Parkinsonism and Dystonia Associated with Adalimumab

We present two cases of parkinsonism secondary to adalimumab, a tumor necrosis factor α (TNF-α) inhibitor.

Case 1: A 30-year-old woman with rheumatoid arthritis (RA) was started on adalimumab 40 mg monthly, which was increased to 40 mg weekly after 7 months. Within days, she developed gait disturbance, bradykinesia, and cognitive slowing.

Brain magnetic resonance imaging (MRI) revealed increased signal in the globus pallidus, putamen, and internal capsule, extending into the subthalamic region (Fig. 1A) with faint putamenal enhancement (Fig. 1B), suggestive of toxic, metabolic or inflammatory causes. Cerebral angiogram showed no evidence of vasculitis. Cerebrospinal fluid examination was normal. The patient continued to deteriorate, and developed urinary incontinence, freezing of gait and falls. High-dose methylprednisone resulted in no improvement.

Examination revealed prominent parkinsonian features, including bilateral rigidity and bradykinesia (Video Segment 1). She scored 50 on the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS).

Adalimumab was discontinued and carbidopa/levodopa was started. She improved and was able to walk independently without freezing after 4 months. Her UPDRS motor score improved to 28 (Video Segment 2). L-dopa was ceased due to nausea, with no worsening of parkinsonism. A repeat brain MRI performed 8 months after the initial scan revealed significant resolution of the high signal changes (Fig. 1C,D). Her symptoms resolved over the next 3 years.

Case 2: A 31-year-old woman with ankylosing spondylitis was referred for evaluation of arm and leg stiffness causing difficulties with hand dexterity and walking, which developed after treatment with adalimumab 40 mg every 2 weeks for 11 months. She experienced recurrent episodes of right-sided painful toe curling. Examination revealed predominantly right-sided cogwheel rigidity and bradykinesia. MRI of the brain was normal. Ceruloplasmin and copper levels were normal. Carbidopa/L-dopa was started. Although her symptoms have improved, reduction in medication resulted in worsening of bradykinesia and rigidity, and she has remained on L-dopa/carbidopa 50/200 mg three times per day.

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

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Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Published online 14 April 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23548

Although the use of inhibitors against TNF-α has advanced the treatment of several inflammatory conditions, troublesome adverse effects associated with these drugs have emerged. We describe two women who developed parkinsonism following adalimumab use. The first case was associated with abnormal radiological findings. The second case was associated with dystonia. There was no significant family history. The cause-and-effect relationship between adalimumab and parkinsonism was supported by the onset after the introduction or increased dosages of the drug in both cases, improvement when the drug was discontinued (Case 1), and the unusual MRI findings (Case 1; Fig. 1A,B).

These two cases represent the first reports of adalimumab-induced movement disorders. We acknowledge that young-onset Parkinson's disease (PD) cannot be definitively excluded in the second case. Chorea in a patient with juvenile RA treated with infliximab for several months followed by adalimumab was previously described.[1] This patient however, apparently had Sydenham's disease, with clinical and serological evidence of streptococcal pharyngitis, which could have caused the observed chorea. Another report describes the development of parkinsonian features 1 week after the introduction of infliximab with rapid deterioration 12 months into the therapy, raising the possibility of infliximab-induced parkinsonism.[2] (Table 1).

TNF-α, regarded as a major regulator of physiological processes within the central nervous system, appears to exert modulating activity on dopaminergic neurons.[3] Elevated levels of TNF-α were seen in postmortem brains of patients with PD and in animal models of PD.[4] Increased density of A_{2A} adenosine receptors were found in the putamen of patients with PD that significantly correlated with UPDRS scores and plasma TNF-α levels .[5] Animal studies indicate that TNF-α causes dopaminergic loss by activating apoptotic transduction pathways.[6] This selective loss may be related to their particular vulnerability to oxidative stress, as dopaminergic neurons produce abundant quantities of reactive oxygen species. These findings suggest that antagonism of TNF-α should improve PD. However, similar to the observed worsening of multiple sclerosis seen with TNF-α antagonists,[7] the mechanisms are likely to be more complex. TNF-α plays both pathogenic and protective roles in the immune response against self-proteins.[7] Whether altered TNF-α signaling is pathogenic in PD, or secondary to disease-related mechanisms is unclear. Further studies into the underlying pathophysiology, pharmacology, and radiological changes are needed to better understand the mechanisms of this newly described movement disorder induced by inhibitors of TNF-α.

Legends to the Video

Segment 1. Case 1. The patient currently on adalimumab manifests marked parkinsonian features including

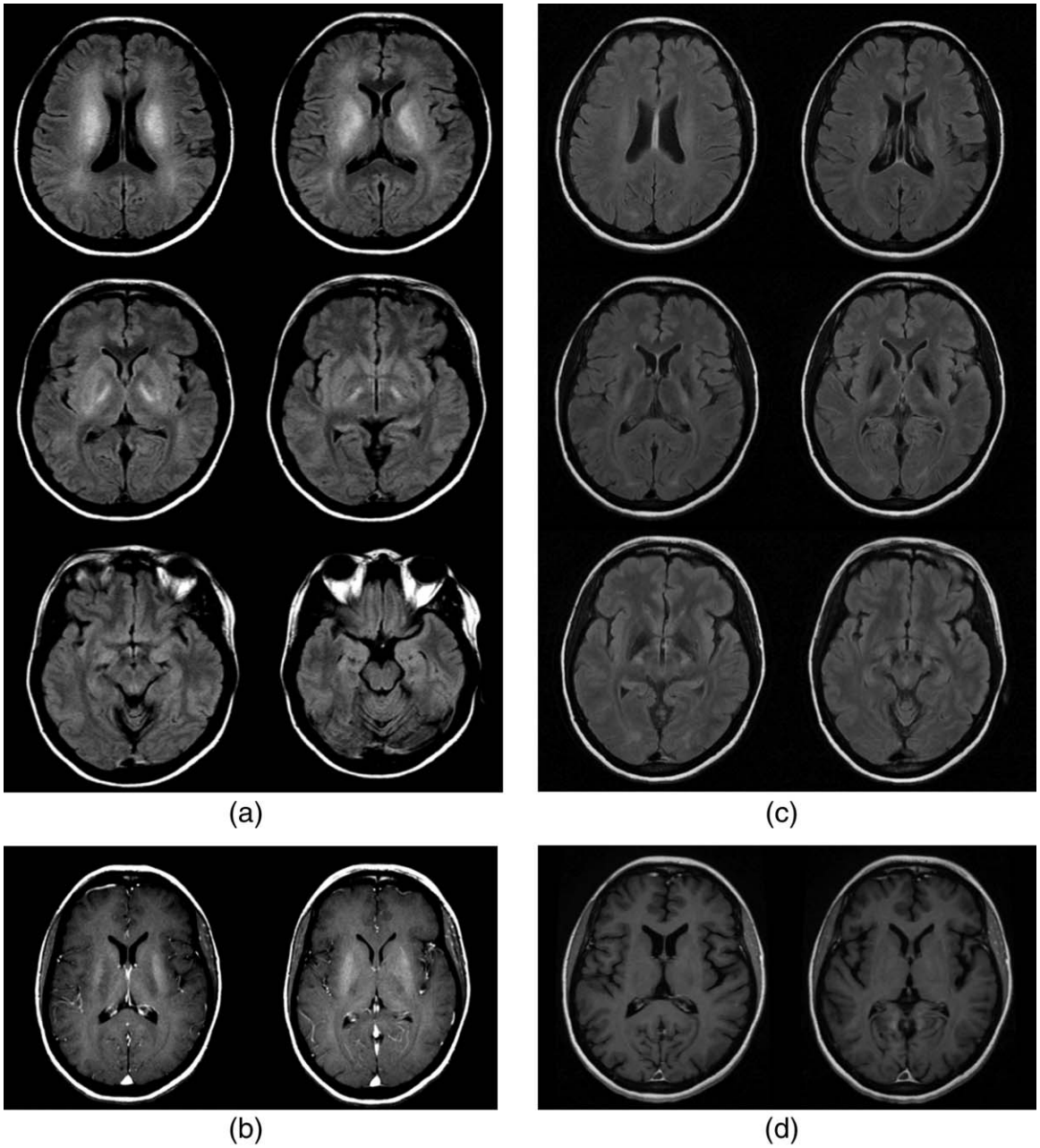

FIG. 1A. (Case 1): Axial flair MRI: Increased signal changes in the globus pallidus, putamen and internal capsule, extending into the subthalamic region. B (Case 1): Axial MRI post-contrast: Bilateral putamenal enhancement. C (Case 1): Repeat axial flair brain MRI (8 months after initial scan) showing improvement in high signal changes. D (Case 1): Repeat axial brain MRI postcontrast (8 months after initial scan) showing resolution of putamenal enhancement.

hypomimia, bradykinesia, difficulty arising from chair, slow and shuffling gait with freezing when turning, and retropulsion.

Segment 2. Case 1. The patient is off adalimumab for 8 months and parkinsonian features are now markedly improved.

Table 1. Movement disorders in patients treated with TNF-α inhibitors

Source	Age (yr)	Underlying condition	TNF-α antagonist	Clinical features
Case 1 (present)	30	Rheumatoid arthritis	Adalimumab (previous infliximab use)	Parkinsonism
Case 2 (present)	31	Ankylosing spondylitis	Adalimumab	Parkinsonism and dystonia
Case 3 (2)	10	Idiopathic juvenile arthritis	Infliximab and Adalimumab	Chorea, intercurrent streptococcal pharyngitis
Case 4 (3)	72	Rheumatoid arthritis	Infliximab	Parkinson's disease (rapidly progressive over 1 yr)

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Deletion in the Tyrosine Hydroxylase Gene in a Patient with a Mild Phenotype

Tyrosine hydroxylase (TH) deficiency causes severe to mild forms of dopa-responsive dystonia.[1] Quantification of biogenic amines and pterins in cerebrospinal fluid (CSF) shows selectively decreased homovanillic acid (HVA) values. Several disease-causing mutations have been reported in the *TH* gene: missense mutations, single-nucleotide deletions, and splice-site mutations.[2,3] We report the first case of dopa-responsive dystonia caused by a deletion in the *TH* gene that encompasses several exons.

A 19-month-old female was referred because of motor delay of unknown etiology. She reached cephalic control at 7 months of age, sat with stability at 9 months, and began crawling at 18 months. No clonic movements, tremor, dystonic posturing of the limbs, facial hypomimia, ptosis, hypersalivation, or diurnal fluctuation were evident in the very early personal history or during follow-up. She always showed good contact, being able to understand and follow simple commands. Physical examination at 20 months of age showed occasional brief periods of eye supraversion. Mild spasticity was perceived; while walking with help, there was a tendency toward toe walking. Cranial MRI, metabolic screening for inborn errors of metabolism, and video-EEG were normal. At 3 years of age, considering that all the etiological studies yielded normal results and that the patient presented with episodes of eye supraversion and mild signs of spasticity, a lumbar puncture was performed to analyze biogenic amines. CSF samples were analyzed as previously reported.[4] Moderate decreases in HVA concentration (151 nmo/L; reference value [RV], 304–658) and in HVA/5-HIAA ratio (1.1; RV, 1.5–3.5) were observed. The other biogenic amines and pterins analyzed disclosed normal results: 3-methoxy-4-hydroxyphenylglycol—20 nmol/L; RV 13–68; 3-orthomethyldopa—8 nmol/L, RV 3–64; 5-hydroxyindoleacetic acid—142 nmol/L, RV 106–316; neopterin—12 nmol/L, RV 9–55; and biopterin—30 nmol/L, RV 10–52.[4]

The patient was started on L-dopa/carbidopa therapy, showing good clinical response. At 5 years of age, the patient is undergoing standard schooling, and physical exploration is normal (see videos with and without treatment). She presents good response to treatment at low doses of L-dopa and long intervals between doses (1.5 mg/kg/12 hours).

Mutational screening of the *TH* gene performed by PCR amplification[5] revealed only a previously reported heterozygous mutation in the promoter region (c.1-70G>A).[6] The analysis of SNPs within the *TH* gene showed heterozygosity at variants located before intron 3 and homozygosity at the subsequent polymorphic sites. The data were compatible with a deletion. Then structural variant analysis of the *TH* gene was performed using the multiplex ligation-dependent probe amplification (MLPA) method (SALSA MLPA kit P099-B2, MRC-Holland. Amsterdam, The Netherlands). Amplicons were separated on a capillary sequencer (ABI 3130 genetic analyzer, Applied Biosystems, Foster City, CA, USA). Peak sizes were analyzed with GeneMapper v4.0 (Applied Biosystems). The results of an MLPA probe in exon 12 showed a deletion, whereas the flanking probes in exons 8 and 14 were in a biallelic status. Primers were designed to PCR-amplify and sequence a region within the *TH* gene spanning exons 11 to 14 in order to define the breakpoints of the deletion. Long-range PCR amplification allowed identification of the 5′ limit of the rearrangement in intron 11 and the 3′ end in exon 13, with the deletion encompassing a segment of 716 bp (c.1197+25_1391del) including exon 12 and part of exon 13 (Fig. 1).

Our patient showed a very mild clinical presentation and also mild biochemical phenotype, with moderately low values of HVA in CSF and even normal values of 3-methoxy-4-hydroxyphenylglycol, which is normally reduced in TH deficiency. Correlation between residual enzyme activity and clinical severity has not been clearly established, but it seems that CSF HVA values may have some correlation with clinical features.[1,7] Given the predictable deleterious effect of the deletion on the enzyme activity, it is tempting to speculate that the promoter mutation provides enough residual activity to explain the mild phenotype and the good response to L-dopa therapy.

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Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.
Support was received from the Biomedical Network Research Centre on Rare Diseases (CIBER-ER, ISCIII), grant FIS PS09/01132, and Agència de Gestió d'Ajuts Universitaris i de Recerca—AGAUR (2009-SGR-00971). Dr. Toma and Dr. Serrano were supported by a CIBER-ER contract and Dr. Artuch by ISCIII (intensificación de la actividad investigadora).

Published online 4 April 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23564

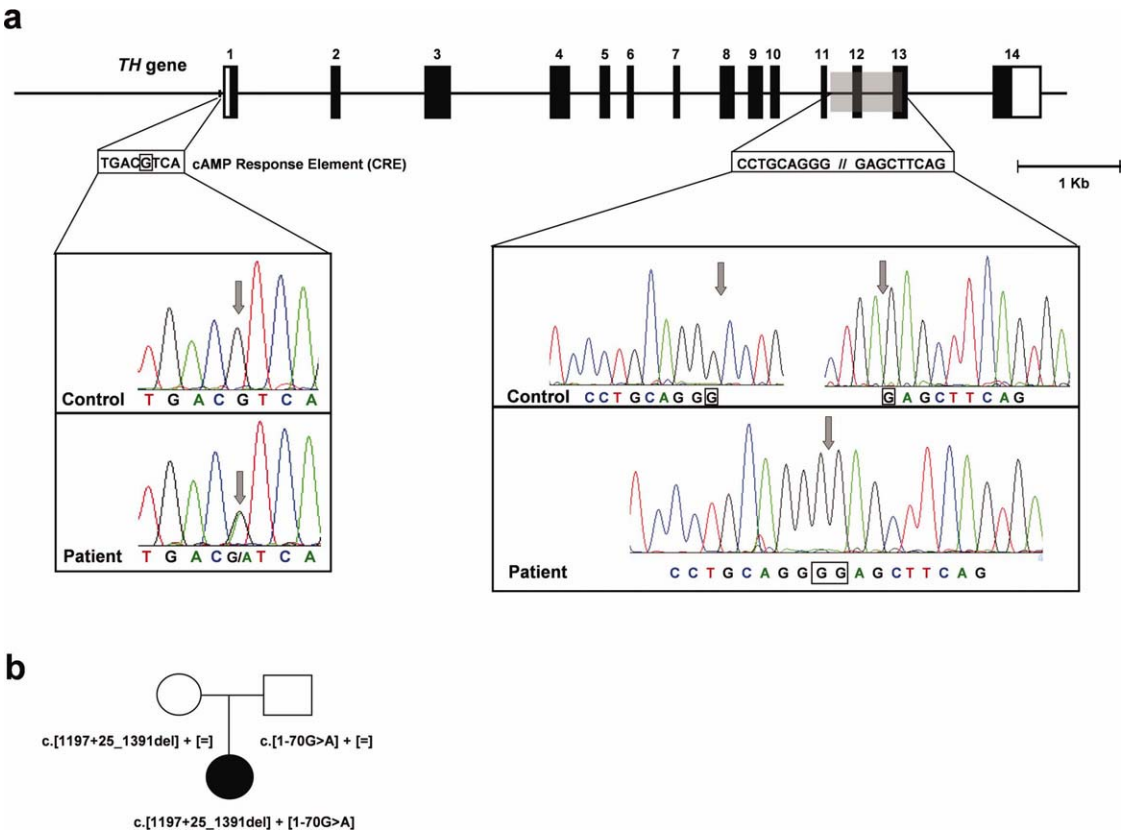

FIG. 1. (**a**) On top, schematic representation of the *TH* gene. Exons are indicated as boxes, with the coding sequences in black. Below left, sequence analysis of a healthy control and the patient showing a G-to-A transition within the cAMP response element (CRE). Below right, sequence analysis of a control and the patient showing a deletion that includes exon 12 and part of exon 13. (**b**) Segregation of the identified *TH* mutations in the pedigree. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TH-deficient patients may present a very mild clinical and biochemical phenotype with an excellent neurological outcome after L-dopa therapy. Our case demonstrates the clinical utility of CSF biogenic amines measurement to diagnose patients with subtle clinical features. Furthermore, after mutation screening of the *TH* gene, some disease-causing mutations are not detected. We recommend the inclusion of structural variant analysis for those patients with clinical and biochemical features of TH deficiency but lacking molecular confirmation by the usual sequencing techniques.

Video 1. Thirty-six hours without treatment. At 5 years and 2 months of age, after identification of 1 disease-causing mutation in the promoter region, good response to treatment at low doses of L-dopa, and good tolerance of large intervals between doses, the patient was hospitalized in an attempt to stop the treatment and reconfirm the deficiency clinically and/or biochemically. After 36 hours without treatment the clinical picture seemed to correspond to that of primary dopamine deficiency: ptosis, hypomimia, bradykinesia. Comprehension was normal.

Video 2. Eight hours after reinitiating treatment: In contrast with video 1, physical exploration shows normal deambulation and coordination maneuvers without the previous bradykinesia. No hypomimia, clear improvement in ptosis, and absence of abnormal movements during the exploration are also evident. Speech and comprehension are normal. Both videos were taken in the early morning.

Acknowledgment: We thank the patient and her family for their collaboration.

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Upright Posture in Parkinsonian Camptocormia Using a High-Frame Walker with Forearm Support

Camptocormia (CC) in Parkinsonian patients is a complex and often painful axial movement disorder that hinders the patient in many ways, including independent mobility, communication, and activities of daily living.[1,2] As pharmacotherapeutic options are rare and more invasive treatments (eg, botulinum toxin, deep brain stimulation) without convincing results,[1] some reports mention external devices such as the use of standard walkers,[3] backpack treatments,[3] or special orthoses[4] to provide beneficial effects. We report a treatment using a high-frame walker with forearm support in 3 camptocormic patients.

The 3 patients had akinetic-rigid Parkinson's disease (PD) according to UK PD brain bank criteria and a dynamic truncal flexion of more than 45°. All had motor fluctuations; hence, all clinical measures were assessed during the best clinical ON conditions. All patients gave informed written consent to have their data included in a scientific article. A video of patient 3 was recorded with a regular DV camera. Informed written consent was obtained from the patient to have his video data published (for detailed patient characteristics, see Table 1).

The high-frame walker (HFW) with forearm support is a semiactive external device. HFWs differ in weight, size, carrying capacity, and how fast and easily they can be assembled. For this report, patients were followed up 5 ± 2 days after their first use of the device.

CC was assessed with a standardized questionnaire.[5] The patients' body heights were measured lying supine and standing upright. Goal attainment scaling (GAS) was applied as described previously.[6]

On first use, posture improved in all patients while standing and walking with the HFW. At follow-up, the walking distance in the upright position had enlarged convincingly, and the occurrence of back pain while standing and walking was reduced in all 3 patients.

Patient 1 presented with forward and lateral flexion and a body height of 163 cm that increased to 170 cm. GAS evaluations demonstrated that he had improved his walking distance in an upright position up to 1500 m. His analgesic medication was reduced more than 50%. CC severity was reduced from 9 to 6 points and pain from 8 to 3 points.

Patient 2 presented with forward and lateral flexion of the trunk and a body height of 135 cm that increased to 153 cm. GAS evaluations indicated that his maximum walking distance had improved up to 1000 m. CC severity improved from 11 to 5 points, the occurrence of back pain had diminished during standing and walking, and the scale value for the occurrence of general back pain changed from 8 to 3 points. The question toward handicaps during ADLs was improved from 8 to 6 points.

Patient 3 presented with forward flexion of the trunk and a slight lateral tilt. His camptocormic body height of 158 cm increased to 175 cm. GAS indicated that his walking distance in an upright position had increased up to 2 km. CC severity improved from 12 to 9 points. His back pain was greatly reduced. Overall occurrence of back pain had been 5 points now was 0 (also see Table 1 and Video).

Upright standing and walking are facilitated by the HFW, and its use is compatible with the actual concepts of camptocormia.[7] The muscular weakness of the erector spinae muscle is compensated for by actively propping up, using the shoulder girdle and trunk musculature, or passively handing weight over to the forearm support. The HFW might also work as a *geste antagoniste* device, as was discussed for the backpack treatment.[3] Learning how to handle the HFW is easy. The capacity of the HFW to effect posture fast and efficiently was clinically striking and seemed more effective the more the sagittal truncal flexion prevailed. The HFW increased the patients' independent mobility and led to impressive pain reduction. Moreover, patients were able to communicate at eye height again.

Viewing over about 20 camptocormic patients using a HFW, we observed sustained therapeutic effects as described with this report. Because this case series was not controlled to any other treatment and followed up for 3 to 7 days only, further data are needed with more patients over longer periods to back up our observations.

Legends to the Video

Video 1. The first segment demonstrates the patient's capacity to achieve the full range of motion of the hip joints while lying supine and his bradykinetic disorder while sitting. The second segment shows the patient getting up and

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Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Published online 25 April 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23585

Table 1. Patient characteristics and baseline/follow-up examination results

	Patient 1	Patient 2	Patient 3
	Patient characteristics		
Age/sex	73.2 y/male	74.4 y/male	54.9 y/male
H&Y/diagnosis of PD/beginning of CC	4/2005/2009	4/1994/2005	3/2001/2009
Concomitant PD medication (daily doses)	LD/CD/EN 400/100/1000 mg; Piribedil 150 mg; Rasagilin 1 mg; apomorphine s.c. 3 mg RPN	LD/BZ 1100/275 mg; LD/CD CR 200/50 mg; apomorphine s.c. 6 mg/h	LD/BZ 200/50 mg; Rotigotin TDP 12 mg; Rasagilin 1 mg; amantadine 50 mg
Previous nondrug treatment	Surgery of lumbar vertebral fracture, 2008	None	BoNT injection into iliopsoas 2010
Autonomic dysfunctions	Urinary urge	Urinary incontinence	Urinary urge, erectile dysfunction
PDQ-39 sum score/Beck depression inventory/dementia screening	35/10/30 (MoCA)	41/6/20 (PANDA)	34/8/30 (MoCA)
UPDRS III/axial subscore (q. 18,19,22a,29,30)	30/8	33/13	19/6
Phenomenology of CC	Forward and lateral flexion	Forward flexion	Forward and lateral flexion
ROM hip joint	140-0-10	145-10-0	160-0-10
Body size lying supine	176 cm	165 cm	182 cm
Mobility aids/falls during last month	Standard walker, walking stick/1	Standard walker/>10	Bicycle/none
	Baseline examination without HFW/follow-up examination with HFW		
Body size standing	163/170 cm	135/153 cm	158/175 cm
CC severity[a]	9/6	11/5	12/9
CC ADL[a]	4/4	8/6	3/3
CC pain[a]	8/3	8/3	5/0
Walking distance in *upright* posture	<1/1500 m	<1/1000 m	<1/2000 m

[a]Higher values indicate higher severity according to reference 5. Abbreviations: ADL, activities of daily living; BoNT, botulinum toxin; BZ, benserazide; CD, carbidopa; CR, continuous release; LD, levodopa; MoCA, Montreal Cognitive Assessment; PANDA, Parkinson Neuropsychometric Dementia Assessment; PDQ-39, Parkinson's Disease Questionnaire; ROM, range of motion; TDP, transdermal patch.

walking around without the HFW. The third segment shows him with the HFW, propping himself up, and walking around in a more upright posture.

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Case Report: Recurrent Parkinsonism-Hyperpyrexia Syndrome Following Discontinuation of Subthalamic Deep Brain Stimulation

Parkinsonism-hyperpyrexia syndrome (PHS) involves increased rigidity, pyrexia, altered consciousness, and autonomic dysfunction associated with sudden withdrawal or reduction of antiparkinsonian drugs during the course of Parkinson's disease (PD).[1]

This report describes the case of a 60-year-old man with a 17-year history of PD who first experienced motor symptoms in 1993. He had a previous episode of minor depression. Nine years after disease onset, he had severe motor dysfunction with motor fluctuations and dyskinesia (Unified Parkinson's Disease Rating Scale [UPDRS] III scores of 54 in the "off" state and 26 in the "on" state). Because the patient's motor symptoms were

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Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles can be found in the online version of this article.

Published online 29 March 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23596

resistant to dopaminergic medications, including levodopa/carbidopa (300 mg) and cabergoline (3 mg), bilateral subthalamic nucleus deep brain stimulation (STN DBS) surgery was performed. The electrodes were stereotactically implanted in the bilateral STN (right, 9.9 mm lateral, 2.7 mm posterior and 6.9 mm inferior; left, 8.3 mm lateral, 1.7 mm posterior and 5.4 mm inferior to the midpoint of the anterior commissure–posterior commissure line). Following bilateral stimulation (2.5 V, 90 μs, 145 Hz, monopolar stimulation; contact 2 negative, case positive), the patient became manic, and his motor symptoms improved (UPDRS III score 20). Two years after surgery, the patient's manic symptoms became more prominent, and he was therefore admitted to our hospital. The bilateral STN DBS devices were switched off after considering their adverse effect. On the third day in the hospital, his manic symptoms disappeared; however, he became somnolent and completely immobile with severe rigidity. He was febrile with a temperature of 38.7°C and a pulse rate of 120/min. Laboratory tests revealed an elevated white blood cell count (12,600/μL) and positive C-reactive protein (1.03 mg/dL). Serum creatine kinase was elevated to 1878 U/L. PHS was considered, and standard infusion therapy was started. On day 6, he was afebrile with a normal consciousness level; STN DBS was switched on with the same settings, resulting in an improvement in rigidity and akinesia. One year later, his medication was discontinued.

The patient developed a manic state in January 2006, October 2006, May 2008, and May 2009. Because applying antipsychotics or changing the stimulating site of the DBS electrode did not ameliorate his manic symptoms, DBS had to be discontinued in each episode, resulting in the recurrence of PHS. Each incidence of PHS was reversed by standard fluid therapy, followed by reintroduction of DBS. In April 2010, he was hospitalized with a similar manic state. We applied low-voltage stimulation (2.0 V, 90 μs, 145 Hz), which prevented the development of PHS and successfully eliminated the manic symptoms.

There are several reports on PHS related to DBS, in which PHS occurred after cessation or reduction of dopaminergic medication in PD patients receiving DBS.[1–3] However, what happened in our case—occurrence of PHS following cessation of DBS—has never been reported.

Acute hypotransmission in the hypothalamus, nigrostriatal system, and mesocortical dopaminergic system is believed to contribute to the development of PHS.[4] Although the exact mechanism by which DBS influences neurotransmission in the brain has yet to be determined, at least in our case, dopaminergic transmission may have been enhanced during the patient's DBS-on given that (1) a manic state was evident before cessation of DBS, (2) PHS developed after cessation of DBS, and (3) the recurrence of PHS was prevented with the use of low-voltage DBS. Recently, the hypothesis that DBS can increase dopamine release in the striatum has been proposed.[5] We suggest that a sudden decrease in enhanced dopamine transmission following the discontinuation of DBS results in the development of PHS.

Although psychiatric side effects could be seen in both DBS of the STN and the globus pallidus internus, some authors have reported a higher incidence of psychiatric changes following STN DBS.[6] In our case, DBS electrodes were placed adjacent to the midbrain, which possibly affected projections from the midbrain to the orbitofrontal or anterior cingulate striato-pallido-thalamo-cortical circuits or fibers from the ventral tegmental area to the limbic system, thus resulting in mania.[7]

Physicians should be aware of the possibility of the development of PHS when STN DBS has to be discontinued.

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Head Drops are Also Observed in McLeod Syndrome

Typical flexion of the neck presenting as head drops along with sudden striking backward extension movements has been recently proposed as a characteristic feature of advanced ''classical'' chorea-acanthocytosis (ChAc, Levine-Critchley), 1 of the 4 major ''core'' neuroacanthocytosis (NA) disorders.[1] According to the authors, these pathognomonic movement disorders may constitute (along with self-mutilatory mouth movements and feeding-related tongue dystonia) ''red flags'' for the diagnosis of ChAc versus Huntington's disease (HD). Sudden and striking flexion movements of the trunk and the head, secondary to a sudden loss of tone, were

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

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Relevant conflicts of interest/financial disclosures: Nothing to report. Supported by the EC-funded (E-Rare JTC 2009 and ANR) EMINA project (European Multidisciplinary Initiative on Neurocanthocytosis). Full financial disclosures and author roles may be found in the online version of this article.

Published online 5 April 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23605

reported in 4 ChAc patients (with sudden extension movements in 1), proven by *VPS 13A* mutations in 3 and absent chorein expression in 1. Here, we report the observation of such a unique movement disorder in a patient with molecularly proven McLeod syndrome (MLS), a less common form and X-linked NA with *XK* gene mutations and weak expression of Kell erythrocyte antigens often associated with cardiomyopathy and neuromuscular involvement.[2]

This 65-year-old patient born from a nonconsanguineous marriage developed nocturnal, then diurnal generalized tonicoclonic epilepsy at age 35, responsive to phenobarbital, then valproic acid. Choreic movements appeared at age 56. HD molecular screening was negative. The diagnosis was established in the presence of blood acanthocytosis, elevated creatine kinase levels (718 UI/L), absent erythrocyte Kp^a and Kp^b expression, and a frame-shift mutation of the *XK* gene: c.722delT (p.ill241fs27X). When last seen, there was a generalized severe and incapacitating chorea of all 4 limbs, the trunk, and the neck. The patient further showed gait instability, generalized hypotonia, severe swallowing difficulties with feeding dystonia and oropharyngeal apraxia, severe dysarthria, and frontal dysexecutive deficits. He also had hypertrophic cardiomyopathy and mild axonal neuropathy. Head drops were very frequent, occurring several times a day regardless of whether he was standing, sitting, or lying down (see Video). That head drops occurred also when lying down with contraction of the sternocleidomastoid (SCM) muscles (see Video 2) and no disappearance of muscle activity on neck extensor muscles (rather, cocontraction with SCM was found on surface EMG recordings during head drops) likely suggests a possible choreic nature of this movement disorder.

We have been impressed by the sense of observation and the careful description by Schneider et al[1] on these striking movement disorders in ChAc. We even retrospectively recognize that the ''severe trunk spasms'' we described and treated with DBS of the motor thalamus in an advanced ChAc patient were probably of the same nature.[3] However, the present observation tells us that these movements may also be found in MLS, thereby being characteristic of NA rather than restricted to ChAc. Thus, in the presence of a male patient with choreic movements, head drops, and negative chorein blot, screening for a blood McLeod phenotype and *XK* gene mutations may be worthwhile.

Legends to the Video

Video 1. Chorea and head drops while the patient is trying to count backward with severe dysarthria.

Video 2. ''Head drops'' while the patient is lying down.

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A Case of Slow Orthostatic Tremor, Responsive to Intravenous Immunoglobulin

A 69-year-old man developed disabling involuntary shaking of both legs while standing. The course progressed gradually: 3 months after onset, he required a walker to ambulate; by the fourth month, he was relegated to a wheelchair. He had no symptoms when seated or supine. His medical and family histories were unremarkable. He had no other neurological or systemic symptoms and denied antecedent illness.

Examination revealed a fit-appearing white man with mild horizontal nystagmus on lateral gaze, rotatory nystagmus on upward gaze, and mildly increased tone in the left leg. Finger-to-nose testing was normal, but subtle dysmetria occurred with heel-knee-shin maneuvers. A severe, coarse, bilateral leg tremor (with superimposed myoclonus) was observed when the patient stood. It abated with time but reemerged with each step. It improved slightly with the patient's head turned to the right. There was no arm tremor, and there were no abnormal findings while he was seated or supine, even with the legs elevated (Video).

Extensive serum and cerebrospinal fluid (CSF) testing was normal (Supplemental Table), as were a brain MRI with gadolinium, electroencephalogram, and nerve conduction with needle electromyography (EMG). Whole-body positron emission tomography and computed tomography failed to reveal occult malignancy. However, surface EMG demonstrated a 3- to 4-Hz tremor in both legs (quadriceps, tibialis anterior, and gastrocnemius) and paraspinal muscles, only on standing (Fig. 1A). Sequential empiric treatments with

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Relevant conflicts of interest/financial disclosures: Dr. Manu Hegde reports no disclosures. Dr. Graham A. Glass has received $8,000 in speaking fees, and the University of California, San Francisco, has an unrestricted educational grant totaling $15,000 from Allergan Inc. Dr. Josep Dalmau has received a research grant from Euroimmun. Dr. Chadwick W. Christine has received research support from Genzyme Corporation, Kyowa Pharmaceutical, Inc., Eisai Inc., and the NIH (NINDS 5U10NS044460 [coinvestigator] and RO1NS046487 [site investigator]) and has received salary and travel support from Avigen, Inc., and Genzyme Corporation through a grant to the University of California. Full financial disclosures and author roles can be found in the online version of this article.

Published online 5 April 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23610

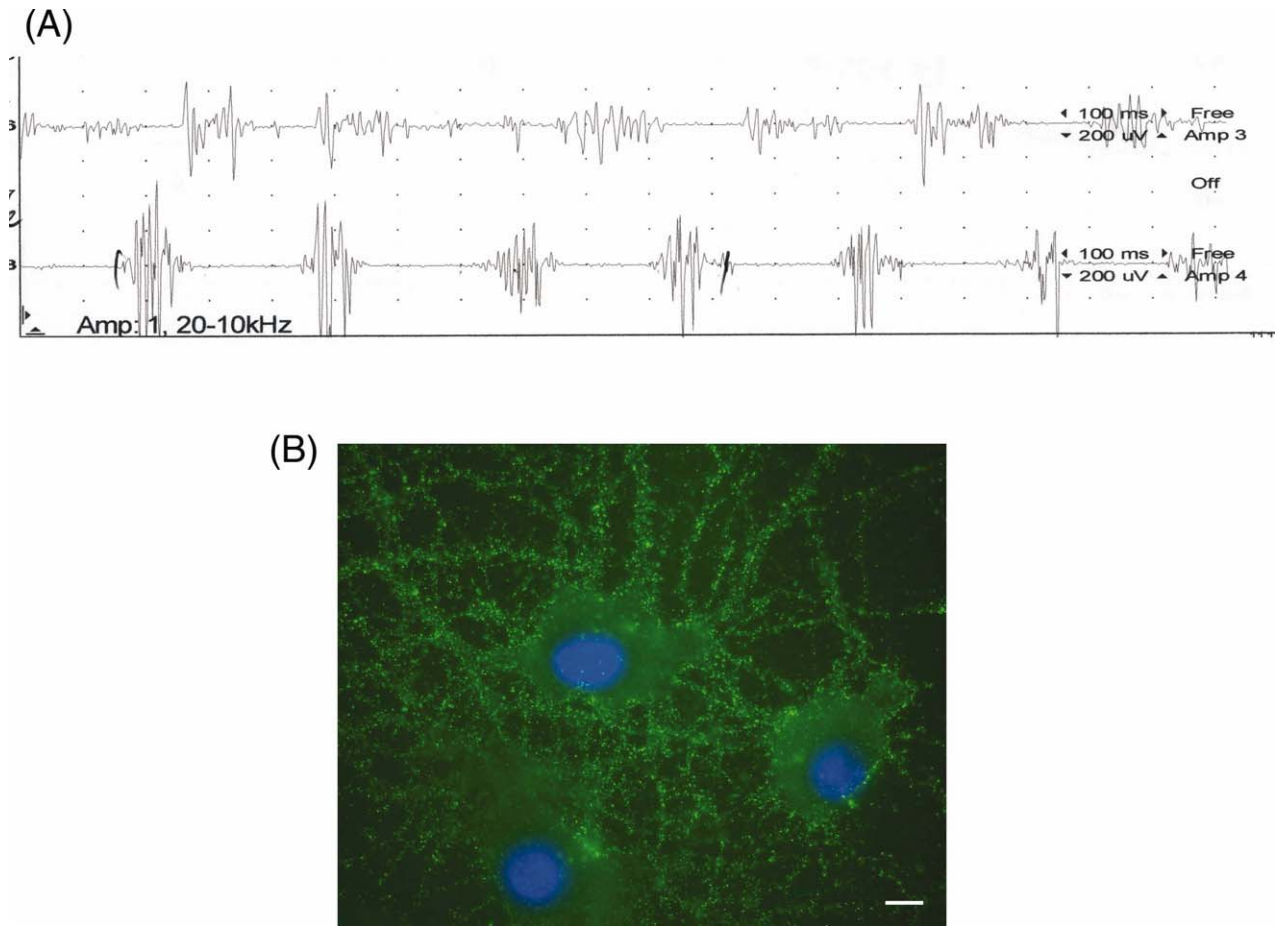

FIG. 1. Surface EMG and immunohistochemistry findings. Recordings from the left (upper tracing) and right (lower tracing) tibialis anterior demonstrate 3- to 4-Hz tremors only on standing (**A**). Fluorescent microscopy demonstrating antibodies from the patient's cerebrospinal fluid (CSF) binding the surface of living rat hippocampal neurons in culture (**B**). Cell nuclei are counterstained in blue with 4′,6-diamidino-2-phenylindole (DAPI). Scale bar = 10 microns. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

valproate, clonazepam, gabapentin, thiamine, parenteral B12, and methylprednisolone all failed to relieve the tremor.

Given the unusual nature, rapid onset, and relentless progression of the patient's tremor, we were concerned he might have a postinfectious or paraneoplastic autoimmune disorder affecting the pons or cerebellum. We therefore examined CSF and serum using immunohistochemical methods described previously.[1] Both contained antibodies to extracellular epitopes on rat hippocampal neurons in vitro (Fig. 1B). No such antibodies have been found in testing of more than 500 control subjects' serum and CSF. Although the antigen remains unidentified, the antibody does not bind to voltage-gated calcium channels, proteins associated with potassium channels (LGI1, CASPR2), or the glutamatergic *N*-methyl-D-aspartate or α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptors.

Given this evidence, we attempted a trial of immunomodulatory therapy. Four months after symptom onset, the patient received 2 g/kg of intravenous immunoglobulin (IVIG) over 3 days. Within hours of the first infusion, he stood from his wheelchair and ambulated with a walker. After 3 days of IVIG, he walked independently. Ten days later, examination was normal except for impaired tandem gait (Video). He remains asymptomatic 21 months after treatment. Repeat imaging was normal, but the antineuronal antibodies were persistent in serum, with unchanged titers (1:3200). The CSF titer (1:800 before treatment) was not repeated.

Discussion

This is the first report of slow orthostatic tremor associated with a novel antineuronal antibody. It is distinguishable from primary orthostatic tremor by its slow frequency (3–4 versus 13–18 Hz) and its poor response to medications.[2] Cerebellar, palatal, and Holmes's tremors may be 3–4 Hz but are clinically different from our case. Slow (<13 Hz) orthostatic tremors have also been reported in patients with homozygous *parkin* mutations,[3] anti-Hu antibody paraneoplastic syndrome,[4] and cerebellar disorders[5] and in demyelinating lesions of the *brachium pontis* in multiple sclerosis.[6] Although our patient demonstrated no evidence of demyelination, other similarities—4 Hz frequency, medication resistance, and restriction to the legs—suggest a pontine localization. A cerebellar localization is also possible, given the association of slow orthostatic tremor with cerebellar pathology, as well as the findings of nystagmus and ataxia (heel-knee-shin and tandem gait).

The dramatic improvement with IVIG and elevated neuronal antibody both support an autoimmune etiology. This could represent a novel paraneoplastic syndrome because affected patients may develop antineuronal antibodies before clinical detection of malignancy[7]; vigilance will be needed to exclude this possibility. A postinfectious autoimmune etiology provides an alternate explanation. However, because the disorder was progressive until treatment, and no antecedent

illness was reported, this is less likely. Finally, because the antibody was found in an assay using rat neurons, the relevance of the elevated titer is uncertain. Nonetheless, we feel this case suggests a novel pathophysiology that may produce slow orthostatic tremor. Characterization of similar cases may lead to identification of the antigen and better understanding of this disorder.

Legend to the Video

Video. The video demonstrates the described patient on examination. No tremor is seen at rest. However, a coarse severe tremor is seen in both legs on standing or walking. Mild dysmetria is seen on heel-to-shin maneuvers, and tone is slightly increased in the left leg. The patient is then shown after treatment with intravenous immunoglobulin. No orthostatic tremor is seen, but difficulty with tandem gait persists.

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Truncating Mutations in THAP1 Define the Nuclear Localization Signal

Mutations in the THAP domain-containing, apoptosis-associated protein 1 (*THAP1*) gene have been identified to cause dystonia 6, a form of primary torsion dystonia that has been linked to chromosome 8 (DYT6).[1] *THAP1* encodes a 213–amino acid (aa) transcription factor featuring a specific DNA-binding THAP (Thanatos-associated protein) zinc finger domain (aa 1–91), a proline-rich region (aa 96–108), and a stretch of 16 aa (146–162) predicted to resemble a bipartite nuclear localization signal.[1]

About 40 different *THAP1* mutations have been reported to date, which are mostly localized in the DNA-binding THAP domain. In addition, nonsense mutations or different small insertions/deletions are predicted to cause premature protein truncation.[1–5] These truncated THAP1 proteins lack the predicted NLS in part or in entirety, presumably resulting in disturbed nuclear import of mutant THAP1.

To further confirm this hypothesis, we tested the intracellular localization of wild-type and mutant THAP1. In a first step, we used confocal laser-scanning microscopy of green fluorescent protein (GFP)–labeled THAP1. Five different truncating mutations (c. 85C>T [p.R29X]; c.134_135insGGGTT/137_139delAAC [p.F45fs73X]; c.388_389delTC [p.V131fs133X]; c.460delC [p.Q154fs180X]; c.474delA [p.L159fs180X]; Fig. 1A)[1–3] were reconstructed in vitro and inserted into the pEGFP-N3 plasmid (Clontech, Saint-Germain-en-Laye, France) to generate appropriate THAP1-GFP fusion proteins. Wild-type THAP1-GFP was used for in vitro mutagenesis to insert 2 missense mutations affecting the THAP domain as controls (c.68A>T [p.H23P]; c.241C>T [p.F81L][1]; Fig. 1A). All GFP fusion constructs were transiently expressed for 48 hours in OVCAR-3 cells, a human ovarian carcinoma cell line. As expected, wild-type THAP1 as well as mutated proteins H23P and F81L were exclusively detected in the nucleus, whereas all 5 truncated forms of THAP1 as well as GFP alone were also found in the cytoplasm (Fig. 1B).

In a second step, to allow for exact quantification of the subcellular distribution, sucrose density gradient centrifugation was used to separate nuclei from all other cellular components (non-nuclear, essentially cytosolic fraction), followed by direct

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Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Published online 14 April 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23611

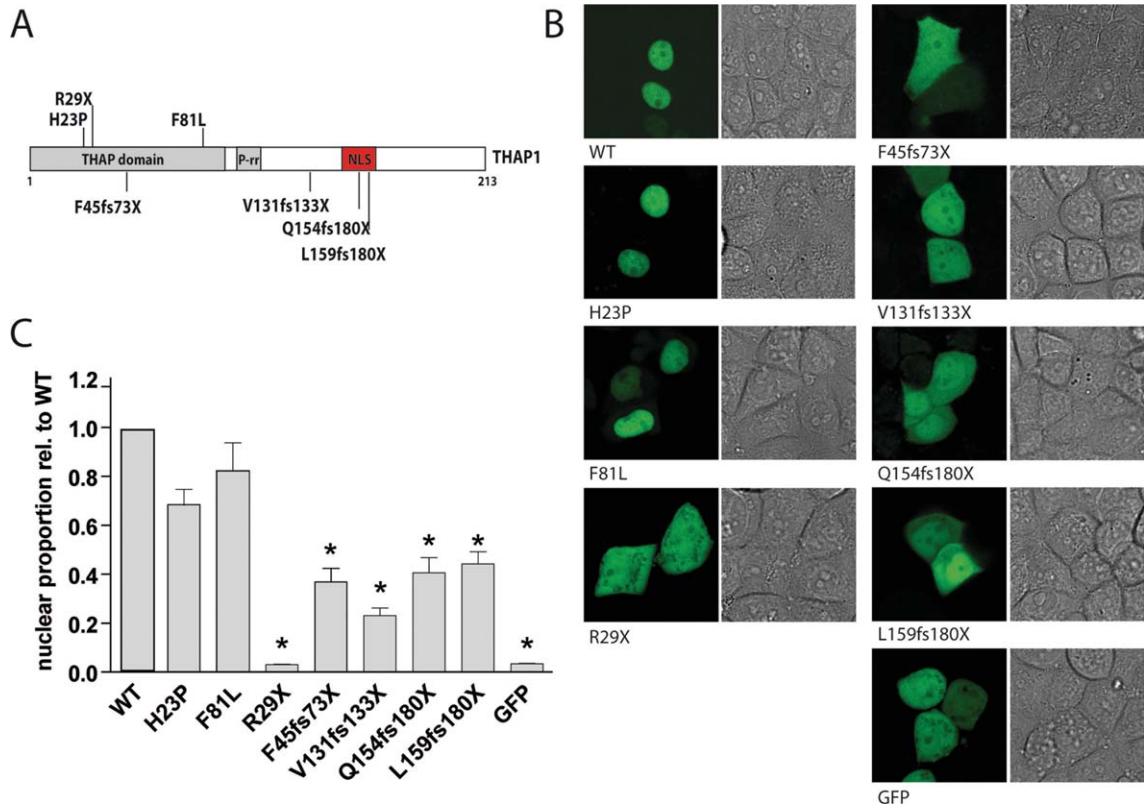

FIG. 1. Subcellular distribution of wild-type and truncated THAP1. **A:** Schematic representation of the THAP1 protein with the investigated mutations. The THAP domain and the proline-rich region (P-rr) are indicated by gray boxes; the bipartite nuclear localization signal (NLS) is illustrated in red. **B:** Intracellular localization of GFP-labeled fusion constructs of THAP1 (green signal) visualized by confocal microscopy in transiently transfected OVCAR-3 cells. THAP1-GFP constructs for wild type, H23P, and F81L are exclusively localized in the nucleus, whereas all truncated THAP1 proteins were clearly present also in the cytosol. The intracellular localization of GFP is shown as a control. **C:** Quantification of the GFP signal of the transfected cells in nuclear versus non-nuclear fractions. Quantification confirmed the lower proportion of nuclearly localized truncated THAP1 compared with its wild-type form (*$P < .05$ vs wild type).

photometric quantification (Kontron SFM25) of GFP-labeled THAP1 proteins. Although missense mutations in the THAP domain do not alter the intracellular distribution of THAP1, the nuclear proportion of all truncated THAP1 proteins was significantly smaller compared with wild-type protein. The nuclear proportion of mutant THAP1 was 3% for R29X, 37% for F45fs73X, 23% for V131fs133X, 40% for Q154fs180X, and 41% for L159fs180X compared with wild-type THAP1 (Fig. 1C).

These data clearly indicate that loss or disruption of the predicted NLS indeed results in dramatically reduced nuclear localization of THAP1. The small proportion of truncated protein entering the nucleus in this overexpression system can be explained by diffusion of small proteins (<60 kD) through the permeable nuclear pore. In contrast with the active transport mechanism, this passive transport is independent of the NLS.

The pathophysiology of *THAP1* mutations in the context of dystonia 6 currently remains poorly understood. However, there are several hints that transcriptional dysregulation may play an important role because THAP1 acts as a transcription factor via its DNA-binding domain.[6,7] Because most of the known mutations are localized in the DNA-binding domain, interaction with DNA seems to be an important feature of THAP1. DNA binding would not only be disturbed by mutations in the THAP domain but also by impaired or abolished nuclear import of the protein. For the first time, we have demonstrated that mutations affecting the predicted NLS indeed result in reduced nuclear import. This underlines the functional relevance of the predicted NLS in THAP1 for its nuclear localization.

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Cortical Origin of Myoclonus in Early Stages of Corticobasal Degeneration

Distal focal myoclonus, spontaneous and/or triggered by movement and sensory stimulation has been observed in 8% of patients with corticobasal degeneration (CBD) at onset and in 57% of patients within 5 years after onset.[1] Clinical features indicate a cortical origin for myoclonus; however, neurophysiological techniques have generally failed to confirm it.[2–5] We investigated the origin of myoclonus in a patient with recent onset CBD and studied the effects of transcranial direct current stimulation (tDCS).

A 74-year-old right-handed woman reported progressive walking difficulty because of jerky movements and right lower limb pain for 1 year. Neurological examination revealed stuttering, dystonia with internal rotation of the right foot, increased muscle tone, hyperreflexia, Babinski's sign, and spontaneous myoclonus restricted to the right lower extremity. Myoclonus was also evoked by voluntary movement, muscle stretch, and taps of the right leg (Video). Magnetic resonance imaging of the brain showed a slightly narrowed postcentral gyrus in the left hemisphere (Fig. 1A). DaTScan documented mild reduced uptake of the left striatum. On the basis of clinical and neuroimaging, a diagnosis of probable CBD was made.[6]

Electrophysiological studies included long latency responses (LLRs), somatosensory evoked potentials (SEPs), electroencephalography with jerk-locked back averaging (JLA), and magnetoencephalography to study corticomuscular coherence (CMC). Motor evoked potentials (MEPs), resting motor threshold (RMT), and silent periods (SPs) were recorded from tibialis anterior (TA) muscles after transcranial magnetic stimulation (TMS). Details on the methods are reported in supplementary material.

A surface EMG recorded from right leg muscles at rest showed continuous background activity with superimposed short-duration (30–50 ms), high-frequency (mean, 7 Hz; range, 5–10 Hz) pseudorhythmic discharges (Fig. 1B). LLRs after stimulation of peroneal, tibial, and sural nerves were recorded only from right TA and gastrocnemius medialis muscles (Fig. 1C).

SEPs after tibial nerve stimulation showed increased amplitudes of P1-N1 and N1-P2 components (Fig. 1D). JLA showed a positive-negative spike at Cz with the latency of myoclonus at 41.5 ms (Fig. 1E). A significant CMC was found during both right and left TA contraction, with a higher value during right contraction (Fig. 1F). Mean amplitude of right TA MEP was higher than that of the left, and RMT was lower in the left hemisphere. Contralateral SPs and ipsilateral SP after left cortex stimulation were shorter than normal values (Table 1, supplementary material).

To assess whether inhibitory neuromodulation is effective in reducing myoclonus in CBD, cathodal tDCS, at a current intensity of 1 mA, was delivered over Cz for 20 minutes and repeated for 5 consecutive days. Furthermore, tDCS effects were compared with pharmacological therapy (2 weeks of levetiracetam 500 mg bid, effective on myoclonic epilepsy,[7] and levodopa-carbidopa 100 + 25 mg tid) by a functional scale and continuous EMG recording from TA muscles. Details on medical treatment and functional scale are reported in the supplementary material. Both tDCS and pharmacological therapy significantly improved the patient's performance and reduced median amplitude and frequency of myoclonus, with the effect persisting for 3 days after the end of tDCS (Table 2, supplementary material; Fig. 1G).

Because electrophysiological features of cortical myoclonus have been rarely demonstrated in CBD, it has been debated whether myoclonus is cortical, subcortical, or an atypical variety.[2–5] The patient we report was studied at an early disease stage, and all electrophysiological findings and cathodal tDCS effects point to a cortical origin. Conflicting electrophysiological results in CBD may be reconciled considering the progressive cortical involvement characteristic of the disease. Therefore, the lack of classical electrophysiological features may be a result of the severity of cortical atrophy. In particular, the absence of giant SEPs in some patients with myoclonus might be explained by the atrophy initially limited to the parietal lobe with relatively intact and less inhibited motor cortex.[3] Moreover, cortical correlates of myoclonus may not be always easy detectable because of small signal amplitude or unfavorable neuronal source location.[4]

In conclusion, we deem that electrophysiological correlates of cortical myoclonus can be identified only in early stages of the disease. In the recent-onset CBD patient we report, the myoclonus is cortical in origin. Cathodal tDCS was tried, and a reduction of myoclonus was noticed, probably by reducing cortical excitability,[8] but further confirmatory

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

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Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Published online 11 April 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23612

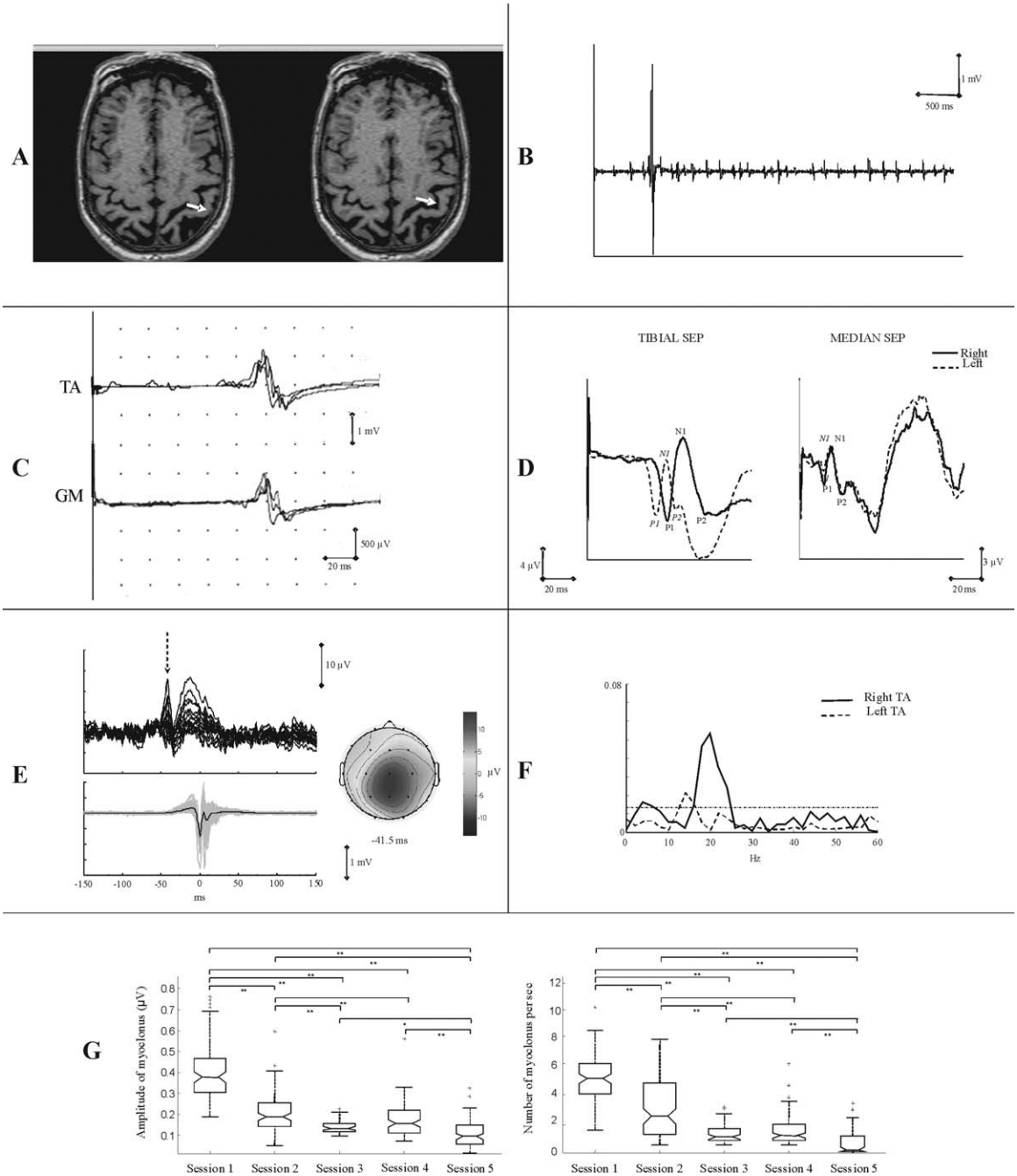

FIG. 1. A: Axial T1-weighted MR images of the brain. Two contiguous slices showing a slightly narrowed postcentral gyrus and an enlarged central sulcus (white arrows) in the left hemisphere compared with the right hemisphere. **B:** Surface EMG of right tibialis anterior (TA) muscle at rest showing high-frequency repetitive bursts of spontaneous myoclonus with a burst of greater amplitude. **C:** Long latency responses recorded from right tibialis anterior (TA) and gastrocnemius medialis (GM) muscles after stimulation of the right peroneal nerve at the ankle with a latency of about 100 ms. The first response was followed by smaller-amplitude responses with intervals of 50–70 ms. **D:** Somatosensory evoked potentials (SEPs) by tibial and median nerves stimulation showing increased amplitude of right and left tibial SEPs of P1-N1 and N1-P2 components, respectively: right = 9.6 and 8.9 μV; left = 5.9 and 5.8 μV (control values: P1-N1 = 1.9 ± 0.7 μV, N1-P2 = 2.0 ± 0.5) and normal amplitude of median SEPs. **E:** Left, superimposition of back-averaged electroencephalography channels (upper) and averaged (bottom, black trace) and single-trial (bottom, gray traces) myoclonic jerks recorded from TA in the time interval (−150, 150) ms, with 0 the time of occurrence of the myoclonus recorded from TA muscle. Right, scalp topography of back-averaged potential at the instant corresponding to the maximal negative peak preceding the myoclonus (dotted arrow, −41.5 ms). **F:** Maximal corticomuscular coherence (CMC) during right and left isometric contraction of TA muscle in the range of 2–60 Hz. Horizontal dotted line indicates the significance level. **G:** Box plot of amplitudes (left) and frequencies of myoclonic bursts with amplitude greater than 0.2 mV (right), displaying the 5–25, 75–95 (dotted lines), 25–75 (boxes) percentiles and the medians (horizontal line) before tDCS (session 1), after the second tDCS (session 2), after the fifth tDCS (session 3), 3 days after the ending of tDCS (session 4), and 2 weeks after the introduction of pharmacological therapy (session 5). The medians of 5 sessions were statistically different ($P < .0001$, Kruskal–Wallis test); $^{**}P < .0001$, $^{*}P < .01$, Mann–Whitney test. The medians between sessions were statistically different except for sessions 3 and 4 ($P > .05$).

studies are required before encouraging tDCS use as a possible therapeutic tool in cortical myoclonus.

Legend to the Video

Shown are spontaneously occurring myoclonic jerks (0–39 seconds), dystonic posture of the right foot (39–41 seconds), myoclonic jerks evoked by foot touch (41–66 seconds), and free walking (66–86 seconds).

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