*Movement Disorders*

Vol. 23, No. 11, 2008, pp. 1613–1627

© 2008 Movement Disorder Society

Letters to the Editor Related to New Topics

# Alexander Disease Causing Hereditary Late-Onset Ataxia with Only Minimal White

Matter Changes: A Report of Two Sibs

Video 

Classic Alexander disease refers to a rare neurodegenerative leukodystrophy, typically manifesting in early childhood with megaloencephaly, seizures, spasticity, and psychomotor regression. Until recently, its diagnosis was based on distinc- tive MRI features, such as white matter lesions that predomi- nantly affect the frontotemporal and periventricular regions. The ﬁnding of causative mutations in the *GFAP* gene has enabled diagnostic conﬁrmation by mutation analysis. This has also lead to the identiﬁcation of atypical and late-onset cases, with a highly variable spectrum of clinical and imag- ing abnormalities.

We report a case of an adult-onset, mutation proven Alexander disease characterized by cerebellar and sensory ataxia, the absence of palatal tremor, and very mild white matter changes.1,2

This 61-year-old man presented at the age of 50 years with slowly progressive gait difﬁculties. His past medical his- tory revealed the onset of static but marked forward ﬂexion of the trunk in his ﬁrst decade, but without any motor abnor- malities until recently. His sister had been diagnosed with progressive cerebellar ataxia; there were no other affected relatives.

Neurological examination (see video) revealed a normal mental status; jerky pursuit, and dysmetric saccades; mild cerebellar dysarthria; mild ataxia of the trunk and extremities that increased upon eye closure; a broad-based, ataxic gait; cervical kyphosis and thoracic scoliosis with ﬂexion contrac- tures of the hips and knees; positive Romberg’s sign; dis- turbed vibration sense in the lower limbs; slightly diminished tendon reﬂexes in the lower extremities with normal plantar responses.

We screened for several of the genetic ataxias, but no mutations were detected in the SCA1/2/3/6/7/14 genes or in the genes responsible for Friedreich’s ataxia and dentato- rubro-pallido-luysian atrophy. Electromyography showed no signs of neuropathy or myopathy. SSEP was not performed. MRI demonstrated subtle white matter lesions anteriorly in both temporal lobes, as well as mild atrophy of the cerebel- lum, brainstem and cervical spinal cord on standard MRI imaging (Fig. 1A–C).

Additional Supporting Information may be found in the online version of this article.

Published online 25 June 2008 in Wiley InterScience [(www.](http://www/) interscience.wiley.com). DOI: 10.1002/mds.22053

The records of the affected sister, who died at the age of 64, mentioned horizontal nystagmus, cerebellar dysarthria, limb ataxia, and progressive gait difﬁculties. In addition, the presence of palatal myoclonus was noted once. While the dysarthria was said to exist from an early age, the gait dif- ﬁculties arose at the age of 30. Brain imaging (at age 58 years) showed cerebellar and marked bulbomedullar atro- phy as well as white matter lesions in the periventricular region, corpus callosum, and right medial cerebellar peduncle (Fig. 1D–F).

As these combined clinical and imaging features were sug- gestive of Alexander disease, we sequenced the *GFAP* gene, and found a novel heterozygous c.692T > A missense muta- tion in exon 4, predicting a p.Leu231His amino acid change; this mutation was not encountered in 210 control chromo- somes.

Several cases of adult-onset Alexander disease have been reported, mostly with an onset in the third or fourth decade of life. Phenotypic heterogeneity is evident from the variable presence of bulbar symptoms, cerebellar signs, palatal tremor, spastic paresis, and autonomic dysfunction.

The index patient reported here displays a rather unique phenotype of adult-onset Alexander disease. First, his age at onset was 50 years, which is one of the latest ever reported.3 Second, his clinical presentation was dominated by the com- bined presence of slowly progressive cerebellar and sensory ataxia, in the absence of palatal tremor. The kyphoscoliosis and his knee-bent posture are very likely related to his Alexander disease, as these features have been observed pre- viously.4–13 Yet, the interval to the onset of ataxia in our case is remarkable. Third, neuroimaging in our patient revealed cerebellar, brainstem, and spinal cord atrophy—all previously reported imaging features of Alexander disease— but the white matter changes were extremely subtle, involv- ing a minor portion of the anterior poles of both temporal lobes only. MRI abnormalities in adult-onset Alexander dis- ease are heterogeneous, but the white matter changes are generally less extensive compared with the classic early-onset disease.17

The give-away in this case was the presence of a PAPT syndrome in the patient’s sister. The combination of cerebel- lar ataxia and palatal tremor is relatively common in adult- onset Alexander disease (43%).4,9–12,14 This clinical constel- lation is presently referred to as PAPT (progressive ataxia and palatal tremor), used to indicate a subgroup of the symp- tomatic palatal tremor in which neurodegenerative diseases are involved. In case of a familial PAPT, the differential diagnosis is quite limited and, in addition to Alexander dis- ease, also includes SCA20 and perhaps other forms of degen- erative cerebellar ataxias.15,16

In conclusion, we report two sibs with late-onset ataxia due to Alexander disease caused by a novel *GFAP* mutation. Alexander disease should thus be considered in the differen- tial diagnosis of otherwise unexplained hereditary late-onset

#### 1613

*1614 LETTERS TO THE EDITOR*

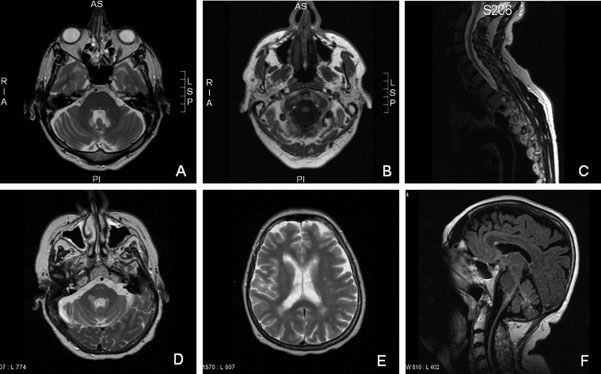
**

FIG. 1. Brain and cervical spine MRI images of the index case (A–C) and affected sister (D–F). (A) Subtle white matter changes in the anterior parts of left more than right temporal lobe; atrophy of the cerebellar hemispheres with enlargement of the 4th ventricle (axial T2). (B) Marked at- rophy of the lower medulla (axial T1). (C) Atrophy of brainstem and upper part of spinal cord; the presence of scoliosis is also evident (axial T2). (D) White matter defect in right medial cerebellar peduncle (axial T2). (E) White matter lesion in the left periventricular region (axial T2).

(F) Cerebellar atrophy and marked atrophy of brainstem (with sparing of the pons) and cervical spinal cord; a small lesion in the anterior part of the corpus callosum; there are in addition high-signal parenchymal changes in the posterior medulla and cerebellar white matter (sagittal FLAIR).

ataxia. Additional—yet not obligate—clinical features (pal- atal tremor, kyphoscoliosis) and more or less distinctive MRI ﬁndings (subtle white matter changes, marked atrophy of brainstem, and spinal cord) might constitute clues that hint towards this speciﬁc diagnosis.

## LEGENDS TO THE VIDEO

Segment 1. Mild ataxic and bouncing gait; note the ﬂex- ion contractures of the knees; difﬁculty tandem walking.

Segment 2. Bent-hip and bent-knee posture.

Segment 3. Ocular pursuit showing jerky pursuit move- ments.

Segment 4. Horizontal saccades showing multi-step sac- cades and ocular dysmetria (both hypometric and hypermet- ric).

Segment 5. Cerebellar dysarthria on repeating the Dutch sentence ‘‘rode ronde appels rollen van de zoldertrap’’ and on repeating ‘‘PATAKA.’’

Segment 6. Mild decomposition of movement during ﬁn- ger-to-nose testing.

Catherine C.S. Delnooz, MD Jurgen H. Schelhaas, MD, PhD

Bart P.C. van de Warrenburg, MD, PhD\*

*Department of Neurology Radboud University Nijmegen Medical Center*

*Nijmegen, The Netherlands*

*\*E-mail:* [*b.vandewarrenburg@neuro.umcn.nl*](mailto:b.vandewarrenburg@neuro.umcn.nl)

Robert-Jan de Graaf, MD

*Department of Neurology Amphia Hospital, Breda/Oosterhout*

*The Netherlands*

Gajja S. Salomons, PhD

*Department of Clinical Chemistry*

*Metabolic Unit VU University Medical Center Amsterdam, The Netherlands*

### References

1. Johnson A. Alexander disease: review of the gene. Int J Dev Neurosci 2002;20:391–394.
2. Li R, Johnson AB, Salomons G, et al. GFAP-mutations in infan- tile, juvenile and adult forms of Alexander disease. Ann Neurol 2005;57:310–326.
3. Howard KL, Hall DA, Moon M, Agarwal P, Newman E, Brenner

M. Adult-onset Alexander disease with progressive ataxia and palatal tremor. Mov Dis 2008;23:118–122.

1. Deprez M, D’Hooghe M, Misson JP, et al. Infantile and juvenile presentations of Alexander disease: a report of two cases. Acta Neurol Scand 1999;99:158–165.
2. Salmaggi A, Botturi A, Lamperti E, et al. A novel mutation in the GFAP gene in a familial adult-onset Alexander disease. J Neurol 2007;254:1278–1280.
3. Schwankhaus J, Parisi JE, Gulledge WR, Chin L, Currier RD. Hereditary adult-onset Alexander disease with palatal myoclonus, spastic paraparesis, and cerebellar ataxia. Neurology 1995;45: 2266–2271.
4. Sawaishii Y, Hatazawa J, Ochi N, et al. PET in juvenile Alexander disease. J Neurol Sci 1999;165:116–120.

15318257, 2008, 11, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.22178 by The University Of Manchester, Wiley Online Library on [22/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

*Movement Disorders, Vol. 23, No. 11, 2008*

#### LETTERS TO THE EDITOR 1615

1. Nonomura Y, Shimizu K, Nishimoto H, Hosoe H, Sakaguchi Y, Miyamoto K. Scoliosis in a patient with Alexander disease. J Spin Dis 2002;15:261–264.
2. Thyagarajan D, Chataway T, Li R, Gai WP, Brenner M. Domi- nantly-inherited adult-onset leukodystrophy with palatal tremor caused by a mutation in the Glial ﬁbrillary acidic protein. Mov Dis 2004;19:1244–1248.
3. Okamoto Y, Mitsuyama H, Hirata K, Arimura K, Osame M, Nakagawa M. Autosomal dominant palatal myoclonus and spinal cord atrophy. J Neurol Sci 2002;195:71–76.
4. Stumpf E, Masson H, Duquette A, et al. Adult Alexander dis- ease with autosomal transmission. Arch Neurol 2003;60:1307– 1320.
5. Borret D, Becker LE. Alexander disease of astrocytes. Brain 1985;108:367–385.
6. Cole G, De Villiers F, Proctor NS, Freiman I, Bill P. Alexander disease: case report including histopathological and electron mi- croscopic features. J Neurol Neurosurg Psych 1979;42:619–624.
7. Kulharni P, Muthane UB, Taly AB, Jayakumar PN, Shetty R, Sathyanarayana Swamy H. Palatal tremor, progressive multiple cranial nerve palsies and cerebellar ataxia: a case report and review of literature of palatal tremors in neurodegenerative dis- ease. Mov Dis 1999;14:689–693.
8. Samuel M, Torun N, Tuite PJ, Sharpe JA, Lang AE. PAPT Clini- cal and MRI assessment with review of palatal tremor. Brain 2004;127:1252–1268.
9. Storey E, Knight MA, Forrest SM, Gardner RJ. Spinocerebellar ataxia type 20. Cerebellum 2005;4:55–57.
10. Van der Knaap MS, Naidu S, Breiter SN, et al. Alexander dis- ease: diagnosis with MRI. Am J Neuroradiol 2001;22:541–552.

# Antihistamine-Associated Myoclonus: A Case Report

Myoclonus is a clinical sign deﬁned as sudden, brief, shock- like, involuntary movements caused by muscular contractions (positive myoclonus) or inhibitions (negative myoclonus, asterixis). Most causes of myoclonus are symptomatic and include posthypoxia, toxic-metabolic disorders, and neurode- generative disorders.1 Various drugs, including neuroleptics, anticonvulsants, and cardiac medications, can cause myoclo- nus,1,2 but antihistamine-associated myoclonus is extremely rare.2,3 Here, we report a case of transient myoclonus trig- gered by an antihistamine, oxatomide.

An 85-year-old man taking amlodipine (5 mg/day), cande- sartan (8 mg/day), arotinolol (20 mg/day), and furosemide (20 mg/day) for hypertension, and allopurinol (200 mg/day) for hyperuricemia, developed an involuntary movement in his right hand. It progressed over his upper limbs and face within several hours, and he was referred to our hospital. On physi- cal examination, he was afebrile without abnormality, except for systolic hypertension (170/80 mm Hg). The mini-mental status test revealed cognitive impairment (score 20). At rest there was myoclonus in the patient’s face, tongue, jaw, neck, and upper limbs, predominantly on the left. There was no palatal tremor. An electrophysiological study revealed 4-Hz rhythmic myoclonic discharges in the left arm muscles with synchronized ocular movement that increased with eyelid closure (see Fig. 1), and suggested that the myoclonus was persistent and time-locked in all locations (generalized myo-

Published online 25 June 2008 in Wiley InterScience [(www.](http://www/) interscience.wiley.com). DOI: 10.1002/mds.22076

clonus). Limb myoclonus was exaggerated when the patient extended his upper limbs, but it was not induced by external sensory stimuli. The involuntary movements were not sup- pressed by mental stress or by alternate pronation and supina- tion of the forearm to an external rhythm. Asterixis was evi- dent when the patient’s upper limbs were extended and his wrists dorsiﬂexed, and it caused the lapse in posture between the positive myoclonic jerks. He was unable to maintain his tongue in the protruded position owing to asterixis of the tongue, and he had difﬁculty speaking. Neurological exami- nation was otherwise normal. Laboratory examination revealed a mild elevation of urea nitrogen (25 mg/dL) and aspartate aminotransferase (40 IU/L), but the plasma ammo- nia concentration and thyroid function were normal. Chest X-ray revealed cardiomegaly, and cardiac ultrasonography showed left ventricular hypertrophy and mild mitral regurgi- tation. The plasma brain natriuretic peptide concentration was 189.0 pg/mL. Abdominal sonography and computed to- mography revealed no abnormality, and there was no portal- systemic shunt. Cerebrospinal ﬂuid analysis was normal. Brain magnetic resonance imaging showed diffuse cerebral atrophy, which was consistent with Alzheimer’s disease, and an old ischemic lesion in the right cerebellum. Electroence- phalography showed a 9-Hz alpha background rhythm with- out epileptiform activity. The involuntary movements dis- appeared immediately after the intravenous administration of 10 mg diazepam.

Five months later, the patient suffered a recurrence of myo-

clonus, but it disappeared within several hours after oral admin- istration of 0.5 mg clonazepam. All of the patient’s medications were reviewed again. The ﬁrst myoclonus occurred after 18 days’ use of oxatomide (120 mg/day), and the second occurred after 8 days’ use of oxatomide (120 mg/day) and epinastine (20 mg/day) for chronic prurigo. The myoclonus has not recurred since the patient stopped the antihistamines.

Our patient ﬁrst presented with acute occurrences of both generalized myoclonus and asterixis, predominantly in the face, neck, and upper limbs. The involuntary movements dis- appeared immediately after benzodiazepine treatment, but he experienced a recurrence. These clinical features are similar to the ‘‘transient myoclonic state with asterixis’’ previously reported by Hashimoto et al.4 The cause of that state is unclear, although aging, chronic diseases, and viral infection could contribute. However, in our patient, the temporal rela- tionship between myoclonus and the antihistamine medica- tion history suggests that oxatomide triggered the movement disorder. Oxatomide, a second-generation antihistamine, is used to treat allergic diseases in Europe and Japan. Its phar- macologic actions include histamine H1-receptor antagonism and suppression of the production and release of chemical mediators, as well as anti-cholinergic and anti-serotonin actions.5 Antihistamines can both stimulate and depress the central nervous system (CNS), but second-generation drugs do not appreciably cross the blood-brain barrier. Therefore, there are few reports of abnormal involuntary movements associated with antihistamines. However, Rajput et al. recently reported a pediatric case of dystonia induced by a second-generation antihistamine (cetirizine), possibly because of dopamine receptor blockade by the drug metabolite.6 Oxatomide can also cause dystonia.7 However, to our knowl- edge, there is only one report of antihistamine-induced myo-

15318257, 2008, 11, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.22178 by The University Of Manchester, Wiley Online Library on [22/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

*Movement Disorders, Vol. 23, No. 11, 2008*

#### 1616 LETTERS TO THE EDITOR

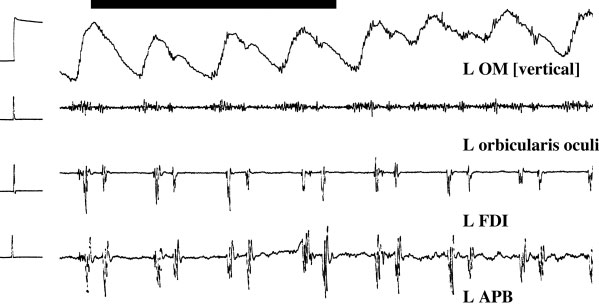
**

FIG. 1. Electrooculography and surface electromyography. Rhythmic ocular movement of the left (L) eye in the vertical direction (L OM [verti- cal]) was synchronous with myoclonus in the L orbicularis oculi. Rhythmic, synchronous myoclonic discharges were also evident in the L ﬁrst dorsal interosseous (FDI) and L abductor pollicis brevis (APB). Calibration: 100 lV in each lane. Time constant: 0.1 s in the ﬁrst lane and

0.001 s in other lanes. Black bar: 1 s.

clonus, in that case caused by abusive overuse of a ﬁrst-gen- eration antihistamine (tripelennamine).3 It remains unclear why oxatomide triggered myoclonus in our patient. We could not determine the plasma concentration of oxatomide when he was suffering from the myoclonus. However, cardiac or renal dysfunction might raise the drug concentration to a toxic level in the CNS, and the drug might affect the seroto- nergic system to cause myoclonus, although the serotonin hy- pothesis of myoclonus remains controversial.8 On the other hand, our patient was demented and being treated with anti- hypertensive agents. Dementia can lower the threshold for myoclonus or can be a cause of myoclonus in and of itself.1 Furthermore, cardiac medications can also cause myoclonus.1 Therefore, the minor toxic-metabolic disturbance caused by antihistamine use might have led our elderly, myoclonus- prone patient into a transient myoclonic state. This is the ﬁrst report of myoclonus triggered by a therapeutic dose of anti- histamines. Clinicians should recognize that antihistamines could trigger this benign but dramatic CNS side effect.

Takashi Irioka, MD, PhD\* Akira Machida, MD Takanori Yokota, MD, PhD

Hidehiro Mizusawa, MD, PhD *Department of Neurology and Neurological Science Graduate School, Tokyo Medical and Dental University*

*Tokyo, Japan*

*\*E-mail:* [*t-irioka.nuro@tmd.ac.jp*](mailto:t-irioka.nuro@tmd.ac.jp)

### References

1. Caviness JN, Brown P. Myoclonus: current concepts and recent advances. Lancet Neurol 2004;3:598–607.
2. Gordon MF. Toxin and drug-induced myoclonus. In: Fahn S, Frucht SJ, Hallett M, Truong DD, editors. Advances in neurol-

ogy, Vol. 89: Myoclonus and paroxysmal dyskinesias. Philadel- phia: Lippincott Williams & Wilkins; 2002. p 49–76.

1. Schipior PG. An unusual case of antihistamine intoxication. J Pediatrics 1967;71:589–591.
2. Hashimoto S, Kawamura J, Yamamoto T, et al. Transient myo- clonic state with asterixis in elderly patients: a new syndrome? J Neurol Sci 1992;109:132–139.
3. Richards DM, Brogden RN, Heel RC, Speight TM, Avery GS. Oxatomide. A review of its pharmacodynamic properties and therapeutic efﬁcacy. Drugs 1984;27:210–231.
4. Rajput A, Baerg K. Cetirizine-induced dystonic movements. Neurology 2006;66:143–144.
5. Casteels-Van Daele M, Eggermont E, Casaer P, Van de Casseye W, De Boeck K. Acute dystonic reactions and long-lasting impaired consciousness associated with oxatomide in children. Lancet 1986;1:1204–1205.
6. Welsh JP, Placantonakis DG, Warsetsky SI, Marquez RG, Bern- stein L, Aicher SA. The serotonin hypothesis of myoclonus from the perspective of neuronal rhythmicity. In: Fahn S, Frucht SJ, Hallett M, Truong DD, editors. Advances in neurology, Vol. 89: Myoclonus and paroxysmal dyskinesias. Philadelphia: Lippincott Williams & Wilkins; 2002. p 307–329.

# Do Parkinson’s Disease and Dementia with Lewy Bodies Differ by Route of Environmental Precipitant?

Braak and colleagues followed their groundbreaking staging classiﬁcation for the brain neuropathology of Alzheimer’s disease with the more recent one for sporadic Parkinson’s disease (PD).1 Their new PD staging system has revolution- ized thinking about the topographic sequence of neuropatho- logical changes as the illness progresses, generally in a cau- dal-rostral direction from lower brainstem to neocortex.

Published online 25 June 2008 in Wiley InterScience [(www.](http://www/) interscience.wiley.com). DOI: 10.1002/mds.22123

15318257, 2008, 11, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.22178 by The University Of Manchester, Wiley Online Library on [22/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

*Movement Disorders, Vol. 23, No. 11, 2008*

#### LETTERS TO THE EDITOR 1617

One of the most important of Braak et al.’s observations may be that olfactory structures are one of the ﬁrst sites of neuropathology in the central nervous system (CNS).2 Coupled with emerging evidence that characteristic synuclei- nopathic changes can be seen in the peripheral autonomic nervous system (including the gastrointestinal tract) even before CNS involvement,3–6 a critical implication of these ﬁndings is that the nose and mouth become suspect as portals of entry for an inciting pathogenic agent.

After nasal entry, transneuronal transmission along olfac- tory pathways is a potential route to the brain. It has been shown, for example, that inhaled ultraﬁne heavy metal par- ticles, which might come from occupational exposures, can pass through the nasal mucosa and be transynaptically trans- ported to deeper brain regions.7 Once a pathogenic agent passes through the gastrointestinal mucosa after oral entry, the pathway via the enteric autonomic nervous system to the vagus nerve and the vagal nuclei in the lower brainstem (also one of the early loci of PD pathology in the CNS1,2) would be open. Thus, environmental factors in the air, water, and food look to be integrally involved in the initial phases of the illness. Potential environmental agents that have been suggested include agricultural pesticides and herbicides reviewed in,8,9 heavy metals,7 viruses,10 and prions.11 Genetic factors might inﬂuence individual susceptibility or response to the offending agents.

Dementia with Lewy bodies (DLB) differs from PD by dif- fuse synucleinopathic degeneration, involving cortex and brain- stem, at onset rather than the initial focal olfactory and lower brainstem pathology of PD.12 It has been debated whether PD and DLB are variants of the same disease or represent distinct entities.13 Based on the differences in their neuropathologic tem- poral proﬁle, I hypothesize that there is an etiological difference that is primarily due to the route of exposure to inciting environ- mental agents. Under this view, PD results from respiratory (air- borne) or gastrointestinal (water/foodborne) exposure while DLB develops following systemic (bloodborne) exposure. Type of toxicant and level of exposure might determine whether signiﬁcant concentrations are achieved in the circulation. Underlying genetic factors might also contribute to which route(s) and levels of exposure result in toxicity. The hypothesis is testable by comparing PD and DLB patients for routes, types, and magnitudes of environmental exposures.

Roger Kurlan, MD

*Department of Neurology, University of Rochester School of Medicine*

*Rochester, New York, USA*

### References

1. Braak H, Del Tredici K, Ru¨b U, de Vos RAI, Jansen Steur ENH, Braak E. Staging of brain pathology related to sporadic Parkin- son’s disease. Neurobiol Aging 2003;24:197–211.
2. Del Tredici K, Rub U, de Vos RAI, Bohl JRE, Braak H. Where does Parkinson disease pathology begin in the brain? J Neuropa- thol Exp Neurol 2002;61:413–426.
3. Wakabayashi K, Takahashi H, Ohama E, Takeda S, Ikuta F. Lewy bodies in the visceral autonomic nervous system in Parkinson’s dis- ease. In: Ikuta F, editor. Neuropathology in brain research. Am- sterdam, London, Tokyo: Excerpta Medica; 1991. p 133–141.
4. Braak H, De Vos RAI, Bohl JR, Del Tredici K. Gastric alpha- synuclein immunoreactive inclusions in Meissner’s and Auer- bach’s plexuses in cases staged for Parkinson’s disease-related brain pathology. Neurosci Lett 2006;396:67–72.
5. Minguez-Castellanos A, Charorro CE, Escamilla-Sevilla F, et al. Do *a*-synuclein aggregates in autonomic plexuses predate Lewy body disorders? A cohort study. Neurology 2007;68:2012–2018.
6. Braak H, Sastre M, Bohl JRE, de Vos RAI, Del Tredici K. Par- kinson’s disease: lesions in dorsal horn layer I, involvement of parasympathetic and sympathetic pre- and postganglionic neu- rons. Acta Neuropathol (Ber) 2007;113:421–429.
7. Oberdo¨rster G, Sharp Z, Atudorei V, et al. Translocation of inhaled ultraﬁne particles to the brain. Inhal Toxicol 2004;16:437–445.
8. Ratner MH, Feldman RG. Environmental toxins and Parkinson’s disease. In: Ebadi M, Pfeiffer RF, editors. Parkinson’s disease. Boca Raton, FL: CRC Press; 2005. p 51–62.
9. Strickland D. Rural environment and Parkinson’s disease. In: Ebadi M, Pfeiffer RF, editors. Parkinson’s disease. Boca Raton, FL: CRC Press; 2005. p 63–71.
10. Braak H, Bohl JR, Mu¨ller CM, Ru¨b U, de Vos RAI, Del Tredici

K. Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson’s disease reconsidered. Mov Disord 2006;21:2042–2051.

1. Klein C, Schlossmacher MG. Parkinson’s disease, 10 years after its genetic revolution: multiple clues to a complex disorder. Neu- rology 2007;69:2093–2104.
2. McKeith IG, Galasko D, Kosaka K. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the Consortium on DLB International Work- shop. Neurology 1996;47:1113–1124.
3. Richard IH, Papka M, Rubio A, et al. Parkinson’s disease and dementia with Lewy bodies: one disease or two? Mov Disord 2002;17:1161–1165.

# Dystonia Associated with Hyperintense Basal Ganglia Lesions on T1-Weighted Brain MRI

Video 

A 43-year-old man presented with cardiac arrest due to an anaphylactic shock after ﬂuorescein application for retinal an- giography. After cardiopulmonary resuscitation, the patient could be weaned from tracheal respiration 2 days later. The initial neurological examination revealed generalized hypoki- nesia, rigidity of extremities, and severe axial dystonia with anterocollis and increased oromandibular tone with almost incapability to open the mouth (Fig. 1A). A mild reduction of hypokinesia occurred due to medication of amantadine and levodopa. The oromandibular dystonia improved consid- erably under repetitive local injections of botulinum toxin type A, and the patient is able to eat and speak without assis- tance. The clinical symptoms are stable since the initial attack over a period of 3.5 years now (see Fig. 1A and video for current clinical state).

The initial CT was regular, but the T1-weighted MRI with- out contrast demonstrated bilateral uniform area-wide hyperin-

Additional Supporting Information may be found in the online version of this article.

Published online 25 June 2008 in Wiley InterScience [(www.](http://www/) interscience.wiley.com). DOI: 10.1002/mds.22128

15318257, 2008, 11, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.22178 by The University Of Manchester, Wiley Online Library on [22/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

*Movement Disorders, Vol. 23, No. 11, 2008*

#### 1618 LETTERS TO THE EDITOR

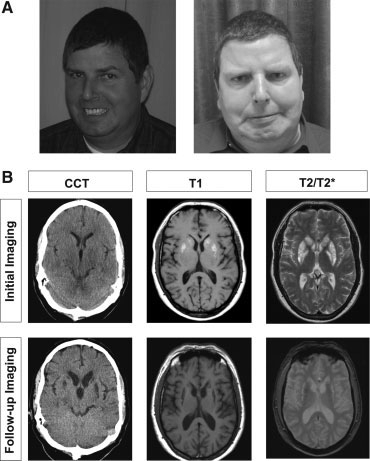


FIG. 1. (A) Photograph of patient showing oromandibular dystonia

~2 months after onset (left picture) and 5 years later following local injections of botulinum toxin type A (right picture). (B) Sequential neuroimaging of T1-hyperintense striatal lesions associated with gen- eralized dystonia after cardiopulmonary resuscitation. Upper row dis- plays initial CT/MRI imaging within the ﬁrst 2 weeks after onset (T1- and T2-weighted images, no contrast), and lower row shows imaging 17 months later (T1- and T2\*-images). Note the hyperin- tense bilateral striatal lesions in initial T1-weighted MRI with no indications of hemorrhages in all images.

tense lesions of the striatum (Fig. 1B, upper row). Imaging showed no indications of hemorrhages. The follow-up imaging 17 months later demonstrated necrosis of both striata without any evidence of hemosiderin deposits (Fig. 1B, lower row).

Similar T1-weighted MRI hyperintensities have been described previously in several patients with chorea after nonketotic hyperglycemia.1,2 and rarely in patients with hypoglycaemic coma3 or chronic hepatic encephalopathy.4 In these cases, postischemic petechial hemorrhage was sus- pected as a possible mechanism, although sporadic postmor- tem pathological studies have reported selective neuronal loss, gliosis, and reactive astrocytosis as common ﬁndings.5,6 Fujioka et al. reported delayed ischemic hyperintensity on T1-weighted MRI in the striatum of rats 7 days after brief focal ischemia.7 Histological preparation of the animal brains showed selective neuronal death and proliferation of reactive astrocytes and microglia without infarct, hemorrhage, lipid accumulation, or apparent calciﬁcation.

Together, the reasons for the initial T1-hyperintensities remain elusive. Theoretically, besides intracellular methemo- globin in hemorrhagic tissue and calciﬁcations, paramagnetic compounds including metal ions (e.g., iron, manganese and copper), molecular oxygen, or free radicals could lead to these

Legend to the Full Video

Time Content

00:00:00–00:00:15 Patient sitting on chair: bradykinesia and hypomimia

00:00:16–00:00:28 Hypomimia and reduced eyelid movement;

forehead dystonia

00:00:29–00:00:37 Listing the days of the week from Monday

to Sunday: dysarthrophonia and oromandibular dystonia (2 weeks after perioral botulinum toxin type A injections)

00:00:38–00:00:47 Patient closing and opening his eyes 00:00:48–00:01:09 Facial innervation: mouth, tongue, and

forehead

00:01:10–00:01:31 Patient putting his ﬁngers on nose; dystonia

of the middle ﬁnger of the left hand 00:01:32–00:02:01 Handmoving: bradykinetic hand-gripping

and pronation-supination test

Legend to the Preview Video

Time Content

00:00:00–00:00:03 Patient sitting on chair: bradykinesia and hypomimia

00:00:04–00:00:07 Hypomimia and reduced eyelid movement;

forehead dystonia

00:00:08–00:00:15 Listing the days of the week from Monday

to Sunday: dysarthrophonia and oromandibular dystonia (2 weeks after perioral botulinum toxin type A injections)

00:00:16–00:00:33 Facial innervation: eyes, mouth, tongue,

and forehead

00:00:34–00:00:46 Patient putting his ﬁngers on nose; dystonia

of the middle ﬁnger of the left hand 00:00:47–00:00:59 Handmoving: bradykinetic hand-gripping

and pronation-supination test

MRI changes. In our case we found no evidence of hemor- rhagic changes or calciﬁcations, so that reported T1-weighted MRI hyperintensities may hypothetically result from hypoxic disruption of the cell/mitochondrial heavy metal metabolism.

Martin Wolz, MD Susann Junghanns, MD Matthias Lo¨hle, MD

*Department of Neurology, Technical University Dresden,*

*Dresden, Germany*

Ru¨diger von Kummer, MD

*Department of Neuroradiology, Technical University*

*Dresden, Dresden, Germany*

Alexander Storch, MD

*Department of Neurology, Technical University Dresden,*

*Dresden, Germany*

*\*E-mail:* [*alexander.storch@neuro.med.tu-dresden.de*](mailto:alexander.storch@neuro.med.tu-dresden.de)

### References

1. Lin JJ, Chang MK. Hemiballism-hemichorea and non-ketotic hyperglycemia. J Neurol Neurosurg Psychiatry 1994;57:748– 750.

15318257, 2008, 11, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.22178 by The University Of Manchester, Wiley Online Library on [22/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

*Movement Disorders, Vol. 23, No. 11, 2008*

#### LETTERS TO THE EDITOR 1619

1. Oh SH, Lee KY, Im JH, Lee MS. Chorea associated with non- ketotic hyperglycemia and hyperintensity basal ganglia lesion on T1-weighted brain MRI study: a meta-analysis of 53 cases including four present cases. J Neurol Sci 2002;200:57–62.
2. Fujioka M, Hiramatsu K, Sakaki T, Sakaguchi S, Ishii Y. Spe- ciﬁc changes in human brain after hypoglycemic injury. Stroke 1997;28:584–587.
3. Krieger D, Krieger S, Jansen O, Gass P, Theilmann L, Licht- necker H. Manganese and chronic hepatic encephalopathy. Lan- cet 1995;346:270–274.
4. Ohara S, Nakagawa S, Tabata K, Hashimoto T. Hemiballism with hyperglycemia and striatal T1-MRI hyperintensity: an au- topsy report. Mov Disord 2001;16:521–525.
5. Shan DE, Ho DM, Chang C, Pan HC, Teng MM. Hemichorea- hemiballism: an explanation for MR signal changes. Am J Neu- roradiol 1998;19:863–870.
6. Fujioka M, Taoka T, Matsuo Y, Hiramatsu KI, Sakaki T. Novel brain ischemic change on MRI. Delayed ischemic hyperintensity on T1-weighted images and selective neuronal death in the cau- doputamen of rats after brief focal ischemia. Stroke 1999;30: 1043–1046.

# Successful Treatment of the Meige Syndrome with Oral Zolpidem Monotherapy

Video 

Zolpidem is an imidazopyridine agonist with a high afﬁnity for the benzodiazepine *a*1 subunit site.1 It has been reported that this drug improves motor symptoms in patients with Par- kinson’s disease, progressive supranuclear palsy, and X- linked dystonia-Parkinsonism syndrome.2–5 Recently, zolpi- dem has been shown to be effective in the treatment of ble- pharospasm and the Meige syndrome in combination with botulinum toxin A.6

Here, we report a patient with Meige syndrome, nonres- ponsive to botulinum toxin A, but successfully treated with oral zolpidem administration.

A 59-year-old man, previously healthy, presented with dis- abling blepharospasm, visual difﬁculty, and facial grimacing that began 6 months before presentation. Before four years, he reported an abnormal feeling of tension in the lower eyelid and subsequently developed involuntary excessive blinking. The dystonic symptoms were usually provoked by speaking or chewing. However, they continued at rest and were relieved by placing a pencil between his teeth. In addition, the patient reported that the symptoms were improved after taking oral zolpidem, prescribed for insomnia by his primary physician; he took this medication a half-hour before going to sleep. The patient had been treated with 50 mg quetiapine, 8 mg trihexi- phenidyl, and 40 mg baclofen without any beneﬁt. In addition, botulinum toxin A treatment was attempted (Botox 40 units, injection in eight sites of the orbicularis oculi muscle and four sites of the orbicularis oris muscle), but this had little effect. The patient reported no history of head trauma, peripheral trau- matic or surgical incidents, or neurological diseases. There was

Additional Supporting Information may be found in the online version of this article.

Published online 25 June 2008 in Wiley InterScience [(www.](http://www/) interscience.wiley.com). DOI: 10.1002/mds.22179

no exposure to neuroleptic medications. There was no family history of movement disorders.

The neurological examination was normal except for ble- pharospasm and oromandibular dystonia appearing synchro- nously. These movements were partially relieved by holding a pencil between the teeth (Segment 1). Neuropsychological testing for memory and frontal lobe functions was within normal limits. The evaluations including magnetic resonance imaging of the brain, electroencephalogram, serum chemis- tries, a complete blood count, serum ceruloplasmin, thyroid function tests, and genetic testing for the DYT1 mutation in the torsion A gene were normal. The dental and ophthalmol- ogy examinations were also normal.

We evaluated whether oral zolpidem treatment could improve the blepharospasm and oromandibular dystonia. These symptoms completely resolved within 1 hour after taking this medicine, and the patient was symptom-free for 4 hours with- out somnolence (Segment 2). A long-acting zolpidem tartrate (12.5 mg four times per day) has been prescribed, and this patient remains symptom free during the daytime.

Meige syndrome is a form of cranial dystonia; it affects the cranial muscles and is characterized by involuntary blinking and chin thrusting.7 This syndrome is considered a variant of idiopathic torsion dystonia. Although botulinum toxin injec- tions are useful for the treatment of blepharospasm as well as facial and oromandibular dystonia, the symptoms are usually refractory or only partially relieved with this medication.8

Zolpidem completely abolished the symptoms associated with the Meige syndrome in our patient without causing som- nolence. The location of the highest density of zolpidem- binding receptors is in the ventral globus pallidus, the sub- stantia nigra pars reticulate, and the subthalamic nucleus.9,10 Recently, zolpidem in the subthalamic nucleus was shown to enhance *g*-aminobutyric acid type A (GABAA) receptor- mediated inhibitory synaptic currents and therefore appears to modulate motor behavior in awake animals11; these results suggested that zolpidem may inhibit the excitability of sub- thalamic neurons and therefore compensate for the excessive inhibition of basal ganglia targets in Parkinsonism, leading to the improvement of symptoms in Parkinson’s disease. How- ever, because other basal ganglia nuclei also express zolpidem-binding sites, zolpidem may also exert electrophysi- ological effects on these other nuclei.12 In addition, other mechanisms may be involved in attenuating dyskinetic symp- toms. For example, GABAergic drugs can be effective in ameliorating experimental orofaical dyskinesia by reinforcing the involvement GABAergic hypofunction,13 and the neuro- protective and antioxidant properties of zolpidem in vivo and in vitro may contribute to the modulation of dyskinesia.14

Although the exact mechanism of binding to these sites is unknown, zolpidem might reverse the pathophysiological changes in the subthalamic nucleus, and therefore the whole basal ganglia circuit. In addition to the direct effects on the basal ganglia, we cannot rule out the possibility that the anx- iolytic inﬂuence of zolpidem may contribute to its beneﬁcial effects on dystonia.

In conclusion, oral zolpidem may be a useful pharmaco- logic alternative for patients with Meige syndrome who do not respond to botulinum toxin treatment. However, special precautions are necessary for long-term management with this drug because of the risk of zolpidem abuse, especially in patients with a previous history of substance abuse.15

15318257, 2008, 11, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.22178 by The University Of Manchester, Wiley Online Library on [22/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

*Movement Disorders, Vol. 23, No. 11, 2008*

*1620 LETTERS TO THE EDITOR*

## LEGENDS TO THE VIDEO

Segment 1. The patient shows a mixture of blepharo- spasm, visual difﬁculty, and facial grimacing. These move- ments were partially relieved by holding a pencil between the teeth.

Segment 2. One hour after oral zolpidem administration, the symptoms were completely resolved in the resting state, while showing his teeth as well as grimacing and whistling.

Jae Young An, MD Joong-Seok Kim, MD\* Yeong-In Kim, MD Kwang Soo Lee, MD *Department of Neurology*

*The Catholic University of Korea, Seoul*

*South Korea*

*\*E-mail:* [*neuronet@catholic.ac.kr*](mailto:neuronet@catholic.ac.kr)

### References

1. Holm KJ, Goa KL. Zolpidem: an update of its pharmacology, therapeutic efﬁcacy, and tolerability in the treatment of insomnia. Drugs 2000;59:865–889.
2. Daniele A, Albanese A, Gainotti G, Gregori B, Bartolomeo P. Zolpidem in Parkinson’s disease. Lancet 1997;349:1222–1223.
3. Daniele A, Moro E, Bentivoglio AR. Zolpidem in progressive supranuclear palsy. N Engl J Med 1999;341:543–544.
4. Evidente VGH. Zolpidem improves dystonia in Lubag or X-linked dystonia-parkinsonism syndrome. Neurology 2002;58:662–663.
5. Ruzicka E, Roth J, Jech R, Busek P. Subhypnotic doses of zolpi- dem oppose dopaminergic-induced dyskinesia in Parkinson’s dis- ease. Mov Disord 2000;15:734–735.
6. Garretto NS, Bueri JA, Rey RD, Arakaki T, Nano GV, Mancuso

M. Improvement of blepharospasm with Zolpidem. Mov Disord 2004;19:967–968.

1. Jankovic J. Clinical features, differential diagnosis and pathoge- nesis of blepharospasm and cranial-cervical dystonia. In: Bosniak L, editor. Blepharospasm advances in ophthalmic plastic recon- structive surgery. New York: Pergamon; 1985. p 67–82.
2. Horn S, Comella C. Treatment of dystonia. In: Jankovic J, Tol- osa E, editors. Parkinson’s disease and movement disorders. Phil- adelphia: Lippincott Williams & Wilkins; 2002. p 358–364.
3. Niddam R, Dubois A, Scatton B, Arbilla S, Langer SZ. Autora- diographic localization of [3H]zolpidem binding sites in the rat CNS: comparison with the distribution of [3H]ﬂunitrazepam binding sites. J Neurochem 1987;49:890–899.
4. Dennis T, Dubois A, Benavides J, Scatton B. Distribution of central omega 1 (benzodiazepine1) and omega 2 (benzodiazepine2) recep- tor subtypes in the monkey and human brain. An autoradiographic study with [3H]ﬂunitrazepam and the omega 1 selective ligand [3H]zolpidem. J Pharmacol Exp Ther 1988;247:309–322.
5. Chen L, Xie JX, Fung KS, Yung WH. Zolpidem modulates GABAA receptor function in subthalamic nucleus. Neurosci Res 2007;58:77–85.
6. Chen L, Savio Chang C, Yung WH. Electrophysiological and be- havioral effects of zolpidem in rat globus pallidus. Exp Neurol 2004;186:212–220.
7. Peixoto MF, Araujo NP, Silva RH, et al. Effects of gabaergic drugs on reserpine-induced oral dyskinesia. Behav Brain Res 2005;160:51–59.
8. Garc´ıa-Santos G, Herrera F, Mart´ın V, et al. Antioxidant activity and neuroprotective effects of zolpidem and several synthesis intermediates. Free Radic Res 2004;38:1289–1299.
9. Madrak LN, Rosenberg M. Zolpidem abuse. Am J Psychiatry 2001;158:1330–1331.

# Torsional Nystagmus Induced by Subthalamic Nucleus Stimulation

Chronic bilateral stimulation of the subthalamic nucleus (STN) is effective in severe Parkinson’s disease (PD).1 How- ever, a few side effects, especially oculomotor manifestations have been reported.2 Understanding their mechanism may help to better deﬁne functional anatomy of this region.

A 66-year-old woman was treated by bilateral STN stimu- lation for PD. A 40% decrease of the Uniﬁed Parkinson Disease Rating Scale (UPDRS) motor score followed STN stimulation alone with the following parameters: left, contact 2: 3.5 V/60 l second/160 Hz; right, contact 7: 3.5 V/90 l second/160 Hz.

During parameters setting, she complained of vertigo, nau- seas, and oscillopsia for high voltages of stimulation (‡3.5 V) on both sides, especially on contacts 1 (left) and 6 (right), at high intensity (respectively, 4.5 V and 3.5 V). We noticed a torsional nystagmus (TN) beating on the side opposite to the stimulation (the direction is given by the upper pole of the eye, relative to patient’s) (Table 1). This completely dis- appeared when the parameters of stimulation were decreased and was reproducible over time. End-of-surgery stereotactic coordinates of each contact were used to locate them within a 3D deformable atlas of the basal ganglia (see Fig. 1).3 This conﬁrmed the unusual medial trajectories of electrodes al- ready suspected on the brain MRI.

Under chronic stimulation parameters, we observed a right sided head tilt and a right skew deviation (i.e. hypotropic right eye). Eye motility was normal and there was no nystag- mus. Subjective visual vertical (SVV) was tilted to the right (*1*3.48), fundi disclosed bilateral right sided ocular torsion. This was consistent with a right sided ocular tilt reaction (OTR). Eye movement recording practiced after the patient gave her written consent, showed hypometric upward sac- cades, normal horizontal vestibulo ocular reﬂex (VOR), and smooth pursuit (Table 2).

1. With right stimulation on contact 6 (3.5 V), a counter- clockwise TN was found. Except for lower gain of VOR, eye movements were not modiﬁed (Table 2). Vertical saccades could not be correctly recorded. The skew deviation increased. SVV slightly decreased (*1*2.048).
2. With left stimulation on contact 1 (4.5 V), we noticed a clockwise TN. Velocities of downward saccades, downward smooth pursuit gain, and horizontal pendular VOR gain decreased (Table 2). The right sided skew deviation decreased, SVV normalized (*1*0.48).

Previously reported oculomotor side effects of STN stimu- lation consisted of eyelid apraxia, binocular diplopia, myosis, mydriasis, and contraversive eye deviation.1,2,4–14 TN has been observed during periaqueductal gray matter,15 but not during STN stimulation.

STN is involved in saccades and smooth pursuit in prima- tes and humans16–23 and its stimulation could explain some ocular motor side effects such as contraversive eye devia- tion.10 However, it is unlikely that STN could have induced the TN as it was not observed at low intensity of stimulation

Published online 10 July 2008 in Wiley InterScience [(www.](http://www/) interscience.wiley.com). DOI: 10.1002/mds.22151

15318257, 2008, 11, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.22178 by The University Of Manchester, Wiley Online Library on [22/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

*Movement Disorders, Vol. 23, No. 11, 2008*

#### LETTER TO THE EDITOR 1621

TABLE 1. *Stimulation parameters and normal complaints*

V Side effects

Contacts and voltages used for chronicle bilateral stimulation LC

2 3.5 No visual complaint RC

7 3.5 No visual complaint Voltages giving a torsional nystagmus

LC

|  |  |  |
| --- | --- | --- |
| 3 |  | No visual complaint |
| 2 | 4.5 | Slight CW TN |
| 1\* | 4.5 | Marked CW TN, nauseas, vertigo |
| 0 | 3.5 | CW TN, nauseas, vertigo |

RC

7 3.5 Slight CCW TN

6\* 3.5 Marked CCW TN, nauseas, vertigo

5 3.5 CCW TN, vertigo

4 3.5 CCW TN, nauseas, vertigo

LC, Left Contacts, 0 is the deepest and 3 is the upper; RC, Right Contacts, 4 is the deepest and 7 is the upper; V, Intensity of the stimulation expressed in Volts; TN, Torsional Nystagmus; CW, Clockwise; CCW, Counterclockwise.

\*Contacts on witch the nystagmus was the more marked and used for the eyes movement recordings.

and as the contacts were medial to the STN. Oculomotor side effects can also be explained by intrafascicular oculomotor nerve stimulation but this could not explain binocular nystagmus.24

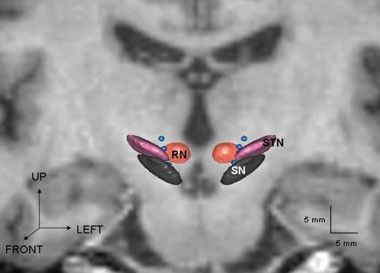


FIG. 1. Axial view of the mesencephalon derived from the deforma- ble 3D atlas (Ref. 3) and anatomic relations between electrodes con- tacts and main mesencephalic structures. The ﬁgure illustrates the unusually medial trajectories of the stimulation electrodes. The four contacts on each side are represented by blue points. Contacts 0 to 3 are left sided, 0 being the deepest and 3 the upper. Contacts 4 to 7 are right sided, 4 being the deepest and 7 the upper. Coordinates of each contact (laterality; below AC–PC line; ahead of CP line in mm) are: left side: 0 (10, 4, 10.5); 1 (11, 4, 12); 2 (11.5, 2.5, 13); 3 (12.5,

1, 14.5); right side: 4 (9, 6.5, 7); 5 (9.5, 5, 8); 6 (10, 3, 9.5); 7 (11,

1, 11). RN, red nucleus; SN, substantia nigra; STN, subthalamic nucleus.

Two prenuclear midbrain structures adjacent to the STN could be implicated in the TN: the rostral interstitial nucleus of the medial longitudinal fascicle (riMLF) and the interstitial nucleus of Cajal (iC). The riMLF is the immediate premotor structure for the generation of torsional and vertical sac- cades.25 On each side, riMLF would encode signals for both upward and downward, but only for ipsitorsional saccades.26 The iC is involved in the control of vertical and ipsilateral torsional VOR and velocity to position integrator.25 In human, lesions of riMLF alone or iC-combined essentially induce a contralesional TN with slowing of vertical saccades, contralesional torsional deviations during saccades and absent quick phases during ipsidirectional head rotations in roll.26–29 Unilateral iC lesion leads to ipsilesional TN and unilateral stimulation of the iC evokes ipsilateral eye torsion and head tilt in nonhuman.30,31 In humans, iC lesion sparing riMLF may induce ipsilesional TN28 and contraversive32,33 or ipsi- versive28 ocular tilt reaction.

Here, the dysfunction of vertical saccades is consistent with an inhibition of the riMLF but modulation of OTR can also suggest a stimulation of the iC. Whether this is explained by nucleus or afferent/efferent ﬁbers is not clear either. To clarify this point, it could be helpful to simulate the current density around the stimulation area.34

According to the close relationship of iC, riMLF, and stimulation contacts, the contralateral TN reported here could be due to an activation of the iC or an inhibition of the riMLF or both, either due to a direct nucleus or an indirect in/out connecting pathways modulation.

Alice Poisson, MD *Universite´ Lyon I Hospices Civils de Lyon*

*Hoˆpital Neurologique Pierre Wertheimer*

*Neurologie C Lyon, France*

Caroline Tilikete, MD, PhD

*Universite´ Lyon I Hospices Civils de Lyon*

*Hoˆpital Neurologique Pierre Wertheimer Unite´ de Neuro-ophtalmologie*

*Lyon, France INSERM UMR-S 864*

*IFR19, Institut Fe´de´ratif des Neurosciences de Lyon*

*Lyon, France*

Patrick Mertens, MD, PhD

*Universite´ Lyon I Hospices Civils de Lyon*

*Hoˆpital Neurologique Pierre Wertheimer*

*Neurochirurgie A Lyon, France*

Je´roˆme Yelnik, MD, PhD

*INSERM U 679*

*Hoˆpital de la Pitie´-Salpetrie`re*

*Paris, France*

15318257, 2008, 11, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.22178 by The University Of Manchester, Wiley Online Library on [22/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

*Movement Disorders, Vol. 23, No. 11, 2008*

*1622*

*LETTERS TO THE EDITOR*

*Movement Disorders, Vol. 23, No. 11, 2008*

TABLE 2. *Eye movements recording with 2D video-oculography (200 Hz frequency, visuo200, synapsys, France)*

Bilateral Stimulation No Stimulation

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | Latency (s) | Vel (8/s) Precision (%) | | Amplitude (8) |  | Latency (s) | Vel (8/s) | | Amplitude (8) | |
| Saccades Horizontal | 158 | Right | 393 (76) | 371 (89) 84 (16) | | 84 (16) |  | 453 (109) | 301 (29) | | 82 (11) | |
|  |  | Left | 373 (68) | 417 (100) 87 (11) | | 87 (11) |  | 605 (89) | 374 (153) | | 79 (19) | |
| Vertical | 108 | Up | 489 (119) | 302 (66) 57 (18) | | 57 (18) |  | 289 (152) | 344 (72) | | 44 (10) | |
|  |  | Down | 388 (167) | 204 (62) 75 (18) | | 75 (18) |  | 438 (60) | 323 (68) | | 70 (14) | |
| Smooth pursuit Horizontal | 158 | Right |  | 52.00 | | 52.00 |  |  |  | | 68,00 | |
|  |  | Left |  | 42.00 | | 42.00 |  |  |  | | 70,00 | |
| Vertical | 108 | Up |  | 71.00 | | 71.00 |  |  |  | | 80,00 | |
|  |  | Down |  | 68.00 | | 68.00 |  |  |  | | 65,00 | |
| VOR Horizontal | Pend | Right |  | 39 | | 39 |  |  |  | | 15 | |
|  |  | Left |  | 43 | | 43 |  |  |  | | 21 | |
| Vertical | HSN |  |  | 56 | |  |  |  | 70 | |  | |
| Torsional | HSN |  |  | 52 | |  |  |  | 75 | |  | |
|  |  |  |  | Right Stimulation | |  |  |  | Left Stimulation | |  | |
|  |  |  | Latency (s) | Vel (8/s) | Precision (%) | Amplitude (8) | Latency (s) | | Vel (8/s) | Precision (%) | | Amplitude (8) |
| Saccades Horizontal | 158 | Right | 408 (234) | 298 (43) | 79 (20) | 79 (20) | 291 (135) | | 402 (63) | 81 (18) | | 81 (18) |
|  |  | Left | 495 (90) | 374 (116) | 64 (12) | 64 (12) | 630 (44) | | 381 (146) | 79 (25) | | 79 (25) |
| Vertical | 108 | Up | N/A | N/A | N/A | N/A | 388 (222) | | 363 (70) | 47 (5) | | 47 (5) |
|  |  | Down | N/A | N/A | N/A | N/A | 328 (42) | | 172 (99) | 71 (10) | | 71 (10) |
| Smooth pursuit Horizontal | 158 | Right |  |  | 64 | 64.00 |  | |  | 56 | | 56.00 |
|  |  | Left |  |  | 57 | 57.00 |  | |  | 59 | | 59.00 |
| Vertical | 108 | Up |  |  | 69 | 69.00 |  | |  | 64 | | 64.00 |
|  |  | Down |  |  | 70 | 70.00 |  | |  | 45 | | 45.00 |
| VOR Horizontal | Pend | Right |  |  | 1 | 1 |  | |  | 4 | | 4 |
|  |  | Left |  |  | 5 | 5 |  | |  | 6 | | 6 |
| Vertical | HSN |  |  | 30 |  |  |  | | 60 |  | |  |
| Torsional | HSN |  |  | 30 |  |  |  | | 50 |  | |  |

Velocity (vel) and gain of horizontal (158) and vertical (108) visually guided saccades; Gain of smooth pursuit (0.15 Hz; 308 horizontal and 208 vertical), pendular Vestibulo-Ocular Reﬂex (VOR) (0.25 Hz; maximum amplitude of 458) and maximal velocity of head shaking nystagmus (HSN) (mean frequency 2 Hz; mean amplitude 258 in horizontal and vertical direc- tions) were recorded.

#### LETTER TO THE EDITOR 1623

Eric Bardinet, PhD

*CNRS UPR 640, UPMC*

*Hoˆpital de la Pitie´-Salpetrie`re*

*Paris, France Centre de Neuro-Imagerie de Recherche*

*UPMC*

*Hoˆpital de la Pitie´-Salpetrie`re*

*Paris, France*

Emmanuel Broussolle, MD, PhD Ste´phane Thobois, MD, PhD\*

*Universite´ Lyon I Hospices Civils de Lyon*

*Hoˆpital Neurologique Pierre Wertheimer*

*Neurologie C, Lyon, France INSERM UMR-S 864*

*IFR19, Institut Fe´de´ratif des Neurosciences de Lyon*

*Lyon, France*

*\*Email: stephane.thobois@chu-lyon*

Acknowledgments: This work was promoted by the Hos- pices Civils de Lyon, project no. HCL/P/2002.303.

### References

1. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Par- kinson’s disease. N Engl J Med 2003;349:1925–1934.
2. Kleiner-Fisman G, Herzog J, Fisman DN, et al. Subthalamic nu- cleus deep brain stimulation: summary and meta-analysis of out- comes. Mov Disord 2006;21 (Suppl 14):S290–S304.
3. Yelnik J, Bardinet E, Dormont D, et al. A three-dimensional, his- tological and deformable atlas of the human basal ganglia. I. Atlas construction based on immunohistochemical and MRI data. Neuroimage 2007;34:618–638.
4. Benabid AL, Koudsie A, Benazzouz A, et al. Deep brain stimula- tion of the corpus luysi (subthalamic nucleus) and other targets in Parkinson’s disease. Extension to new indications such as dys- tonia and epilepsy. J Neurol 2001;248 (Suppl 3):III37–III47.
5. Broggi G, Franzini A, Ferroli P, et al. Effect of bilateral subtha- lamic electrical stimulation in Parkinson’s disease. Surg Neurol 2001;56:89–94; discussion 94–86.
6. Herzog J, Volkmann J, Krack P, et al. Two-year follow-up of subthalamic deep brain stimulation in Parkinson’s disease. Mov Disord 2003;18:1332–1337.
7. Iansek R, Rosenfeld JV, Huxham FE. Deep brain stimulation of the subthalamic nucleus in Parkinson’s disease. Med J Aust 2002;177:142–146.
8. Ostergaard K, Sunde N, Dupont E. Effects of bilateral stimulation of the subthalamic nucleus in patients with severe Parkinson’s dis- ease and motor ﬂuctuations. Mov Disord 2002;17:693–700.
9. Romito LM, Scerrati M, Contarino MF, Bentivoglio AR, Tonali P, Albanese A. Long-term follow up of subthalamic nucleus stimulation in Parkinson’s disease. Neurology 2002;58:1546– 1550.
10. Sauleau P, Pollak P, Krack P, et al. Contraversive eye deviation during stimulation of the subthalamic region. Mov Disord 2007;22:1810–1813.
11. Tamma F, Rampini P, Egidi M, et al. Deep brain stimulation for Parkinson’s disease: the experience of the Policlinico-San Paolo Group in Milan. Neurol Sci 2003;24 (Suppl 1):S41–S42.
12. Tavella A, Bergamasco B, Bosticco E, et al. Deep brain stimula- tion of the subthalamic nucleus in Parkinson’s disease: long-term follow-up. Neurol Sci 2002;23 (Suppl 2):S111–S112.
13. Thobois S, Mertens P, Guenot M, et al. Subthalamic nucleus stimulation in Parkinson’s disease: clinical evaluation of 18 patients. J Neurol. 2002;249:529–534.
14. Volkmann J, Allert N, Voges J, Weiss PH, Freund HJ, Sturm V. Safety and efﬁcacy of pallidal or subthalamic nucleus stimulation in advanced PD. Neurology 2001;56:548–551.
15. Lueck CJ, Hasmlyn P, Crawford TJ, Levy IS, Brindley GS, Wat- kins ES, Kennard C. A case of ocular tilt reaction and torsional nystagmus due to direct stimulation of the midbrain in man. Brain 1991;114 (Pt 5):2069–2079.
16. Huerta MF, Krubitzer LA, Kaas JH. Frontal eye ﬁeld as deﬁned by intracortical microstimulation in squirrel monkeys, owl mon- keys, and macaque monkeys. I. Subcortical connections. J Comp Neurol 1986;253:415–439.
17. Huerta MF, Pons TP. Primary motor cortex receives input from area 3a in macaques. Brain Res 1990;537:367–371.
18. Stanton GB, Goldberg ME, Bruce CJ. Frontal eye ﬁeld efferents in the macaque monkey. II. Topography of terminal ﬁelds in midbrain and pons. J Comp Neurol 1988;271:493–506.
19. Basso MA, Pokorny JJ, Liu P. Activity of substantia nigra pars reticulata neurons during smooth pursuit eye movements in mon- keys. Eur J Neurosci 2005;22:448–464.
20. Matsumura M, Kojima J, Gardiner TW, Hikosaka O. Visual and oculomotor functions of monkey subthalamic nucleus. J Neuro- physiol 1992;67:1615–1632.
21. Fawcett AP, Cunic D, Hamani C, et al. Saccade-related poten- tials recorded from human subthalamic nucleus. Clin Neurophy- siol 2007;118:155–163.
22. Fawcett AP, Dostrovsky JO, Lozano AM, Hutchison WD. Eye movement-related responses of neurons in human subthalamic nucleus. Exp Brain Res 2005;162:357–365.
23. Rivaud-Pechoux S, Vermersch AI, Gaymard B, et al. Improve- ment of memory guided saccades in parkinsonian patients by high frequency subthalamic nucleus stimulation. J Neurol Neuro- surg Psychiatry 2000;68:381–384.
24. Bejjani BP, Arnulf I, Houeto JL, et al. Concurrent excitatory and inhibitory effects of high frequency stimulation: an oculomotor study. J Neurol Neurosurg Psychiatry 2002;72:517–522.
25. Buuttner U, Buuttner-Ennever JA, Rambold H, Helmchen C. The contribution of midbrain circuits in the control of gaze. Ann N Y Acad Sci 2002;956:99–110.
26. Kremmyda O, Bu¨ttner-Ennever JA, Bu¨ttner U, Glasauer S. Torsional deviations with voluntary saccades caused by a unilateral midbrain lesion. J Neurol Neurosurg Psychiatry. 2007;78:1155–1157.
27. Bhidayasiri R, Plant GT, Leigh RJ. A hypothetical scheme for the brainstem control of vertical gaze. Neurology 2000;54:1985–1993.
28. Helmchen C, Rambold H, Kempermann U, Buttner-Ennever JA, Buttner U. Localizing value of torsional nystagmus in small mid- brain lesions. Neurology 2002;59:1956–1964.
29. Riordan-Eva P, Faldon M, Buttner-Ennever JA, Gass A, Bron- stein AM, Gresty MA. Abnormalities of torsional fast phase eye movements in unilateral rostral midbrain disease. Neurology 1996;47:201–207.
30. Farshadmanesh F, Klier EM, Chang P, Wang H, Crawford JD. Three-dimensional eye-head coordination after injection of mus- cimol into the interstitial nucleus of Cajal (INC). J Neurophysiol 2007;97:2322–2338.
31. Klier EM, Wang H, Crawford JD. Interstitial nucleus of cajal encodes three-dimensional head orientations in Fick-like coordi- nates. J Neurophysiol 2007;97:604–617.
32. Dieterich M, Brandt T. Thalamic infarctions: differential effects on vestibular function in the roll plane (35 patients). Neurology 1993;43:1732–1740.
33. Halmagyi GM, Brandt T, Dieterich M, Curthoys IS, Stark RJ, Hoyt WF. Tonic contraversive ocular tilt reaction due to unilateral meso-diencephalic lesion. Neurology 1990;40:1503–1509.

15318257, 2008, 11, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.22178 by The University Of Manchester, Wiley Online Library on [22/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

*Movement Disorders, Vol. 23, No. 11, 2008*

#### 1624 LETTERS TO THE EDITOR

1. Butson CR, Cooper SE, Henderson JM, McIntyre CC. Patient- speciﬁc analysis of the volume of tissue activated during deep brain stimulation. Neuroimage 2007;34:661–670.

# Palatal Tremor and Facial Dyskinesia in a Patient with *POLG1* Mutation

Recently, a progressive ataxic syndrome (MSCAE) caused by zA467T and W748S *POLG1* mutations was reported.1–4 The nuclear gene, *POLG1* encodes the catalytic subunit of the mitochondrial DNA dependent polymerase, polymerase *g*5. The catalytic subunit comprises three domains, a poly- merase and 30-50 exonuclease domain and an intervening linker region. Over 70 mutations have been reported in the catalytic subunit with both dominant and recessive modes of inheritance. The carrier frequency of these two mutations is high in Northern Europe, particularly Scandinavia.3 The clini- cal features associated with *POLG1* mutation include pro- gressive external ophthalmoplegia (PEO),6 Alpers’ syn- drome,7 parkinsonism,8 or a syndrome with sensory ataxia, neuropathy, dysarthria, and ophthalmoplegia (SANDO).9 We present a young woman, homozygous for the W748S muta- tion and MSCAE that developed palatal tremor and facial dyskinesia and hypertrophic degeneration of the inferior oli- vary nuclei.

The patient is now 35-years old without family history of epilepsy or movement disorder. She was ﬁrst seen at the age of 19 with focal epileptic seizures. Five years later external ophthalmoplegia and gait unsteadiness were noted and aged 28, during her ﬁrst pregnancy, she was admitted with focal epileptic seizures that were highly resistant to treatment. Two months later her symptoms worsened and included myoclonic jerks in the extremities and facial dyskinesias. Treatment with sodium valproate resulted in acute severe hepatic failure and she underwent a successful liver transplantation. Two years later a cerebral MRI scan showed marked hypertrophic degeneration of the inferior olives (Fig. 1). She denied symp- toms of ear clicking.

On examination at age 35, she had a mild cognitive deﬁ- cit, cerebellar dysarthria, mild external ophthalmoplegia, no nystagmus and no facial nerve dysfunction. She had an asymptomatic palatal tremor, consisting of soundless, bilat- eral, synchronous and symmetrical 2 Hz contractions of the soft palate plus facial dyskinesias consisting of continuous, rhythmic, undulating wave-like, bilateral periorbital move- ments.

Intermittent, asymmetric limb myoclonus, cerebellar and sensory ataxia and signs of peripheral neuropathy with loss of reﬂexes and sensory disturbance were also present. Muscle bulk, tone, and power appeared normal. DNA analysis con- ﬁrmed that she was homozygous for the *c.* 2243G>C (*p.* W748S) mutation in *POLG1*.

Our patient demonstrates the typical features of MSCAE with the combination of focal epilepsy, myoclonus and ataxia as well as sensitivity to sodium valproate.3,10 The interesting features are the rhythmical facial dyskinesia and the asymp-

Published online 25 June 2008 in Wiley InterScience [(www.](http://www/) interscience.wiley.com). DOI: 10.1002/mds.22178

tomatic palatal tremor with its structural correlate of inferior olivary nuclei involvement.

Hypertrophic olivary degeneration (HOD) is clinically associated with palatal tremor and is often caused by pa- thology in the dentato-rubro-olivary pathways or also called Guillain-Mollaret triangle. Usually the lesion is caused by vascular ischemia, hemorrhage, infection, trauma, neoplasm or demyelination.11 A syndrome called progressive ataxia and palatal tremor (PAPT) has been reported and shows similarities to our case. Even though sporadic PAPT cases had a heterogeneous clinical picture, the cerebellar degen- eration was the most symptomatic feature and HOD was common in the presented cases.12 In the familiar forms of PAPT, however, olivary pathology was absent. Palatal tremor with olivary hypertrophy and dentate calciﬁcation has also been described in a form of spinocerebellar ataxia, SCA 20.13

In our patient HOD was an incidental MRI ﬁnding with- out any obvious clinical symptoms. It occurred several years after disease onset. The lack of ear clicks or other symptoms may explain why this clinical picture has not been reported by other authors. Asymptomatic palatal tremor may also be easily overlooked in a routine clinical examination.

Facial dyskinesia appeared as wave-like periorbital invol- untary movements on both sides, but not perioral. These asymmetric movements, alternating from one side to the other were most prominent when she was in a resting posi- tion. She had never been treated with neuroleptic or antipar- kinsonian drugs that might have induced this feature. EEG recorded routinely due to her epilepsy has not shown any correlate with these movements. Orofacial dyskinesia is reported in chorea acanthocytosis together with other symp- toms like dysphagia, dysarthria, areﬂexia, seizures, and de- mentia.14 Facial myorhythmia is also pathognomic for Whip- ple’s disease mostly localized around the eyes and jaw. Other symptoms as seizures, myoclonus, ophthalmoplegia, and dys- arthria are also common. A diagnostic criterion for this entity is small intestine biopsy that excluded the disease.

We present a case with the typical clinical features of *POLG1* mutation and additional novel ﬁndings of palatal tremor with HOD on MRI and facial dyskinesia. These ﬁnd- ings expand the clinical spectrum of the syndromes caused by mutation in this gene. Moreover, since palatal tremor is a rare disorder, and often reported as a sporadic entity, we sug- gest that *POLG1* mutation should be considered in patients with this disorder.

## LEGENDS TO THE VIDEO

Segment 1. The patient shows gait ataxia and mild external ophthalmoplegia. She has bilateral, asymmetrical rhythmical facial dyskinesias, mainly in the periorbital regions. The asymptomatic palatal tremor: soundless, bilat- eral, synchronous and symmetrical 2Hz contractions of the soft palate.

Krisztina K. Johansen, MD

*Department of Neuroscience Norwegian University of Science and Technology*

*Trondheim, Norway*

15318257, 2008, 11, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.22178 by The University Of Manchester, Wiley Online Library on [22/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

*Movement Disorders, Vol. 23, No. 11, 2008*

#### LETTERS TO THE EDITOR 1625

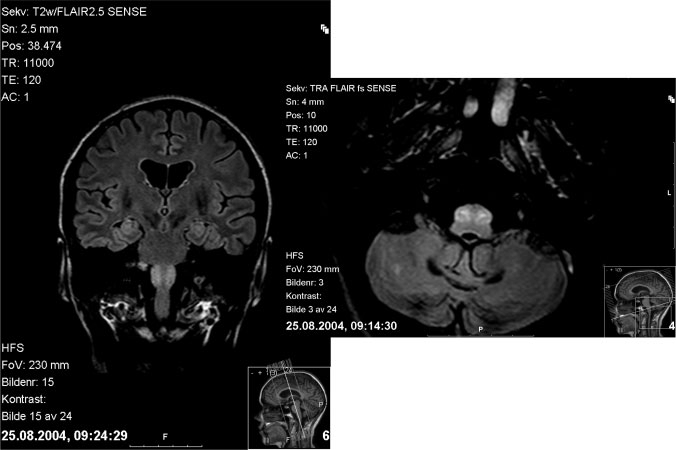
**

FIG. 1. Marked hypertrophic degeneration of the inferior olives.

Laurence A. Bindoff, MD, PhD

*Department of Neurology Haukeland University Hospital, Bergen; Institute of Clinical Medicine*

*University of Bergen, Norway*

Jana Rydland, MD

*Department of Radiology, St Olavs Hospital*

*Trondheim, Norway*

Jan O. Aasly, MD, PhD\*

*Department of Neurology St Olavs Hospital, Trondheim Department of Neuroscience*

*Norwegian University of Science and Technology*

*Trondheim, Norway*

*\*E-mail:* [*jan.aasly@ntnu.no*](mailto:jan.aasly@ntnu.no)

### References

1. Van Goethem G, Luoma P, Rantamaki M, et al. POLG mutations in neurodegenerative disorders with ataxia but no muscle involvement. Neurology 2004;63:1251–1257.
2. Hakonen AH, Heiskanen S, Juvonen V, et al. Mitochondrial DNA polymerase W748S mutation: a common cause of autoso- mal recessive ataxia with ancient European origin. Am J Hum Genet 2005;77:430–441.
3. Winterthun S, Ferrari G, He L, et al. Autosomal recessive mito- chondrial ataxic syndrome due to mitochondrial polymerase gamma mutations. Neurology 2005;64:1204–1208.
4. Tzoulis C, Engelsen BA, Telstad W, et al. The spectrum of clini- cal disease caused by the A467T and W748S POLG mutations: a study of 26 cases. Brain 2006;129:1685–1692.
5. Kaguni LS. DNA polymerase gamma, the mitochondrial repli- case. Ann Rev Biochem 2004;73:293–320.
6. Lamantea E, Tiranti V, Bordoni A, et al. Mutations of mitochon- drial DNA polymerase gammaA are a frequent cause of autoso- mal dominant or recessive progressive external ophthalmoplegia. Ann Neurol 2002;52:211–219.
7. Naviaux RK, Nguyen KV. POLG mutations associated with Alpers’ syndrome and mitochondrial DNA depletion. Ann Neurol 2004;55:706–712.
8. Luoma PT, Eerola J, Ahola S, et al. Mitochondrial DNA poly- merase gamma variants in idiopathic sporadic Parkinson disease. Neurology 2007;69:1152–1159.
9. Fadic R, Russell JA, Vedanarayanan VV, Lehar M, Kuncl RW, Johns DR. Sensory ataxic neuropathy as the presenting feature of a novel mitochondrial disease. Neurology 1997;49: 239–245.
10. Engelsen BA, Tzoulis C, Karlsen B, et al. POLG1 mutations cause a syndromic epilepsy with occipital lobe predilection. Brain 2008;131:818–28.
11. Yokota T, Hirashima F, Furukawa T, Tsukagoshi H, Yoshikawa

H. MRI ﬁndings of inferior olives in palatal myoclonus. J Neurol 1989;236:115–116.

1. Samuel M, Torun N, Tuite PJ, Sharpe JA, Lang AE. Progres- sive ataxia and palatal tremor (PAPT): clinical and MRI assess- ment with review of palatal tremors. Brain 2004;127:1252– 1268.

15318257, 2008, 11, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.22178 by The University Of Manchester, Wiley Online Library on [22/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

*Movement Disorders, Vol. 23, No. 11, 2008*

#### 1626 LETTERS TO THE EDITOR

1. Knight MA, Gardner RJ, Bahlo M, et al. Dominantly inherited ataxia and dysphonia with dentate calciﬁcation: spinocerebellar ataxia type 20. Brain 2004;127:1172–1181.
2. Rampoldi L, Danek A, Monaco AP. Clinical features and mo- lecular bases of neuroacanthocytosis. J Mol Med 2002;80:475– 491.

# Thalamic Stimulation Does Not Involve a High Rate of Suicide

I read with some concern the paper of Appleby et al. pub- lished in the September issue of MDJ.1 The authors write in the abstract, ‘‘Reported rates of depression, cognitive impair- ment, mania, and behavior change are low, but there is a high rate of suicide in patients treated with DBS, particularly with thalamic and GPi stimulation.’’ In the Results section, the authors provide numbers and percentage of ‘‘those patients that expressed suicidality (deﬁned as suicidal idea- tion, suicide attempt, or completed suicide).’’ They wrote, ‘‘Most patients underwent DBS for the treatment of Parkin- son’s disease (26; 81%); 4 had dystonia (12.5%), 1 had essential tremor (3%), and another had OCD (3%).’’ Then the authors provide details of the brain target for DBS in these patients: ‘‘26 patients (81%) were implanted in the STN, 4 (12.5%) had GPi implants, and 1 (3%) had a VIM implant, and the last patient received an anterior limb of the internal capsule implant.’’ Then, toward the end of the Results section, they wrote, ‘‘The rate of completed suicide was highest in the thalamus group (5.4%).’’

In my reading, these results simply do not add up and the drawn conclusions expressed both in the abstract and in the discussion of that paper do not substantiate, in fact contra- dict, the ﬁgures and percentage cited. This article is supposed to be a review of the literature and a meta-analysis, but nowhere can one read how the meta-analysis was statistically conducted. To start with, there is no information about the number of patients with the various diagnoses or the number of patients operated on in the various brain targets. There is instead information about number of publications, their geo- graphical origin, gender of patients, etc. There is no mention of any data providing the percentage of patients with suici- dality in relation to the number of patients operated on, in any of the brain targets, or for any of the diagnoses.

In the quoted references, I cannot ﬁnd any reference that supports the authors’ claim that thalamic stimulation carries the highest risk for suicidality, and the authors do not give the citation reference numbers to back up their conclusions. To name but one example, the last patient who committed suicide and who ‘‘received an anterior limb of the internal capsule implant’’ is certainly the patient described by Abel- son et al. in the (nonquoted) paper on four patients with OCD treated with DBS.2

The authors wrote, ‘‘Since its approval by the FDA in 1997 for use in Parkinson’s disease, DBS has been used to treat essential tremor, dystonia, cluster headaches, and chronic pain1–4’’ and among these 4 quoted references, one (Ref. 4) was actually about DBS for epilepsy. Besides, it is

true that FDA granted approval for thalamic DBS for parkin- sonian and essential tremor in 1997, then pallidal DBS and STN DBS for advanced PD in 2001. However, for dystonia, the FDA granted in 2003 a humanitarian device exemption, which is not a full approval.

Instead of providing several tables detailing device-related adverse events (Table 3) and somatic adverse events (table 4), both of which are evidently out of the scope of this paper on psychiatric and neuropsychiatric adverse events, it would have been more helpful to provide tables of the percentage or prevalence of suicides according to target and diagnosis. In my review of the literature, suicidality following DBS is overall rare, and its prevalence is higher in patients with sub- thalamic DBS compared to thalamic DBS, a ﬁnding contrary to their statement (in the abstract and on page 1726).

The ﬁnal conclusion of this article reads, ‘‘Our ﬁndings are optimistic regarding the use of DBS for psychiatric disor- ders.’’ Which ﬁndings? I looked repeatedly in the paper for any results, ﬁgures, or tables that would justify such a con- clusion but could ﬁnd none. In the context of this study, such a conclusion seems to me in need of reconsideration, and the data need to be clearly provided.

In my view, we are left with a published study that could potentially have been an extremely informative analysis had the authors separated thalamus and subthalamus and had they carefully evaluated the literature that they set themselves to review. The meta-analysis promised in the title of this work was not provided, and the authors fall short of answering the issues at stake.

Marwan I. Hariz, MD, PhD

*Professor of Functional Neurosurgery*

*Institute of Neurology Queen Square, London, United Kingdom*

*E-mail:* [*m.hariz@ion.ucl.ac.uk*](mailto:m.hariz@ion.ucl.ac.uk) *or* [*marwan.hariz@neuro.umu.se*](mailto:marwan.hariz@neuro.umu.se)

### References

1. Appleby BS, Duggan PS, Regenberg A, Rabins PV. Psychiatric and neuropsychiatric adverse events associated with deep brain stimulation: a meta-analysis of ten years’ experience. Mov Dis- ord 2007;22:1722–1728.
2. Abelson JL, Curtis GC, Sagher O, Albucher RC, Harrigan M, Taylor MF, Martis B, Giordani B. Deep brain stimulation for re- fractory obsessive-compulsive disorder. Biol Psychiatry 2005;57: 510–516.

# Dystonia with Superimposed Myasthenia Gravis: An Experiment in Nature

Neuromuscular junctional (NMJ) paralysis induced by botuli- num toxin injection is currently the preferred treatment for focal or segmental dystonia, whereas NMJ paralysis due to depletion of postjunctional acetylcholine receptors is the pathogenetic mechanism of myasthenia gravis (MG). A

Published online 25 June 2008 in Wiley InterScience [(www.](http://www/) interscience.wiley.com). DOI: 10.1002/mds.22138

Published online 25 June 2008 in Wiley InterScience [(www.](http://www/) interscience.wiley.com). DOI: 10.1002/mds.22166

15318257, 2008, 11, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.22178 by The University Of Manchester, Wiley Online Library on [22/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

*Movement Disorders, Vol. 23, No. 11, 2008*

#### LETTERS TO THE EDITOR 1627

patient with dystonia developing MG may, therefore, show improvement of dystonic symptoms. Here, we present 2 patients with coexisting dystonia and MG.

A 69-year-old woman, 19 years earlier, noticed intermit- tent turning of her head to the right side which had begun suddenly following a motor vehicle accident. She had side- to-side movement of her head with rotation and tilt to the right side. It was aggravated by stress and suppressed with sensory tricks. There was no family history of dystonia or of prior treatment with neuroleptic medications. She was diag- nosed with cervical dystonia with mild head tremor. She tried various oral medications with no improvement. She was never treated with botulinum toxin.

Seven years ago, she developed double vision, drooping of the eyelids, and generalized weakness. She also noted marked reduction of dystonic movements at the same time. Neurological examination revealed bilateral ptosis and di- plopia, which worsened on fatigue. She had minimal dys- tonic head tremor, with torticollis to the right of 208 and right laterocollis of 158. She also had bilateral orbicularis oculi and generalized proximal muscle weakness. The remainder of her neurological examination disclosed no abnormalities. She was diagnosed with generalized seropos- itive myasthenia gravis and started on pyridostigmine and corticosteroids, which resulted in the improvement of the myasthenic symptoms and signs. On recent follow up, she had minimal head tremor in the side-to-side direction, mild residual weakness of the cervical muscles, and no relapse of cervical dystonia.

A 61-year-old man with cerebral palsy developed ble- pharospasm several years prior to presentation to our facil- ity. One year earlier, he received botulinum toxin treatment which provided temporary improvement of this disorder. About 6 months before evaluation, he complained of pro- gressive bilateral lower extremity weakness and dysphagia to both solids and liquids. Neurological examination revealed bilateral ptosis, ophthalmoparesis, and mild gener- alized proximal muscle weakness. His blepharospasm dis- appeared and none was observed during the examination. Following further investigations including neurophysiologi- cal testing (which showed a signiﬁcant decremental response on repetitive nerve stimulation at 3 Hz), he was diagnosed with seropositive generalized myasthenia gravis. He was treated with pyridostigmine, corticosteroids, and azathioprine. A follow-up examination 2 years later showed marked improvement of myasthenic symptoms but with mild residual weakness of the orbicularis oculi. He had no recurrence of blepharospasm.

Approximately 33% of patients diagnosed with focal or seg- mental dystonia and treated with anticholinergic drugs show a modest improvement in symptoms compared with signiﬁcant improvement in 90% treated with local intramuscular botuli- num toxin.1 Botulinum toxin binds at the neuromuscular junc- tion and prevents the release of acetylcholine from the presyn- aptic terminal. It results in temporary weakness of the skeletal muscles into which it is injected, which can ameliorate the symptoms and signs of dystonia. The median duration of

effect is about 12.5 weeks.2 It is the treatment of choice for cervical dystonia, blepharospasm, spasmodic dysphonia, oro- mandibular dystonia, and limb dystonia.3

Myasthenia gravis is an autoimmune disorder caused by autoantibodies against the nicotinic acetylcholine receptor on the postsynaptic membrane at the neuromuscular junc- tion.4 Both our patients had acetylcholine receptor anti- body positive generalized myasthenia gravis and both had improvement of their movement disorders. There was marked improvement of torticollis in our ﬁrst patient and resolution of blepharospasm in the second after the devel- opment of generalized myasthenia gravis. A review of the literature reveals two reports of patients who had both gen- eralized myasthenia gravis and dystonia. Interestingly, in contrast to our patients, both of them developed only tem- porary improvement of the dystonia.5,6 Furthermore, in one of these patients, the recurrent dystonia was successfully treated with botulinum toxin.6 It is possible that our patients did not develop a recurrence of dystonia due to mild residual muscle weakness secondary to the myasthenia gravis.

Clinical improvement of dystonia after the onset of MG attests to an intriguing relationship between dystonia and MG serving as another example of an experiment of nature. Spon- taneous improvement of symptoms in a dystonic patient should direct attention to the possibility of developing a NMJ disorder.

Archana Hinduja, MD Sudhanshu Chokroverty, MD, FRCP

Philip Hanna, MD Raji P. Grewal, MD\*

*NJ Neuroscience Institute Seton Hall University*

*School of Graduate Medical Education*

*JFK Medical Center Edison, New Jersey, USA*

*\*E-mail:* [*rgrewal@solarishs.org*](mailto:rgrewal@solarishs.org)

### References

1. Jankovic J, Leder S, Warner D, Schwartz K. Cervical dystonia: Clinical ﬁndings and associated movement disorders. Neurology 1991;41:1088–1091.
2. Jankovic J. Botulinum toxin therapy for cervical dystonia. Neuro- tox Res 2006;9:145–148.
3. Jankovic J. Botulinum toxin in clinical practice. J Neurol Neuro- surg Psychiatry 2004;75:951–957.
4. Thanvi BR, Lo TCN. Update on myasthenia gravis. Postgrad Med J 2004;80:690–700.
5. Hoffman LM, Robinson J, Hannah H. Loss of dystonia as a sign of myasthenia. South Med J 1991;84:1159–1160.
6. Tarsay D, Bhattacharyya N, Borodic G. Myasthenia gravis after botulinum toxin A for Meige syndrome. Movement Disord 2000; 15:736–738.

15318257, 2008, 11, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.22178 by The University Of Manchester, Wiley Online Library on [22/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

*Movement Disorders, Vol. 23, No. 11, 2008*