clinical (relapse frequency) and imaging end points (new T2-lesions and gadolinium-enhancing lesions) used in clinical trials of relapsing remitting (RR) MS are less applicable in SPMS trials. Hence new imaging biomarkers visualizing the SPMS-relevant pathology are greatly needed for treatment studies of progressive MS.

Objectives: To evaluate, whether *in vivo* positron emission tomography (PET) imaging could be reliably used to obtain information about the underlying neuropathology in patients with SPMS.

Methods: Ten SPMS patients and eight controls were studied using the radioligand [11C]PK11195 binding to the 18-kDa translocator protein (TSPO) expressed on activated microglial cells. T1-hypointense lesions were classified as [11C]PK11195-positive, chronic active lesions if there was increased [11C]PK11195-DVR covering more than half of the lesion's circumference (in all axial slices) compared to the adjacent or contralateral NAWM. To evaluate the binding pattern of TSPO-ligands in more detail, autoradiography experiments using postmortem human MS brain tissue sections and TSPO radioligands were performed. In addition, immunohistochemical staining for CD68 was performed to visualize activated microglial cells in serial sections.

Results: The DVR of [11C]PK11195 was significantly increased in the NAWM (p< 0.001) and thalamic ROIs (p=0.027) of SPMS patients compared to the control group. Increased perilesional TSPO-uptake was present in 57% of the chronic T1-lesions in MRI, giving thus *in vivo* proof of a significant proportion of chronic active lesions among SPMS patients. Autoradiography confirmed specific TSPO-ligand binding in the plaque edge, which was co-localized with activated, CD68-positive microglial cells/macrophages.

Conclusions: PET imaging enables the detection of microglial activation in brains of SPMS patients *in vivo*, thus revealing the diffuse pathology and the presence of chronic active lesions more sensitively

than conventional MRI imaging can do. This suggests that visualization of microglial activation with PET imaging could be used as an outcome measure in treatment trials of progressive MS.

P446
In vivo characterization of axonal damage in multiple sclerosis using high-gradient diffusion magnetic resonance imaging

SY Huang[1,2], SM Tobyne[3], A Nummenmaa[2], T Witzel[2], LL Wald[2], JA Mcnab[4], EC Klawiter[3]
[1]Massachusetts General Hospital, Department of Radiology, Boston, MA, United States, [2]Massachusetts General Hospital, Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Boston, MA, United States, [3]Massachusetts General Hospital, Department of Neurology, Boston, MA, United States, [4]Stanford University, Richard M. Lucas Center for Imaging, Department of Radiology, Stanford, CA, United States

Background: Axonal damage is considered the pathologic substrate of disability in multiple sclerosis (MS). However, *in vivo* imaging biomarkers specific for axonal degeneration remain elusive. Q-space diffusion magnetic resonance imaging (MRI) techniques demonstrate potential for determining axon diameter and density but require high gradient strengths to gain sensitivity to the smallest axons.

Objectives: To measure differences in axon diameter and density in the corpus callosum of patients with MS compared to healthy controls (HCs) using a novel high-gradient 3T human MRI scanner developed for the Human Connectome Project equipped with 300 mT/m gradients, more than 7 times stronger than those available on clinical MRI scanners.

Methods: Six relapsing-remitting MS subjects and six age- and gender-matched healthy HCs were scanned using a novel high-gradient 3T MRI scanner (MAGNETOM Skyra CONNECTOM, Siemens Healthcare) with a maximum gradient strength of 300 mT/m. Clinical characteristics of the MS subjects were as follows: median Expanded Disability Status Scale (EDSS) 1.83 (range 1.0-3.0) and disease duration 7.3 ± 4.8 years.

Sagittal 2-mm diffusion-weighted stimulated-echo echo planar images were acquired with 17 diffusion gradient increments (30-272 mT/m) and 5 diffusion times (11-96 ms) (b-values 400-10,000 s/mm^{2}). Diffusion gradients were applied in the z-direction, perpendicular to the callosal fibers. Total acquisition time was 52 minutes.

The AxCaliber model of diffusion in intra- and extra-axonal compartments was used to estimate axon diameter and density in the mid-sagittal corpus callosum within regions of interest (ROIs) drawn in T2 hyperintense lesions in MS subjects, normal-appearing white matter (NAWM) of the genu, body and splenium in MS subjects and similar locations in HCs. Mean axon diameter and density were compared between MS lesion ROIs and NAWM ROIs in the same MS subjects using the Wilcoxon matched-pair sign-rank test and between groups using the Mann-Whitney U test.

Results: MS lesions showed significantly reduced mean axon diameter (2.31 vs. 2.74 um, p< 0.05) and density (0.24 vs. 0.48, p< 0.05) compared to corresponding NAWM. No significant difference in mean axon diameter or density was seen for NAWM in MS subjects compared to HCs in the genu, body or splenium.

Conclusions: High-gradient diffusion MRI provides specific *in vivo* characterization of axonal damage in MS and demonstrates decreased mean axon diameter and density in MS lesions relative to corresponding NAWM.

P447
Bi-directional trans-synaptic degeneration in the visual pathway in multiple sclerosis

LJ Balk[1], MD Steenwijk[1], P Tewarie[1], M Daams[1], J Killestein[1], MP Wattjes[1], H Vrenken[1], F Barkhof[1], CH Polman[1], BM Uitdehaag[1], A Petzold[1]
[1]VU University Medical Centre, Amsterdam, Netherlands

Background: In order to investigate the dynamics of neuroaxonal degeneration in Multiple sclerosis (MS), the visual pathway is a particularly suitable model, as it is a hard-wired, single pathway model. The relation between retrograde and anterograde trans-synaptic degeneration in the visual pathway of patients with MS (as a result of either lesions is the optic nerve or elsewhere in the visual pathway), and its relationship with whole brain atrophy, is however not entirely clear.

Objectives: To investigate the co-existence of antero- and retrograde trans-synaptic axonal degeneration and to explore the relationship between selective visual pathway damage and global brain involvement in longstanding MS.

Methods: In this single-center, cross sectional study, patients with long-standing MS (N=222) and healthy controls (HCs, N=62) were included. Thickness of retinal layers (optical coherence tomography), optic radiations (diffusion tensor imaging), visual cortex and whole brain gray and white matter volumes (structural MRI) were used to quantify atrophy. Linear regression analyses were used to assess associations between the different components and for comparing patients with and without optic neuritis and HC.

Results: In patients with MS, an episode of optic neuritis (MSON) was significantly associated with decreased integrity of the optic radiations (OR) and thinning of the peripapillary retinal nerve fibre layer (pRNFL) and macular ganglion cell complex (GCC). Lesion volume in the OR was negatively associated with pRNFL and GCC thickness in patients without optic neuritis (MSNON). The pRNFL and GCC showed associations with integrity of the OR, thickness of the primary visual cortex (only in patients with MSON), and also with global white and gray matter atrophy. In HCs, no such relationships were demonstrated.

Conclusions: This study provides evidence for presence of bi-directional (both antero- and retrograde) trans-synaptic axonal degeneration in the visual pathway of patients with MS. Additionally, thinning of the retinal pRNFL and GCC are related to global white and gray matter atrophy in addition to pathology of the visual pathway.

P448
Evidence of resting-state fMRI functional connectivity abnormalities in pediatric-onset MS and the relation to structural damage and cognition

N Akbar[1,2], C Till[3], J Sled[1], SM Doesburg[1], M Binns[4], AR McIntosh[4], B Aubert-Broche[5], L Collins[5], D Araujo[5], M Lysenko[3], B Banwell[1,6]
[1]The Hospital for Sick Children, Toronto, ON, Canada, [2]University of Toronto, Institute of Medical Science, Toronto,

ON, Canada, ³York University, Psychology, Toronto, ON, Canada, ⁴Rotman Research Institute, Baycrest, Toronto, ON, Canada, ⁵Montreal Neurological Institute, Montreal, QC, Canada, ⁶Children's Hospital of Philadelphia, Philadelphia, PA, United States

Background: Functional connectivity between brain regions may be disrupted by MS, especially if the disease begins in childhood and adolescence. How these disruptions may relate to structural damage and cognitive outcomes remains unclear.

Objectives: To evaluate brain network connectivity and its relation to structural damage and cognition in pediatric-onset MS.

Methods: Nineteen pediatric-onset relapsing-remitting MS individuals aged 13-23 (mean age=18 years, 14 female, mean disease duration=65 months, median EDSS=1.5) and 16 healthy controls matched by age, sex, and socio-economic status underwent cognitive testing as well as structural and functional imaging on a 3.0 Tesla MRI scanner. Resting-state functional connectivity patterns were examined using seed-based analyses via time-series correlations.

Results: Cognitive impairment was documented in 5 of 19 patients. Compared to the control group, the MS group demonstrated higher functional connectivity between the posterior cingulate seed region and the following areas: anterior cingulate, left middle frontal gyrus, cerebellum and right insula and additionally between the thalamus seed region and anterior cingulate (all z>3.51, p< .001). Log-transformed T_2 lesion volume was negatively correlated with functional connectivity of the thalamus and right superior lateral occipital region (z=-4.21, p=.0006). Normalized thalamic volume was positively correlated with functional connectivity of the thalamus and the following regions: right superior lateral occipital (z=2.76, p=.013), left middle frontal gyrus (z=2.32, p=.033), and precuneus (z=2.14, p=.047). Functional connectivity of the frontomedial seed was negatively correlated with mean composite cognitive z-score across multiple regions including the left insula (z=-5.27, p=.0001), paracingulate (z=-3.71, p=.0017), and posterior cingulate (z=-3.57, p=.0023).

Conclusions: Pediatric-onset MS individuals show greater resting-state functional connectivity of the posterior cingulate and thalamus as compared with controls. However, within the MS group, lower connectivity is demonstrated among patients with greater disease related pathology (higher lesion volume, reduced thalamic volume) suggesting a disruption of thalamo-cortical functional connectivity with greater disease burden. Furthermore, in this MS group with a relatively low prevalence of cognitive impairment, enhanced connectivity of the frontomedial cortex was associated with poorer cognitive performance suggesting a potential maladaptive mechanism.

P449

Improved white matter integrity with natalizumab treatment in multiple sclerosis

OT Wiebenga¹,², MM Schoonheim², HE Hulst², GJA Nagtegaal¹,², EM Strijbis³, MD Steenwijk¹, CH Polman³, PJW Pouwels⁴, F Barkhof¹, JJG Geurts²

¹VU University Medical Center, Radiology and Nuclear Medicine, Amsterdam, Netherlands, ²VU University Medical Center, Anatomy and Neurosciences, Amsterdam, Netherlands, ³VU University Medical Center, Neurology, Amsterdam,

Netherlands, ⁴VU University Medical Center, Physics & Medical Technology, Amsterdam, Netherlands

Background: Multiple sclerosis (MS) is characterized by progressive white matter (WM) and grey matter damage. Natalizumab is a relatively new treatment option that strongly suppresses inflammation in the brain, and has been shown to strongly reduce relapse rate and lesion formation. The strong clinical effect of natalizumab can only partly be explained by its effect on lesion formation, given the poor relationship between lesion load and physical disability. The clinical effect of natalizumab might rather be understood in terms of restraining more subtle damage in normal appearing WM as can be measured with diffusion tensor imaging (DTI).

Objectives: To investigate the effect of natalizumab treatment on the extent and severity of WM damage over time, compared to standard disease modifying drugs in relapsing-remitting MS (RRMS).

Methods: The study included 22 RRMS patients initiating natalizumab at baseline, 17 matched RRMS patients continuing interferon-beta or glatiramer acetate (IFNb/GA) and 12 matched healthy controls. DTI and conventional MRI sequences were obtained at baseline and month 12. Tract-Based-Spatial-Statistics (TBSS) was used at both time-points to compare diffusion measures between patients and controls, investigating the extent and severity of WM damage. Severity of fractional anisotropy (FA) abnormalities was expressed as a Z-score (compared to controls). Subjects also underwent comprehensive neuropsychological investigation.

Results: Natalizumab patients showed abnormalities in 56.8% of the WM voxels at baseline ('extent of damage'), which was reduced to 47.2% at month 12. In IFNb/GA patients, 41.4% of the WM voxels at baseline was abnormal in terms of FA, which was 39.1% at month 12. The severity did not differ between patient groups at baseline (Z= -0.67 for natalizumab patients and Z= -0.64 for IFNb/GA patients, p=1.0). In natalizumab patients the FA-damage improved over time to Z= -0.59 at month 12 (p=0.04). In IFNb/GA patients, severity of FA-damage remained stable over time, where it was Z=-0.67 at month 12 (p=1.0). In all patients, the severity of FA damage was correlated with overall cognitive performance (r=0.525, p=< 0.001; at month 12)

Conclusions: Severity of DTI-measured WM damage improved significantly under natalizumab treatment over 12 months. No improvement of WM damage was observed in the patients continuing IFNb/GA. This may have important implications for restriction cognitive impairment in the future.

P450

Unraveling the relationship between regional gray matter atrophy and pathology in connected white matter tracts in long-standing multiple sclerosis

MD Steenwijk¹, M Daams¹,², PJW Pouwels³, LJ Balk⁴, PK Tewarie⁴, JJG Geurts², F Barkhof¹, H Vrenken¹,³

¹VU University Medical Center, Dept of Radiology and Nuclear Medicine, Amsterdam, Netherlands, ²VU University Medical Center, Dept of Anatomy and Neurosciences, Amsterdam, Netherlands, ³VU University Medical Center, Dept of Physics and Medical Technology, Amsterdam, Netherlands, ⁴VU University Medical Center, Dept of Neurology, Amsterdam, Netherlands

Background: Gray matter (GM) atrophy is common in multiple sclerosis (MS), but the relationship with white matter (WM) pathology is largely unknown. Some studies found co-occurrence of GM atrophy and WM pathology in specific systems, but a regional analysis across the brain in different clinical phenotypes is necessary to further understand disease mechanisms underlying GM atrophy in MS.

Objectives: To investigate the association between regional GM atrophy and pathology in anatomically connected WM tracts at the whole-brain level in a large cohort of patients with long-standing MS.

Methods: MRI was performed at 3T in 208 long-standing MS patients and 60 healthy controls. Deep and cortical GM regions were segmented and quantified. An atlas based on the healthy controls was used to measure lesion volume and tissue integrity in the WM tracts connected to the GM regions. Linear regression was performed to quantify the amount of regional GM atrophy that can be explained by WM pathology in the connected tracts.

Results: MS patients showed extensive deep and cortical GM atrophy. Cortical atrophy was particularly present in frontal and temporal regions. Pathology in connected WM tracts statistically explained both regional deep and cortical GM atrophy in relapsing-remitting (RR) patients, but only deep GM atrophy in secondary-progressive (SP) patients.

Conclusions: In RRMS patients, both deep and cortical GM atrophy were associated with pathology in connected WM tracts. In SPMS patients, only regional deep GM atrophy could be explained by pathology in connected WM tracts. This suggests that in SPMS patients cortical GM atrophy and WM damage are (at least partly) independent disease processes.

P451

Attenuated BOLD hemodynamic response predicted by degree of white matter insult, slows cognition in multiple sclerosis

NA Hubbard[1], MP Turner[1], DM Robinson[2], S Sundaram[1], L Oasay[1], JL Hutchison[1], A Ouyang[2], H Huang[2], B Rypma[1,2]
[1]University of Texas at Dallas, Dallas, TX, United States, [2]University of Texas Southwestern Medical Center, Dallas, TX, United States

Background: Multiple Sclerosis (MS) is characterized by a high degree of white matter insult, brain activity changes, and cognitive slowing (Genova et al., 2009). Understanding the interactions between white matter and brain activity changes is paramount for understanding MS-related differences in cognitive slowing (cf. Rypma et al., 2006).

Objectives:

1. To examine the extent to which functional magnetic resonance imaging (fMRI) activity within executive brain regions differs during cognition for patients with MS (MSPs) compared to healthy controls (HCs).
2. To examine if differences in activity in MSPs are predicted by their degree of white matter insult.
3. To examine if brain activity or white matter insult mediate cognitive slowing in MSPs.

Methods: 28 patients with relapsing remitting MS (MSPs) and 23 age- and sex-matched healthy controls (HCs) underwent fMRI and diffusion tensor imaging (DTI). Participants completed a processing speed measure, which examined the speed of mental operations, during fMRI scanning. Blood-oxygen-level dependent (BOLD) signal was measured in dorsolateral prefrontal cortex during fMRI scanning. DTI examined the degree of white matter insult at the time of each scan using the radial diffusivity (RD) metric.

Results:

1. MSPs were slower than HCs on processing speed performance, $t(49) = 2.31$, $p = .025$. Further, MSPs had a significantly attenuated BOLD-hemodynamic response compared to HCs in DLPFC during processing speed performance $t(49) = -3.42$, $p = .001$.
2. In MSPs increasing white matter insult significantly decreased the BOLD-hemodynamic response, $r = -.52$, $p < .001$[1].
3. Using multivariate regression, we found that the BOLD-hemodynamic response in DLPFC significantly predicted processing speed performance when controlling for white matter insult, partial $r = -.464$, $p = .019$[1].

[1]Two multivariate outliers ($x > 95\%$ UCL) were excluded from these analyses.

Conclusions:

1. Cognitive slowing and accompanying decreased DLPFC BOLD-hemodynamic response for patients with relapsing-remitting MS compared HCs were confirmed in the present study.
2. Decreased BOLD-hemodynamic activity was predicted by increased individual differences in white matter insult in patients with relapsing-remitting MS.
3. Although, the degree of white matter integrity predicted DLPFC BOLD-hemodynamic activity, it did not mediate the relationship between activity and cognitive slowing. Such a difference suggests that MS-related cognitive slowing might be related to the break down of functional neural mechanisms, rather than structural.

P452

Disrupted distant functional connectivity within the temporoparietal junction is linked to impaired attention in multiple sclerosis

SM Tobyne[1], D Boratyn[1], J Sherman[1,2], B Rosen[3], C Mainero[3], EC Klawiter[1]
[1]Massachusetts General Hospital, Harvard Medical School, Neurology, Boston, MA, United States, [2]Massachusetts General Hospital, Harvard Medical School, Psychiatry, Boston, MA, United States, [3]Massachusetts General Hospital, Harvard Medical School, Radiology, Boston, MA, United States

Background: When used in conjunction with resting state functional connectivity (RSFC), graph theory is a powerful tool for investigating brain networks. The balance of local functional connectivity (LFC) and distant functional connectivity (DFC) throughout the brain is important for maintaining efficient network organization and performing cognitive tasks such as sustained attention. The temporal parietal junction (TPJ) is associated with effortful deployment of attention, a commonly observed cognitive deficit in multiple sclerosis (MS). Imaging biomarkers of LFC and DFC network integrity could aid in determining those at risk for cognitive impairment.

Objectives: To explore the relationship between impaired attention and changes in LFC and DFC in relapsing-remitting (RR) MS compared to healthy controls (HC).

Methods: Anatomical and RSFC data in 24 RRMS (mean disease duration 8.48 years; median EDSS=2.0, range 1-6.5) and 37 age- and gender-matched HC subjects were acquired at 3T. LFC and DFC maps were generated by summing suprathreshold (rho>0.3) voxels after correlating each voxel's timecouse to all other voxels inside (LFC) and outside (DFC) a 14mm spherical neighborhood. Normalized metrics were extracted from ventral attention (vATT), dorsal attention (dATT), and frontoparietal control (FPC) networks using a functionally defined network parcellation and compared to HC using a Student´s t-test. Performance on the Symbol Digit Modality Test (SDMT), Paced Auditory Serial Addition Task (PASAT) and Brief Test of Attention (BTA) tests were correlated to RSFC metrics using a Pearson´s correlation.

Results: Performance on attention tests was impaired in the RRMS group, as compared to normative data (SDMT mean Z=-0.228; 2s-PASAT mean Z=-0.387; BTA mean Z=-0.499). Average LFC was decreased in RRMS in areas representing the vATT (p=0.007) and dATT (p=0.036) networks. Average DFC was decreased in the vATT (p=0.002) and dATT (p< 0.001) and FPC (p=0.013) networks. Decreased DFC in posterior components of the vATT functional parcellation, corresponding to the TPJ, was significantly correlated with impaired performance on the 2-second delay PASAT (rho=0.602, p=0.005).

Conclusions: LFC and DFC in RRMS were significantly reduced in the vATT/TPJ. Impaired performance on the 2-second PASAT positively correlated with decreased DFC within the vATT/TPJ, suggesting impaired performance on attention tasks is linked to the vATT network in MS. Decreased vATT/TPJ DFC may represent a promising biomarker for cognitive impairment in RRMS.

P453

The natural history of brain volume loss among patients with multiple sclerosis: a systematic literature review and meta-analysis

T Vollmer[1], JE Signorovitch[2], L Huynh[2], P Galebach[2], C Kelley[2], J Marvel[3], A Di Bernardo[3], R Sasane[3]
[1]University of Colorado School of Medicine, Department of Neurology, Aurora, CO, United States, [2]Analysis Group, Inc., Boston, MA, United States, [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States

Background: Multiple sclerosis (MS) has been associated with progressive brain volume (BV) loss in multiple studies.

Objectives: We aimed to systematically summarize reported rates of BV loss in MS, to develop consensus estimates of the annual rate of BV loss in MS, to stratify by treatment, and to explore associations between BV loss and other markers of MS severity.

Methods: A systematic literature search (2003-2013) was conducted to identify longitudinal studies of MS patients with at least 12 months of follow-up and reported changes in BV measures, including percentage BV change (PBVC), T1 lesion volume (T1LV), or T2LV. Patients receiving no treatment or receiving first-generation disease modifying treatment (DMT) with interferon-beta (IB) or glatiramer acetate (GA) were included. Two reviewers independently extracted data on study designs, patient characteristics, BV algorithm, and rates of BV change. Meta-analyses allowed

for random effects across studies. Associations between annualized PBVC, changes in LV and MS disease duration were examined in pre-specified meta-regression models.

Results: We identified 36 studies (N=5006 MS and non-MS patients). Eight studies were clinical trials; 28 were observational studies. Study durations ranged from 12 to 69.6 months. Mean ages ranged from 30 to 51 years. Half of the studies (N=18 studies) recruited only relapsing-remitting (RR) MS patients. In 12 studies for which PBVC was reported (N=676 MS patients) based on the SIENA algorithm, annualized PBVC ranged from -1.34% to -0.46% per year. In meta-analyses, the annualized PBVC was -0.69% (95%CI= -0.87% to -0.50%) in study arms receiving first-generation DMT (N=1 CT and N=5 observational) and -0.71% (95%CI= -0.81% to -0.61%) in untreated study arms (N=6 observational). In meta-regression analyses, no significant relationships were observed between annualized PBVC and study-level average MS duration or changes in T1LV or T2LV (all p>0.05).

Conclusions: In this systematic review of data from multiple studies, the average MS patient receiving first-generation DMT or no DMT lost approximately 0.7% of BV per year, well above rates associated with normal aging (0.1%-0.3% of BV per year).

P454

Multivoxel MR spectroscopy in a pilot crossover study of natalizumab to dimethyl fumerate therapy

DD Blatter[1], JF Foley[2], T Hoyt[2]
[1]LDS Hospital and Intermountain Health Care, Radiology, Salt Lake City, UT, United States, [2]Rocky Mountain MS Research Group, Salt Lake City, UT, United States

Background: The greater efficacy of Natalizumab (NAB) in the treatment of patients with Multiple sclerosis (MS) also brings significant risk of progressive multifocal Leukoencephalopathy (PML) in patients with a history of immunosuppression, more than 24 NAB doses, and JCV index of greater than 1.5. MRI is often insensitive to early relapse.

Objectives: Asses the ability of multiple voxel Magnetic Resonance Spectroscopy (MV MRS) for determining relapse in patients after withdrawal of NAB therapy.

Methods: 30 subjects at high risk for developing PML were enrolled in a study to monitor their transition to dimethyl fumarate (DF). In addition to enhanced MRI, each patient underwent MVMRS at the time of last NAB infusion, and at 4, 16, and 24 weeks. All studies were obtained at 1.5 T with 4-D technique. 4 slices included from the basal ganglia (BG) to above the ventricles. Metabolite peaks corresponding to Choline (Ch), Creatine (Cr), n-acetyl aspartate (NAA) and amino acids (AA) were measured and statistical analysis of corresponding ratios performed.

Results: At the time of final NAB infusion, the global sum of Ch/Cr plus NAA/Cr were significantly negatively correlated (r=-0.43, p< 0.01) with the expanded disability status scale (EDSS). No significant differences were observed between baseline and 4 week spectra. By 16 weeks a reduction in the AA/Cr was observed only in the basal ganglia slice (0.224 vs 0.184, P=0.029). At submission only 17 of 30 patients have completed 24 weeks. In these, the reduction in the average AA/Cr ratio persists without further change. The BG Ch/Cr had increased (1.42 vs 1.56, p=0.0002). A correlation was observed between the change in EDSS and the combined BG change in Ch and NAA (change in Ch/Cr + change

in NAA/Cr, r=-0.69). Among patients crossing back to NAB therapy a reduction in basal ganglia AA/Cr was seen.

Conclusions: Significant differences in MVMRS are seen in patients with MS compared with controls. Ch/Cr and NAA/Cr are correlated with EDSS. After crossing over to DF significant reduction in AA/NAA and increase in Ch/Cr in the basal ganglia slice only. EDSS change correlated negatively with Ch + NAA/Cr and with AA/Cr in the basal ganglia slice only. Results are incomplete but MVMRS may be able to detect clinical relapse.

P455

Normal appearing white matter injury in MS is affected by the distance to the nearest cortical lesion

N Evangelou[1], R Abdel-Fahim[1], O Mougin[2], J Rukseneita[3], A Lazenbury[4], P Gowland[2], A Pitiot[5]
[1]University of Nottingham, Division of Clinical Neurosciences, Nottingham, United Kingdom, [2]University of Nottingham, Sir Peter Mansfield MR Centre, Nottingham, United Kingdom, [3]Leicester Royal Infirmary, Leicester, United Kingdom, [4]University of Nottingham, Nottingham, United Kingdom, [5]University of Nottingham, School of Psychology, Nottingham, United Kingdom

Background: Disability in MS patients has been correlated to Grey Matter (GM) pathology and to Normal Appearing White Matter (NAWM) injury. GM lesions volume has been correlated to the NAWM magnetization transfer ratio (MTR) suggesting that GM lesions cause NAWM degeneration.

Objectives: To examine whether changes in NAWM vary with distance to focal GM lesions.

Methods: Forty two MS patients (8 CIS, 12 RRMS, 10 PPMS, and 12 SPMS) were scanned at 7T using PSIR and B1 corrected MTR sequences. GM and white matter (WM) lesions were segmented by two trained neurologists. We estimated GM and WM tissue maps from the PSIR images using the SPM software. For each patient, we then computed the average NAWM MTR value as a function of the distance to the nearest GM lesion. To remove the influence of WM lesion on WM MTR, we excluded all WM closer than 5 voxels (3mm) from the nearest WM lesion.

Results: For each patient, we estimated the parameters for a robust linear regression of the average NAWM MTR value on the distance to the nearest GM lesion using iteratively reweighted least squares.

A one sample Wilcoxon signed rank showed that the regression slopes were significantly positive (p < 0.0123), suggesting a significant linear dependence of NAWM MTR values on the distance to GM lesions.

Conclusions: The observed distance effect between NAWM and GM lesions suggests cortical lesions are important in the pathogenesis of NAWM damage. As GM lesions and NAWM correlate strongly with disease progression, this study strengthens further the evidence for the role of focal GM lesions in causing disability progression in MS.

P456

Dynamics of brain iron accumulation differ between clinically isolated syndrome and definite multiple sclerosis: a longitudinal 3T MRI study

M Khalil[1], C Langkammer[1], A Pichler[1], D Pinter[1], T Gattringer[1], G Bachmaier[1], S Ropele[1], S Fuchs[1], C Enzinger[1], F Fazekas[1]

[1]Medical University of Graz, Graz, Austria

Background: Increased iron concentration in cerebral deep grey matter is a consistent finding in multiple sclerosis (MS) while respective results have been controversial in patients with a clinically isolated syndrome (CIS). This suggests a temporal dynamic of iron accumulation.

Objectives: To investigate longitudinal changes of iron concentration in the subcortical gray matter of patients with different stages of MS and their relation to clinical and other morphologic variables.

Methods: We followed 144 patients (76 CIS; mean age 32.0 (SD 8.3) years, median EDSS 1.0 (IQR 0.0-2.0); 68 MS (62 relapsing remitting MS, 6 secondary progressive MS), mean age 34.2 (SD 9.3) years, median EDSS 2.0 (IQR 1.0-3.3)) with 3T MRI over a median period of 2.9 (IQR 1.3-4.0) years. Iron concentration was estimated from R2* relaxation rates in the caudate nucleus, globus pallidus, putamen and thalamus at baseline and last follow-up.

Results: At baseline, iron deposition was higher in MS compared to CIS. In CIS, R2* rates increased in the globus pallidus (p< 0.001), putamen (p< 0.001) and caudate nucleus (p< 0.005), whereas R2* rates in the thalamus decreased (p< 0.05). In MS, R2* rates only slightly increased in the putamen (p< 0.05), remained stable in the globus pallidus and caudate nucleus, and decreased in the thalamus (p< 0.01). Changes of R2* relaxation rates were unrelated to respective volume changes. Only in MS, baseline R2* rates of the caudate nucleus and putamen correlated with the change of EDSS scores over time (r=0.4, p< 0.005), however the change of R2* relaxation rates in deep gray matter areas was unrelated to the change of EDSS scores during the follow-up period.

Conclusions: Iron accumulation is an early and region specific phenomenon in MS, which plateaus over time and occurs independent from other morphologic brain changes. The long-term clinical impact of this phenomenon and its relation to treatment deserve further clarification.

P457

Region of interest based grey matter volumetry identifies clinically meaningful atrophy in early relapsing forms of multiple sclerosis

R Opfer[1], A Tewes[1], L Spies[1], LY Reitz[2], R Martin[3], S Schippling[3]
[1]Jung Diagnostics GmbH, Hamburg, Germany, [2]University Medical Center Hamburg Eppendorf, Institute for Neuroimmunology and Clinical Multiple Sclerosis Research (INIMS), Hamburg, Germany, [3]University Hospital Zurich, Neuroimmunology and Multiple Sclerosis Research Section (nims), Department of Neurology, Zurich, Switzerland

Background: Brain atrophy occurs early and in different subtypes of multiple sclerosis (MS). Neuro-axonal damage in MS is thought to be the structural analogue of permanent disability. Thus reliable detection of focal atrophy is of increasing value for clinical follow up and may guide treatment decisions in MS patients.

Objectives: To investigate in which brain regions grey matter (GM) loss is most pronounced in patients with early forms of

relapsing remitting MS and whether they are detectable on an individual patient level. Finally, to which extend longitudinal changes are correlated with clinical findings.

Methods: A cohort of 60 untreated patients with a clinically isolated syndrome or early relapsing remitting MS (mean disease duration 3.2 years) with cranial high-resolution 3D T1-MPRAGE imaging at baseline and after an interval of 6 to 12 months was studied. Clinical testing comprised the expanded disability status scale, parts of the MS functional composite test, namely the 9 hole peg test (NHPT) and the 7.5 m walking test (T7.5) as well as the timed tandem walk. We deployed a region-of-interest (ROI) based volumetry using Statistical Parametric Mapping 12b. We quantified percentage volume changes (PVC) for BPV and various deep as well as cortical GM regions. PVC values were correlated with clinical parameters.

Results: Regional atrophy measures, such as temporal lobe GM showed a more pronounced PVC than BPV, i.e. -1.75% (p< 0.0001) and -0.82% (p< 0.001), respectively. Taking intra-scanner variability into account, a significant PVC could be demonstrated for 10 out of 60 individual patients based on BPV as opposed to 16/60 individual patients based on the temporal lobe GM (5% error probability). Patients with significant PVC in the temporal lobe GM had poorer clinical outcomes for hand motor function (NHPT; p=0.001) and walking abilities (T7.5; p=0.001).

Conclusions: ROI based GM volumetry is able to detect regional GM volume loss on short time scales in early MS patients on group but also on an individual patient level. On a group level the temporal cortical GM shows higher PVC than the BPV and is stronger correlated with clinical measures of disability. Individual PVC of the temporal lobe GM allows stratification of patients into clinically distinct subgroups.

P458
Comparison of spinal cord area between spinal cord measurements using different coils in multiple sclerosis patients with 3.0T MRI

F-X Aymerich[1], D Pareto[1], M Alberich[1], J Alonso[1], J Sastre-Garriga[2], X Montalban[2], Á Rovira[1]
[1]Vall Hebron University Hospital, Magnetic Resonance Unit, Neuroradiology Dept., Barcelona, Spain, [2]Vall Hebron University Hospital, Multiple Sclerosis Centre of Catalonia, Neuroimmunology Dept., Barcelona, Spain

Background: 3-D magnetization prepared rapid gradient echo (MPRAGE) sequences are frequently applied to brain and spinal cord studies. Although the use of neck coils is the common choice to study spinal cord, MPRAGE sequences using head coils also enable to study the spinal cord down to C4 level.

Objectives: To compare cross-sectional area (CSA) measurements in MS patients using head and neck coils.

Methods: 36 patients (19 women; median age, 34.5 years; age range [19, 50] years, median EDSS, 1.5; EDSS range, [0, 4.0]) presenting with a clinically isolated syndrome (CIS), underwent 3.0 T MRI (Trio, Siemens) including sagittal T1-weighted 3D MPRAGE sequences using head and neck coils. In both sequences we carried out axial reconstructions centred at C2-C3 level. Cross-sectional areas were evaluated using the spinal cord toolkit included in Jim 6.0 software. We studied two regions: first (SP1) from the odontoid down to C4 superior margin; and second (SP2),

down to C7 superior margin. Neck coil was used to study both regions (SP1 and SP2), whereas head coil (HC) only for SP1. In these regions we measured global CSA spinal cord, i.e. spinal cord volume divided by cord length, and CSA measurements at C2-C3 and C3-C4 levels. Student t-test was applied to test for differences in CSA measurements using different coils. Mean squared error (MSE) was also calculated in order to measure the differences in CSA measurements along all the common length. Finally the agreement was evaluated by using the Bland-Altman plots.

Results: Images acquired using the head coil presented a lower CSA (in mm2 global: HC, 77.90; SP1, 80.30; SP2: 80.07. C2-C3: HC, 75.06; SP1, 78.01; SP2: 78.70. C3-C4: HC, 76.35; SP1, 79.93; SP2: 80.91). However, differences only reached significance at C3-C4 level between HC and SP2 (p< 0.024). A higher MSE was also observed comparing HC and spinal measurements (in mm2 HC-SP1, 21.27; HC-SP2, 22.27; SP1-SP2, 4.90), and statistical differences (p< 0.001) were found in cases involving SP2 measurements. Finally, Bland-Altman plots showed a bias in [-4.56, -2.17] comparing between head and neck coil measurements, and a poor agreement between measurements, mainly when head coil is used.

Conclusions: Results suggest a better performance using neck coil than head coil, and a poor agreement between measurements, mainly for global CSA measurements.

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Increased gray matter lesion detection in MS with 7 Tesla MRI: a post-mortem verification study

LE Jonkman[1], ID Kilsdonk[2], JJM Zwanenburg[3], R Klaver[1], S van Veluw[4], PJW Pouwels[5], PR Luijten[3], JJG Geurts[1], F Barkhof[2]
[1]VU University Medical Center, Anatomy and Neurosciences, Amsterdam, Netherlands, [2]VU University Medical Center, Radiology, Amsterdam, Netherlands, [3]University Medical Center Utrecht, Radiology, Utrecht, Netherlands, [4]University Medical Center Utrecht, Neurology, Utrecht, Netherlands, [5]VU University Medical Center, Physics and Medical Technology, Amsterdam, Netherlands

Background: The relevance of grey matter (GM) pathology in MS has become increasingly recognised over the past decade. GM lesions relate better to cognitive and clinical disability than white matter (WM) lesions, and might even facilitate early diagnosis. Unfortunately, a large part of cortical GM lesions go undetected on conventional MRI using standard field strength due to their small size, scarcity of inflammation and partial volume effects from adjacent CSF and WM. In vivo studies suggested improved detection of cortical GM lesions by using high field 3T and ultra-high field 7T MRI systems. So far, however, histopathological verification of clinically applied MRI sequences has been lacking.

Objectives: To determine the sensitivity of 3T and 7T MRI T1w, T2w, FLAIR, DIR and SWI sequences for the detection of GM lesions by directly comparing them to histopathology (gold standard).

Methods: Coronal brain sections of 19 patients with MS (10 females) were obtained after rapid autopsy, formalin-fixed and scanned according to a multi-contrast MRI protocol on 3T and 7T

Philips MRI systems. The scan protocol included T1w, T2w, FLAIR, DIR and SWI sequences. GM lesions were scored on all sequences separately by an experienced rater blinded to histopathology and clinical data. Staining was performed with antibodies against proteolipid protein (PLP) and scored by a pathological reader who was blinded to the MR and clinical data. Subsequently, MR images were matched to histopathology and sensitivity of MRI systems and sequences were statistically evaluated. Additionally, a second unblinded (retrospective) scoring of MR images was performed.

Results: In MS brain slices of 17 patients, we identified 99 lesions; 16 WM and 83 GM lesions (6 type I lesions, 27 type II lesions, 28 type III lesions and 22 type IV lesions). Overall, 7T MRI detected significantly (59%) more lesions than 3T MRI (Z=-5.493, p < 0.001). Focusing on GM lesions only, 7T FLAIR detected 225% more lesions than 3T FLAIR (sensitivity 31 vs. 10%, Z=-3.499, p < 0.001), 7T SWI detected 200% more lesions than 3T SWI (sensitivity 29 vs. 10%, Z=-3.025, p = 0.002), and 7T T2w detected 107% more than 3T T2w (sensitivity 35 vs. 17%, Z=-2,949, p = 0.003). Regarding WM lesion detection, no significant differences were found between 3T and 7T on all sequences.

Conclusions: Ultra-high field 7T MRI leads to an increased detection of GM lesions in MS, compared to 3T MRI. This is especially true for FLAIR, SWI and T2w sequences.

*Both authors contributed equally to this work

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Thalamus structure and function determines severity of cognitive impairment in multiple sclerosis

MM Schoonheim[1], HE Hulst[1], RB Brandt[2], M Strik[1], AM Wink[2], BMJ Uitdehaag[3], F Barkhof[2], JJG Geurts[1]
[1]VU University Medical Center, Anatomy and Neurosciences, Amsterdam, Netherlands, [2]VU University Medical Center, Radiology, Amsterdam, Netherlands, [3]VU University Medical Center, Neurology, Amsterdam, Netherlands

Background: Cognitive impairment is prominent in multiple sclerosis (MS) and is strongly influenced by thalamic damage.

Objectives: This study investigates whether changes in functional connectivity (FC), diffusivity and volume of the thalamus explain different severities of cognitive impairment in early multiple sclerosis.

Methods: A homogeneous cohort of 157 early MS patients (104 women), six years post-diagnosis, was divided into three groups based on cognitive testing with an expanded BRB-N: cognitively preserved (CP, n=108), mildly cognitively impaired (MCI, n=22), and more severely cognitively impaired (CI, n=27) and compared to 47 matched healthy controls (28 women). MRI-based thalamic volume, thalamic fractional anisotropy (FA), thalamic mean diffusivity (MD) and thalamic resting-state FC were compared between groups.

Results: Thalamic volume was significantly lower in all patient groups compared to controls, with lowest volumes in CI, and no difference between CP and MCI. Thalamic FA was decreased in CI compared to controls only; MD was increased in CI compared to all other groups. Thalamic FC was increased in CI with mainly sensorimotor, frontal and occipital regions. Thalamic volume was the primary thalamic predictor of cognition, together with

thalamic FC and MD. This linear regression model of cognition (adjusted R[2] 0.47) also included male sex and a lower level of education.

Conclusions: These findings indicate that thalamic changes in structure and function are highly informative regarding overall cognitive performance in multiple sclerosis. Increased thalamic functional connectivity only became apparent in more severe cognitive impairment, possibly as a sign of maladaption.

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Regional white matter abnormalities and cognitive impairment in MS: a multicenter TBSS study

A Bisecco[1], MA Rocca[1,2], E Pagani[1], F Barkhof[3], DL Thomas[4], N De Stefano[5], C Enzinger[6], A Gallo[7], HE Hulst[3], L Mancini[4], ML Stromillo[5], F Fazekas[6], G Tedeschi[7], G Comi[2], M Filippi[1,2]
[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Institute of Experimental Neurology, Milan, Italy, [2]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy, [3]VU Medical Centre, Radiology and Image Analysis Centre (IAC), Amsterdam, Netherlands, [4]Institute of Neurology, UCL, Department of Brain Repair and Rehabilitation, London, United Kingdom, [5]University of Siena, Dept. of Medicine, Surgery & Neuroscience, Siena, Italy, [6]Medical University of Graz, Department of Neurology, Graz, Austria, [7]Second University of Naples, Department of Neurology, Naples, Italy

Background: Previous single center studies have shown an association between disrupted white matter (WM) integrity and clinical manifestations, including cognitive impairment, in MS patients.

Objectives: Aim of this study was to apply Tract Based Spatial Statistics (TBSS) in a multi-center setting to assess the spatial distribution of WM damage in MS and its relationship with global cognitive impairment as well as deficits in selected cognitive domains.

Methods: This study was conducted at six European sites using 3.0 Tesla scanners. Fifty-one MS patients and 57 sex-matched healthy controls (HC) underwent MR imaging examination including diffusion tensor imaging (DTI). MS patients underwent the Rao battery and the Wisconsin Card Sorting test (WSCT). Patients with at least two abnormal tests were considered as cognitively impaired (CI). TBSS was applied for voxel-wise analysis of fractional anisotropy (FA) and mean diffusivity (MD) maps. T2 lesion probability maps (LPM) were also created. Significant differences were reported at a threshold of 0.01, age corrected.

Results: Twenty-two MS patients were CI. Compared to HC, MS patients had decreased FA of the majority of skeleton voxels. Compared to cognitively preserved patients, CI patients showed bilateral decreased FA and increased MD of the corpus callosum, superior and inferior longitudinal fasciculus, corticospinal tract, inferior fronto-occipital fasciculus, posterior thalamic radiation, and cingulum as well as the right uncinate fasciculus. Only a partial overlap was found between regional DT MRI abnormalities and T2 LPM differences between CI and CP patients. Significant correlations (p< 0.01) were found between:

1) global cognitive and attention Z score *vs* FA/MD abnormalities of most of the damaged areas described above;

2) visual memory Z score *vs* FA of the corpus callosum and right inferior fronto-occipital fasciculus;

3) verbal memory Z score *vs* MD abnormalities of most of the damaged areas; and

4) WCST scores *vs* MD of the corticospinal tract, superior longitudinal fasciculus, left inferior fronto-occipital fasciculus, forceps major, fornix, anterior thalamic radiation and left cingulum.

Conclusions: The application of TBSS to define the regional distribution of WM damage in a multicenter setting in MS patients is feasible and contributes to better characterize disease cognitive manifestations.

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Thalamic tract integrity changes are associated with cognition and disinhibition in multiple sclerosis

HE Hulst[1], RHB Benedict[2], MD Steenwijk[3], MM Schoonheim[1], MG Dwyer[2,4], N Bergsland[4,5], F Barkhof[3], B Weinstock-Guttman[2], R Zivadinov[4,6], JJG Geurts[1]
[1]VU University Medical Center, Anatomy and Neurosciences, Amsterdam, Netherlands, [2]University at Buffalo State University of New York, Department of Neurology, School of Medicine and Biomedical Sciences, Buffalo, NY, United States, [3]VU University Medical Center, Radiology, Amsterdam, Netherlands, [4]University at Buffalo State University of New York, Buffalo Neuroimaging Analysis Center, Department of Neurology, School of Medicine and Biomedical Sciences, Buffalo, NY, United States, [5]Don Gnocchi Foundation, IRCCS, Milan, Italy, [6]MRI Clinical Translational Research Center, School of Medicine and Biomedical Sciences, Buffalo, NY, United States

Background: Thalamic pathology is frequently found in multiple sclerosis (MS). These thalamic abnormalities are highly correlated with conversion to clinically definite MS, physical disability and cognitive impairment. Anatomically, the thalamus can be subdivided into a number of different thalamic nuclei, each with their own specific (sub) cortical output and input areas. This implies that damage to specific thalamic nuclei and/or their associated tracts should result in disparate symptoms.

Objectives: To investigate groups of thalamic nuclei (anterior, posterior, medial, lateral) and the integrity of their associated tracts with regard to cognitive impairment and neuropsychiatric symptoms in MS patients.

Methods: Conventional MRI and diffusion tensor imaging (DTI) was acquired in 73 MS patients and 18 healthy controls (HC). The Minimal Assessment of Cognitive Function in MS (MACFIMS) was used to investigate cognitive functioning; neuropsychiatric symptoms were assessed using the Neuropsychiatric inventory. Based on a histological atlas, the thalamus was parcellated into an anterior, lateral, medial and posterior part. The associated tracts were derived using an atlas obtained by probabilistic tractography in the HCs and integrity of the tracts was expressed by fractional anisotropy (FA) and mean diffusivity (MD).

Results: In MS patients, cognitive impairment, disinhibition and agitation were related to MD and lesion volume in tracts emanating from all four thalamic nuclei. No correlations were detected between FA and cognitive and neuropsychiatric measures in the posterior, medial and lateral thalamic tracts. However, FA was positively correlated with cognitive test scores and negatively

with disinhibition, *exclusively* in the tract of the anterior part of the thalamus.

Conclusions: FA changes in the anterior thalamic tract were the most specific marker for cognitive impairment and disinhibition. This finding provides a highly specific biological explanation for cognitive deterioration and neuropsychiatric changes common to MS.

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Multimodal quantitative magnetic resonance imaging of thalamus in multiple sclerosis and neuromyelitis optica

J Wang[1], Y Liu[2,3], Y Duan[2], H Dong[2], J Ye[2], F Barkhof[3], K Li[2]
[1]Hangzhou Normal University, Hangzhou, China, [2]Xuanwu Hospital, Beijing, China, [3]VU Medical Center, Amsterdam, Netherlands

Background: The thalamus, a key node of the deep grey matter has been convergently found to show MS-related abnormalities, while thalamus implication in NMO patients were also reported with controversial results. Whether and how the MS/NMO differentially affects thalamus is unclear.

Objectives: To compare the structural and functional alterations in thalamus between MS and NMO by a combination of multimodal MRI techniques.

Methods: We recruited 33 MS, 38 NMO patients and 40 well-matched healthy controls (HC) with multimodality MRI data obtained at a 3T MRI. Six measurements were obtained for the whole thalamus for each participant including the gray matter volume (GMV), fractional anisotropy (FA), mean diffusivity (MD), amplitude of low-frequency fluctuation (ALFF), cross-correlation coefficient of spontaneous low-frequency (COSLOF) and weighted functional connectivity strength (wFCS). All of the measurements were compared among groups using multiple one-way analyses of covariance (ANCOVA). Correlations between MRI-based measures and clinical variables were investigated by multiple partial correlation analyses. At last we performed a receiver operating characteristic curve analysis to determine the power of the observed between-group differences to classify the groups.

Results: Significant group effects were detected in the GMV and WM integrity (FA and MD) of the thalamus ($P < 10^{-3}$), while only MS patients showed decreased COSLOF and wFCS than HC, no significant functional parameters were found between NMO and HC. Significant correlation was identified between structural measurements, but not between structural and functional measurement in both MS and NMO. The observed differences in structural GMV and FA/MD of the whole thalamus exhibited fair-to-good-excellent discriminative power indistinguishing the three groups.

Conclusions: Structural and functional alterations in thalamus were identified in MS, while NMO showed similar pattern but much milder. The disassociation between structural and functional changes in both MS and NMO implies that structural and functional abnormalities in thalamus may occur independently and may provide complementary information about MS/NMO pathophysiology. The thalamic structural parameters showed fair-to-good-excellent discriminative power with very high specificity in three groups, which serves

as potential MRI biomarkers to distinguish MS, NMO and HC.

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Memory impairment in multiple sclerosis: relevance of hippocampal activation and hippocampal connectivity

HE Hulst[1], MM Schoonheim[1], Q van Geest[1], BMJ Uitdehaag[2], F Barkhof[3], JJG Geurts[1]

[1]VU University Medical Center, Anatomy and Neurosciences, Amsterdam, Netherlands, [2]VU University Medical Center, Neurology, Amsterdam, Netherlands, [3]VU University Medical Center, Radiology, Amsterdam, Netherlands

Background: Memory deficits develop in 40-65% of the patients with multiple sclerosis (MS) and generally lead to problems in daily life activities and to unemployment. The hippocampus plays an essential role in memory function and is therefore a crucial structure to study to understand the underlying neurobiological substrates of memory impairment in MS.

Objectives: The aim of our study was to investigate structural hippocampal changes, functional hippocampal activation and functional hippocampal connectivity in MS and to identify the most important hippocampal parameter(s) for memory performance in MS.

Methods: Structural and functional (resting-state and task-based) MRI data were acquired in 57 MS patients (39 women) and 28 healthy controls (HCs, 19 women). Hippocampal volume, hippocampal lesions, hippocampal functional connectivity at rest, and hippocampal activation during a memory task were determined. A composite memory score was calculated based on three subtests of a larger neuropsychological test battery. A linear regression analysis was used to predict this score of memory function.

Results: Hippocampal volume was significantly lower in MS patients compared to HCs. In MS, increased hippocampal connectivity was detected between the left hippocampus and the right posterior cingulate. Hippocampal activation during a memory task was decreased in cognitively impaired patients only; hippocampal activation in the entire patient group did not differ from HCs. Linear regression showed that 30% of the variance in memory impairment in MS was explained by sex, hippocampal activation and hippocampal connectivity with the posterior cingulate (p< 0.001).

Conclusions: *Increased connectivity* and *decreased task-related activation* of the hippocampus and *male sex* were associated with worse memory performance in MS. These results indicate that functional activation and functional connectivity of the hippocampus reflect two different processes in the brain with distinct effects on memory performance in MS.

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Volumetric imaging of grey and white matter in the human brain

S Buch[1], Y Ye[2], S McDonald[3], EM Haacke[1,2,4]

[1]McMaster University, School of Biomedical Imaging, Hamilton, ON, Canada, [2]Wayne State University, MR Research Facility, Detroit, MI, United States, [3]Royal Victoria Regional Health Center, Barrie, ON, Canada, [4]MRI Institute of Biomedical Research, Detroit, MI, United States

Background: Whole brain grey matter (GM) and white matter (WM) atrophy have been shown to correlate with dysfunction and disability in MS. Applying the registration and segmentation processing to provide these measurements using the conventional MR images is very resource intensive; and the partial volume effect at the interface of these tissues makes it harder to extract accurately.

Objectives: Our goal was to perform a volumetric measurement of GM/WM using double inversion recovery (DIR) sequence. There is currently a "gap" between our academic ability to study atrophy and applying this concept in a routine clinical environment. The solution may lie in the use of this specialized MR pulse sequence that highlights either GM or WM alone. In this study, we tested the DIR sequence and a special processing methodology, to provide a simpler means by which to calculate the longitudinal measurement of GM/WM atrophy.

Methods: Inversion times for the DIR-sequence depend on the T_1 relaxation time of the tissue of interest to be suppressed. Using the theoretical values and an experimental approach, where five healthy participants were studied, the sequence parameters were optimized for GM-only DIR (GM-DIR): TI_1/TI_2=1400/500ms, and WM-only DIR (WM-DIR): TI_1/TI_2=2320/380ms, with B_0=3T and the voxel resolution=1x1x1mm³. Masks generated from WM-DIR and GM-DIR are subtracted to discard the common fat layer and to ensure that the extraction is done efficiently.

Results: For GM-DIR, the measured mean contrast ratios for the tissue pairs are: i) GM and WM=0.88, ii) GM and CSF=0.81, and iii) GM and air=0.95. Similarly, for WM-DIR: i) WM and GM=0.87, ii) WM and CSF=0.85 and iii) WM and air=0.92. The brain GM and WM volumes ± mean differences for volunteers were measured as (in mm³): GM = 558 ± 28, WM = 373 ± 35, whole brain = 915 ± 40, similarly, for patients (in mm³): GM = 599 ± 48, WM = 339 ± 55, whole brain = 939 ± 65.

Conclusions: Contrast ratio values of both GM-DIR and WM-DIR images are similar in their mean values. Relatively larger standard deviation is seen in the white matter for patients. This could indicate the variability in the demyelination across the given patient population. However not expected, the presence of overlapping pixels in the extracted masks may represent the myelinated grey matter regions, situated at the GM-WM interfaces, in the brain. In summary, DIR provides the potential for a complete assessment of total WM and GM volumes to follow patients over time.

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Brain sodium MRI in multiple sclerosis: a promising tool to monitor disability

A Maarouf[1], A Faivre[1], B Audoin[1], A Rico[1], E Soulier[1], S Confort-Gouny[1], M Guye[1], L Schad[2], J-P Ranjeva[1], J Pelletier[1], W Zaaraoui[1]

[1]CRMBM UMR 7339 CNRS Aix-Marseille Universite, Marseille, France, [2]Computer Assisted Clinical Medicine, Heidelberg University, Mannheim, Germany

Background: Brain sodium MRI is an emerging tool that enables depiction of cerebral sodium accumulation related to neuronal injury. In MS, demyelination, inflammation and subsequent mitochondrial energy failure result in axonal sodium accumulation, which leads to axonal calcium overload, causing structural and functional axonal injury that is the major substrate of disability in patients.

Objectives: This study aimed to assess sodium accumulation in patients at several stages of MS and the potential relationships between sodium concentration and their level of disability.

Methods: Forty-six MS patients including 14 early RRMS (median disease duration 1.2 years), 12 advanced RRMS (MDD 13 years), 20 progressive MS and 15 healthy controls were enrolled. They underwent 3D-quantitative total brain sodium MRI, conventional MRI (T2-weighted and 3D- T1-MPRAGE) at 3T and clinical assessment of disability using EDSS. Statistical mapping analyses of total sodium concentration abnormalities were performed using SPM8.

Results: Patients with early RRMS showed restricted sodium accumulation involving only the brainstem, the cerebellum and the left temporal pole whereas patients with advanced RRMS showed widespread sodium accumulation affecting both the white matter and the cortical and deep grey matter (caudate, thalami, insula, parietal, temporal, and prefrontal cortices, corpus callosum and cerebellum).

Patients with progressive MS showed diffuse sodium accumulation only in the grey matter, and especially in regions involved in motor and cognitive functions predominantly altered in this form of MS (primary motor cortices, premotor cortices, cerebellum, thalami, limbic and frontal networks).

Interestingly, higher was the level of disability in patients whatever the stage of MS, higher was the local sodium concentration inside the following grey matter regions: right primary motor area, right middle frontal gyrus, left premotor cortex, bilateral superior frontal gyri and the bilateral cerebellum.

Conclusions: Sodium accumulation in MS depicted by brain sodium MRI seems to be a dynamical phenomenon related to the stage of the disease, with restricted accumulation at the onset of MS which dramatically extends at later stages in white and grey matter in RRMS and only in grey matter in progressive MS. The relationship between motor performances and sodium accumulation depicted here emphasizes that brain sodium MRI is a promising tool to monitor disability in MS patients whatever the stage of the disease.

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Measurement of cortical thickness and volume of subcortical structures in multiple sclerosis: agreement between 2D and 3D T1-weighted images

À Vidal-Jordana[1], D Pareto[2], J Sastre-Garriga[1], C Auger[2], E Ciampi[1], X Montalban[1], Á Rovira[2]
[1]Vall Hebron University Hospital, Multiple Sclerosis Centre of Catalonia, Neuroimmunology Department, Barcelona, Spain, [2]Vall Hebron University Hospital, Magnetic Resonance Unit, Neuroradiology Department, Barcelona, Spain

Background: Grey matter pathology is known to occur in multiple sclerosis (MS) patients early during the disease course. It has been related to disease outcomes more reliably than global or white matter volumes. Interest in grey matter has grown in the last years and newer software tools to measure grey matter pathology as glanced by MRI have been developed. FreeSurfer measures cortical thickness as well as subcortical volumes in 3D T1-weighted images. Unfortunately, most classical MS cohorts with long-term follow-up do not have 3D but 2D T1-weighted images.

Objectives: We aimed to evaluate if cortical thickness and subcortical volumes obtained with FreeSurfer software could be reliably measured in 2D T1-weighted images as compared to the same measures obtained with 3D T1 sequences.

Methods: Thirty-eight patients with MS and 2D and 3D T1-weighted images obtained at the same time were included in the analysis. FreeSurfer software was used to obtain cortical thickness and subcortical structures volumes in all 2D and 3D images. To assess reliability, the intraclass correlation coefficient (ICC) between these two measures was calculated. ICC measures were classified as: slight (0.01 to 0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), substantial (0.61 to 0.80), and almost perfect agreement (0.81 to 1.0). Two-tailed chi-square tests were used for group comparison.

Results: Subcortical volumes showed good agreement between 2D and 3D images, with 53% of the structures having either a substantial or almost perfect agreement. The highest ICCs values included important structures for MS patients such as: thalamus, pallidum, caudate, brainstem, putamen, and corpus callosum. Cortical thickness had the lowest ICCs values, with 38.6% and 37.1% of the structures having a moderate or slight agreement respectively, and only 1 structure (right superior temporal gyrus) had a substantial agreement. Cortical thickness of lateral structures had higher proportions of moderate ICCs values than medial structures (58.3% vs. 13.3%, p=0.001).

Conclusions: Measuring subcortical volumes with FreeSurfer software in 2D images seems to produce reliable results. Measurement of cortical thickness with 2D images, although better for lateral than medial structures, is inaccurate and unreliable.

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Diffusion tensor imaging reveals distinct patterns of white matter changes in pediatric monophasic demyelinating disorders and multiple sclerosis

<u>G Longoni</u>[1,2], P Momayyezsiahkal[2], RA Brown[2], C Elliott[3], S Narayanan[2], B Brenda[4], M Filippi[1], DL Arnold[2]
[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience and Department of Neurology, Milano, Italy, [2]McGill University, Montreal Neurological Institute, McConnell Brain Imaging Centre, Montreal, QC, Canada, [3]McGill University, Centre for Intelligent Machines, Montreal, QC, Canada, [4]Children's Hospital of Philadelphia, University of Pennsylvania, Division of Neurology, Philadelphia, PA, United States

Background: In contrast to the multifocal nature of multiple sclerosis (MS), monophasic acquired demyelinating syndromes (mADS) during childhood may be expected to have normal white matter (WM) in regions not involved in the acute attack.

Objectives: To determine whether normal appearing WM (NAWM) microstructure, as indicated by fractional anisotropy (FA) and mean diffusivity (MD), differs between pediatric MS and the main mADS presentations (acute disseminated encephalomyelitis (ADEM), monofocal mADS ($mADS_m$), polyfocal mADS ($mADS_p$), and mADS with and without brain lesions ($mADS_{T2}$+, $_mADEM$ excluded; $mADS_{T2}$-).

Methods: Children with pediatric onset MS (McDonald 2005 criteria) or mADS (a single demyelinating event with no further clinical or radiological disease; follow-up > 2 years) were identified from the prospective Canadian Pediatric Demyelinating Disease Study. The temporal changes in FA and MD were modeled using serial diffusion tensor imaging and linear mixed effects models (using fixed effects for *age at onset* and for the

interactions of *disease duration* with *group*, and a random effects *subject* to account for within-subject variability). The *age at onset* term in each model estimates the effect of age on FA or MD at clinical presentation; the trajectory described by this term was used to measure whether FA or MD trajectories were different before and after the initial clinical event. Results are reported for $p < 0.05$.

Results: 517 scans from 75 mADS patients and 53 MS patients were selected (mean age at onset 10.0 and 12.1 years, respectively; mean follow: 4.8 and 5.2 years, respectively).

(A) As expected, FA decreased and MD increased more steeply over time in MS compared to children with mADS; nonetheless, FA and MD trajectories in both groups significantly differed from those expected from their age-dependent baseline trajectories.

(B) FA trajectories were similar between $mADS_p$ (n=11) and MS, both decreasing significantly faster than ADEM (n=18) and baseline trajectories.

(C) Longitudinal FA and MD were not significantly different between $mADS_{T2}+$ (n=17) and MS; in both groups, longitudinal FA decreased more steeply than $mADS_{T2}-$, and differed significantly from the baseline trajectory.

Conclusions: Pediatric mADS syndromes other than ADEM are associated with significant disruption of NAWM integrity and subsequent development. Patients with $mADS_{T2}+$, most of whom may ultimately be diagnosed with MS, showed loss of NAWM integrity comparable to that in MS patients.

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Effective connectivity of the default mode network in MS patients: increased self-inhibition of the posterior cingulate cortex

M Tonietto[1,2], M Calabrese[1], I Mazzonetto[2], M Castellaro[2], S Monaco[1], A Bertoldo[2]
[1]University of Verona, Department of Neurological and Movement Sciences, Verona, Italy, [2]University of Padova, Department of Information Engineering, Padova, Italy

Background: Differences in the functional connectivity were vastly reported in Multiple Sclerosis (MS), however there is no evidence on how they relate to changes in the underlying neural coupling. Dynamic Causal Models (DCM) were developed to explicitly model the neuronal coupling and to derive effective connectivity information.

Objectives: This study presents the preliminary results obtained analysing for the first time the effective connectivity in MS using DCM.

Methods: Resting state fMRI was acquired in 12 healthy subjects (age 25.4±2.3y) and 53 Relapsing Remitting MS patient (age 41.6±10.4y). MS patients were divided in 3 paired groups: by age (30.1±5.7 vs 48.5±5.6 y), by disease duration (3.5±1.8 vs 17.7±3.9 y) and EDSS (1.1±0.4 vs 2.6±0.7). After standard pre-processing, fMRI data were analysed through probabilistic Independent Component Analysis using FSL in order to separate artefacts from resting state networks. The Default Mode Network (DMN) component was used as guide to extract the principal eigenvariate from the prefrontal cortex (PFC), posterior cingulate cortex (PCC), left and right inferior parietal lobule (LIPL, RIPL). Seven

different DCMs describing the effective connectivity between the DMN regions were chosen based on anatomical information or derived from literature. Parameters were estimated with SPM8 and the most likely model was selected using Bayesian Model Selection (BMS). Using this as reference, population networks were calculated for healthy, MS and each subgroup of MS patients using the posterior variance-weighted averaging method. Differences between the population connectivity parameters were tested calculating the z-scores of their differences. Values greater than 3 were considered significant (99.7% confidence).

Results: BMS selected a model with connections from the PCC, LIPL and RIPL to the PFC. As regards the connectivity estimates, a significant difference was found in the PCC self-inhibition between controls and MS patients. In particular, MS patients presented stronger (faster) self-inhibition. This difference was consistent comparing controls with the different subgroups of MS patients, included the age matched subgroup. However, no differences were found between any of the MS subgroups.

Conclusions: Our results on effective connectivity obtained with DCM are remarkable as they are in line with several neuropathological and structural MRI studies showing that the PCC is mainly affected by the disease. The increased self-inhibition might constitute a potential MS marker.

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Evolution of gadolinium-enhancing lesions into chronic black holes in patients treated with subcutaneous interferon β-1a in PRISMS and SPECTRIMS

A Traboulsee[1], D Li[1], Y Zhao[1], R Tam[1], G Zhao[1], Y Cheng[1], A Riddehough[1], F Dangond[2], J Fang[2], L Kappos[3], on behalf of the PRISMS and SPECTRIMS Working Groups
[1]University of British Columbia, Vancouver, BC, Canada, [2]EMD Serono, Inc., Rockland, MA, United States, [3]University Hospital Basel, Basel, Switzerland

Background: Chronic black holes (CBHs) indicate irreversible axonal loss in multiple sclerosis (MS).

Objectives: To assess the evolution of gadolinium-enhancing (Gd+) lesions into CBHs in patients with relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) treated with subcutaneous (sc) interferon (IFN) β-1a.

Methods: The treatment arms of two controlled studies, PRISMS (RRMS; baseline Expanded Disability Status Scale [EDSS] score 0-5.0) and SPECTRIMS (SPMS; baseline EDSS score 3.0-6.5 and pyramidal functional score ≥2), were retrospectively analyzed. Patients receiving sc IFN β-1a (44 and 22 μg three-times-weekly groups combined) were included if they had monthly magnetic resonance imaging scans from Months -1 to 9 and ≥1 new T1 Gd+ lesion from Months -1 to 3. Images were reanalyzed to assess evolution of new Gd+ lesions from Months -1 to 3 into CBHs by Month 9 (Months -1 to 2 and 8 were analyzed for patients without a Month 9 scan), and evolved CBH volume at Month 9. CBHs were defined as new T1 Gd+ lesions that evolved into T1 hypointense lesions that were visible ≥6 months later.

Results: Overall, 73 patients were included from PRISMS (mean [standard deviation, SD] age 34.7 [7.0] yrs; 69.9% female) and 79 from SPECTRIMS (mean [SD] age 42.2 [7.3] yrs; 60.8% female). For RRMS vs SPMS, the mean (SD) total number of new T1 Gd+ lesions from Months -1 to 3 was 7.5 (16.5) vs 4.6 (5.4); median

(Q1, Q3), 4.0 (1.0, 7.0) and 3.0 (1.0, 6.0). The proportion of new Gd+ lesions (lesion level) evolving into CBHs at Month 8/9 was lower for RRMS vs SPMS: 11.0% (60/544) vs 28.8% (105/365); odds ratio (95% confidence interval; CI) 0.31 (0.18, 0.53); p< 0.0001. For RRMS vs SPMS, a lower proportion of Gd+ lesions evolved into CBHs (patient level) at Month 8/9: mean (SD), 12.6% (24.7%) vs 34.7% (35.8%); median (Q1, Q3), 0.0 (0.0, 12.5) vs 25.0 (0.0, 60.0); p< 0.0001. The rate of Gd+ lesions evolving into CBHs was lower for patients with RRMS vs SPMS (rate ratio [95% CI] 0.38 [0.26, 0.58]; p< 0.0001). For RRMS vs SPMS, the mean (SD) evolved CBH volume (mm^3) was lower for RRMS vs SPMS: 66.0 (172.60) vs 120.3 (224.57); median (Q1, Q3), 0.0 (0.0, 52.4) vs 33.5 (0.0, 173.4); p=0.0008.

Conclusions: According to this analysis, the evolution of CBHs was significantly lower in sc IFN β-1a treated patients with RRMS vs SPMS.

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Ultra-high field MRI of intra- and extra-cellular sodium concentration in multiple sclerosis

M Petracca[1,2], R Teodorescu[1], L Fleysher[3], L Jonkman[1], I De Kouchkovsky[4], N Oesingmann[3], J Herbert[5], M Inglese[1,3,6]
[1]*Mount Sinai School of Medicine, Neurology, New York, NY, United States,* [2]*Federico II University, Neuroscience, Naples, Italy,* [3]*Mount Sinai School of Medicine, Radiology, New York, NY, United States,* [4]*New York University, Radiology, New York, NY, United States,* [5]*New York University, Neurology, New York, NY, United States,* [6]*Mount Sinai School of Medicine, Neuroscience, New York, NY, United States*

Background: Measurement of total sodium concentration (TSC) is useful in the assessment of brain tissue injury in Multiple Sclerosis (MS) patients[1,2,3,4]. However, it does not allow discrimination of the extra-cellular (ESC) from the intra-cellular sodium concentration (ISC) that might be a marker of delayed axonal damage[5].

Objectives:

1) To measure TSC, ISC and ESC in MS patients using triple-quantum sodium MRI at 7 Tesla (7T);
2) to investigate the associations between TSC, ISC and ESC and measures of lesion and brain volume;
3) to assess the clinical significance of ISC and ESC.

Methods: Nineteen MS patients with a relapsing-remitting course (11F; mean age: 40.0 ±11.2 yrs; median EDSS: 2.0; range: 1.0-5-5; disease duration 9.1 ± 7.4 yrs) and 17 healthy controls (CTRLs) (8F; mean age: 46.16 ±11.65 yrs) underwent sodium MRI at 7T and proton MRI at 3T. The 7T MRI protocol included a modified GRE sequence with a new 12-step phase-cycling TQF scheme[6,7]. The 3T MRI protocol included DE-TSE and 3D T1W-MPRAGE. After creation of the TSC (mM), ISC (mM) and intracellular sodium volume fraction (ISVF-an indirect measure of ESC; %) maps[7], mean TSC, ISC and ISVF were measured with a histogram analysis over the entire gray and white matter (GM, WM) and with a regional voxel-based approach using SPM8.

Between groups comparison was performed with an ANCOVA test controlling for age, gender and intra-cranial volume. The correlation between sodium MRI-derived parameters, proton MRI-derived measures and clinical scores were assessed using Spearman´s rank correlation coefficient.

Results: Compared to CTRLs, MS patients showed higher global GM and WM TSC (p< 0.05) and lower global GM and WM ISVF (p< 0.01). Global GM and WM ISC were higher in patients than CTRLs but the difference was not statistically significant (p>0.1). ISC resulted significantly higher and ISVF lower in thalamus, frontal middle gyrus, precentral gyrus and superior longitudinal fasciculus bilaterally, in the left insula and cortico-spinal tract and in the forceps minor (p< 0.05, Ke=10). Global GM ISVF showed a correlation trend with EDSS (r=-0.47, p=0.054) and global GM ISC showed a correlation with T2 lesion volume (r=0.50, p< 0.05).

Conclusions: Brain ISC and ESC abnormalities are widespread in MS patients; while both metrics are moderately associated with lesion volume, only ESC correlates with EDSS.

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Cervical cord area measurement using volumetric brain magnetic resonance imaging

Z Liu[1,2], Ö Yaldizli[1], M Pardini[1,3], V Sethi[1], H Kearney[1], N Muhlert[1], C Wheeler-Kingshott[1], DH Miller[1], DT Chard[1,4]
[1]*Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Institute of Neurology, London, United Kingdom,* [2]*Xuanwu Hospital of Capital Medical University, Department of Neurology, Beijing, China,* [3]*University of Genoa, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Genoa, Italy,* [4]*National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre, London, United Kingdom*

Background: In multiple sclerosis (MS), combined clinical and MRI studies have shown that cervical cord atrophy, especially the measure of cross-sectional cord area at the C2/3 level, is more strongly associated with physical disability than either brain lesion load or atrophy. Spinal cord imaging is not routinely obtained in research studies and clinical trials. However, brain volumetric imaging is often acquired and usually includes the upper cervical cord.

Objectives: In this study, using volumetric brain images, we investigated cross-sectional areas in the uppermost cervical cord and compared them with areas at the standard C2/3 level. Our aims were:

[1] to determine if an active surface model frequently used to measure cord cross-sectional area at C2/3 could be reliably used at to measure the cord area at higher levels in short (0.5cm) segments; and

[2] to explore whether cord area measures at these higher levels would be a plausible alternative to the area obtained at the standard C2/3 level.

Methods: Using volumetric T1-weighted brain scans from 13 healthy controls and 37 people with MS that included the upper cervical cord in the filed of view, an active surface technique was applied to obtain cross-sectional area measurements at C2/3, below the level of the odontoid peg (OP), and 2cm (P2) and 2.5cm (P2.5) below the pons.

Results: Reproducibility assessment for C2/3, P2.5, P2 and OP levels showed cord area measurements were most reliable at 2.5 cm below the pons (inter-rater coefficient of variation 2.3%, 1.5%, 3.7% and 14.6%, and intraclass correlation coefficient 0.97, 0.99,

0.95 and 0.24 for P2.5, P2 and OP respectively). Cord areas at P2.5, P2 and OP were all significantly correlated with that at C2/3 (the Pearson correlation coefficient r=0.811, 0.731 and 0.741 respectively, each P< 0.001).

Conclusions: Whereas the standard C2/3 level is often not within the field of view on brain images, the level 2.5cm below the pons almost always is, and measurement at this level may be a good way to investigate upper cervical cord atrophy when only brain images are available.

P473

Natural evolution of gadolinium-enhancing lesions into chronic black holes in multiple sclerosis: analysis of PRISMS and SPECTRIMS placebo arms

A Traboulsee[1], D Li[1], Y Zhao[1], R Tam[1], G Zhao[1], Y Cheng[1], A Riddehough[1], F Dangond[2], J Fang[2], L Kappos[3], on behalf of the PRISMS and SPECTRIMS Working Groups
[1]*University of British Columbia, Vancouver, BC, Canada*, [2]*EMD Serono, Inc., Rockland, MA, United States*, [3]*University Hospital Basel, Basel, Switzerland*

Background: Chronic black holes (CBHs) represent irreversible axonal loss.

Objectives: To assess the evolution of gadolinium-enhancing (Gd+) lesions into CBHs in relapsing-remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis (SPMS).

Methods: The PRISMS (RRMS; baseline Expanded Disability Status Scale [EDSS] score 0-5.0) and SPECTRIMS (SPMS; baseline EDSS score 3.0-6.5 and pyramidal functional score ≥2) subcutaneous interferon β-1a studies, which had parallel recruitment, were retrospectively analyzed. Patients receiving placebo were included if they had monthly magnetic resonance imaging scans to Month 9 and ≥1 new Gd+ lesion from Months -1 to 3. Images were reanalyzed to assess evolution of new Gd+ lesions from Months -1 to 3 into CBHs by Month 9, and evolved CBH volume at Month 9 (Months -1 to 2 and Month 8 were analyzed if a Month 9 scan was unavailable). CBHs were defined as new T1 hypointense lesions (initially Gd+) persisting for ≥6 months.

Results: In total, 49 patients were included from PRISMS (mean [standard deviation, SD] age 34.7 [8.4] years; 36 [73.5%] female) and 52 from SPECTRIMS (mean [SD] age 41.4 [5.9] years; 33 [63.5%] female). For RRMS and SPMS, respectively, mean (SD) total number of new Gd+ lesions per patient from Months -1 to 3 was 8.7 (12.7) and 9.9 (15.4); median (Q1, Q3) was 4.0 (2.0, 11.0) and 4.0 (2.0, 11.0). The proportion of new Gd+ lesions (lesion-level) evolving into CBHs at Month 8/9 was lower for patients with RRMS vs SPMS: 11.6% (49/424 lesions) vs 27.2% (140/514 lesions); odds ratio 0.35; 95% confidence interval (CI) 0.19, 0.65; p=0.001. Analyses of patient-level data suggested a similar trend. The rate of lesions evolving into CBHs was lower in patients with RRMS versus SPMS (rate ratio 0.54; 95% CI 0.34, 0.86; p=0.01). There was a trend towards a lower proportion of Gd+ lesions evolving into CBHs per patient at Month 8/9 for RRMS vs SPMS: mean (SD), 19.8% (28.9%) vs 27.7% (31.9%); median (Q1, Q3), 6.3 (0.0, 28.6) vs 16.5 (0.0, 50.0); p=0.20. For RRMS and SPMS, mean (SD) evolved CBH volume (mm³) was 118.3 (329.5) vs 246.4 (589.6); median (Q1, Q3) was 6.6 (0.0, 83.0) vs 12.1 (0.0, 171.5); p=0.32.

Conclusions: The risk of a new Gd+ lesion evolving into a CBH was significantly higher in placebo patients with SPMS vs RRMS. Patients with SPMS tended to have a higher proportion of new Gd+ lesions evolving into CBHs and higher evolved CBH volume than those with RRMS.

P474

Unraveling the neuroimaging markers of motor dysfunction in long-standing multiple sclerosis

M Daams[1,2], MD Steenwijk[1], MP Wattjes[1], JJG Geurts[2], BM Uitdehaag[3], PK Tewarie[3], LJ Balk[3], J Killestein[3], F Barkhof[1]
[1]*VU University Medical Center, Radiology and Nuclear Medicine, Amsterdam, Netherlands*, [2]*VU University Medical Center, Anatomy and Neurosciences, Amsterdam, Netherlands*, [3]*VU University Medical Center, Neurology, Amsterdam, Netherlands*

Background: Motor dysfunction is well described in multiple sclerosis (MS) but its pathological substrate is not fully understood.

Objectives: To investigate the influence of conventional MRI measures and quantitative imaging measures in the corticospinal tract (CST) on motor dysfunction in a large cohort of patients with long-standing MS.

Methods: A total of 195 MS patients and 54 healthy controls were included. A wide spectrum of neuroimaging measures at the whole-brain, cervical and CST level were quantified, including whole-brain, cerebellar, brainstem and brain white matter lesion volumes, (juxta)cortical lesion count, mean upper cervical cord area (MUCCA), cervical cord lesion count, and CST lesion volume, CST tract integrity (as measured using diffusion tensor imaging), and thickness of the cortex connected to the CST. Motor function was assessed using the Expanded Disability Status Scale (EDSS), Nine-Hole-Peg test (9-HPT), and 25 feet Timed-Walk Test (TWT). Stepwise linear regression was used to assess the association between damage in different parts of the motor system and motor functioning.

Results: Worse motor functioning was associated with smaller MUCCA, lower brain- cerebellum- and brainstem volume, higher brain lesion volume, cortical and infratentorial lesion count, cervical cord lesion count and several CST measures, including lesion volume in the CST, mean-, axial- and radial diffusivity in the CST, and thickness of the cortex connected to the CST. More specifically, EDSS score was associated with infratentorial and cervical cord lesion count, lesion volume in the CST and MUCCA (explaining 40.3% of the variance). The model for 9-HPT score included infratentorial lesion count and thickness of the cortex connected to the CST (explaining 24.5% of the variance). TWT score was associated with infratentorial lesion count and cerebellar volume (explaining 15.0% of the variance).

Conclusions: In this study, we mapped damage in different parts of the motor system in long-standing MS using comprehensive brain and cervical measures in relation to motor dysfunction. We show that motor dysfunction is a complex mechanism and cannot be explained by a single neuroimaging marker, but is the consequence of an interplay of both whole-brain, cerebellar, and spinal cord pathology, as well as damage in the corticospinal tract.

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MRI correlates of disability: neuroimaging substudy at 20-years in the ongoing US glatiramer acetate open-label extension study

O Khan[1,2], F Bao[2], G Ramesh[2], K Thakore[2], C Caon[1], C Santiago[1], Z Latif[3], R Aronov[3], I Zak[3], Y Sidi[4], S Kolodny[5], The MRI Sub-Study of the US Open-Label Glatiramer Acetate Study Group

[1]Multiple Sclerosis Center, Wayne State University School of Medicine, Detroit, MI, United States, [2]Sastry Foundation Advanced Imaging Laboratory, Wayne State University School of Medicine, Detroit, MI, United States, [3]Wayne State University School of Medicine, Department of Diagnostic Radiology, Detroit, MI, United States, [4]Teva Pharmaceutical Industries, Netanya, Israel, [5]Teva Pharmaceutical Industries, Cleveland, OH, United States

Background: Identifying MRI outcomes that correlate with disability remains an MS research priority.

Objectives: To characterize MRI-EDSS associations in a subset of subjects treated for up to 20 years in the US Glatiramer Acetate open-label (OL) extension trial.

Methods: Following the placebo-controlled phase of the US Glatiramer Acetate pivotal trial, subjects entered the GA 20mg daily open-label extension in 1994. MRI scans were obtained in a subset of these patients in 2012. EDSS closest to the MRI scan was used for cross-sectional Spearman rank-correlation coefficient analyses.

Results: Sixty-four of 74 subjects (86%) participated in this MRI substudy. EDSS scores (mean 3.42; 0-8) were correlated with whole brain (WB) volume (r= -0.42, P= .001), gray matter (GM) volume (r= -0.35, P= .005), tNAA/tCr levels (r= -0.54, P< .001), cingulate cortical thickness (r= -0.31, P= .014), T1 lesion volume (r= 0.41, P= .001), and T2 lesion volume (r= 0.35, P= .005). There was no significant correlation with white matter volume, WB MTR, WB DTI metrics including FA and MD, or global cortical thickness.

Conclusions: The strongest cross-sectional MRI correlate of MS-related disability in this cohort was tNAA/tCr, followed by WB volume, T1 lesion volume, GM volume, T2 lesion volume, and cingulate cortical thickness.

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MS cortex-study: the association of cortical thickness and cortical lesions with clinical symptoms in multiple sclerosis

K Reuter[1], O Geisseler[1], T Pflugshaupt[1,2], L Bezzola[3], B Schuknecht[4], P Brugger[1], M Linnebank[1]

[1]University Hospital Zurich, Department of Neurology, Zurich, Switzerland, [2]Luzerner Kantonsspital, Department of Internal Medicine, Centre of Neurology and Neurorehabilitation, Luzern, Switzerland, [3]University of Zurich, Institute of Psychology, Division of Neuropsychology, Zurich, Switzerland, [4]Medizinisch Radiologisches Institut, Zurich, Switzerland

Background: Inflammatory lesions and brain atrophy in multiple sclerosis (MS) impact the central nervous system white matter as well as the cortex. Recent studies report conflicting results whether cortical thinning and cortical lesions are associated with the Expanded Disability Status Scale (EDSS) and disease duration. Few data are available concerning the association between cortical lesions, cortical thickness and more specific clinical parameters like the Multiple Sclerosis Functional Composite (MSFC).

Objectives: To analyse the association of T1, T2 and cortical lesion volume as well as cortical thickness and the clinical parameters EDSS and MSFC.

Methods: A structural MRI including a double inversion recovery sequence was conducted in 48 patients with relapsing-remitting MS. Within four weeks before or after MRI, patients were clinically examined. Lesion burden was analysed with *MRIcron*, cortical thickness with *Freesurfer*. Multivariate linear regression analysis was used to analyse the association of T1, T2 and cortical lesion volume as well as cortical thickness and EDSS and the three MSFC components. Due to multiple testing, threshold was set as α=0.0125.

Results: T1 lesion volume was associated with the nine-hole peg test of the dominant hand (domNHPT; p=0.009) but not with EDSS (p=0.132), the timed 25-foot walk (T25-FW; p=0.157) and with the nine-hole peg test of the non-dominant hand (ndomNHPT; p=0.076). T2 lesion volume was associated with the domNHPT for trend (p=0.016), but not with T25-FW (p=0.238), ndomNHPT (p=0.061) and EDSS (p=0.097). Cortical thickness was associated with domNHPT (p=0.004), ndomNHPT (p=0.014 for trend), T25-FW (p=0.002) and EDSS (p=0.039 for trend). Cortical lesion volume was not associated with any of the clinical parameters. The paced auditory serial addition test (PASAT) result was not associated with any of the MRI parameters. In addition, explorative analyses suggested region-specific associations of cortical thickness and clinical parameters, whereas global cortical thickness was associated with age (p=0.001), but not disease duration (p=0.553).

Conclusions: This study suggests that cortical thickness might be more relevant for clinical impairment in MS patients than the T1 or T2 lesion volumes. MSFC might be more suited for such analyses than EDSS. Such associations become clearer when compared with MSFC than with EDSS. This should be considered for the design of clinical studies and clinical practise.

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Tissue-specific brain volume changes on natalizumab: a 36-month follow-up study using VBM

E Ciampi[1], D Pareto[2], J Sastre-Garriga[1], À Vidal-Jordana[1], C Tur[1], J Río[1], M Tintoré[1], C Auger[2], Á Rovira[2], X Montalban[1]

[1]Vall Hebron University Hospital, Multiple Sclerosis Centre of Catalonia, Neuroimmunology Department, Barcelona, Spain, [2]Vall Hebron University Hospital, Magnetic Resonance Unit, Neuroradiology Department, Barcelona, Spain

Background: Global and regional GM loss occurs only during the first year of NTZ treatment in distinctive cortical and subcortical areas. GM loss is not influenced by the presence of inflammatory activity at baseline.

Objectives: To describe tissue-specific global brain volume and regional Gray Matter (GM) changes in MS patients receiving NTZ for at least 36 months and their correlation with radiological baseline and follow-up characteristics.

Methods: 38 patients on NTZ for at least 3 years were assessed radiologically (baseline, 12, 24, 36 months brain MRI including

2D pre/post Gad, 3D T1-weighted sequences) using a 1.5T magnet. Transversal and longitudinal Voxel Based Morphometry (VBM) analyses were performed with Statistical Parametric Mapping (SPM8), using a lesion mask to avoid segmentation errors due to black holes misclassification as GM. Longitudinal regional changes were assessed using a Flexible Factorial design; differences were considered significant at a FWE-corrected level for p< 0.001 and k=10 voxels. Global and tissue-specific GM, white matter (WM) and CSF) volumes and their correlations were analyzed using SPSS v21.

Results: Significant GM fraction (F), WMF and brain parenchymal (BP) F decreases were observed during the first year (p=0.002, p=0.001 and p< 0.001, respectively); only WMF changes were found in the second year (p=0.015) and no significant changes were observed in the third year. Baseline Gad enhancement influenced WMF and BPF change in the first year (R^2=0.40, p=0.03; R^2=0.40, p=0.03 respectively) but not GMF changes; no significant impact was observed beyond the first year. Clusters of significant GM loss in the first 12 months were located in bilateral cerebellum, cingulum, left>right fronto-parietal cortex, right>left hippocampus, and left caudate; no areas of GM increase were observed. No significant areas of GM loss or increase were observed during the second/third year.

Conclusions: Global and regional GM loss occurs only during the first year of NTZ treatment in distinctive cortical and subcortical areas. GM loss is not influenced by the presence of inflammatory activity at baseline.

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Slowly expanding lesions in MS: a histopathological mirage?

V Sethi[1], G Nair[1], CD Shea[1], BE Dewey[1], DS Reich[1]
[1]NINDS, NIH, Translational Neuroradiology Unit, Neuroimmunology Branch, Bethesda, MD, United States

Background: The pathological characteristics of chronic multiple sclerosis (MS) lesions have been studied extensively. At autopsy, particularly in progressive MS, approximately 40% of lesions are described to be "slowly expanding," characterized by the presence of immune cells at the lesion edge with ongoing myelin phagocytosis. However, as pathological lesion classification relies on analysis of a single time point, the rate of "expansion," or even whether they truly enlarge over time, cannot be directly inferred. In this study, we marshaled long-term (up to 20 years) in vivo MRI data to study the evolution of chronic WML with proton density-weighted (PD) MRI.

Objectives: To study the long-term evolution of individual white matter lesions (WML) in patients with MS using MRI.

Methods: 5 progressive MS patients were studied. Data were acquired on several different scanners between 1994 and 2014, using a variety of protocols. All images underwent rigid registration to the average T1 scan in MNI space, resampling to 1x1x1 mm, and intensity normalization. 11 discrete WML (at least 2 lesions each) were identified and tracked over time using both manual and automatic methods. For automatic tracking, a pairwise subtraction-based method for detecting new and enlarging lesions was used.

Results: All analyzed WML were found to shrink consistently on longitudinal PD MRI, with no evidence for an inflection point.

Over a mean duration of 15.2 years, the change in lesion volume was 50-61%, 32-54%, 79-88%, 39-98%, and 17-33% in the five patients. The estimation of lesion volume using manual and automatic methods did not differ (p=0.35). Lesions that were smaller at the first time point demonstrated the greatest relative change over time.

Conclusions: In contrast to the pathological finding that ~40% WML are slowly expanding, we found no evidence of radiological enlargement of lesions in progressive MS, and noted a sustained contraction in lesion volume over time. Although pathological classification was not possible here, it is unlikely that all of the lesions were undergoing gradual remyelination and repair in these progressive MS cases. Instead, a more likely explanation for our findings is that the rate of enlargement of chronic lesions, if lesion expansion is indeed a real phenomenon, is slow relative to the rates of tissue resorption and atrophy at the lesion core. Further work will examine the clinical determinants and correlates of long-term changes in lesion size.

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MRI reveals connectivity of cortical lesions to deep white matter lesions in multiple sclerosis

J-M Tillema[1], S Weigand[2], J Port[3], Y Shu[3,4], J Mandrekar[2], C Lucchinetti[1], I Pirko[1]
[1]Mayo Clinic, Neurology, Rochester, MN, United States, [2]Mayo Clinic, Biomedical Statistics and Informatics, Rochester, MN, United States, [3]Mayo Clinic, Radiology, Rochester, MN, United States, [4]Mayo Clinic, Biomedical Engineering and Medical Physics, Rochester, MN, United States

Background: The relationship between cortical lesions (CL) and white matter lesions (WML) in MS is poorly understood. In addition to their association with disease progression, CL may also play a role in disease initiation. We hypothesized that WML-s develop along tracts directly connected with CL.

Objectives: Our aim was to demonstrate this connectivity using double inversion recovery (DIR) sequences for CL detection coupled with DTI-based probabilistic tractography.

Methods: Relapsing-remitting MS patients with relative mild disease (EDSS < =4) and matched controls were scanned using the same 3T MRI protocol (3D-MPRAGE, DTI (41 directions) and 3D-DIR). Freesurfer was used for segmentation of the cortex. Semi-automated outlining of WM and CL (on DIR) was performed. FSL was used for connectivity analysis. WMLs were used as individual seeds for tractography. Connectivity to the cortex for each individual tract was obtained. These connected cortical regions were combined, dividing the entire cortex into "WML connected" and "non-connected" cortex. We calculated the fraction of CL volume within the connected and non-connected cortex, quantified as the connected vs. non-connected lesion ratio (CNCLR). Automated cluster analysis was performed to include randomly selected, non-specific DIR cortical hyperintensities in patients and controls. For comparative analysis we placed topographically comparable WM seeds in each controls from matched patients via affine registration.

Results: 25 patients (median age 33) and 24 controls (median age 35) were included. Connected vs Non-connected lesion ratios were elevated in MS patients (median 2.7 [IQR 2.0-3.6]) compared to their nonspecific cortical areas (median 1.2 [IQR

1.0-1.5]; p< 0.001) and compared to nonspecific cortical areas in controls (median 1.0 [IQR 0.8-1.2]; p< 0.001). These non-specific cortical areas in MS patients had slightly higher CNCLRs than controls (p=0.10).

Conclusions: CL on DIR are nearly 3 times as likely to be found in cortex that is connected to WML, providing evidence that CL and WML are topographically related. Non-specific DIR hyperintensities may be found slightly more frequently in connected cortex, suggesting that some of these non-specific regions may also represent poorly visualized CL due to sensitivity limitations. These findings are consistent with our hypothesis of CL-WML connectivity. Additional MRI and experimental pathology studies are underway to further investigate our hypothesis.

P480

Can MS lesion stages be distinguished with MRI? A postmortem MRI and histopathology study

LE Jonkman[1], A Lopez Soriano[2], H Vrenken[2], P van der Valk[3], F Barkhof[2], JJG Geurts[1]
[1]VU University Medical Center, Anatomy and Neurosciences, Amsterdam, Netherlands, [2]VU University Medical Center, Radiology, Amsterdam, Netherlands, [3]VU University Medical Center, Pathology, Amsterdam, Netherlands

Background: Multiple sclerosis (MS) is mostly characterized by its white matter lesions (WM) resulting from demyelination. Pathologically, a distinction can be made between different stages of WM lesions; preactive, active, chronic active and chronic inactive, depending on their degree of microglia, inflammation and demyelination. Unfortunately, conventional MR Imaging cannot distinguish between lesion stages, so clinical correlates cannot be directly investigated. However, there are a few quantitative MR imaging (qMRI) techniques which have shown to be far more sensitive and pathologically specific.

Objectives: To verify if different stages of WM lesion can be sufficiently differentiated by means of T1-RT in post mortem MS samples.

Methods: Coronal brain sections of 20 patients with MS (11 females) were obtained after rapid autopsy. The scan protocol included conventional Pd/T2 weighted images and six sets of images for T1 mapping (covering the same volume as the Pd/T2-w images). WM abnormalities visible on T2-w imaging were sampled and used for further examination. Staining and immunohistochemestry were performed on adjacent sections with antibodies against microglia/macrophages (anti-HLA-DR, clone LN3) and proteolipid protein (PLP). Sections containing WM lesions were matched to corresponding T2-w MR images. Lesions were outlined and copied onto T1 qMRI maps. For analysis between lesion types we used the unstructured General Estimated Equation (GEE) for correlated data.

Results: In total, 72 WM lesions were selected: 9 preactive, 18 active, 30 chronic active and 14 chronic inactive. Additionally, 38 areas of normal appearing WM (NAWM) were selected. Both NAWM and preactive lesions differed significantly from all other lesion types (p< 0.001), but did not differ significantly from each other (P=0.655). Active lesions differed significantly from chronic inactive lesions (p< 0.05), but not from chronic active lesions (p=0.147). Chronic active and chronic inactive lesions did not differ significantly from each other (p=0.155). However, when WM lesions were divided into three groups: 'NAWM/preactive', 'active'

and 'chronic' (including chronic active and chronic inactive lesions), all groups differed significantly from each other (p< 0.05).

Conclusions: We demonstrated that although not all four pathologically defined types of WM lesions can be sufficiently distinguished from each other, a MRI distinction can be made between NAWM/preactive, active and chronic lesions.

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Corpus callosum atrophy is associated with cognitive impairment in multiple sclerosis: results of a 17-year longitudinal study

T Granberg[1], J Martola[1], G Bergendal[2], S Shams[1], P Aspelin[1], S Fredrikson[2], M Kristoffersen-Wiberg[1]
[1]Karolinska Institutet, Department of Clinical Science, Intervention and Technology, Stockholm, Sweden, [2]Karolinska Institutet, Department of Clinical Neuroscience, Stockholm, Sweden

Background: Cognitive impairment is common in MS and may be subtle. The corpus callosum connects the cerebral hemispheres, is involved in connectivity-demanding cognitive tasks and is normally resistant to age-dependent change. However, due to its high myelin content it is affected in MS by lesions and Wallerian degeneration and may therefore serve as a sensitive and specific marker for cognitive function in MS.

Objectives: To study corpus callosum area (CCA) as a marker and predictor of cognitive function and disability in multiple sclerosis (MS).

Methods: In this longitudinal study, 45 MS patients were followed clinically and with magnetic resonance imaging (MRI) from 1995. Follow-ups were performed in 2004 (n=37) and 2013 (n=23). Mean follow-up time in 2013 was 17.2 years. A matched control group was recruited in 2013. Disability was assessed with expanded disability status scale (EDSS) and information processing speed with symbol digit modalities test (SDMT). CCA was measured on sagittal MRI. Volumetric measurements were obtained in Freesurfer.

Results: Disease duration spanned over five decades (1.6-46) years and EDSS increased with disease duration. In neuropsychological testing, 82% of the patients performed subnormally. The annual corpus callosal atrophy rate was 6.6 mm^2 (1.2%), and decreased with increased disease duration. After correcting for disease duration, age, sex, and multiple testing, only grey matter volume was significantly correlated to EDSS. Brain volume and grey matter measurements were strongly correlated to SDMT. CCA, at all time points, showed strong to very strong correlations to the final SDMT score (r=0.682, p=0.003; r=0.838, p< 0.001 and r=0.855, p< 0.001 respectively).

Conclusions: Corpus callosal atrophy rate decreases with increasing disease duration. CCA outperforms volumetric measurements in correlation to current and future performance in complex information processing. CCA is feasible for clinical practice and is thus suitable for identifying and predicting MS patients with current and future cognitive impairment.

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Functional and structural connectivity abnormalities underlying clinical disability in multiple sclerosis

E Sbardella[1,2], N Filippi[3], F Tona[1], C Piattella[1], N Petsas[1,2], L Prosperini[1], C Pozzilli[1], P Pantano[1]

[1]University Sapienza, Neurology and Psychiatry, Rome, Italy,
[2]Santa Lucia Fundation, Rome, Italy, [3]FMRIB Centre, Oxford,
United Kingdom

Background: Functional and structural MRI have been widely applied in Multiple Sclerosis (MS) patients to better understand pathophysiology of clinical impairment. So far, few studies combined the two methods to detect damage underlying disability.

Objectives: To investigate the effects of functional (FC) and structural (SC) connectivity abnormalities in determining clinical impairment in a MS population.

Methods: Thirty Relapsing-Remitting MS patients and 24 sex- and age-matched healthy subjects (HS) underwent a multimodal MRI using a 3T magnet. Resting state (RS) and DTI data were analysed by using MELODIC and Tract-Based Spatial Statistics (TBSS), respectively. A voxelwise General Linear Model was applied to assess group differences and clinical correlations (cluster-based threshold, family-wise-error corrected, $p=/< 0.05$). In all subjects we obtained measures of hand dexterity (9-hole peg test), ambulation function (25-foot test), cognitive performance (Paced Auditory Serial Addiction test) and balance capability (stabilometry).

Results: Patients poorly performed in cognitive and balance exercises with respect to HS. Out of the 11 RS networks (RSNs) identified, 5 [cerebellum (CB), executive function (EF), dorsal attention (DA), basal ganglia (BG) and sensori-motor (SM)] showed lower FC in patients than in HS. No RSN showed increased FC in patients. Cognitive performance inversely correlated with FC in right fronto-parietal (rFP), EF and DA networks and directly correlated with FC in the CB, temporal, BG and SM networks. Balance capability inversely correlated with FC in the rFP and visual networks. DTI parameters were altered in patients with respect to HS in most of white matter tracts, where a direct correlation was found with cognitive performance and hand dexterity. Moreover, reduced SC in the corpus callosum was related to higher FC in the temporal and CB networks.

Conclusions: In MS, both FC and SC abnormalities were detected and were found to correlate with different clinical domains. Only the cognitive impairment was related with both structural damage and FC changes. A better cognitive performance was associated with higher FC in 4 RSNs: FC in two of them (CB and temporal) was inversely related to corpus callosum damage. Despite the complex relationship between FC and SC, our data suggest an attempt of higher FC to compensate structural damage and to limit clinical impairment.

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Longitudinal DMN changes in cognitively preserved MS patients

R Docimo[1,2], A Bisecco[1,2], F Esposito[2,3], G Muzzo[1,2], G Pontillo[1,2], S Bonavita[1,2], L Lavorgna[1,2], M Cirillo[1,2], G Tedeschi[1,2], A Gallo[1,2]
[1]Second University of Naples, Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, Naples, Italy, [2]MRI Research Centre SUN-FISM - Neurological Institute for Diagnosis and Care 'Hermitage Capodimonte', Naples, Italy, [3]University of Salerno, Department of Medicine and Surgery, Salerno, Italy

Background: Resting-state networks (RSNs) explored by functional MRI (fMRI) during resting conditions allow to assess cortical reorganization in MS. Among different RSNs, the Default Mode Network (DMN) is strictly related to the cognitive status of MS patients.

Objectives: To assess DMN changes over 2 years in a group of persistent cognitively preserved MS (CP-MS) and Healthy Controls (HC).

To compare DMN functional connectivity (FC) between CP-MS and HC at baseline (BL) and at 2-year follow-up (FU).

Methods: Inclusion criteria for MS patients were: MS diagnosis (2010 McDonald criteria); age < 55; relapsing-remitting phenotype; no relapses or steroid therapy within the month before the study; low fatigue and depression scores as assessed by the Fatigue Severity Scale and the Chicago Multiscale Depression Inventory; absence of cognitive deficits at the Rao´s brief repeatable battery and Stroop Test as defined by ≤1 failed test (i.e. score ≤2SD normative values).

The HC group was matched for age, sex and education.

Both groups were re-assessed after 2 years and only persistent CP subjects - 12 out of 16 MS patients and 12 out of 13 HC - were retained in the study for the analysis.

The MRI data were acquired by a 3 Tesla GE scanner equipped with a 8-channel coil.

The preprocessing of resting state-fMRI (rs-fMRI) data, statistical analysis and visualization were performed by BrainVoyager QX. The individual and group-level ICA analysis was carried out on functional time series preprocessed by fast-ICA and sog-ICA algorithms.

Results: At FU, compared with BL, both HC and CP-MS showed a reduced functional connectivity (FC) in the core region of the posterior node (PN) of the DMN; this finding was more evident in CP-MS. Concomitantly, only CP-MS showed an increased FC in a few peripheral areas of the PN of the DMN.

CP-MS compared to HC at each time-point showed: at BL, a reduced FC in the anterior node (AN), as well as an increased FC in the peripheral PN of the DMN; at FU no differences within the AN, and a persistent increased FC in the peripheral PN of the DMN.

Conclusions: The group-independent longitudinal reduction of FC in the core region of the PN of the DMN, might be attributed to the effect of aging on network efficiency. Contrariwise, the increased FC in the peripheral PN of the DMN observed in CP-MS *vs* HC (at both time points) and at FU *vs* BL, seems to suggest that strengthening and expanding the FC of this region might be crucial to maintain a normal cognitive output.

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White matter lesion central veins: an interscanner comparison of patients with multiple sclerosis and ischemic lesions at 3-Tesla MRI

A Samaraweera[1], PS Morgan[2], R Dineen[3], I Driver[4], N Evangelou[1]
[1]University of Nottingham, Division of Clinical Neuroscience, Nottingham, United Kingdom, [2]Nottingham University Hospitals NHS Trust, Department of Medical Physics, Nottingham, United Kingdom, [3]University of Nottingham, Division of Radiological and Imaging Sciences, Nottingham, United Kingdom, [4]University of Nottingham, Sir Peter Mansfield Magnetic Resonance Centre, Nottingham, United Kingdom

Background: The value of detecting intralesional white matter (WM) veins in MS has been increasingly recognised. Whether this

can be used as an imaging biomarker needs further clarification. If used in clinical practice, it is important to achieve the same results for the same patients when scanned in different MRI scanners.

Objectives: To assess the visibility of WM intralesional veins when the same patient with either MS or ischemic lesions is scanned on two different 3T MRI scanners using different "vein sequences".

Methods: Each patient was scanned on two different manufacturer's (GE and Philips) 3T MRI scanners, referred to as A and B. The core MRI protocol included 3D fluid-attenuated inversion recovery (FLAIR) and 3D T2*-weighted gradient echo. In addition a 3D T2*-weighted gradient echo with high-EPI (echo planar imaging) factor was acquired on the Philips. WM intralesional veins were identified on all T2* imaging. WM lesion numbers were counted using FLAIR and T2* sequences.

Results: Eight patients with relapsing remitting MS and 3 with WM ischemic lesions have been included so far. Intralesional veins could be identified in more MS than ischemic lesions, no matter which scanner was used. Scans were identified correctly as MS or ischemic in all patients based on the proportion of lesions with intralesional veins. Mean numbers of intralesional veins in the ischemic group were virtually the same irrespective of scanner or sequence used (mean =0.9).

Intralesional vein numbers in the MS group differed between scanners despite the same core gradient echo sequence being used. The mean number identified using scanner A, standard T2* was 15.3 (range 2-36) vs 5.5 (range 0-11) using scanner B. T2* with EPI factor allowed the most number of veins to be identified (mean 45.6, range 5-101) compared to the standard T2* gradient echo on the same scanner. WM lesion numbers differed between scanners. The mean lesion number in the MS group on scanner A, standard T2* being 49.7 vs 14 using scanner B. T2* with EPI factor allowed higher lesion counts (mean 71.2). FLAIR allowed the highest lesion counts but numbers differed between scanners (78.7 vs 46.6, MS group). Similar findings were seen in the ischemic group.

Conclusions: All MS and ischemic scans were correctly classified irrespective of scanner or sequence used. T2* with high EPI factor is more sensitive in identifying intralesional veins. WM lesion central veins continue to show promise in differentiating MS from ischemia, irrespective of the exact 3T scanner used.

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Inflammation does not cause chronic global neurodegeneration in NMO? A longitudinal multimodel quantitative MRI study comparing NMO and MS

L Matthews[1,2], S Kolind[3], A Brazier[1], MI Leite[1], J Brooks[4], M Jenkinson[1], H Johansen-Berg[1], J Palace[1,2]
[1]University of Oxford, Nuffield Department of Clinical Neurosciences, Oxford, United Kingdom, [2]Oxford University Hospitals NHS Trust, Department of Neurology, Oxford, United Kingdom, [3]University of British Columbia, Vancouver, BC, Canada, [4]University of Bristol, Clinical Research and Imaging Centre, Bristol, United Kingdom

Background: Inflammatory demyelinating central nervous system lesions are a common feature of both neuromyelitis optica (NMO) and MS. However accrual of disability in MS is predominantly due to a progressive neurodegenerative process, whereas in NMO it appears solely relapse related. Prospective imaging studies are needed to assess if there is any evidence of progressive, non-lesional neurodegeneration outside of relapses in NMO as occurs in MS. If not, this would question the theory that neurodegeneration occurs as a chronic sequelae to prior inflammatory and demyelinating pathology.

Objectives: Using longitudinal quantitative MRI of the brain and spinal cord we aimed to assess whether seropositive NMO is associated with imaging markers of neurodegeneration over one year.

Methods: 18 patients with aquaporin-4 antibody positive NMO, 15 with relapsing remitting MS (RRMS) and 17 healthy controls had a brain and cervical spinal cord MRI at baseline that included structural imaging, diffusion tensor imaging (DTI) and myelin water imaging (MWI)). 16 NMO patients, 13 RRMS patients and 16 controls returned at one year. Data was analysed using the FMRIB software library of tools. Lesions were excluded from the analysis. Statistical testing was conducted with a voxelwise method (showing the spatial location of significant differences) and ANCOVA analysis with age and time between scans as covariates.

Results: Cross-sectional: RRMS had significant a.) thalamic atrophy b.) cervical cord atrophy c.) diffuse DTI and MWI abnormalities compared to controls and NMO patients. There was a localised reduction in the DTI metric fractional anisotropy within the optic pathways of NMO patients, ten of whom where blind or had severe visual impairment in one or both eyes.

Longitudinal: Reduction in brain volume over the year was greatest in the RRMS group but did not reach statistical significance. Significant atrophy of the temporal lobes and thalami along with areas of progressive change in DTI and MWI metrics were found in the RRMS only.

Conclusions: The findings from all of the quantitative MRI modalities corroborate to support a lack of non-lesional and progressive neurodegeneration in NMO, in contrast to MS. The results highlight the uncertainty about the true relationship between inflammation and neurodegeneration.

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Functional changes in default mode network activity - the most sensitive resting state fMRI parameter for short-term longitudinal changes in MS

D Pinter[1], C Beckmann[2], M Loitfelder[1], N Filippini[3], A Pichler[1], S Fuchs[1], F Fazekas[1], C Enzinger[1]
[1]Medical University Graz, Graz, Austria, [2]Radboud University Nijmegen, Nijmegen, Netherlands, [3]University of Oxford, Oxford, United Kingdom

Background: The implementation of resting state fMRI (RS-fMRI) in patient cohorts bears great potential to explore processes of functional reorganization, since changes in multiple functional networks can be investigated without any bias of task performance even in patients with impairments. RS-fMRI has recently been increasingly suggested to monitor effects of therapies and intervention or track dynamics of disease in multiple sclerosis (MS). However, to date limited longitudinal data of RS-fMRI in MS patients exists to conclude which RS-network would be most sensitive to change.

Objectives: Here, we hence aimed to test (a) the stability of findings and (b) the sensitivity towards change of different RS-networks, by repeated RS-fMRI in MS, as a role model disease characterized by dynamic evolution of tissue changes.

Methods: Structural, functional MRI and neuropsychological testing was assessed in 20 patients stratified by aggressiveness of disease and efficacy of drugs, i.e. 11 MS patients with Natalizumab treatment (NAT), and 9 MS patients receiving common disease-modifying treatment (DMT) at baseline and a 3 month follow-up.

Results: Nine baseline components/networks were identified in both groups using an ICA approach. Three visual networks, a sensorimotor network, the auditory network, the executive control network, the left and right fronto-parietal network and the default mode network (DMN). Longitudinal analyses revealed no significant changes in disease progression (assessed by T2-lesion load, global and regional volume loss), processing speed, sustained attention, and concentration over three months for both groups. Slight improvements in episodic memory performance were observed in both groups. Over three months significant changes were exclusively observed in a single network, i.e. the DMN. Increases in the group with less efficacious treatment (DMT group), compared to the NAT group, in the cerebellum, occipital pole, middle frontal gyrus, supramarginal gyrus, anterior and posterior cingulate were observed.

Conclusions: This study suggests that changes of RS activation could be observed already at a short follow-up duration (3 months) independent of disease progression and that functional connectivity within the DMN seems to be particularly sensitive to changes and thus could be a target to monitor changes in future studies.

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Functional MRI encoding task for faces in multiple sclerosis

L Vacchi[1], MA Rocca[1,2], GC Riccitelli[1], M Rodegher[2], V Martinelli[2], F Possa[2], A Falini[3], G Comi[2], M Filippi[1,2]
[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Institute of Experimental Neurology, Milan, Italy, [2]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy, [3]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neuroradiology, Milan, Italy

Background: Encoding difficulties are among the causes of memory deficits often affecting MS patients. To date, no study has investigated encoding difficulties for social non-verbal stimuli as faces in these patients.

Objectives: We assessed behavioral and functional MRI correlates of face encoding (FE) in MS patients and their correlation with cognitive impairment.

Methods: Using a 3.0 Tesla scanner, a block-design episodic FE paradigm was administered to 78 MS patients (14 with clinically isolated syndromes, 40 with relapsing-remitting and 24 with secondary progressive) and 22 healthy controls (HC). A face recognition (FR) test was performed outside the scanner. Patients with abnormal performance at Paced Auditory Serial Addition Test were considered cognitively impaired. Analyses of fMRI data was performed using SPM8. T2 lesions volumes, normalized gray matter (GM) and white matter (WM) volumes were assessed and correlated with fMRI abnormalities.

Results: All groups activated areas involved in face perception and encoding tasks, including the bilateral inferior occipital and temporal gyri, fusiform gyri and (para)hippocampi, as well as regions in

frontal lobes. Compared to HC, MS patients had reduced activations of the left angular gyrus, left superior and inferior frontal gyrus, left inferior occipital and right inferior temporal gyrus. Twenty-nine (37%) patients were CI. FR performance was lower in CI patients *vs* HC (p=0.002) and cognitively preserved (CP) patients (p=0.03). Compared to HC and CI patients, CP patients had increased activations of several regions located in the temporo-occipital lobes, bilaterally, including the hippocampus and fusiform gyrus and the orbital cortex. Compared to the other two groups, CI MS patients had increased recruitment of several regions located in the parietal lobes, bilaterally and the left middle frontal gyrus. In MS patients, significant correlations (p< 0.001) were found between: 1) FR performance *vs* left hippocampal activity (r=0.42); 2) GMV *vs* activity in the left temporo-occipital lobes (including the hippocampus and fusiform gyrus) (r values between 0.45 and 0.52); and 3) WMV *vs* right angular gyrus activity (r=-0.40).

Conclusions: Abnormalities of face encoding and recognition occur in MS patients. While increased recruitment of regions of the temporo-occipital lobes contributes to better performance at these tasks, engagement of parietal lobe regions (related to tissue loss) is associated to poor cognitive outcome.

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Brain atrophy quantification in multiple sclerosis

S Jain[1], D Smeets[1], DM Sima[1], A Ribbens[1], K Janssens[1], M Daams[2], M Steenwijk[2], H Vrenken[2], F Barkhof[2], W Van Hecke[1,3]
[1]icoMetrix, Leuven, Belgium, [2]VU University Medical Center, Amsterdam, Netherlands, [3]Antwerp University Hospital, Antwerp, Belgium

Background: Magnetic Resonance Imaging (MRI) of the brain has become a standard radiological tool for examining multiple sclerosis patients. Apart from the presence and location of lesions, grey matter atrophy is an important indicator for the diagnosis and prognosis of cognitive impairment. Current brain segmentation methods such as SIENAX provide volumetric measures for white matter (WM), grey matter (GM) and cerebrospinal fluid (CSF), but are inaccurate when applied to MS patients, due to the presence of lesions. In these cases the GM volume is typically overestimated, and thus the GM atrophy is underestimated.

Objectives: We propose an automatic method for quantifying brain volumes in MS patients by compensating for the presence of lesions.

Methods: 3D T1-weighted and FLAIR MR images are used simultaneously in a probabilistic model to segment the brain tissue into grey matter, white matter and cerebrospinal fluid using expectation-maximization, allowing for an outlier class in order to accommodate the lesions. Subsequently, the T1-weighted images are used for lesion filling, which means that pixels labeled as lesion are replaced by artificially generated intensities using the statistical distribution of neighbouring WM pixels. Brain segmentation is performed again only with the WM, GM and CSF classes. 20 multiple sclerosis patients participated in a study at VU University Medical Center, Amsterdam, the Netherlands. They were scanned on a 3T whole body scanner (GE Signa HDxt, Milwaukee, WI, USA). Expert lesion identification and manual segmentation was performed based on the FLAIR images by a highly trained neuroradiological team.

WM, GM and CSF percentages within the expert-segmented lesions are compared between the segmentation of the 3D T1-weighted images before and after lesion filling using unpaired t-tests.

Results: Before lesion filling, we found a very low percentage of WM (9 ± 10%) within lesions, because a high percentage of lesion volume was attributed to GM (65 ± 17%) and CSF (26 ± 17%). After lesion filling, WM percentage within lesions became very high (77 ± 7%), followed by GM (20 ± 6%) and CSF (3 ± 3%). These volume differences before and after lesion filling are highly significant ($p < 0.0001$).

Conclusions: We propose a fully automatic method to quantify WM, GM and CSF volumes in MR images of MS patients. The method compensates for the presence of lesions and substantially reduces the underestimation of GM atrophy.

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Sample-size calculations for short-term proof-of-concept studies of tissue protection and repair in MS lesions via conventional clinical imaging

DS Reich[1], R White[2], ICM Cortese[1], L Vuolo[1,3], CD Shea[1], TL Collins[4], AJ Petkau[2]
[1]National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD, United States, [2]University of British Columbia, Statistics, Vancouver, BC, Canada, [3]University of Florence, Neurology and Radiology, Florence, Italy, [4]Myelin Repair Foundation, Saratoga, CA, United States

Background: New lesion activity on MRI is used to test immunomodulatory therapies in MS proof-of-concept trials, but comparably powerful endpoints to assess tissue protection or repair are lacking.

Objectives: To report sample-size calculations for assessment of new lesion recovery in highly active MS.

Methods: In 6 active MS cases, new lesions were observed by monthly 3 tesla (T) MRI for ≥12 months. Similar data were obtained from a historical set of 6 active MS cases observed by monthly 1.5T MRI for a similar time period. Averages and quartiles of normalized (proton density/T1/T2 weighted) and quantitative (T1/T2 maps and mean diffusivity in the 3T dataset, T2 maps and magnetization transfer ratio in the 1.5T dataset) measures were used to compare the lesion area before lesion appearance to afterward. A linear mixed effects model incorporating lesion- and participant-specific random effects estimated average levels and variance components for sample-size simulations.

Results: In both datasets, the greatest statistical sensitivity was observed for the 25th percentile of lesion-by-lesion normalized proton density-weighted signal. Based on the 3T dataset, using new lesions ≥15 mm³, 9 participants/arm are required for a 6-month, placebo-controlled, add-on trial postulating a therapeutic effect size of 20% and statistical power of 90%. For the same effect size and power, when considering all incident lesions in a 12-month trial, the 3T and 1.5T datasets yielded similar results, with sample sizes of 8 to 10 participants/arm. In general, normalized measures derived from conventional imaging performed far better than quantitative measures, including those derived from relaxation mapping, diffusion imaging, and magnetization transfer.

Conclusions: Lesion recovery is a powerful outcome measure for proof-of-concept clinical trials of tissue protection and repair in MS. Such trials require active cases and are therefore best implemented near disease onset. The extent to which success in this type of trial will predict efficacy in trials of progressive MS remains to be demonstrated.

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The value of MRS, a novel MRI technique, as a predictor of disability: analysis at 20-years of RRMS patients treated long-term with glatiramer acetate

O Khan[1,2], F Bao[2], C Ford[3], S Kolodny[4], A Vainstein[5], Y Sidi[5]
[1]Multiple Sclerosis Center, Wayne State University School of Medicine, Detroit, MI, United States, [2]Sastry Foundation Advanced Imaging Laboratory, Wayne State University School of Medicine, Detroit, MI, United States, [3]University of New Mexico Health Sciences Center, Albuquerque, NM, United States, [4]Teva Pharmaceutical Industries, Cleveland, OH, United States, [5]Teva Pharmaceutical Industries, Netanya, Israel

Background: Finding MRI metrics and techniques to serve as validated surrogate markers for disability in MS patients (pts) has been a research priority for decades.

Objectives: To explore potential correlations between various MRI measurements and disability in RRMS pts receiving long-term (~20 years) treatment with glatiramer acetate (GA).

Methods: At approximately 20 years from the initiation of the US Glatiramer Acetate open-label long-term extension study (GA 9004), pts continuing in the trial in November, 2012, were invited to undergo MRI assessment (the first MRI examination in this study). MRI data and clinical data reported at the time closest to the MRI scan date were evaluated for correlations between the two disease outcomes. The Elastic Net model selection algorithm using a criterion of minimum mean square error (MSE) was applied to select variables that contribute to the odds at the 20-year follow-up of a pt belonging to either the higher or lower disability subgroup, defined by EDSS score of ≥ 2 steps vs EDSS < 2, pyramidal functional system score (FSS) ≥ 2 vs < 2, and pyramidal FSS ≥ 3 vs < 3. The following MRI variables, whole brain (WB), grey matter (GM), and white matter (WM) volumes; total N-acetylaspartate/total creatine (tNAA/tCr) ratio on MRS; T1 and T2 lesions volumes; along with gender, disease duration, exposure to GA, and age at MRI scan, were added as candidates for selection. In cases when variables with high correlations (correlation coefficient ≥ 0.7) were selected, a model with next smallest MSE that eliminated 1 of these variables was chosen. In the final selection model, the relative contribution of each selected variable to the predicted odds was calculated.

Results: Of 64 pts who underwent MRI after 20 years on-study, 39 (61%) were included in the MRS assessment. The selection methodology showed MRS was the most influential parameter (98%, 97%, 81%) for predicting the odds of belonging to a specific disability subgroup using the cutoffs EDSS ≥ 2 vs < 2, pyramidal FSS ≥ 2 vs < 2, and pyramidal FSS ≥ 3 vs < 3, respectively. An increase of 1 point in tNAA/tCr level decreased the odds of being in the higher disability subgroup for each parameter by 74%, 91%, and 98% for EDSS ≥ 2, pyramidal FSS ≥ 2 and pyramidal FSS ≥ 3, respectively (odds ratios: 0.26, 0.09, and 0.02, respectively). Several other selected variables were found to correlate with disability prediction, but at minimal levels.

Conclusions: MRS should be considered as a tool for measuring disability in MS patients.