Movement Disorders
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Letters to the Editor Related to New Topics

Transient Exacerbation of Ataxia with Smoking: A Prevalence Survey

Some cerebellar ataxic patients complain of transient, but marked, exacerbation of ataxia after smoking cigarettes. The prevalence of this phenomenon is unknown, although it has been reported previously, mostly among patients with multiple system atrophy (MSA).[1–4] The finding is reproduced by intravenous injection of nicotine tartrate,[1] but the mechanism is not established. We distributed a self-reporting questionnaire to patients with various types of chronic cerebellar ataxia to determine the prevalence of ataxia exacerbation by smoking, and whether sensitivity to cigarette smoking is specific to certain subtypes of ataxia.

Written surveys were mailed to adults with cerebellar ataxia evaluated in the Massachusetts General Hospital (MGH) Ataxia Unit from 8/2005 to 7/2007 (n = 140), and to the Emory University National Ataxia Registry (n = 305). The survey assessed smoking status, and whether cigarettes transiently exacerbated or alleviated symptoms of ataxia by the patient's own report. Eleven symptoms were assessed as follows: (1) balance, (2) coordination, (3) slurred speech, (4) choking/coughing, (5) tremor, (6) slowed movement, (7) lightheadedness (as though about to pass out), (8) dizziness (spinning sensation), (9) urinary urgency, frequency, or incontinence, (10) muscle weakness, and (11) impaired handwriting. An open-ended question provided respondents an opportunity to elaborate upon their smoking-related symptoms.

Telephone interviews were conducted for MGH Ataxia Unit patients who did not return the survey. Medical records were reviewed to determine smoking status in MGH patients who could not be contacted. This study was approved by the Partners Human Research Committee.

MGH Ataxia Unit patients were clinically evaluated by the authors. Registry patients provided a copy of genetic tests or a physician's note elucidating the diagnosis. The registry released the respondents' diagnoses after receipt of medical record release forms included with the mailed surveys.

Patients were grouped into five diagnostic categories as follows: (1) Friedreich's Ataxia (FA), (2) Autosomal dominant genetic and familial ataxias (Genetic), including spinocerebellar ataxia (SCA) 1, 2, 3, 5, 6, 7, 8, and autosomal dominant ataxias gene unknown, (3) Idiopathic Late Onset Cerebellar Ataxia (ILOCA), including sporadic ataxias of unknown etiology, (4) Multiple System Atrophy (MSA), and (5) Miscellaneous ataxias of known causes (Misc), including toxic/metabolic cerebellar ataxia, gluten ataxia, postinfectious cerebellar ataxia, paraneoplastic cerebellar ataxia, cerebellar hypoplasia, autoimmune ataxias, superficial siderosis, fragile X-associated tremor ataxia syndrome, and Gerstmann-Straussler-Schenker disease.

Of 405 survey recipients, 21 were deceased, had changed address, or received duplicate surveys. Of the remainder, 304 responded to the survey, for a total response rate of 72%. One hundred and thirty-nine (46%) of the respondents had ever smoked cigarettes. Of these, 53 reported quitting smoking before ataxia developed. Of the 86 patients, who smoked after ataxia onset, 36 (42%) reported transient exacerbation of ataxia from cigarettes. Patients in all diagnostic categories reported this phenomenon, with no difference in smoking effect rate between diagnostic groups ($P > 0.5$).

The effect rate was similar for the 2 patient cohorts: 41% of MGH patients (n = 9) and 42% of registry patients (n = 27) reported transient exacerbation of ataxia from cigarettes.

Most patients who reported an effect noted transient exacerbation of ataxia symptoms with smoking, but 6 patients reported transient improvement (Table 1).

This study confirms the previously reported effect of smoking on cerebellar ataxia.[1–4] Our questionnaire, completed by 304 patients, shows a deleterious symptomatic effect of smoking in 42% of patients with ataxia, regardless of etiology.

The mechanism by which smoking worsens cerebellar ataxia is unknown. Although there are >4,000 candidate chemicals in tobacco smoke,[5] this phenomenon is likely nicotine-induced given the exacerbation of ataxia following injection of nicotine tartrate.[1] There are abundant nicotinic receptors in the cerebellum,[6] nicotine has been shown to inhibit cerebellar Purkinje cells in animal models,[7] and it increases blood flow to cerebellum.[8] Intranasal administration of nicotine can induce nystagmus, dizziness, nausea, and postural imbalance in healthy subjects, possibly by an effect on the vestibular system.[9]

Limitations of this study are that patients were not examined after smoking; we relied entirely on their self-report of worsening symptoms; and most (n = 218) of our cohort either never smoked or stopped smoking before developing ataxia.

Given the high prevalence (42%) of the deleterious effect of cigarette smoking in patients with ataxia, we conclude that ataxic patients have yet another reason not to smoke. We did not inquire about second hand smoke, but appropriate caution seems justified. The relationship of nicotine to exacerbation of cerebellar ataxia raises the possibility that treatment with nicotinic receptor modulators should be explored.

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TABLE 1. *Prevalence of smoking-induced transient exacerbation and alleviation of specific symptoms of ataxia among smoking ataxic patients*

Prevalence of effect	FA		Genetic		ILOCA		MSA		Misc		All	
Total survey responders	49		102		94		31		28		304	
Smokers (% of total survey responders)	21 (43%)		27 (26%)		25 (27%)		8 (26%)		5 (18%)		86 (28%)	
Smokers with sx exacerbation (% of smokers)	11 (52%)		9 (33%)		12 (48%)		3 (38%)		1 (20%)		36 (42%)	
Smokers with sx alleviation (% of smokers)	2 (10%)		3 (11%)		0 (0%)		0 (0%)		1 (20%)		6 (7%)	
Specific symptoms	E	A	E	A	E	A	E	A	E	A	E	A
Balance	3	1	6	1	7	–	3	–	1	1	20	3
Coordination	4	2	4	2	6	–	3	–	–	1	17	5
Slurring of speech	–	1	3	–	6	–	3	–	1	–	13	1
Choking	5	–	1	–	5	–	1	–	–	–	12	–
Tremor	2	1	4	1	3	–	2	–	–	1	11	3
Slowness of movement	3	–	1	1	3	–	1	–	–	–	8	1
Lightheadedness	8	–	5	–	5	–	1	–	1	1	20	1
Dizziness	3	–	3	–	6	–	1	–	1	1	14	1
Urinary symptoms	1	–	1	1	2	–	–	–	–	–	4	1
Muscle weakness	4	–	4	2	3	–	–	–	–	–	11	2
Impairment of handwriting	1	–	5	–	3	–	3	–	–	1	12	1

FA, Friedreich's Ataxia; Genetic, genetic and familial ataxias; ILOCA, idiopathic late onset cerebellar ataxia or other undiagnosed idiopathic ataxia; MSA, multiple system atrophy; Misc, miscellaneous ataxia. Total survey responders, all subjects who responded to the survey. Smokers, subjects who were active smokers or used to smoke while demonstrating symptoms of ataxia. Sx, symptom. The specific symptoms listed are those that were listed on the surveys. E, number of patients who experienced exacerbation of the symptom. A, number of patients who experienced alleviation of the symptom.

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Multiple System Atrophy with Antecollis That Later Changed to an Extended Posture: A Case Report

Antecollis in multiple system atrophy (MSA) first was described by Quinn in 1989.[1] It impairs the patient's quality of life, because it disturbs eye contact, conversation, swallowing, and walking. It causes neck and back pain and produces cosmetic problems that prevent the person from joining in social activities. Anti-parkinsonian drugs may reverse symptoms, but in MSA usually the effect is not satisfactory. We report a patient with MSA who had predominant motor symptoms of Parkinsonism (MSA-P) and antecollis, but later the neck posture changed to hyperextension.

A 60-year-old woman visited our hospital complaining of abnormal forward neck flexion. It had developed suddenly after she used a motor-driven weed cutter that was handheld but had a support strap suspended from the neck. Several months after the emergence of neck flexion, postural dizziness, urinary incontinence, and difficulty in using the right hand developed. Five months after the onset of neck flexion, she experienced gait disturbance and visited our hospital. She presented with rigidity and akinesia of the neck and extremities and postural instability. Her neck was extremely flexed with her chin on the chest (Fig. 1A). There was no neck muscle weakness, and instead the neck extensor muscles were prominently contracted. A head-up tilt test showed marked reduction of systolic blood pressure (75 mm Hg drop within 3 min after standing). T2*-weighted MR images showed low signal intensity lesions in the putamen with slit-like low signals bilaterally along the outside ridges. The cerebellum was slightly atrophic on the T2-weighted MR images. MR images of the cervical spine and neck muscles were normal. Surface EMG showed increased discharges from electrodes placed on the sternocleidomastoid and trapezius muscles simultaneously when she tried to extend the neck (see Fig. 2). The clinical symptoms and MR findings prompted a diagnosis of MSA-P.

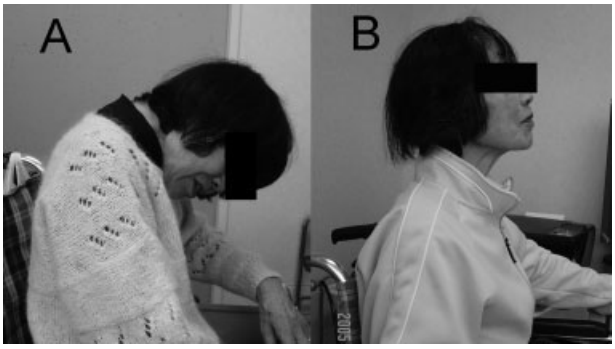

FIG. 1. The patient's antecollis (A) is somewhat changed to hyperextended posture (B) 3 years after its onset.

Anti-parkinsonian drugs partially improved her motor symptoms. Antecollis, however, was aggravated on the addition of cabergoline (up to 3 mg per day) or pramipexole (up to 4.5 mg per day). Antecollis was reduced slightly by levodopa/carbidopa. Her antecollis caused disturbed vision and neck/back pain.

Three years after antecollis onset, forward neck flexion had reversed to hyperextension posture within 3 months (Fig. 1B). Her medication had not been changed either before or near the time of the postural change. The severity of her Parkinsonism at that time corresponded to Hoehn and Yahr stage 4. Antecollis has not reoccurred for more than 2 years.

Antecollis may be a frequent complication of MSA.[1,2] Hyperextension of the neck, on the other hand, often is present in progressive supranuclear palsy.[1,2] The longitudinal course of antecollis in MSA has yet to be reported, but usually it appears to be refractory to reversal[3] except when induced by medication.[4] Antecollis in MSA and Parkinson's disease has been suggested to be caused by neck extensor myopathy, imbalanced rigidity of the anterior and

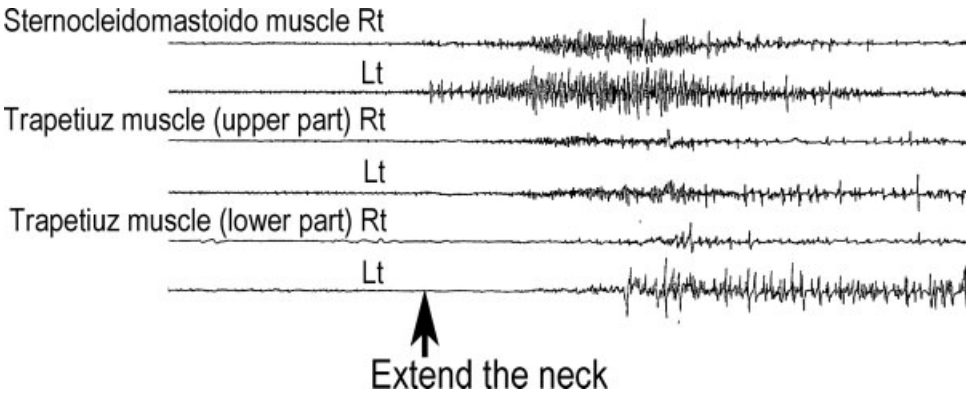

FIG. 2. Results of surface EMG study of the patient. Electrodes were placed on the bilateral sternocleidomastoid and upper and lower part of trapezius muscles. Discharges from all electrodes increased simultaneously when the patient attempted to extend the neck.

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posterior neck muscles, or dystonia.[3,5–7] Needle EMG of the neck muscles have not been performed in our patient, however, no neck muscle weakness and surface EMG results suggesting simultaneous and equal overactivation of flexor and extensor muscles on neck extension of the patient support the imbalanced tonus hypothesis. That is, imbalance of muscle tonus might have shifted from flexor- to extensor-neck muscle predominance as the disease progressed.

The change in our patient's neck posture from the flexed to extended neck position indicates that antecollis in basal ganglia diseases may be reversed in the natural course of the illness.

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Pantothenate Kinase-Associated Neurodegeneration in Two Taiwanese Siblings: Identification of a Novel *PANK2* Gene Mutation

Video 

Pantothenate kinase-associated neurodegeneration (PKAN) is an autosomal recessive disorder characterized by accumulation of iron in the basal ganglia due to mutation of the pantothenate kinase 2 gene (*PANK2*).[1] The hallmark of neuroradiological finding is "eye of the tiger sign." Classic PKAN presents in the first decade with dystonia, dysarthria, intellectual impairment, retinopathy, optic atrophy and progresses rapidly, leading to loss of ambulation by mid-adolescence. The atypical form of PKAN presents in late adolescence (around aged 20), manifesting as a progressive picture of dementia, Parkinsonism, dystonia, anarthria, and aphonia.[2] Herein, we report a compound heterozygote *PAKN2* mutation in two Taiwanese siblings with atypical PKAN.

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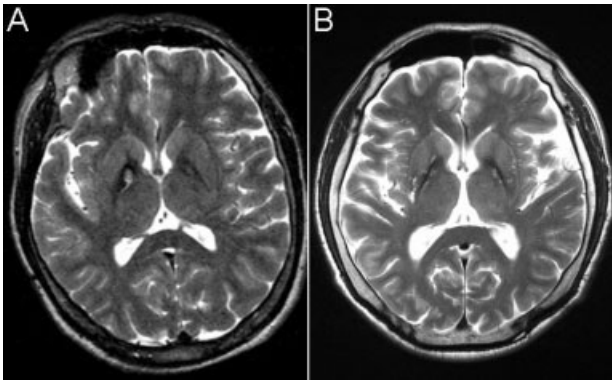

FIG. 1. Magnetic resonance imaging of the brain showing hypointensity with a central region of hyperintensity in the medial globus pallidus, the eye of the tiger sign (Case 1, **A**) or a faint hyperintensity region within a slit hypointensity region in the medial globus pallidus (Case 2, **B**).

A 48-year-old male (Case 1) had slight mental retardation since childhood. He had right hand tremor and progressive gait disturbance for two years. Neurological examination revealed severe dysarthria, stuttering, torticollis, and tongue tremor. Mild rigidity, bradykinesia, and postural instability were found. During walking, he had wide base gait along with right foot dystonia (see video, Segment 1). His 59-year-old elder brother (Case 2) experienced progressive gait disturbance and frequent falls for 8 years. Mild dysarthria, typical parkinsonian tremor in the jaw, tongue, and all four limbs, generalized rigidity and bradykinesia, dystonia at feet, wide base gait, and postural instability were noted (see video, Segment 2). Therapeutic trials with levodopa, trihexyphenidyl, baclofen, and propranolol have been ineffective. Their grandfather had history of tremor and gait disturbance. There were no other family members with similar symptoms. Brain T2-weighted magnetic resonance imaging (MRI) showed low signal intensity in the pallidum with a slight anteromedial core of high signal intensity, as so-called "eye of the tiger" sign in Case 1, which was less typical in Case 2 (Fig. 1). 99mTc-TRODAT-1 brain SPECT (single-photon emission tomography) studies of both siblings demonstrated symmetrical mild decline of dopamine transporter in bilateral striatum, which was normally seen for their age. There was no significant benefit of L-dopa also made the diagnosis of PD unlikely.

Automated DNA sequence analyses revealed compound heterozygous mutations in the exon 3 (c.1133A>G)[3] and 4 (c.1355A>G). Both mutations predict the replacement of an aspartic acid residue with glycine (p.D378G and p.D452G). RT-PCR and cDNA sequencing further revealed that the novel c.1355A>G primarily creates a potential 5′ splice signal, leading to a 58-bp deletion in exon 4 (c.1355_1412del).

To our knowledge, this would be the first *PANK2* mutation reported in Taiwan with atypical PKAN.

Numerous mutations underlying PKAN have been reported, generally nonsense mutations with typical form and missense mutations with atypical form.[4,5] Reports in ethnic Chinese are relatively sparse; only compound missense *PANK2* mutations for a Chinese patient with atypical PKAN were reported.[6] Both p.D378G and p.D452G are likely pathogenic being highly conserved across species. Moreover the major product of c.1355A>G is c.1355_1412del, resulting in predicted protein truncation and no residual activity. PANK2 is primarily localized to mitochondria of neurons in human brain. Its deficiency is thought to cause mitochondrial accumulation of cysteine or cysteine-containing substrate, resulting in free radical generation and cell death.[7] The MRI of Case 2 did not revealed typical "eye of the tiger sign," which is reminiscent of the findings reported by Baumeister et al., in which the central hyperintensity continues to diminish and may ultimately disappear.[8]

In this report, we identified a novel mutation in the *PANK2* gene responsible for PKAN and confirmed that PKAN has a board spectrum of phenotype, even among siblings with same mutations.

Legends to the Video

Segment 1. Patient 1 has tongue and right hand tremor. The tremor has a very low-frequency and in one sequence a resting tremor on the right can be detected. Furthermore, he shows a low-frequency intention-tremor, resembling in combination with the resting tremor and a Holmes-Tremor. He has right big toe dystonia, mild bradykinesia, and impaired rapid alternative movement. During walking, he had wide base gait along with right foot dystonia. Postural instability was detected by the pull test (see Video, Segment 1).

Segment 2. Patient 2 has typical Parkinsonian tremor in the four limbs, mild bradykinesia, dystonia of left big toe, wide base gait, and postural instability.

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Dopamine Transporter Binding is Reduced Following Disulfiram-Induced Striatal Damage

Disulfiram is an aldehyde dehydrogenase inhibitor, which is used as an adjunctive agent in severe chronic alcoholism because of its antabuse effect. It has neurotoxic properties resulting in neuropathy, optic neuritis, encephalopathy, and pallidoputaminal necrosis.[1] In the latter case, delayed-onset movement disorders such as akinesia and dystonia have been observed.[2–4]

We report 2 patients who showed striatopallidal damage with involvement of the dopaminergic nigrostriatal pathway in disulfiram-induced encephalopathy.

A 70-year-old woman with chronic alcohol abuse was admitted for acute encephalopathy. She had already presented 2 weeks before at the emergency room because of a fall due to acute ethanol intoxication. A CT scan was normal. As she was motivated to stop drinking, disulfiram (500 mg/day) was started for the first time. The patient left the emergency room without obvious signs of encephalopathy or Parkinsonism.

Clinical evaluation showed a somnolent patient with gait difficulties, mild bradykinesia of the upper left limb, and a bilateral extensor plantar response. Blood tests revealed macrocytosis (106 fl) and slightly below-range serum cobalamin (190 pmol/L, N > 197), but no signs of acute alcohol

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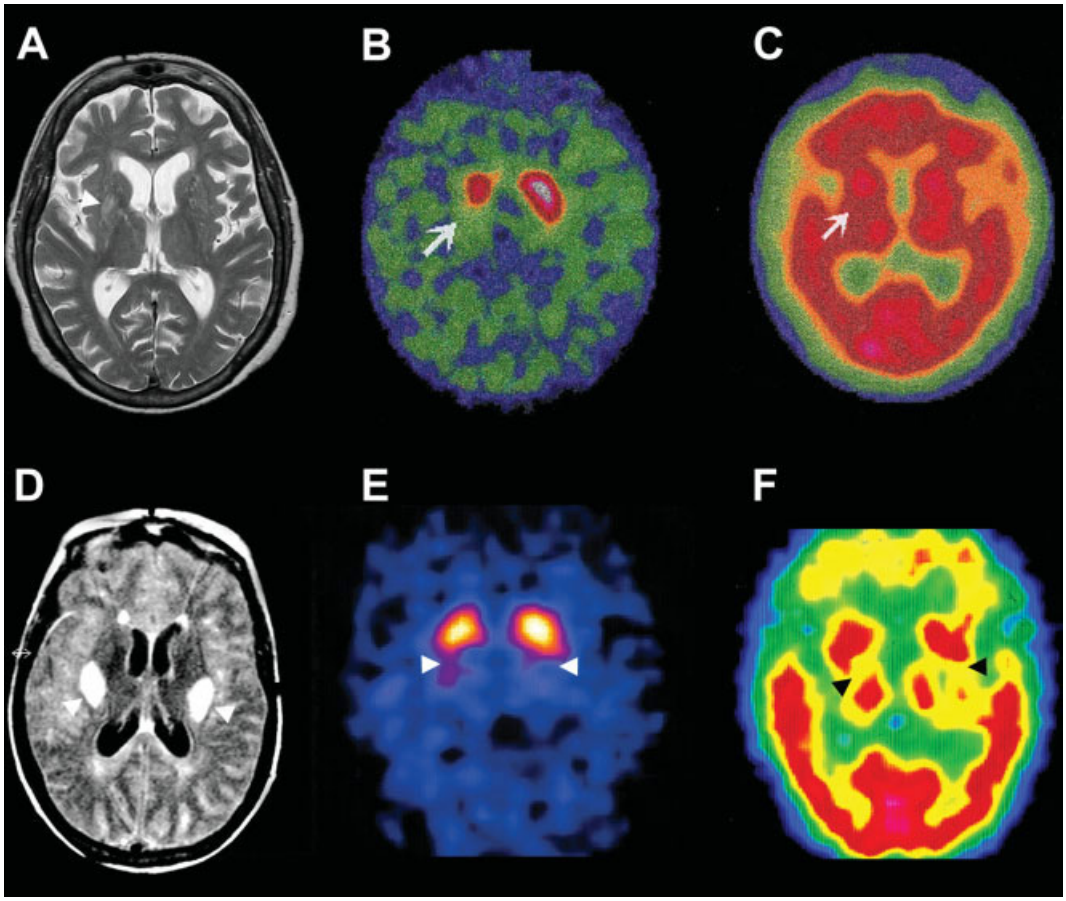

FIG. 1. Patient 1: (**A**) T2-weighted imaging shows an abnormal hypersignal mainly in the right putamen (arrowhead). (**B**) Low uptake in the right posterior putamen on β-CIT-SPECT (arrow). (**C**) HMPAO-SPECT shows low uptake in the right posterior putamen (arrow). Patient 2: (**D**) T2-weighted imaging shows an abnormal hypersignal in both posterior putamena (arrowheads). (**E**) Low uptake in both putamena on β-CIT-SPECT (arrowheads). (**F**) HMPAO-SPECT shows low uptake in left posterior putamen (arrowhead). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

intoxication. EEG showed diffuse slowing. Brain MRI disclosed T1-hypointense and T2-hyperintense signal abnormalities of the right pallidum (Fig. 1A), which were less pronounced on a control MRI 1 year later. HMPAO-SPECT showed a reduced signal in this area and β-CIT-SPECT revealed reduced dopamine transporter density in the right posterior putamen (Fig. 1B,C). The patient progressively recovered, but mild bradykinesia of the upper left limb, gait difficulties, and cognitive impairment persisted at the patient's discharge. Six months later, mild bradykinesia was still observed and levodopa treatment was initiated (300 mg/day) allowing perfect symptom control.

A 54-year-old woman was found comatose at home with mild signs of hypoxemia. She was subsequently admitted to the intensive care unit for acute encephalopathy and aspiration pneumonia requiring artificial ventilation. She suffered from chronic alcoholism and had already been admitted to the emergency room 2 months earlier with acute ethanol intoxication and dehydration. At that time, a CT scan was normal. She decided to stop drinking, and disulfiram was initiated (500 mg/day) for the first time. The patient returned home after several days without obvious signs of encephalopathy or Parkinsonism.

Lab testing for acute alcohol intoxication was not performed in the emergency room. MRI disclosed a bilateral T1-hypointense and T2-hyperintense signal in the posterior putamen (Fig. 1D), partly extending to the left pallidum. The extent of the pallidoputaminal lesion had considerably decreased on a control MRI 2 months after admission. HMPAO-SPECT showed a reduced signal in the left posterior putamen, whereas β-CIT-SPECT revealed a reduced signal in both posterior putamena (Fig. 1E,F), which was more pronounced on the left. She recovered from coma 6 days after admittance and was found to be mildly tetraparetic, predominantly on the right with an extensor plantar response on the same side. Mild postural tremor of both upper limbs, dysarthria, and difficulties of swallowing were noted, requiring transient feeding through a nasogastric tube. The patient almost completely recovered after 3 months with a persisting extensor plantar response on the right side.

We report 2 new cases of pallidoputaminal damage in relation to disulfiram intake. Concomitant aggravating factors

may have been slight cobalamin deficiency in the first patient and mild hypoxemia in the second. Disulfiram neurotoxicity is frequent and can occur during regular treatment without alcohol consumption or vitamin deficiency.[1]

The MRI lesion was almost restricted to the right putamen in patient 1 and her bradykinesia responded well to L-dopa. This suggests a specific toxic affinity of disulfiram to dopaminergic terminals in this patient. By contrast, the lesion largely exceeded the area of dopaminergic terminals in patient 2, which is in agreement with previous observations and argues against an exclusive toxicity of disulfiram on dopaminergic terminals.[2–4] Because postmortem studies are missing, the exact mechanisms of disulfiram-induced dopaminergic denervation remain unclear. Acute disulfiram intoxication increases dopamine release, probably by affecting the Mg^{2+}/ATPase activity-dependent uptake of dopamine.[5] It is noteworthy that the uptake of gamma-aminobutylic acid (GABA) and glutamate also relies on Mg^{2+}/ATPase activity. Thus, disulfiram may increase extracellular concentrations of glutamate in the basal ganglia leading to unspecific glutamate-induced excitotoxicity.[6] Disulfiram further impairs proper functioning of cell enzymes by forming mixed disulfides and chelating metal ions. In this view, diethyldithiocarbamate, a disulfiram metabolite, inhibits superoxide dismutase activity[7] and causes nigral cell loss in mice with nontoxic doses of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.[8]

Although we cannot completely exclude pre-existing infraclinical Parkinsonism in both patients, the present observations suggest that disulfiram may have toxic effects on striatal dopaminergic fibers.

Contributor Roles: W. Meissner wrote the first draft of the manuscript. All other authors (F. Macia, A. Foubert-Samier, M. Guyot, E. Bussy, M. Allard, and F. Tison) reviewed the first draft and their critique has been integrated in the final version of the manuscript.

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Infantile Hypokinetic-Hypotonic Syndrome due to Two Novel Mutations of the Tyrosine Hydroxylase Gene

Video 

Tyrosine hydroxylase (TH) deficiency is an autosomal recessive disorder varying in both phenotype and response to L-dopa. We report the case of an infant with an unusual phenotype and two novel *TH* mutations.

Born in Guatemala, the girl had not acquired head control, had axial hypotonia and limb hypertonia at the age of 9 months when she was adopted. At 13 months, she was able to sit. During infectious episodes, her motor abilities temporarily worsened and she became floppy, could not hold her head and had bilateral ptosis. She presented no excessive sweating, temperature instability, or oculogyris crises. At 23 months, she had normal cognitive development, but persistent axial hypotonia with limited ability to maintain an

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upright position while sitting. She had marked amimia and akinesia with few spontaneous limb movements (Video segment 1). During voluntary movements, symmetrical dystonia and tremor of the extremities appeared with pes equinovarus and an inability to pick up small objects. Dystonia was present throughout the day, whereas axial hypotonia showed diurnal variation, worsening in the evening and improving in the morning or after a nap when she was able to stand up if helped.

Although limb dystonia only partially improved following initiation of low dose L-dopa (0.7 mg/kg/d) treatment, axial tone dramatically improved allowing independent walking one month later (Video segment 2). Higher dose L-dopa was tried but induced dyskinesia and irritability. Brain MRI, routine blood tests, and metabolic investigations were normal. No mutation was found in the GCH1 gene. During a one week treatment interruption period necessary for the analysis of pterins and biogenic amines in the cerebrospinal fluid (CSF) by high-performance liquid chromatography, the patient lost the ability to walk. Pterins, 5 hydroxyindoleacetic (5HIAA) and 3 ortho-methyl-dopa concentrations were normal; homovanillic acid (HVA) concentration was in the lower range: 254 nmol/L (normal range 211−871) and the ratio HVA/5HIAA was low: 0.7 (normal 1.5−3.5) suggesting a TH deficiency. Sequencing of the TH gene revealed two heterozygous mutations: p.Phe375Leu/p.Ser467Gly not encountered in 85 controls. During follow-up, L-dopa was slowly increased up to 1.7 mg/kg/d. Motor abilities were normal at 6 years, except for the persistence of mild dystonic movements of the hands, and L-dopa induced hyperkinesia and dyskinesia resulting in impaired handwriting. IQ, measured by Weschsler Preschool and Primary Scale of Intelligence, was within normal range (VIQ 105, PIQ 103), but executive speed was below average (77).

Since the first description of TH deficiency in 1995,[1] 29 cases have been reported with a wide range of phenotypes falling into three main categories: Dopa Responsive Dystonia (DRD) (9/29), severe progressive encephalopathy in infancy (6/29), and infantile Parkinsonism (14/29). DRD begins between 1 and 5 years of age[1,2] with the phenotype initially described by Segawa showing dramatic and sustained improvement with low dose L-dopa therapy. Severe progressive encephalopathy occurs within the first few months of life with marked truncal hypotonia, peripheral rigidity, tremor, and myoclonic jerks.[3] Symptoms of catecholamine deficiency with lethargic episodes, excessive sweating and salivation, ptosis, and oculogyric crises are frequent, with mild to moderate mental retardation. Response to L-dopa therapy is null or limited by intolerable side effects such as hyperkinesia and irritability. Infantile Parkinsonism starts before the age of one year[4] and shows better response to L-dopa. Patients have no or mild mental retardation and less severe dysautonomic symptoms.

The present case, associating prominent severe axial hypotonia, normal cognitive functions, and an absence of severe dysautonomia, therefore represents an unusual phenotype. The diurnal fluctuation of axial hypotonia and increased floppiness during infectious episodes with ptosis are the hallmarks of our observation.[5] The decreased HVA/5HIAA ratio rather than a decreased HVA level in the CSF led to the diagnosis of TH deficiency. Other possible diseases such as juvenile Parkinson's disease or mitochondrial disorders were considered[6,7] but rejected based on the age at onset, the clinical features and the normal lactate levels in plasma and CSF. Moreover, this patient has two missense mutations, absent in controls and located in the catalytic domain of the protein thereby predicting deficient activity.

The diagnosis of this often treatable rare condition needs to be made from a large spectrum of early onset movement disorders. Diurnal fluctuations of axial hypotonia and dysautonomic symptoms are suggestive of the diagnosis and should lead to the study of biogenic amines in the CSF and the complete analysis of the TH gene.[8]

Legends to the Video

Segment 1. At age 23 months, she presented hypokinesia and axial hypotonia and could not stand up unaided.

Segment 2. After one month of L-dopa therapy, she was able to walk independently.

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Life-Threatening Hypothermia in Parkinson's Disease

Hyperthermia has been described as the symptom of neuroleptic malignant syndrome. However, it is rare to find a patient with Parkinson's disease (PD) developing life-threatening hypothermia. A 58-year-old man with PD had been treated with levodopa/carbidopa, cabergoline, and quetiapine fumarate developed life-threatening hypothermia. The common causes of hypothermia have not been determined. It is possible to speculate that his thermoregulation breakdown and/or the drugs administered to him such as dopamine D2 receptor agonist may affect the thermal homeostasis mechanisms. Although it is rare to see a patient with PD with life-threatening hypothermia, the awareness of clinical entity of hypothermia should be kept in mind.

In patients with PD, hyperthermia is a symptom that needs careful treatment because it is the core symptom of neuroleptic malignant syndrome. However, it is rare to find a patient with PD developing recurrent, life-threatening hypothermia.

Case report: A 58-year-old man with PD was admitted to our emergency room for impairment of consciousness on 15 December. He had been diagnosed with PD at the age 45, and had since been treated with dopamine replacement therapy. At the time of admission, he was being treated with L-dopa/carbidopa 500 mg per day, cabergoline 2 mg per day, and quetiapine fumarate 50 mg per day. He had been treated with quetiapine for 3 years to control visual hallucinations; without inducing any prominent deterioration of his motor symptoms. His daily activities were limited because of motor fluctuations, which were about Hoehn–Yahr Stage III during "on" and stage V during "off". Over the last few years, his cognitive function had gradually deteriorated (MMSE = 20). Further increasing the dose of his dopamine replacement therapy had resulted in deterioration of his psychiatric symptoms. In the weeks before admission, his caregivers had occasionally noticed that his temperature was extremely low (below 35°C), but did not take him to hospital because he looked well, as usual. On admission, his temperature was 32°C and blood pressure 107/68 mm Hg, pulse rate 45/min, and respiratory rate 15/min. He was in a stupor with his eyes opening spontaneously. No voluntary movements of limbs or body were noted. There was marked muscular rigidity but no overt tremor or shivering. Results of routine laboratory tests, including thyroid function, were normal. Brain CT was normal. EKG demonstrated J waves as described by Osborn, known to be characteristic in hypothermia. He suddenly developed ventricular tachycardia, resulting in cardiopulmonary arrest, but he was soon resuscitated. His rectal body temperature was found 33.1°C. To improve his life-threatening hypothermia, warming with an electric blanket and intravenous administration of warm saline was immediately started. Subsequently, his rectal temperature slowly improved, and he eventually recovered without any sequelae, suggesting that hypothermia was the primary problem. His caregivers stated that he preferred to wear light clothing but was never exposed for long to low temperatures. Indeed, he usually spent the daytime in a nursing home and the evening at his home, both had air-conditioning and heating systems. His caregivers were asked to check his body temperature regularly after he was discharged and not let him wear light clothes. In the 18 months following this event, he never developed a similar episode.

The exact cause of the life-threatening hypothermia in the present patient was unclear, although it was suggested that PD could be a predisposing factor of hypothermia.[1,2] We think that hypothermia should not be regarded as an accidental event or as unrelated to PD or its treatment. This is because the common causes of hypothermia, such as prolonged exposure to low temperatures, serious endocrine disease, and malnutrition have not all been determined. Additionally, from Japan Meteorological Agency records, the average temperatures in the area, that is December, was 8.8°C, suggesting that cold circumstances did not cause his hypothermia. It is also interesting to note that he never complained of feeling cold, despite the low body temperature, and that he did not exhibit shivering, suggesting that there might be some derangement of his thermal homeostasis systems. It is possible to speculate that his thermoregulation breakdown might have involved the hypothalamus or hypothalamic outflows to the brainstem. Another possibility is that the drugs administered to him may have worsened his hypothermia. There are reports suggesting that dopamine D2 receptor stimulation may affect the thermal homeostasis mechanisms.[3] Experimentally, in rats, dopamine D2 receptor agonist-induced hypothermia in cold environments may be mainly due to decreased heat production, rather than to increased heat loss.[4] Atypical neuroleptics might also may be involved in hypothermia[5]; however, to our knowledge, quetiapine has not been reported in this regard.

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Although it is rare to see a patient with PD with life-threatening hypothermia, the possibility that hypothermia can occur during the course of PD should be kept in mind, because it may be potentially fatal if undetected or overlooked.

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A Multimodal Approach to Physical Therapy in Parkinson's Disease: Optimizing Strategies

The recent systematic review of exercise interventions for Parkinson's disease (PD) by Goodwin and colleagues[1] reinforces the evidence supporting a role of exercise in the management of PD.[2,3] The authors focused solely on exercise-based interventions in experimental, randomized designs. Studies explicitly evaluating cueing strategies were excluded as such techniques were considered external temporal or spatial stimulation to facilitate gait separate from the act of exercising. Using such criteria, Goodwin and colleagues conclude that exercise benefits physical functioning, balance, gait speed, strength, and health-related quality of life.

We commend the authors' methodology in addressing the important issue of the lack of homogeneity in the interventions and study designs used to ascertain effect of physical therapy in PD. Although the exclusion of studies explicitly evaluating cueing strategies homogenizes the intervention and enables extracting information regarding the individual contribution of exercise, we wonder how to place such findings in the context of the recent recommendations of physical therapy in PD published in this journal by Keus and colleagues.[4] These evidence-based recommendations were more inclusive of physiotherapeutic techniques, and included cueing strategies, cognitive movement strategies to improve transfers, specific exercises to improve balance, and training of joint mobility as well as muscle power.

In planning future studies of physiotherapeutic interventions in PD, both methodologies have their merits and different goals. Restricting interventions allows one to ascertain the efficacy of specific techniques while risking smaller effect size and thus non-significant findings. Combining multiple modalities at once (i.e., cueing and exercise) may maximize treatment effect at the cost of not knowing the contribution of an individual technique. It is possible that simultaneous interventions (i.e., cueing and exercise) are redundant, additive, or synergistic. However, it would not be possible to know if each potential therapeutic component were tested only in isolation. One approach may be to first test interventions that simultaneously employ multiple modalities. If these seem effective, one may then test each modality in isolation to determine its individual contribution to therapeutic benefit. However, such an approach carries its own risk, as it is conceivable that combined interventions may be less effective than individual techniques. For example, psychomotor difficulties or complications that occur in the later stages of PD may make it too difficult for participants to engage in both cueing strategies and exercise simultaneously.

We appreciate the work of Goodwin, Keus and others as they have highlighted the limitations and fragilities of past trials regarding trial design, patient selection, and duration of therapeutic effect. Such reviews assist in planning future studies in physiotherapeutic interventions for PD.

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Corticobasal Degeneration Presenting as Complex Regional Pain Syndrome

Video 

Corticobasal degeneration (CBD) is a neurodegenerative disorder characterized by progressive asymmetric motor signs including rigidity, bradykinesia, myoclonus, and dystonia, unresponsive to levodopa, together with asymmetric apraxia, alien limb phenomenon and cortical sensory loss, suggesting cortical and basal ganglia dysfunction.[1,2] Despite a high specificity of CBD clinical diagnosis, sensitivity is low (35%).[3] In fact, several cases of PSP, Alzheimer's disease, Creutzfeldt-Jakob disease, frontotemporal dementia, parkinsonism linked to chromosome 17 (FTDP-17I) and multi-infarct disorder can present with a CBD-like syndrome (CBS).[1,4] Conversely, there is a substantial overlap of clinical symptoms with other entities.[1]

Complex Regional Pain Syndrome Type I (CRPS I) is a systemic disease characterized by sensory and autonomic disturbances of an extremity, usually after a noxious event.[5] Interestingly, in the subacute and chronic phase of CRPS Type I, patients may develop motor changes including weakness, bradykinesia, dystonia, myoclonus and tremor.[6]

We report a patient who met clinical criteria of CBD, mimicking CPRS.

A 71-year-old right-handed man noticed progressive writing impairment 4 yr before presentation. During his twenties, he was an amateur boxer who restarted this practice a few months before noticing writing and signature abnormalities. His personal history was relevant for arterial hypertension, brain lacunar state without thalamic involvement, duodenectomy, gallblader surgery, and post-transfusional hepatitis C. The family history was irrelevant. Several treatments were all unresponsive (levodopa, dopamine agonists, selegiline, baclofen, and benzodiazepines).

After 2 yr, he reported severe paroxysmal pain, stiffness, jerking tremor, and a dystonic posture of the right upper limb. Fourteen days before admission, he suffered a right clavicle fracture. Neurological examination showed a patient with right flexed elbow, intense pain and skin maceration with nails digging into the palm, a clenched fist, characterized by wrist flexion, thumb in palm, extension at the second finger and flexion at the third, fourth, and fifth metacarpophalangeal joints. He had paroxystic painful accesses, either spontaneous or induced by any attempt to extend the fingers. A levitation phenomenon, myoclonus, tremulousness, and dystonia were evident in the right upper limb at rest and aggravated during action, with a stimulus-sensitive component. Dysautonomic phenomena such as skin discoloration, temperature changes, abnormal sudomotor function, and edema were also evident.

A brain and cervical MRI showed temporoparietal atrophy predominantly on the left hemisphere, multiple gliotic ischemic lesions, and a degenerative spinal C5–C6 discopathy.

TABLE 1. *Common CBD and CRPS symptoms*

	CBD	CRPS
Age onset	6th–8th decades	6th–8th decades
W/M ratio	Women>Men	Women>Men
Prevalence	4.9–7.3/10[5]	0.002–40%
Presentation	Asymmetrical	Asymmetrical
Anatomical	Cortical, basal ganglia	Cortical, basal ganglia
Mov	Parkinsonism	–
Dystonia	71%	20%(91%)[a]
Myoclonus	Stimulus-sensitive and action	30–36% at rest worsening during action
Pain	3%	100%
Clenched fist	Thumb included and thumb and fingers held	Flextion of the 3rd, 4th, 5th, thumb adducted and second extension

[a]20% of patients with CRPS showed movement disorders, 91% presented dystonia.

The X-ray of right arm, routine blood tests, and CSF examination were normal. A diagnosis of CRPS I was suggested. Although, BTXA injections improved the dystonic posture, a severe increase of paroxysmal pain was identified. Over the last year, balance, postural instability, and motor symptoms progressed to involve all limbs. Progressive mood disturbance, cognitive impairment, ideomotor apraxia, confusional state, and fluctuating visual hallucinations responsive to quetiapine 50 mg/day were identified. Gabapentin 1,200 mg/day and levetiracetam 500 mg/day induced moderate pain relief and myoclonus improvement, respectively.

Six years after onset, a CBS was evident; the patient was dependent for all daily life activities and remained with occasional pain.

The disproportionate character of complaints, paroxystic painful accesses, limited active range of motion and temperature asymmetry would provide in this patient a good indication of CRPS I with high sensitivity (94–100%).[5] However, the writing impairment at the beginning of the symptoms and the subsequent clinical course were also consistent with the diagnosis of CBD according to Riley and Lang's criteria.[3]

CRPS and CBD share common features (Table 1); both syndromes involve cortex, basal ganglia, and thalamus.[1,6] In fact, dystonia represents 91% and 71% of movement disorders identified in CRPS and CBD, other than parkinsonism,[4] whereas myoclonic jerks have been observed in 30% of patients with CRPS and in more than half of individuals with CBD.[2]

On the other hand, pain is the main symptom of CRPS, whereas in CBD, it occurs in only 3% of cases.[4]

Finally, the low prevalence estimated for both conditions (CBS: 4·9–7·3 per 100,000; CRPS: 0.002–40%), seems to make a casual or random association improbable.[7] In summary, even if one of the most important limitations of our case is related to the absence of an anatomopathological study confirming the diagnosis, we suggest that CRPS Type I should be included in atypical CBD presentations.

Legends to the Videotape

Segment 1. This segment shows a patient who presented with right upper rigidity, jerking tremor and myoclonus and

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dystonia. He complained of pain and difficulty in using his right hand; the intention to open his hand or extend his arm induced pain and myoclonus. A clenched right fist is observed with changes in blood flow and edema. Levitation phenomena was present. The same patient after botulinum toxin A injections with moderate improvement in the hand posture.

Segment 2. One year after previous examination. The video shows upper limb flexor posture, myoclonus, and apraxia in lower limb foot tapping.

Segment 3. The patient today, 6 year after onset of symptoms.

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