

## Letters to the Editor Related to New Topics

### Paroxysmal Nonkinesigenic Dyskinesias due to Recurrent Hypoglycemia Caused by an Insulinoma

Paroxysmal dyskinesias are characterized by recurrent attacks of dystonic, choreatic, or ballistic movements. They can be sporadic or inherited and are classified traditionally into three subtypes. Paroxysmal kinesigenic dyskinesias (PKD) typically present with brief (seconds to minutes) dyskinetic episodes triggered by sudden movements. Attacks of paroxysmal exertional dyskinesias (PED) are provoked by prolonged physical exercise and typically last between 5 min and 2 h. Paroxysmal nonkinesigenic dyskinesias (PNKD) usually last from 5 min to 4 h, are not induced by movement or exercise but sometimes by fatigue, alcohol or caffeine. The distinction between sporadic PNKD and psychogenic movement disorders is often difficult.

Recently, several groups including ours identified mutations in the glucose transporter of the blood brain barrier, GLUT1, as a cause of familial PED.<sup>1,2</sup> These mutations decrease the ability of GLUT1 to transport glucose, leading to a reduced cerebrospinal fluid (CSF)/serum glucose ratio. Here, we describe a patient with sporadic PNKD due to recurrent hypoglycemia caused by an insulinoma. This further strengthens the emerging connection between paroxysmal dyskinesias and disturbed brain glucose homeostasis.

A 39-year-old woman was admitted to the emergency department because of involuntary movements of arms and legs with acute onset. On admission, there were random, non-rhythmic, nonsynchronous movements of arms and legs, which clinically seemed to be choreatic and ballistic rather than epileptic in nature. Clinical examination revealed no other significant abnormalities. In particular, consciousness and orientation were normal. Approximately 1 h after onset the dyskinesias ceased spontaneously.

The patient reported approximately five similar dyskinetic episodes over the preceding 2 yr, each lasting approximately 30 min. Consciousness was always preserved although she sometimes felt “dreamy” during attacks. There was no amnesia. Apart from psychological stress and fatigue, she identified no provoking factors. Her medical history was otherwise unremarkable. She occasionally took ibuprofen for left arm pain. She denied any substance abuse. She had no family history of neurological disorders.

Blood sampling 10 min after admission revealed hypoglycemia (42 mg/dL; normal: 55–100 mg/dL) and insulin (5 mU/L) and C-peptide (0.57 nmol/L) levels that were inappropriately high for the degree of hypoglycemia, but no other abnormalities. Toxicological urine screening, cranial CT and MRI were

normal. EEG on the following day was normal except for a slight excess in beta activity. Daily controls also revealed frequent asymptomatic hypoglycemic episodes (with glucose levels as low as 35 mg/dL). The CSF/serum glucose ratio after overnight fasting was normal (0.64; CSF glucose: 34 mg/dL; serum glucose: 53 mg/dL). Abdominal CT and endoscopic ultrasound visualised a 0.7-cm diameter lesion in the pancreatic tail. After laparoscopic enucleation the suspected diagnosis of an insulinoma was confirmed pathologically. No more hypoglycemic and dyskinetic attacks occurred in the 12 months between insulinoma removal and manuscript submission.

Our patient suffered from sporadic PNKD, which resolved after removal of an insulinoma. Although dyskinesia during hypoglycemia has been described,<sup>3</sup> it is an uncommon manifestation of hypoglycemia compared with typical neuroglycopenic symptoms such as confusion, behavioural changes, dizziness, weakness, loss of consciousness, seizures, and amnesia.<sup>3,4</sup> Reports of paroxysmal dyskinesias caused by recurrent hypoglycemia are scarce. Marsden and coworkers described a patient with a suspected insulinoma who adopted dystonic postures when recovering from hypoglycemic episodes.<sup>5</sup> To our knowledge, there have been only two published reports of patients with paroxysmal dyskinesias, a pathologically confirmed insulinoma and documented remission of the attacks following insulinoma removal.<sup>6,7</sup> In one of these two cases the patient had a structural lesion in the globus pallidus, which may have contributed to the dyskinesias.<sup>6</sup> In both published cases, however, the patient had typical PED,<sup>6,7</sup> whereas our patient had PNKD. Our findings suggest that the possibility of an insulinoma should be considered in every patient with sporadic PNKD, especially since insulinomas are often curable.

Interestingly, our patient also had documented hypoglycemic episodes without dyskinesias, consistent with the known lack of a tight correlation between plasma glucose levels and hypoglycemic neurological symptoms in general.<sup>3</sup>

Adequate glucose delivery to the brain does not only depend on plasma glucose levels, but also on efficient glucose transport across the blood brain barrier. The latter process is impaired by GLUT1 mutations, a recently identified cause of familial PED.<sup>1,2</sup> Thus, recurrent shortage of glucose supply to the brain may represent a common mechanism underlying several subtypes of paroxysmal dyskinesias, including familial PED,<sup>1,2</sup> sporadic PED,<sup>6,7</sup> and sporadic PNKD.

**Acknowledgments:** Dr. Vandenberghe is a Senior Clinical Investigator of the Fund for Scientific Research—Flanders (FWO).

Frederik Debruyne, MD  
Wim Van Paesschen, MD, PhD  
Department of Neurology  
University Hospital Leuven  
Leuven, Belgium

Peter Van Eyken, MD, PhD  
*Department of Pathology  
 University Hospital Leuven  
 Leuven, Belgium*

Marie Bex, MD  
*Department of Endocrinology  
 University Hospital Leuven  
 Leuven, Belgium*

Wim Vandenberghe, MD, PhD\*  
*Department of Neurology  
 University Hospital Leuven  
 Leuven, Belgium*

\*E-mail: [wim.vandenberghe@uz.kuleuven.ac.be](mailto:wim.vandenberghe@uz.kuleuven.ac.be)

### References

1. Weber YG, Storch A, Wuttke TV, et al. GLUT1 mutations are a cause of paroxysmal exertion-induced dyskinesias and induce haemolytic anemia by a cation leak. *J Clin Invest* 2008;118:2157–2168.
2. Suls A, Dedeken P, Goffin K, et al. Paroxysmal exercise-induced dyskinesia and epilepsy is due to mutations in *SCL2A1*, encoding the glucose transporter, GLUT1. *Brain* 2008;131:1831–1844.
3. Windebank AJ, McEvoy KM. Diabetes and the nervous system. In: Aminoff MJ, editor. *Neurology and general medicine*. Philadelphia: Churchill Livingstone; 1995. p 349–381.
4. Dizon AM, Kowalyk S, Hoogwerf BJ. Neuroglycopenic and other symptoms in patients with insulinomas. *Am J Med* 1999;106:307–310.
5. Winer J, Fish D, Sawyers D, Marsden CD. A movement disorder as a presenting feature of recurrent hypoglycaemia. *Mov Disord* 1990;5:176–177.
6. Shaw C, Haas L, Miller D, Delahun J. A case report of paroxysmal dystonic choreoathetosis due to hypoglycaemia induced by an insulinoma. *J Neurol Neurosurg Psychiatry* 1996;61:194–195.
7. Tan NCK, Tan AKY, Sitoh YY, Loh KC, Leow MKS, Tjia HTL. Paroxysmal exercise-induced dystonia associated with hypoglycaemia induced by an insulinoma. *J Neurol* 2002;249:1615–1616.

### Erdheim-Chester Disease: A Rare Clinical Presentation as Multiple System Atrophy

Evaluation of late onset nonfamilial progressive ataxia is a challenge with numerous diagnostic possibilities. We report a patient who initially presented with bladder dysfunction and sporadic progressive ataxia but later development of non-neurological manifestations helped to make a diagnosis of Erdheim-Chester disease (ECD). ECD is a rare non-Langerhans histiocytic disorder with multisystem involvement,<sup>1</sup> and initial presentation with ataxia is rare.

The patient was a 51-year-old gentleman who was well till 2003 when he noticed increased urinary frequency and urgency. He was diagnosed to have urethral stricture but did not benefit from urethral dilatation. Two years later, he

started having imbalance while walking and multiple lobular eruptions over face, and over next year developed dysarthria, difficulty swallowing, slowness of activities, generalized body aches, and arthralgias. At this time, he was seen at our Neurology clinic and found to have multiple soft, nontender lobular cutaneous lesions over face (Fig. 1a). Neurological evaluation revealed normal cognition, spastic dysarthria, nasal intonation of voice, jerky pursuits, slow saccades, and bilateral horizontal nystagmus. He had increased tone of both lower limbs and left upper limb, normal power and sensations, exaggerated stretch reflexes, brisk jaw jerk, bilateral Babinski's sign, mild heel-knee and left finger-nose incoordination, broad-based gait, and impaired tandem walking. He had generalized slowness that could be partly attributed to musculoskeletal pain.

Blood investigations showed mild anemia, persistently elevated ESR, mildly elevated alkaline phosphatase, and reversal of albumin-globulin ratio. MRI brain showed hyperintense lesions of pons and midbrain on T2 and flair sequences, not enhancing with contrast (Fig. 1b). Nerve conductions were normal, but visual, brainstem, and median somatosensory-evoked potentials showed prolonged latencies. He had mild parasympathetic and moderate sympathetic involvement on autonomic function tests, and urodynamic studies showed impaired detrusor contractibility with unstable bladder secondary to neurogenic bladder. Cerebrospinal fluid analysis was normal.

Presence of systemic features, elevated ESR, and MRI not typical of MSA made us search for an alternative diagnosis. A biopsy of the skin lesions confirmed cutaneous xanthoma (Fig. 1e). X-ray of knee joints showed diffuse sclerosis predominantly involving the diaphysis of femur and tibia (Fig. 1c) and corresponding MRI findings were diffuse marrow signal changes (Fig. 1d). Bone scintigraphy (740 MBQ 99m Tc MDP) showed bilateral symmetrical increased tracer uptake in the metaphysis extending into the diaphysis of long bones, clavicles, left acetabulum, and acromial ends of both scapulae. Finally, a bone biopsy of left tibia below the tibial tuberosity confirmed a non-Langerhans cell histiocytic disorder (Fig. 1f–h).

The overall clinical presentation supported by the above investigations established the diagnosis of ECD. He was treated with parenteral methyl prednisolone followed by oral steroids and analgesics. He did not show any significant improvement and succumbed to his illness 2 years later.

ECD is a rare multisystem disorder with clinical spectrum ranging from asymptomatic tissue infiltration to fulminant multisystem organ failure. An early diagnosis is often difficult in those presenting with an isolated system involvement, especially of the nervous system. In the latter, imaging may be normal particularly in those with diabetes insipidus (DI)<sup>2,3</sup> or misleading,<sup>4</sup> tissue diagnosis requires a highly invasive procedure, and intra-axial lesions may not show the characteristic histopathological findings of the disease.<sup>4</sup> Therefore, the true prevalence of neurological involvement in ECD may not be accurate. In a recent meta-analysis of 110 patients<sup>2</sup> of ECD with neurological manifestations, the most common neurological presentation was DI followed by cerebellar involvement in 27 patients (24.5%); 18 did not have involvement of other systems, and 2 of them did not even have radi-



**FIG. 1.** (a) Photograph of patient's face, showing yellowish colored lobular and papular lesions predominantly over the nose and perioral areas. (b) T2-weighted MRI of brain showing hyperintense lesions involving the pons (arrows). (c) X-ray (AP view) of both knees showing diffuse sclerosis of the diaphysis of femur and tibia extending up to the metaphysis. (d) T2-weighted MRI of both knees showing diffuse marrow signal changes (hypointensity) in femoral and tibial diaphysis. (e) Biopsy of skin xanthoma showing thinning of epidermis and infiltration of the entire thickness of dermis by sheets of finely vacuolated foamy histiocytes interspersed with Touton type of multinucleate giant cells (arrowheads). Moderate numbers of admixed lymphocytes and a rare eosinophil are also present. (f) Bone biopsy (tibia) showing bone sclerosis and widespread infiltration of marrow spaces by large foamy lipid laden histiocytes admixed with few eosinophils similar to the skin lesions. Inset: Histiocytes with abundant finely vacuolated cytoplasm and small nuclei. Touton giant cells were inconspicuous and the nuclei were small and bland. There was no nuclear grooving. (g) Immunohistochemistry showing strong expression of CD68 macrophage marker in the histiocytes. Inset: Higher magnification showing Touton giant cell positivity. (h) The histiocytes are CD1a and S-100 negative. The findings indicated a non-Langerhans cell histiocytic disorder. [(e, f) HE stain; (g, h) Immunohistochemistry; Original magnifications: (e) 40 $\times$ , inset 320 $\times$ ; (f) 160 $\times$ ; (g) 80 $\times$ , inset 320 $\times$ ; (h) 320 $\times$ ].

ological evidence of ECD. Ataxia may result from dural mass lesions compressing the brainstem and cerebellum<sup>5</sup> or intra-axial infiltration of the dentate nucleus, basis pontis, and middle cerebellar peduncle,<sup>2-4,6,7</sup> which is similar to the MRI findings in our patient. However, as these intra-axial lesions do not show evidence of mass effect, they may be easily mistaken for demyelinating lesions or even infarcts.<sup>4</sup>

In summary, we have reported a patient presenting with bladder dysfunction, late onset sporadic ataxia, and pyramidal signs, a syndrome mimicking MSA resulting from ECD, which is a rare disorder uncommonly seen by neurologists. Musculoskeletal pains, recent onset of skin xanthomas, and elevated ESR warranted further investigations for an alternative diagnosis. The diagnosis was confirmed by histopathological findings from skin and bone. It may be increasingly relevant to identify this small group of patients as recent reports suggest improvement of exophthalmos, DI, and bone lesions in ECD following treatment with interferon.<sup>8</sup> Our report emphasizes the importance of looking for evidence of involvement of other organ systems in patients with progressive sporadic neurologic dysfunction.

Vijay Chandran, MBBS  
 Pramod Kumar Pal, MD, DM\*  
 Aumir Moin, MD, DM  
 Department of Neurology, National Institute of Mental  
 Health and Neurosciences  
 Bangalore, Karnataka, India  
 \*E-mail: pal.pramod@rediffmail.com

Yasha T. Chickabasaviah, MD  
 Department of Neuropathology  
 National Institute of Mental Health and Neurosciences  
 Bangalore, Karnataka, India

Shivashankar Ravishankar, MD  
 Department of Neuroimaging and Interventional Radiology  
 National Institute of Mental Health and Neurosciences  
 Bangalore, Karnataka, India

Samhita Panda, MD, DM  
 Department of Neurology  
 National Institute of Mental Health and Neurosciences  
 Bangalore, Karnataka, India

## References

1. Veyssier-Belot C, Cacoub P, Caparros-Lefebvre D, et al. Erdheim-Chester disease. Clinical and radiologic characteristics of 59 cases. *Medicine* 1996;75:157-169.
2. Brodtkin CL, Wszolek ZK. Neurologic presentation of Erdheim-Chester disease. *Neurol Neurochir Pol* 2006;40:397-403.
3. Wright RA, Hermann RC, Parisi JE. Neurological manifestations of Erdheim-Chester disease. *J Neurol Neurosurg Psychiatry* 1999; 66:72-75.
4. Evidente VG, Adler CH, Giannini C, Conley CR, Parisi JE, Fletcher GP. Erdheim-Chester disease with extensive intraaxial brain stem lesions presenting as a progressive cerebellar syndrome. *Mov Disord* 1998;13:576-581.

5. Kujat C, Junk B, Hermes M, Martin J, Dewes W. Cerebral manifestations of Erdheim-Chester disease. *Radiologie* 1991;31:307–309.
6. Fukazawa T, Tsukishima E, Sasaki H, Hamada K, Hamada T, Tashiro K. Erdheim-Chester disease and slowly progressive cerebellar dysfunction. *J Neurol Neurosurg Psychiatry* 1995;58:238–240.
7. Weidauer S, Stuckrad-Barre S, Dettmann E, Zanella FE, Lanfermann H. Cerebral Erdheim-Chester disease: case report and review of the literature. *Neuroradiology* 2003;45:241–245.
8. Braith F, Boxrud C, Esmaeli B, Kurzrock R. Successful treatment of Erdheim-Chester disease, a non-Langerhans-cell histiocytosis, with interferon- $\alpha$ . *Blood* 2005;106:2992–2994.

### Development of Holmes' Tremor in a Patient with Parkinson's Disease Following Acute Cerebellar Infarction



Holmes' tremor (HT) is categorized as intention, rest, and sometimes postural tremor with a frequency below 4.5 Hz by the Consensus Statement of the Movement Disorder Society on tremors.<sup>1</sup> It is caused by various neurological diseases, such as stroke or tumors involving the brainstem.<sup>1</sup> Recent pathoanatomical study suggests that the combined damage of the cerebellothalamic and nigrostriatal system is required for the genesis of HT.<sup>2,3</sup> Here, we present a case with Parkinson's disease (PD) developing HT after acute cerebellar infarction.

An 81-year-old female was admitted for severe action tremor in left arm for 10 days. Three weeks prior to admission, transient dizziness and gait disturbance were developed. The patient had previous histories of hypertension, diabetes mellitus, and atrial fibrillation 5 years prior. The patient was diagnosed with PD for progressive left-side dominant rest tremor and bradykinesia in a local clinic 2 years ago, but had refused treatment. The family history was unremarkable.

The cognitive, cranial nerve, motor, or sensory functions were normal. There was left sway on the tandem gait. There was masked face. In a resting condition, there was rhythmic flexion and extension of the left hand (Fahn-Tolosa-Martin rating scale (FTM) score = 2). Tremulous activity at jaw was observed in a resting condition. The intensity of the tremor was accentuated in arm stretching condition (FTM score = 3) and was maximal in goal-directed movement (FTM score = 4). The action tremor was too severe to perform activities of daily living with left hand. Other PD features were left-side dominant bradykinesia, rigidity, and parkinsonian gait (UPDRS part III motor score = 38). A surface polomyographic study showed rhythmic bursts between the

arm flexor and extensor with a frequency of 4 to 4.3 Hz in a resting and arm stretching condition (Fig. 1A).

A brain diffusion-weighted image (DWI) study 3 days after admission disclosed acute multifocal infarctions in the left cerebellar hemisphere (Fig. 1B). There were mild ischemic changes on bilateral periventricular white matter. Medication with levodopa (Sinemet<sup>®</sup> (25/100), 300 mg, t.i.d.) and antiplatelet agent (Astrix<sup>®</sup>, 100 mg, daily) was initiated.

One month after discharge, the rest tremor in the left arm and jaw almost disappeared (FTM score = 0) and other PD symptoms were slightly improved (UPDRS part III = 27). However, postural or kinetic tremor did not change (FTM score = 3 and 4, respectively) despite the combined treatments with L-dopa (Sinemet<sup>®</sup> (25/250), 750 mg, t.i.d.), arotinolol HCl (Almarl<sup>®</sup>, 20 mg, b.i.d.), and clonazepam (Rivotril<sup>®</sup>, 1.5 mg, t.i.d.) over 6 months.

The tremor of our case fulfills the criteria for a HT: unilateral intention and rest tremor of the arm with a frequency below 4.5 Hz. Our case had a preexisting PD tremor, and postural and kinetic tremor developed abruptly after acute cerebellar infarction. One could assume that action tremor of our case is a part of essential tremor, found in less than 10% of patients with PD,<sup>4</sup> or parkinsonian tremor of postural type during the natural course of PD.<sup>1</sup> However, we think that the etiology of action tremor is of symptomatic origin because it developed abruptly and unilaterally after cerebellar infarction.

Although the pathological mechanism of HT is still unclear, there has been evidence to suggest that combined damage of the nigrostriatal and cerebellothalamic pathways is the possible mechanism of HT.<sup>2,3</sup> The most single responsible lesion is the midbrain where an anatomical proximity between the two pathways exists. However, there were several cases with HT caused by preexisting cerebellar deficits and subsequent nigrostriatal dysfunction.<sup>5–7</sup> These findings suggest that separate lesion of each pathway from different etiology or at different time also induces HT. Development of HT in our case is attributed to the combined effect of the preexisting nigrostriatal dysfunction and subsequent cerebellothalamic dysfunction.

Although the response of HT to medical treatment is highly variable, treatment with L-dopa has occasionally been reported to be effective.<sup>2,8,9</sup> Our case showed dramatic response to L-dopa in rest tremor but not in postural and kinetic tremor, suggesting that nigrostriatal dysfunction partly plays a role in HT. However, it has been found that patients with typical rest tremor do not usually respond to L-dopa,<sup>1</sup> whereas other patients with predominantly action tremor respond satisfactorily,<sup>2,5,6</sup> indicating that complex pathological mechanism may exist in HT.

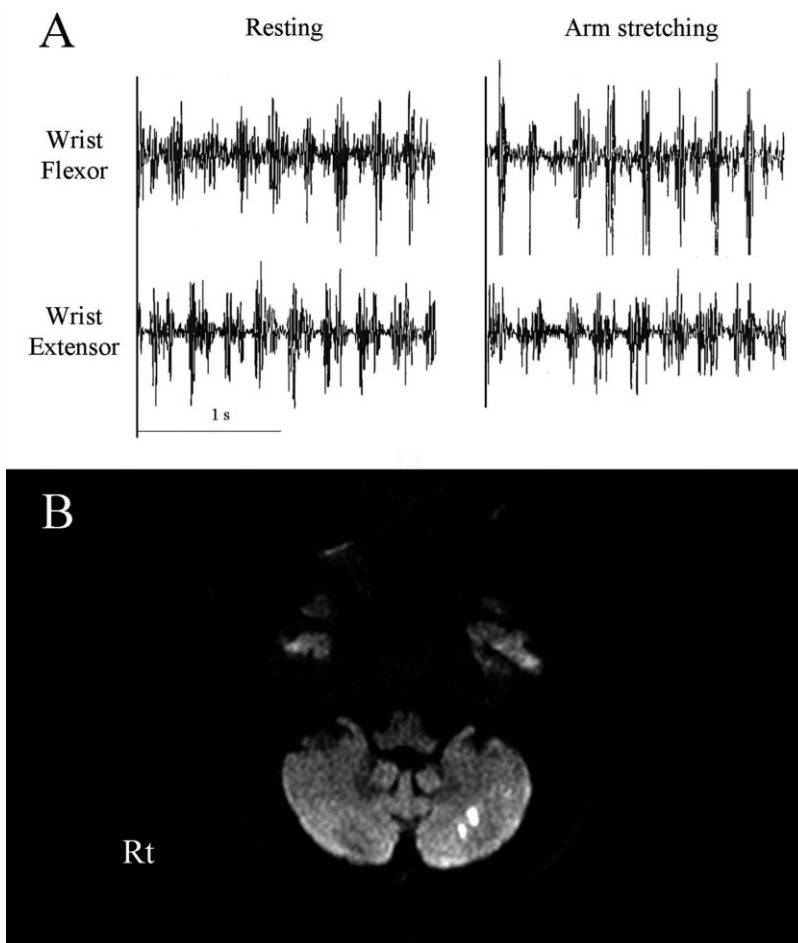
### LEGENDS TO THE VIDEO

**Segment 1.** (0–1 minute 31 seconds). There is a rhythmic flexion-extension movement in the left arm. The tremor worsens in arm stretching or the finger-to-nose test. A jaw tremor is also found in the resting condition.

**Segment 2.** (1 minute 31 seconds–2 minutes 59 seconds). Three months after medication (levodopa, beta blocker, and

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

Published online 11 December 2008 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22394



**FIG. 1.** (A) Surface polymyography in the left arm in a resting and postural condition. (B) Diffusion-weighted image of the brain MR study.

clonazepam), the rest tremor previously seen in the left arm and jaw is almost absent. However, the postural and kinetic tremor still persist.

Dong-Gun Kim, MD  
 Young-Ho Koo, MD  
 Ok-Joon Kim, MD  
 Seung-Hun Oh, MD\*  
*Department of Neurology*  
*Pochon CHA University College of Medicine*  
*Seongnam, Korea*  
 \*E-mail: ohsh72@chamc.ac.kr

### References

1. Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. *Mov Disord* 1998;13(Suppl 3):2–23.
2. Remy P, de Recondo A, Defer G, et al. Peduncular ‘rubral’ tremor and dopaminergic denervation: a PET study. *Neurology* 1995;45:472–477.
3. Paviour DC, Jager HR, Wilkinson L, Jahanshahi M, Lees AJ. Holmes tremor: application of modern neuroimaging techniques. *Mov Disord* 2006;21:2260–2262.
4. Louis ED, Frucht SJ. Prevalence of essential tremor in patients with Parkinson’s disease vs. Parkinson-plus syndromes. *Mov Disord* 2007;22:1402–1407.
5. Krack P, Deuschl G, Kaps M, Warnke P, Schneider S, Traupe H. Delayed onset of “rubral tremor” 23 years after brainstem trauma. *Mov Disord* 1994;9:240–242.
6. Deuschl G, Wilms H, Krack P, Wurker M, Heiss WD. Function of the cerebellum in parkinsonian rest tremor and Holmes’ tremor. *Ann Neurol* 1999;46:126–128.
7. Friedman JH. “Rubral” tremor induced by a neuroleptic drug. *Mov Disord* 1992;7:281–282.
8. Samie MR, Selhorst JB, Koller WC. Post-traumatic midbrain tremors. *Neurology* 1990;40:62–66.
9. Velez M, Cosentino C, Torres L. Levodopa-responsive rubral (Holmes’) tremor. *Mov Disord* 2002;17:741–742.

## Beneficial Effect of Deep Brain Stimulation of GPi in a Patient with Dystonia-Deafness Phenotype

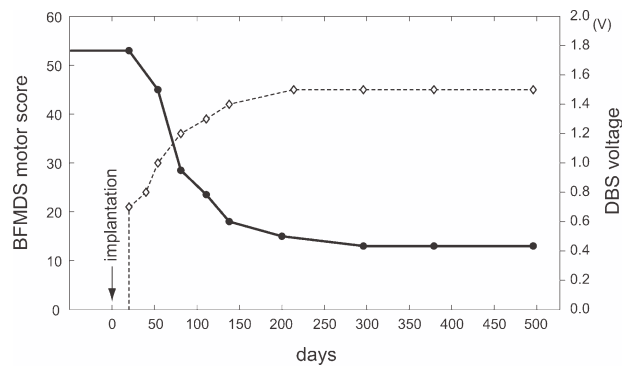
Video 

We present the first case of the successful treatment of dystonia-deafness syndrome by deep brain stimulation (DBS) of the globus pallidus interna (GPi).

The case concerns a 30-year-old male patient who had a negative family history of dystonia or hearing loss. At about 3 years of age, he was found to have a severe sensorineural hearing impairment, which remained stable until the age of 24. At that time, the patient noticed occasional involuntary twisting of his head toward left. The hearing impairment progressed to total deafness. Notably, there was no previous exposure to neuroleptics until 28 years of age, when he had a psychotic episode with paranoid delusions. The deafness and severe truncal and cervical dystonia accompanied by dysphagia and severe dysarthria further predominated in the clinical picture. Visual evoked potentials were significantly prolonged bilaterally. The ophthalmologic examination and magnetic resonance imaging of the brain were normal. Neuropsychological tests revealed no cognitive deficit.

By clinical examination and genetic testing, we ruled out the DYT1, PKAN, Wilson disease, spinocerebellar ataxias, as well as rare syndromes of deafness with generalized dystonia. A comorbidity of primary sporadic non-DYT1 dystonia compounded by deafness due to other causes appeared rather speculative. Finally, severe sensorineural hearing disorder from early childhood followed by generalized dystonia developing in early adulthood made us suspect the dystonia-deafness (Mohr-Tranebjaerg) syndrome.<sup>1</sup> Several additional symptoms such as history of behavioral disorder and subclinical involvement of the visual system supported this diagnosis. Even if genetic testing showed no evidence of mutation<sup>2-5</sup> (frameshift, deletion, stop, missense, splice-site, or intronic mutation) of the gene *TIMM8A/DDP1*, a novel mutation could not be excluded. Therefore, we still believe that the present case is the dystonia-deafness syndrome.

The patient received repeated local injections of botulinum toxin into dystonic neck muscles with only partial relief. Oral treatments by biperidene, tiapride, amantadine, and clonazepam were subsequently given with no or minor improvement. At the age of 29, his cervical and truncal dystonia further progressed with dystonic involvement spreading to his lower extremities. Extreme retrocollis soon led to compromised respiration forcing the patient to sleep in a semirecumbent position. After the failed use of all available pharmacological treatment, we resorted to GPi DBS as to the ultimate option. The patient then had the electrodes (Model 3389, Medtronic, Minneapolis, MN) implanted into the posteroventral portion of the GPi bilaterally. The coordinates of the distal (active) contacts were as follows: 19-mm lateral from the midline in



**FIG. 1.** Clinical improvement in a patient with the dystonia-deafness phenotype is documented by a gradual decrease of the BFMDS-motor score (closed circles) following bilateral GPi DBS. To find optimal parameters of neurostimulation, the voltage (open diamonds) was gradually increased to 1.5V with the pulse duration (450  $\mu$ s) and frequency (130Hz) being constant. As a result of the slow start of the clinical benefit, the optimum was reached 10 months after implantation.

the left and 21-mm lateral in the right hemisphere; 3.5-mm below the level of the intercommissural line in the left and 2.5-mm below this line in the right hemisphere; and 3-mm anterior to its middle on both sides. A Kinetra neurostimulator was implanted into the subclavicular region.

Like in other generalized dystonias, the antidystonic effect of GPi DBS began to show gradually over a course of several months (Fig. 1). Maximum improvement was expressed by a 75% decrease in the motor score of the Burke-Fahn-Marsden scale (BFMDS),<sup>6</sup> which was reached 10 months after surgery. This is comparable with the effects of GPi DBS commonly seen in patients with DYT1-positive primary dystonia.<sup>7</sup> There was marked abatement of cervical and truncal dystonia as well as improvement of gait (see video). Swallowing and speech showed only little improvement. The hearing loss remained unchanged as expected.

As our experience suggests, bilateral GPi DBS can be a suitable symptomatic therapy in patients with the dystonia-deafness phenotype. Now, 21 months after the implantation, the patient is experiencing the stable clinical effects of neurostimulation.

### LEGENDS TO THE VIDEO

**Segment 1.** Before the implantation of DBS electrodes: severe cervical and truncal dystonia, impairment of gait.

**Segment 2.** One month after the implantation, a day before the start of the chronic GPi DBS: same clinical picture as before surgery.

**Segment 3.** Three months after the implantation: cervical and truncal dystonia shows improvement.

**Segment 4.** Ten months after the implantation: minor cervical dystonia, gait markedly improved.

Petra Havránková, MD  
 Robert Jech, MD, PhD\*  
 Jan Roth, MD, PhD  
 Department of Neurology  
 1st Faculty of Medicine  
 Charles University  
 Prague, Czech Republic  
 \*Email: jech@cesnet.cz

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

Published online 2 December 2008 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22317

Dušan Urgošík, MD, PhD  
*Stereotactic and Radiation Neurosurgery  
 Na Homolce Hospital  
 Prague, Czech Republic*

Evžen Růžička, MD, DSc  
*Department of Neurology, 1st Faculty of Medicine  
 Charles University  
 Prague, Czech Republic*

**Acknowledgments:** Supported by grant from the Czech Ministry of Health (IGA MZCR 1A/8629-5) and by research program of the Czech Ministry of Education (MSM 0021620849).

### References

- Mohr J, Mageroy K. Sex-linked deafness of a possibly new type. *Acta Genetica et Statistica Medica* 1960;10:54–62.
- Jin H, May M, Tranebjaerg L, et al. A novel X-linked gene, DDP, shows mutations in families with deafness (DFN-1), dystonia, mental deficiency and blindness. *Nat Gen* 1996;14:177–180.
- Tranebjaerg L, Hamel BC, Gabreels FJ, Renier WO, Van Ghelue M. A de novo missense mutation in a critical domain of the X-linked DDP gene causes the typical deafness-dystonia-optic atrophy syndrome. *Eur J Hum Genet* 2000;8:464–467.
- Ezquerria M, Campdelacreu J, Munoz E, Tolosa E, Marti MJ. A novel intronic mutation in the DDP1 gene in a family with X-linked dystonia-deafness syndrome. *Arch Neurol* 2005;62:306–308.
- Kim HT, Edwards MJ, Tyson J, Quinn NP, Bitner-Glindzicz M, Bhatia KP. Blepharospasm and limb dystonia caused by Mohr-Tranebjaerg syndrome with a novel splice-site mutation in the deafness/dystonia peptide gene. *Mov Disord* 2007;22:1328–1331.
- Burke RE, Fahn S, Marsden CD, Bressman SB, Moskowitz C, Friedman J. Validity and reliability of a rating scale for the primary torsion dystonias. *Neurology* 1985;35:73–77.
- Coubes P, Cif L, El Fertit H, et al. Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: Long-term results. *J Neurosurg* 2004;101:189–194.

### Cervical Dystonia Presenting as a Phenocopy in an Irish SCA2 Family

Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant neurodegenerative disorder caused by an unstable CAG repeat in the *ataxin-2* gene on chromosome 12q.<sup>1</sup>

Ataxia is almost invariable and may be accompanied by pyramidal and extrapyramidal signs, peripheral neuropathy, and oculomotor abnormalities. Cervical dystonia has been described in SCA1,<sup>2</sup> 3,<sup>3</sup> and 6,<sup>4</sup> as well as in genetically undetermined cases.<sup>5</sup> Recently a number of reports have described the association of SCA2 with cervical dystonia.<sup>6,7</sup> In a series of 11 patients with SCA2 and cervical dystonia, seven had an isolated laterocollis and in one case dystonia preceded the onset of ataxia by 3 years.<sup>8</sup>

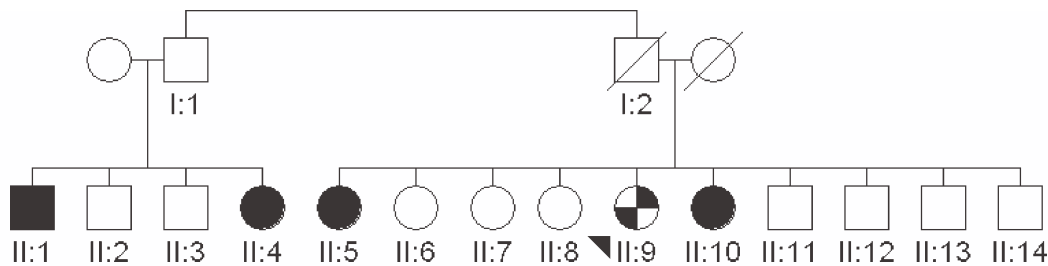
Normal SCA2 alleles contain between 14 and 31 CAG repeats; the 22 repeat normal allele accounts for up to 86.4% of alleles.<sup>9</sup> Clinical signs compatible with SCA2 have been described in a patient with 33 repeats.<sup>10</sup> We report on an Irish SCA2 pedigree in which four members have varying combinations of adult onset dystonia and ataxia; one sibling with cervical dystonia, originally presumed to have inherited a pathogenic SCA2 allele, was later found to represent a disease phenocopy.

A truncated pedigree drawing is provided in Figure 1. The proband (II:9) is a 74-year-old woman who reported the gradual onset of shoulder pain and neck stiffness at the age of 57. There was no history of preceding trauma or neuroleptic exposure. At presentation, she had a moderate to severe right laterocollis and a “no-no” head tremor that precluded MRI examination. No limb or laryngeal dystonia was identified. Gait and saccadic eye movements were normal and there was no sensory neuropathy or pyramidal signs. She has been treated with botulinum toxin every 3 months with a moderate response.

Both II:1 and II:4 are cousins of the proband currently living in the UK. They are both ataxic with onset after 30 years of age. The older of the pair, II:1, is now wheelchair bound. II:5 is a 78-year-old woman who developed cervical dystonia (laterocollis) of sudden onset at 40 years of age. At 69 years, she reported deterioration of her gait with the need to use a stick due to imbalance. In the last decade, she has developed a severely disabling spasmodic dysphonia (adductor type) and writer’s cramp of her right hand. Clinically evident slowing of saccadic eye movements was observed with a moderate truncal and limb ataxia. She has had a poor response to botulinum toxin treatment. II:10 is a 71-year-old woman who developed an insidious onset of gait imbalance in her fourth decade. She has required the assistance of a stick to walk since her late sixties. Since childhood she describes having “poor writing” and currently has evidence of a writer’s cramp on the right side as well as an adductor-type spasmodic dysphonia since the age of 68 years. She has a moderately severe truncal ataxia, limb ataxia, and slow saccadic eye movements on examination. Ankle jerks are absent and there is distal loss of vibration sensation in the lower limbs. No cervical dystonia is present. MRI brain showed moderately severe cerebellar atrophy.

II:1, II:5, and II:10 were found to have single pathological allelic expansions with 36, 34, and 35 CAG repeats respectively at the SCA2 locus on chromosome 12. Individual II:4 also had confirmed pathological SCA2 expansion although no further details are available to us. Gene sequencing on II:10 identified an uninterrupted expansion suggesting a greater possibility of instability of this region when transmitted between generations. Analysis of the SCA2 gene in the proband, II:9, surprisingly revealed normal alleles of 22 repeats. A further sample taken for reanalysis confirmed the result. It is therefore highly unlikely that she has inherited the SCA2 genotype.

Genetic testing for inherited neurological diseases has hugely improved our ability to provide patients with a diagnosis and genetic counselling. The ability to test for known mutations has also enabled the description of a more complete phenotypic spectrum in some conditions. The presence of phenocopies within pedigrees is a well-known hazard of linkage analysis and has the ability to confound genetic stud-



**FIG. 1.** A truncated representation of an Irish SCA2 pedigree. Filled in symbols represent family members with genetically confirmed SCA2. The proband (II:9) is identified by the black arrow.

ies as well as provide diagnostic confusion.<sup>11</sup> In these situations careful review of clinical features and appropriate use of genetic testing may be helpful.

Richard Walsh, MRCPI\*  
John P. O'Dwyer, MRCPI  
Sean O'Riordan, MD, MRCPI  
David Bradley, MRCPI  
Department of Neurology  
St. Vincent's University Hospital  
Dublin, Ireland  
\*E-mail: richardawalsh@gmail.com

Joan Moroney, MD, MRCPI  
Department of Neurology  
Beaumont Hospital  
Dublin, Ireland

Michael Hutchinson, FRCP, FRCPI  
Department of Neurology  
St. Vincent's University Hospital  
Dublin, Ireland

## References

1. Imbert G, Saudou F, Yvert G, et al. Cloning of the gene for spinocerebellar ataxia 2 reveals a locus with high sensitivity to expanded CAG/glutamine repeats. *Nat Genet* 1996;14:285–291.
2. Wu YR, Lee-Chen GJ, Lang AE, Chen CM, Lin HY, Chen ST. Dystonia as a presenting sign of spinocerebellar ataxia type 1. *Mov Disord* 2004;19:586–587.
3. Lang AE, Rogaeva EA, Tsuda T, Hutterer J, St. George-Hyslop P. Homozygous inheritance of the Machado-Joseph disease gene. *Ann Neurol* 1994;36:443–447.
4. Arpa J, Cuesta A, Cruz-Martinez A, Santiago S, Sarria J, Palau F. Clinical features and genetic analysis of a Spanish family with spinocerebellar ataxia 6. *Acta Neurol Scand* 1999;99:43–47.
5. Kuoppamaki M, Giunti P, Quinn N, Wood NW, Bhatia KP. Slowly progressive cerebellar ataxia and cervical dystonia: clinical presentation of a new form of spinocerebellar ataxia? *Mov Disord* 2003;18:200–206.
6. Dragasevic NT, Culjkovic B, Klein C, et al. Frequency analysis and clinical characterization of different types of spinocerebellar ataxia in Serbian patients. *Mov Disord* 2006;21:187–191.
7. Zarubova K, Ruzicka E. Cervical dystonia in spinocerebellar ataxia type 2. *Mov Disord* 2006;21:1295–1296.
8. Boesch SM, Muller J, Wenning GK, Poewe W. Cervical dystonia in spinocerebellar ataxia type 2: clinical and polymyo-

graphic findings. *J Neurol Neurosurg Psychiatry* 2007;78:520–522.

9. Cancel G, Durr A, Didierjean O, et al. Molecular and clinical correlations in spinocerebellar ataxia 2: a study of 32 families. *Hum Mol Genet* 1997;6:709–715.
10. Fernandez M, McClain ME, Martinez BS, et al. Late-onset sca2: 33 CAG repeats are sufficient to cause disease. *Neurology* 2000; 55:569–572.
11. Wilder C, Melquist S, Hauf M, et al. Study of a Swiss dopa-responsive dystonia family with a deletion in gch1: redefining DYT14 as DYT5. *Neurology* 2008;70:1377–1383.

## Thalamic Stimulation Restores Defective Cerebellocortical Inhibition in Multiple Sclerosis Tremor

Action tremor is a frequent complication of multiple sclerosis (MS)<sup>1</sup> that can be treated by deep brain stimulation (DBS) of the ventralis intermedius (VIM) thalamic nucleus, a structure receiving cerebellar projections.<sup>2</sup> However, the mechanism of action of VIM-DBS is still a matter of debate.

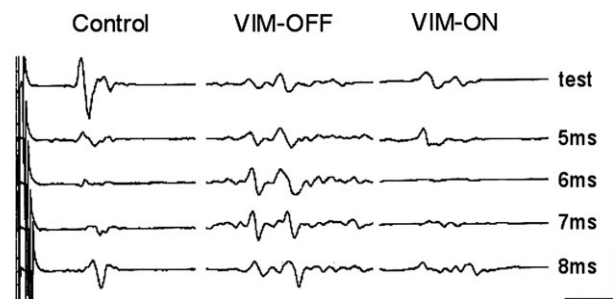
By activating the cerebellothalamic cortical (CTC) pathway,<sup>3</sup> transcranial magnetic stimulation (TMS) of the cerebellum reduces motor-evoked potential (MEP) amplitude (in response to M1 stimulation) by more than 40% (according to our normative data). Inhibition is reduced or absent when the dentate nucleus or the CTC pathway is lesioned.<sup>4</sup> In a series of 6 patients with essential tremor, VIM-DBS was found to partially restore the defective CTC-mediated inhibition.<sup>5</sup> The goal of this work was to determine whether VIM-DBS can produce the same effect in a case of MS tremor.

A 49-year-old man with secondary progressive MS was severely disabled by left upper limb tremor for more than 2 years. Tremor was mostly triggered by posture and further exacerbated by any attempted movement, interfering with daily-life activities. The right upper extremity was mildly affected. Brain magnetic resonance imaging (MRI) showed multiple T2-weighted hyperintense signal changes, including a lesion located at the junction between the pons and lower midbrain on the right side.

The patient underwent right VIM-DBS implantation<sup>6</sup> and his tremor remarkably improved. Tremor severity score on

Published online 18 December 2008 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22416





**FIG. 1.** Motor-evoked potentials (MEPs) recorded at the left hand in response to right motor cortex stimulation conditioned by preceding left cerebellar stimulation. From left to right are presented data from an illustrative control subject (43-year-old man) and from a patient with multiple sclerosis tremor treated by VIM thalamic nucleus stimulation in “OFF-” and “ON-stimulation” condition. Note that MEPs are frankly dispersed because of demyelination. From top to bottom are presented the averaged MEPs obtained to M1 stimulation performed alone (test) or conditioned by cerebellar stimulation at interstimuli intervals ranging from 5 to 8 milliseconds. Horizontal bar: 20 milliseconds. Vertical bar: 1 mV.

Fahn-Tolosa-Marin rating scale was reduced from 4/4 (severe tremor, amplitude > 4 cm) to 1/4 (slight, intermittent tremor) when VIM-DBS was turned from “OFF” to “ON” (voltage: 3 V, pulse width: 90 microseconds, frequency: 130 Hz, mode: bipolar, cyclic).

The patient gave informed consent for a TMS study of CTC pathways. Stimulation of the left cerebellum was performed with a double-cone coil centered 3–4 cm lateral to theinion. Stimulus intensity was set at 5–10% below the active motor threshold. Stimulation of the left hand representation in the right M1 was performed with a figure-of-eight coil oriented at 45° to the midsagittal line. Stimulus intensity was adjusted to elicit MEPs with peak-to-peak amplitude of 0.5–1 mV in the relaxed first dorsal interosseous (FDI) muscle. Interstimulus intervals between cerebellar and M1 stimulation ranged from 5 to 8 milliseconds. Eight trials of test pulse alone and four trials of paired pulses at each interval were performed and averaged. The amplitude of FDI-MEPs to M1 stimulation was compared between conditioned and unconditioned trials to assess the effect of CTC pathway activation resulting from cerebellar stimulation. The TMS study was performed in “ON-” then “OFF-stimulation” condition. In these conditions, VIM-DBS was switched “ON” or “OFF” for more than 30 minutes.

The results are illustrated in Figure 1. Statistical comparisons were not performed because there were too few values (single case). First, we found that VIM-DBS did not modify M1 excitability because test MEP amplitude (0.6 mV) and stimulus intensity (52%) were identical in “OFF-” and “ON-stimulation” conditions. In contrast, conditioned MEP amplitude varied with stimulation condition: MEP inhibition to cerebellar stimulation was absent in “OFF-stimulation” condition (conditioned MEP size ranged from 100 to 130% of test MEP size, mean  $\pm$  SD: 125.4  $\pm$  17.4) and was restored to normal when VIM-DBS was switched “ON” (conditioned MEP size ranged from 17 to 95% of test MEP size, mean  $\pm$  SD: 47.9  $\pm$  33.7). Because of tremor, the background muscular activity was greater in “OFF-” than “ON-stimulation”

condition. However, this was unlikely to contribute to the lack of inhibition in “OFF-stimulation” condition, because MEP amplitude was the same with the stimulator turned “OFF” or “ON.” Therefore, we hypothesized that the difference observed between stimulation conditions mostly reflected the restoration of CTC-mediated inhibition by VIM-DBS, as previously shown in patients with essential tremor.<sup>5</sup>

The clinical presentation of MS tremor suggests cerebellar dysfunction, but MS tremor amplitude was found to correlate with the lesion load in the contralateral pons rather than in the cerebellum.<sup>7</sup> In our patient, the lack of inhibition from cerebellar output to M1 at baseline favored the hypothesis of a lesion affecting the ascending efferent CTC pathways. The localization of MRI signal abnormality in the right brainstem further supported a lesion distal to CTC pathway decussation.

Thalamic stimulation restored motor inhibition from the CTC pathway, but we cannot ascertain that tremor suppression was the direct consequence of this restored inhibition. Nevertheless, this finding strengthens the hypothesis that VIM-DBS suppresses tremor by activating circuits and therefore may differ from ablative thalamotomy. Reactivation of the CTC pathways may be a common mechanism of action of VIM-DBS on tremor of various origins, including MS and essential tremor.

Samar S. Ayache, MD

*Department of Physiology*

*Hôpital Henri Mondor*

*Assistance Publique-Hôpitaux de Paris*

*Créteil, France*

*Department of Neurosurgery*

*Hôpital Henri Mondor*

*Assistance Publique-Hôpitaux de Paris*

*Créteil, France*

Rechdi Ahdab, MD

*Department of Physiology*

*Hôpital Henri Mondor*

*Assistance Publique-Hôpitaux de Paris*

*Créteil, France*

Danusa O. Neves, MD

*Department of Physiology*

*Hôpital Henri Mondor*

*Assistance Publique-Hôpitaux de Paris*

*Créteil, France*

*Department of Neurosurgery*

*Hôpital Henri Mondor*

*Assistance Publique-Hôpitaux de Paris*

*Créteil, France*

Jean-Paul Nguyen, MD

*Department of Neurosurgery*

*Hôpital Henri Mondor*

*Assistance Publique-Hôpitaux de Paris*

*Créteil, France*

Jean-Pascal Lefaucheur, MD, PhD\*

*Department of Physiology*

*Hôpital Henri Mondor*

*Assistance Publique-Hôpitaux de Paris*

*Créteil, France*

\*E-mail: jean-pascal.lefaucheur@hmn.aphp.fr

## References

1. Koch M, Mostert J, Heersema D, De Keyser J. Tremor in multiple sclerosis. *J Neurol* 2007;254:133–145.
2. Wishart HA, Roberts DW, Roth RM, et al. Chronic deep brain stimulation for the treatment of tremor in multiple sclerosis: review and case reports. *J Neurol Neurosurg Psychiatry* 2003;74:1392–1397.
3. Ugawa Y, Yoshikazu U, Terao Y, Hanajima R, Kanazawa I. Magnetic stimulation over the cerebellum. *Ann Neurol* 1995;37:703–713.
4. Ugawa Y, Terao Y, Hanajima R, et al. Magnetic stimulation over the cerebellum in patients with ataxia. *Electroencephalogr Clin Neurophysiol* 1997;104:453–456.
5. Molnar GF, Sailer A, Gunraj CA, Lang AE, Lozano AM, Chen R. Thalamic deep brain stimulation activates the cerebellothalamocortical pathway. *Neurology* 2004;63:907–909.
6. Geny C, Nguyen JP, Pollin B, et al. Improvement of severe postural cerebellar tremor in multiple sclerosis by chronic thalamic stimulation. *Mov Disord* 1996;11:489–494.
7. Feys P, Maes F, Nuttin B, et al. Relationship between multiple sclerosis intention tremor severity and lesion load in the brainstem. *Neuroreport* 2005;16:1379–1382.

## Psychogenic Nocturnal Stridor in a Child: A Case Report

Video 

Stridor is a harsh/strained, high-pitched respiratory noise that may be congenital or acquired, acute, intermittent or chronic, daily or nocturnal, and whose sound is usually distinguishable from snoring.

In pediatric age, stridor may be the main symptom of airway obstruction,<sup>1</sup> whereas its nocturnal recurrence in adulthood is often an early sign of a neurodegenerative disease.<sup>2,3</sup> Psychological factors may also cause stridor, in the absence of obvious anatomic or physiologic disorders, that is, psychogenic stridor.<sup>4</sup>

A 13-year-old boy was admitted with a 5-month history of nightly recurring heavy noisy breathing that had begun after an episode of common pharyngitis. In particular, a donkey-like respiratory noise appeared repetitively whenever he attempted to fall asleep, every night, disrupting sleep onset with consequent insomnia. After 5 to 10 noisy respiratory cycles, the patient would get out of bed coughing and complaining of headache, excessive salivation, and sometimes vomiting. Family history was unremarkable. Respiratory function tests performed through static and dynamic spirometry, chest-abdomen computed tomography, and laboratory investigations were all normal.

Daytime otolaryngologic examinations including fibroscopy of the upper airways with static and dynamic vocal cord evaluation and CT/MRI of brain and neck did not disclose any abnormality.

Laryngomalacia and laryngopharyngeal reflux were excluded. When asked to, the patient was able to reproduce the noise that the parents recognized as the same their son displayed at home during the night. On flexible video-nose-endoscopy, an abnormal and paradoxical adduction of the vocal cords during inspiration was observed while the patient, on demand, reproduced the respiratory noise. The latter was stridorous and inspiratory, with prompt resumption of normal vocal cord conditions and disappearance of the inspiratory stridor as soon as he was asked to stop.

Drug-induced sleep endoscopy<sup>5</sup> documented normal vocal cord motion while asleep.

A videopolysomnographic study (VPSG) was performed. While awake, EEG showed a posterior alpha rhythm at 9 to 10 c/s; the patient was eupnoic (18–20 breaths per minute) with O<sub>2</sub> saturation at 98%. Heart rate (HR) was 82 and regular. During wake preceding sleep onset, between 12:15 p.m. and 3:30 a.m., five episodes (3 with the patient on right side posture and 2 in prone posture) were recorded, stereotypic and characterized by a slowing down of respiratory rate (now 14–16 breaths per minute) accompanied by a sort of expiratory blow and culminating into 5 to 10 consecutive respiratory cycles with heavy inspiratory noisy stridor, until the patient abruptly got up anxious and reporting headache. During such episodes, the EEG showed diffuse fast activity, typical of wakefulness, accelerated HR, and unchanged oxygen saturation. Paradoxical thoraco-abdominal movements were not present (Fig. 1). After each episode, the patient resumed normal breathing and behavior in less than 1 minute (Video).

The patient was diagnosed with psychogenic stridor, and parents and patient were reassured about the benign nature of the respiratory noise and the lack of structural airway abnormality. The patient was then managed through psychotherapy and, upon follow-up, the nocturnal stridorous breathing vanished after a few weeks.

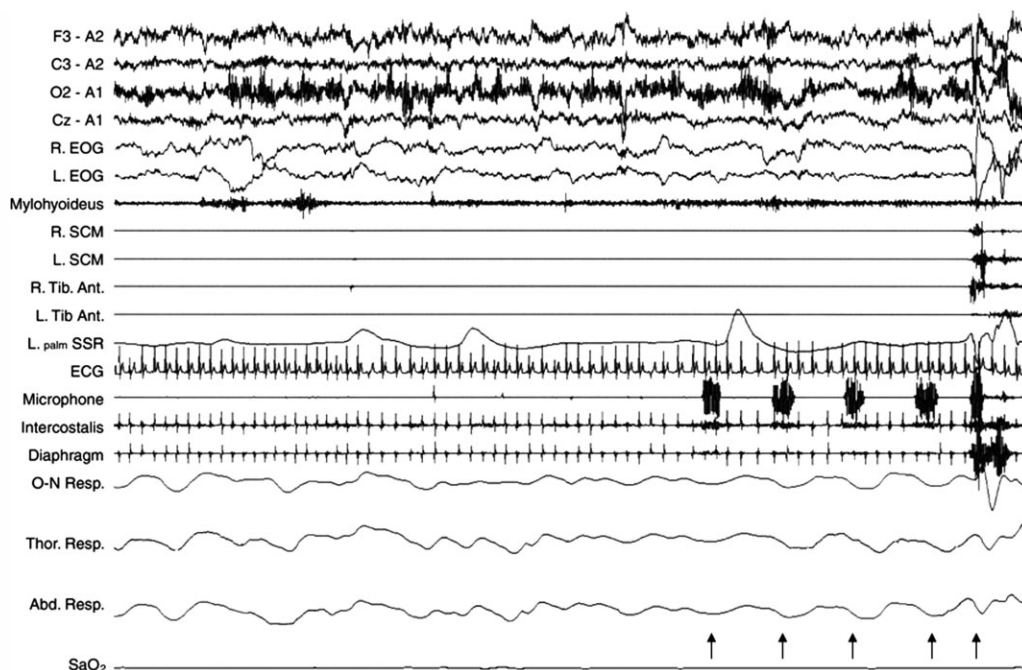
Stridor is often a worrisome symptom to patients and physicians alike. Our patient complained of nocturnal recurring respiratory noise arising during a behavioral condition resembling sleep but characterized by EEG wake activity. The breathing noise made by the patient was frightening to himself and his relatives and led to medical consults. Structural and functional abnormalities of the upper airways and lung were excluded by the normal clinical, radiological, spirometric, and fiberoptic findings, including drug-induced sleep endoscopy. Fibroscopy during attempts at voluntary reproducing the respiratory noise showed no obvious disorder, but rather a paradoxical adduction of the vocal folds during inspiration as indeed happens in psychogenic stridor.<sup>4</sup> Our report also highlights the importance of VPSG as a useful diagnostic tool in atypical forms of respiratory-related nocturnal noises, because it excluded possible sleep-related breathing disorders/noises such as snoring, catathrenia, nocturnal laryngospasm, and epileptic moaning.<sup>6,7</sup>

## LEGENDS TO THE VIDEO

**Segment 1.** To the left, audiovisual recordings of stridorous, nocturnal breathing in a 13-year-old boy. To the right, PSG recordings document EEG (F3-A2, C3-A2, O2-A1, Cz-A1) alpha activity. Five stridor episodes (Mic, microphone) are followed by behavioral arousal with coughing. R, right; L, left; EOG, electroculogram; Mylo, mylohyoidus; SCM,

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

Published online 31 December 2008 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22422



**FIG. 1.** PSG recordings of psychogenic stridor. The polysomnographic trace reveals that the respiratory noise (arrows) appears while wake-related fast rhythms on EEG channels and an accelerated HR on ECG are present; neither oxygen desaturation nor paradoxical thoraco-abdominal movements are evident during the “stridorous phase.” EEG (F3-A2, C3-A2, O2-A1, Cz-A1); R, right; L, left; EOG, electrooculogram; Mylohyoideus; SCM, sternocleidomastoideus; Tib. Ant., tibialis anterior; L<sub>palm</sub> SSR, left palm spontaneous sympathetic skin response; ECG, electrocardiogram; Microphone; Intercostalis; Diaphragm; O-N Resp., oro-nasal respirogram; Thor. Resp., thoracic respirogram; Abd. Resp.: abdominal respirogram; SaO<sub>2</sub>: oxygen saturation (%).

sternocleidomastoideus; Tib Ant, tibialis anterior; L<sub>palm</sub> SSR, left palm spontaneous sympathetic skin response; ECG, electrocardiogram; Mic, microphone; Interc, intercostalis; Diaph, diaphragm; O-N Resp., oro-nasal respirogram; Abd. Resp., abdominal respirogram; SaO<sub>2</sub>, oxygen saturation (%).

**Segment 2.** Another episode of inspiratory stridorous breaths, again followed by behavioral arousal. PSG legend as per segment 1; Thor Resp, thoracic respirogram.

**Acknowledgments:** Ms. A. Laffi provided help with manuscript’s editing. We also thank Mr. M. Armaroli and Ms. E. Zoni for the video editing.

**Author Roles:** Roberto Vetrugno, MD, PhD: *Research Project:* Conception, organization and execution; *Manuscript:* Writing of the first draft, review and critique.

Christian Franceschini, PsyD: *Research Project:* Conception, organization and execution; *Manuscript:* Writing of the first draft, review and critique.

Roberto D’Angelo, MD: *Research Project:* Conception, organization and execution; *Manuscript:* Writing of the first draft, review and critique.

Elena Antelmi, MD: *Research Project:* organization; *Manuscript:* critique.

Keivan Kaveh Moghadam, MD: *Research Project:* organization; *Manuscript:* critique.

Pasquale Montagna, MD: *Research Project:* Conception, organization; *Manuscript:* review and critique.

Claudio Vicini, MD: *Research Project:* execution; *Manuscript:* review and critique.

Giuseppe Plazzi, MD: *Research Project:* Conception, organization and execution; *Manuscript:* Writing of the first draft, review and critique.

Roberto Vetrugno, MD  
 Christian Franceschini, PsyD  
 Roberto D’Angelo, MD  
 Elena Antelmi, MD  
 Keivan Kaveh Moghadam, MD  
 Pasquale Montagna, MD  
 Claudio Vicini, MD  
 Giuseppe Plazzi, MD\*  
*Department of Neurological Sciences*  
*University of Bologna*  
*Bologna, Italy*  
 \*E-mail: giuseppe.plazzi@unibo.it

## References

- Holinger LD. Etiology of stridor in the neonate, infant and child. *Ann Otol Rhinol Laryngol* 1980;89:397–400.
- Plazzi G, Corsini R, Provini F, et al. REM sleep behavior disorders in multiple system atrophy. *Neurology* 1997;48:1094–1097.
- Vetrugno R, Liguori R, Cortelli P, et al. Sleep-related stridor due to dystonic vocal cord motion and neurogenic tachypnea/tachycardia in multiple system atrophy. *Mov Disord* 2007;22:673–678.
- Wareing MJ, Mitchell D. Psychogenic stridor: diagnosis and management. *J Accid Emerg Med* 1997;14:330–332.

5. Hessel NS, de Vries N. Dostic work-up of socially unacceptable snoring. II Sleep endoscopy. *Eur Arch Otorhinolaryngol* 2002;259:158–161.
6. Vetrugno R, Lugaresi E, Plazzi G, Provini F, D'Angelo R, Montagna P. Catathrenia (nocturnal groaning): an abnormal respiratory pattern during sleep. *Eur J Neurol* 2007;14:1236–1243.
7. Fusco L, Specchio N. Non-epileptic paroxysmal manifestations during sleep in infancy and childhood. *Neurol Sci* 2005;26:s205–s209.

### Increased Medial Temporal Blood Flow in Parkinson's Disease with Pathological Hypersexuality

Parkinson's disease (PD) is characterized by motor and nonmotor features, including cognitive, neuropsychiatric, and autonomic disturbances. PD can also be accompanied by various pathological behaviors such as pathological hypersexuality (PHS), excessive gambling or shopping. These impulse control behaviors have devastating psychosocial consequences. Recently, PHS has been associated with antiparkinsonian medication. However, the brain region responsible for PHS remains unknown, in part because of few neuroimaging studies. We describe a PD patient with PHS who showed activation in the medial temporal regions on technetium-99m-ethyl cysteinate dimer (Tc-ECD) SPECT.

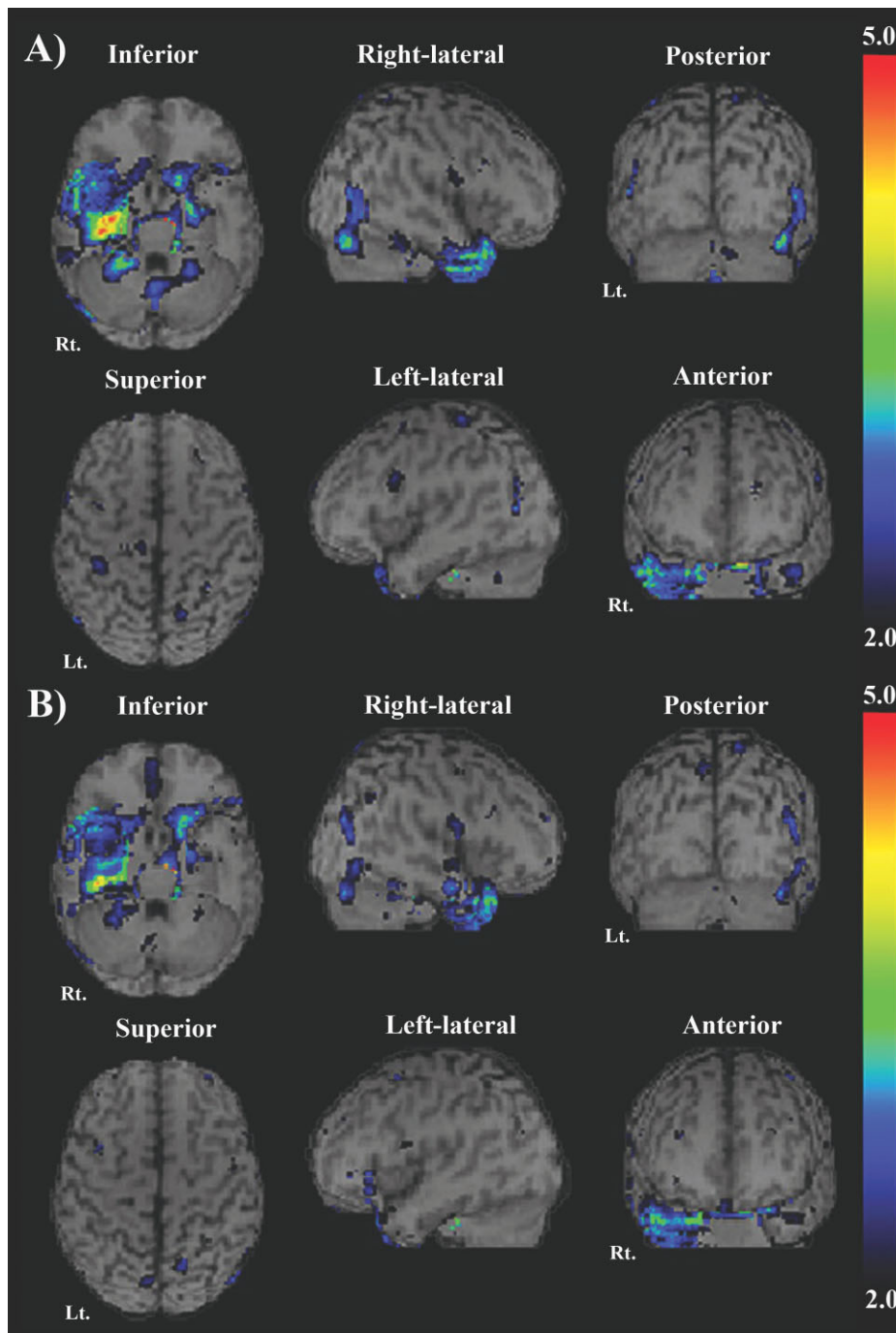
In October 2001, a 74-year-old right-handed man noticed gait difficulty and hand tremor. He received levodopa, and symptoms improved moderately. However, slowness of movements, rigidity, and tremor worsened, and he was given other antiparkinsonian medications, including pergolide and trihexyphenidyl. In March 2006, he presented at our hospital. The patient was given L-dopa (300 mg/day), pergolide (1500 µg/day), selegiline (5 mg/day), trihexyphenidyl (2 mg/day), and droxydopa (200 mg/day). He showed features of moderate Parkinsonism, including masked face, stooped posture, retropulsion, bradykinesia, left-side-dominant rigidity, and resting tremor. Because slowness of movement and gait difficulty progressively worsened, the doses of L-dopa (400 mg/day) and pergolide (1,750 µg/day) were increased. Symptom severity decreased, but obsessive behavior developed in February 2008. Every night he demanded sex several times and touched his wife's genitals many times per night, even though he could not achieve an erection. He was uninterested in other women. He also changed clothes many times per day. The patient had a serious personality, with no history of hypersexuality. In March, his sexual urges increased despite treatment with quetiapine (25 mg/day). In April, he desired sex constantly, not only at night but also during the daytime. The results of EEG and cranial MRI examinations were normal. The easy Z-score imaging system (eZIS) images on initial Tc-ECD SPECT showed increased regional cerebral blood flow (rCBF) in the right medial temporal regions (Fig. 1A). There was decreased rCBF in the

occipital lobes (data not shown). At the time of SPECT imaging, the patient was receiving L-dopa (400 mg/day), pergolide (1,750 µg/day), selegiline (5 mg/day), trihexyphenidyl (2 mg/day), droxydopa (200 mg/day), and quetiapine (25 mg/day). The scores of neuropsychological assessments were 1 (out of a possible 54) on the Hamilton Depression Scale, 3 (out of 56) on the Hamilton Anxiety Scale, and (3 out of 60) on the Young Mania Rating Scale. The score on the Mini-Mental Status Examination was normal (26/30). The scores on parts I, II, III, and IV of the Unified Parkinson's Disease Rating Scale were 0, 7, 14, and 1, respectively. The dose of only pergolide was decreased (1,250 µg/day), and the obsessive touching of his wife's genitals and excessive punding-like behavior resolved, but he still demanded sex many times per day. In May, the dose of pergolide was decreased to 500 µg/day. The doses of the other medications remained unchanged. His desire to have sex resolved during the daytime, but persisted at night. At the time, a second series of eZIS images on SPECT revealed that the increased rCBF in the right medial temporal regions had diminished (Fig. 1B).

PHS in our patient was ascribed to pergolide since such behavior decreased after lowering the dose. Impulse control behavior involves increased dopaminergic stimulation of non-motor basal ganglia loops, including the nucleus accumbens, mesolimbic and mesocortical circuits, and the anterior cingulate loop.<sup>1</sup> Dopamine agonists can influence nonmotor basal ganglia loops.<sup>2</sup> Dopamine D3 receptor is involved in reward, craving, emotional, and cognitive processes and related to impulse control behavior.<sup>3</sup> Pergolide has a high affinity for D3 receptor. The relation of drug usage to PHS remains uncertain, but the association of pathological gambling in PD with the use of dopamine D3-selective agonists<sup>4</sup> and our observations suggest a link between PHS and treatment with this type of drug.

The region responsible for PHS remains unclear because of difficulty in evaluating the underlying causes by techniques such as functional MRI. Some neuroimaging studies of impulse control behavior showed reduced activity in the mesial frontal areas in medicated PD patients performing the Iowa Gambling task.<sup>5</sup> Functional MRI showed a negative correlation of gambling severity with activation of the ventromedial prefrontal cortex and ventral striatum in individuals with pathological gambling without PD.<sup>6</sup> The increased medial temporal blood flow in our patient may provide initial evidence of primary regions associated with PHS. The mesolimbic system, an integral part of nonmotor basal ganglia loops, regulates responses to natural rewards such as sex.<sup>7</sup> The dopamine D3 receptors, temporally associated with PHS in our patient, are primarily localized to brain limbic regions.<sup>3</sup> Although the effects of other antiparkinsonian medications being received at the time of scanning cannot be ruled out, our observations suggest that excessive stimulation of D3 receptors in medial temporal regions may contribute to PHS in PD.

Hiroshi Kataoka, MD, PhD\*  
 Department of Neurology  
 Nara Medical University, Kashihara  
 Nara, Japan  
 \*E-mail: hk55@naramed-u.ac.jp



**FIG. 1.** SPECT study performed with technetium-99m-ethyl cysteinate dimer. The images were analyzed with an easy Z-score (eZIS) imaging system. The first eZIS images on SPECT showed increased rCBF in the right medial temporal lobe (A). The second eZIS images on SPECT revealed that the increased rCBF in the right medial temporal regions had diminished (B).

Takayuki Shinkai, MD, PhD  
 Department of Radiation Oncology  
 Nara Medical University,  
 Kashihara,  
 Nara, Japan

Makoto Inoue, MD, PhD  
 Department of Psychiatry  
 Nara Medical University,  
 Kashihara  
 Nara, Japan

Ueno Satoshi, MD, PhD  
 Department of Neurology  
 Nara Medical University, Kashihara  
 Nara, Japan

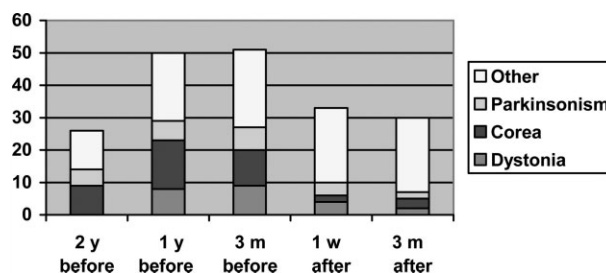
### References

- Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Prog Brain Res* 1990;85: 119–146.
- Shapiro MA, Chang YL, Munson SK, Okun MS, Fernandez HH. Hypersexuality and paraphilia induced by selegiline in Parkinson's disease: report of 2 cases. *Parkinsonism Relat Disord* 2006;12: 392–395.
- Dodd ML, Klos KJ, Bower JH, Geda YE, Josephs KA, Ahlskog JE. Pathological gambling caused by drugs used to treat Parkinson's disease. *Arch Neurol* 2005;62:1377–1381.
- Klos KJ, Bower JH, Josephs KA, Matsumoto JY, Ahlskog JE. Pathological hypersexuality predominantly linked to adjuvant dopamine agonist therapy in Parkinson's disease and multiple system atrophy. *Parkinsonism Relat Disord* 2005;11:381–386.
- Thiel A, Hilker R, Kessler J, Habedank B, Herholz K, Heiss WD. Activation of basal ganglia loops in idiopathic Parkinson's disease: a PET study. *J Neural Transm* 2003;110:1289–1301.
- Reuter J, Raedler T, Rose M, Hand I, Gläscher J, Büchel C. Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nat Neurosci* 2005;8:147–148.
- Evans AH, Lees AJ. Dopamine dysregulation syndrome in Parkinson's disease. *Curr Opin Neurol* 2004;17:393–398.

## The Impact of an Intense Religious Experience on Motor Symptoms in Huntington's Disease

The effects of placebo and psychological factors on movement disorders are intriguing. Voluntary suppression of tics is a common finding in Gilles de la Tourette syndrome.<sup>1</sup> In Parkinson's disease the placebo effect plays a very important role in the response to medical and surgical treatments and it is known to be associated with substantial release of endogenous dopamine in the striatum.<sup>2</sup> Very little is known about the impact of psychological factors on clinical scores in Huntington's disease (HD). We now report the impact on motor disorders of an intense religious experience in a patient with HD.

The patient is a 36-year old lady with a predominant motor syndrome, mostly characterized by chorea and dystonia, and little cognitive or psychiatric impairment. There is family history of HD in several siblings and other relatives, and the diagnosis has been confirmed by molecular analysis of the CAG repeats in the huntingtin gene (long allele: 55 CAG repeats; short allele: 19 CAG repeats). We have followed this patient for the last 3 years and we have recorded her clinical deficits according to the Unified Huntington's Disease Rating Scale (UHDRS) since 2006, (Fig. 1).



**FIG. 1.** Evolution on chorea, dystonia, Parkinsonism (rigidity, bradykinesia, and tapping) subscores and rest of items of the UHDRS, from 2 years before up to 3 months after an intense religious experience, showing marked improvement, mostly of chorea and dystonia. (y, years; m, months; w, weeks).

In May 2008, the patient visited the pilgrimage shrine of Lourdes, in the French Pyrenees, a site with a long standing fame of miraculous cures for patients with untreatable disorders. According to the patient, during the visit, the Virgin Mary spoke to her and told her she was cured of HD. During the next few days she felt she was able to move much better, much faster, and with better coordination. Therefore, she requested a nonscheduled appointment in our HD clinic which took place in the middle of June, 1 week after her visit to Lourdes.

The patient continued to take the same medications and doses as in previous visits, (bromocriptine 5 mg twice daily and sertraline 20 mg once daily). She was euphoric about her "miraculous cure" and requested that the molecular analysis of the number of CAG repeats in the huntingtin gene would be repeated, as she expected that it should now be normal. Her neurological examination failed to detect any cure of her disease but there was a very important reduction of chorea and dystonia scores with respect to previous exams. The application of the UHDRS was performed independently by two examiners (J.L.S. and J.G.Y.) with good interindividual agreement. The rest of the items included in the UHDRS did not improve with respect to previous exams (Fig. 1). In summary, the UHDRS motor scores of our patient improved 40%, from a score of 51 in the last visit, 3 months before her trip to Lourdes, to a 31 score 1 week after and a 33 score 3 months after the visit. The improvement was limited to the subscores of chorea and dystonia without significant changes in other items.

UHDRS-motor scale is a compound, unbalanced scale, which scores several motor abnormalities often present in patients with HD.<sup>3</sup> The maximal total score is 124 points. Maximal scores for chorea and dystonia are 28 and 20, respectively. Other items include ocular movement (maximal score: 24 points), dysarthria (maximal score: 4), tongue protrusion (maximal score: 4), bradykinesia and rigidity (maximal score: 12), finger tapping, hand pronosupination and Luria's test (maximal score: 20), gait, tandem, walking, and pull test (maximal score: 12). Our findings, an almost complete disappearance of chorea and dystonia despite negligible effects on other clinical motor deficits, suggest that both chorea and dystonia are greatly susceptible to placebo effect.

Dystonia is known to be reduced by sensorial stimulation (the “geste antagoniste” effect) and increased by action and anxiety.<sup>4,5</sup> Chorea increases with anxiety.<sup>5</sup> Our report suggest that the placebo effect has a strong effect on these symptoms and should be particularly considered in studies, which investigate the course of the disease and modifying factors in HD.

Jose Luis López-Sendón Moreno, MD\*  
Justo García de Yébenes, MD, PhD  
*Department of Neurology*  
*Hospital Ramon y Cajal*  
*Madrid, Spain*  
\*E-mail: [joselopezendon@hotmail.com](mailto:joselopezendon@hotmail.com)

### References

1. Jankovic J. Tourette syndrome: phenomenology and classification of tics. *Neurol Clin Neurophysiol* 1997;15:267–275.
2. de la Fuente-Fernandez R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ. Expectation and dopamine release: mechanism of the placebo effect in Parkinson’s disease. *Science* 2001;293:1164–1166.
3. Hogarth P, Kayson E, Kieburz K, et al. Interrater agreement in the assessment of motor manifestations of Huntington’s disease. *Mov Disord* 2005;20:293–297.
4. Lesser RP, Fahn S. Dystonia: a disorder often misdiagnosed as a conversion reaction. *Am J Psychiatry* 1978;135:349–352.
5. Jankovic J, Tolosa E, editors. *Parkinson’s disease and movement disorders*, 5th ed. Baltimore: Lippincott Williams and Wilkins; 2007.