Frontotemporal Dementia with Parkinsonism Presenting as Posterior Cortical Atrophy

Posterior cortical atrophy (PCA) represents a degenerative disorder characterized by the development of higher-order visual deficit.[1] PCA may result from heterogeneous pathologies that make up tauopathies. An increasing number of mutations in the *tau* gene (microtubule-associated protein tau [MAPT]) causes a wide spectrum of clinical presentations known as frontotemporal dementia with parkinsonism linked to chromosome-17 (FTDP-17).[2] Symptomatology usually involves executive dysfunction and altered personality and behavior, with patients displaying parkinsonian features.

We describe the case of a woman with PCA who further developed asymmetric motor signs. A mutation in the *MAPT* gene was detected, and a diagnosis of FTDP-17 was formulated. To our knowledge, this is the very first report of a patient suffering from FTDP-17 diagnosed with posterior cortical atrophy.

Case Report

A 55-year-old woman started suffering in 2006 from altered perception of human faces. Initially the visual distortion was fluctuating; over the following year it became constant, and she could not recognize her husband and children by their faces anymore. She further developed visuospatial deficits, with difficulty in localizing stimuli, judging distances, or orienting herself in familiar surroundings. A first neurological examination revealed visual agnosia. She had no visual hallucinations or personality changes. Biochemical investigations and CSF analysis were normal. Her mother suffered from dementia that started when she was 80. Genetic tests for Alzheimer's disease genes (betaPP, PS1, PS2) were performed, revealing normal alleles.

As the disease progressed, she developed difficulties manipulating objects with her left hand. On further neurological examination, she showed marked ocular apraxia, and she appeared to be cortically blind. Motor signs appeared and were confined to her left arm, with plastic rigidity, bradykinesia, and postural tremor; dopaminergic treatment was not tolerated.

Brain magnetic resonance imaging (MRI) showed slight signal alteration in parieto-occipital white matter bilaterally without significant atrophy; an 18F-FDG PET brain study demonstrated decreased metabolism in the posterior parietal and occipital regions, compatible with PCA. To investigate her asymmetrical motor signs, a quantitative analysis was performed, revealing asymmetrical dysfunction of the nigrostriatal system (Fig. 1). Over the following years she developed complete blindness except for lights, with marked asymmetrical motor signs and apraxia, initially interpreted as a corticobasal syndrome (CBS). Second-level genetic testing revealed a missense mutation, V363I, in exon 12 of the microtubule-associated protein tau (*MAPT*) gene. To date, her cognitive functions and insight are still preserved.

Discussion

There have been no reports so far of patients with mutations in the *MAPT* gene who were diagnosed with PCA. Moreover, to our knowledge, this is the first reported case of PCA documenting an "in vivo" dopaminergic system deficit, indicative of a "PD-like" neuron terminal loss.

In our patient prosopagnosia progressively evolved into a complex visuospatial disorder compatible with PCA. The right temporal lobe has been implicated in prosopagnosia in patients with semantic dementia[3]; nonetheless, in our patient the temporal lobe was relatively spared from degeneration (Fig. 1). For some time, motor dysfunction was reminiscent of CBS. To date more than 30 mutations have been identified in the *MAPT* gene as causes of familial FTD, usually referred to as FTD with parkinsonism linked to chromosome 17 (FTDP-17).[4] In our case, genetic testing revealed a mutation in a highly conserved *MAPT*-gene region. Apraxia and visuospatial dysfunction have been rarely depicted in the course of FTDP-17, and they usually occur in progranulin (PGRN) mutations.[5]

The described missense mutation, V363I in the *tau* gene, so far has been associated with semantic dementia[6] and with progressive nonfluent aphasia.[7] Interestingly, Bessi and coworkers described a woman developing severe impairment in language who presented with prosopagnosia just at the beginning of her neurological deterioration.[6]

In our case, the pattern of degeneration started dorsally, from occipital cortical areas, progressing ventrally to involve the parietal-frontal regions and the deep gray matter. Why different brain regions are so sensitive to small changes in tau is still a challenge.

Our case report suggests considering FTDP-17 in the differential diagnosis of patients suffering from PCA with parkinsonism, even without striking behavioral/cognitive changes.

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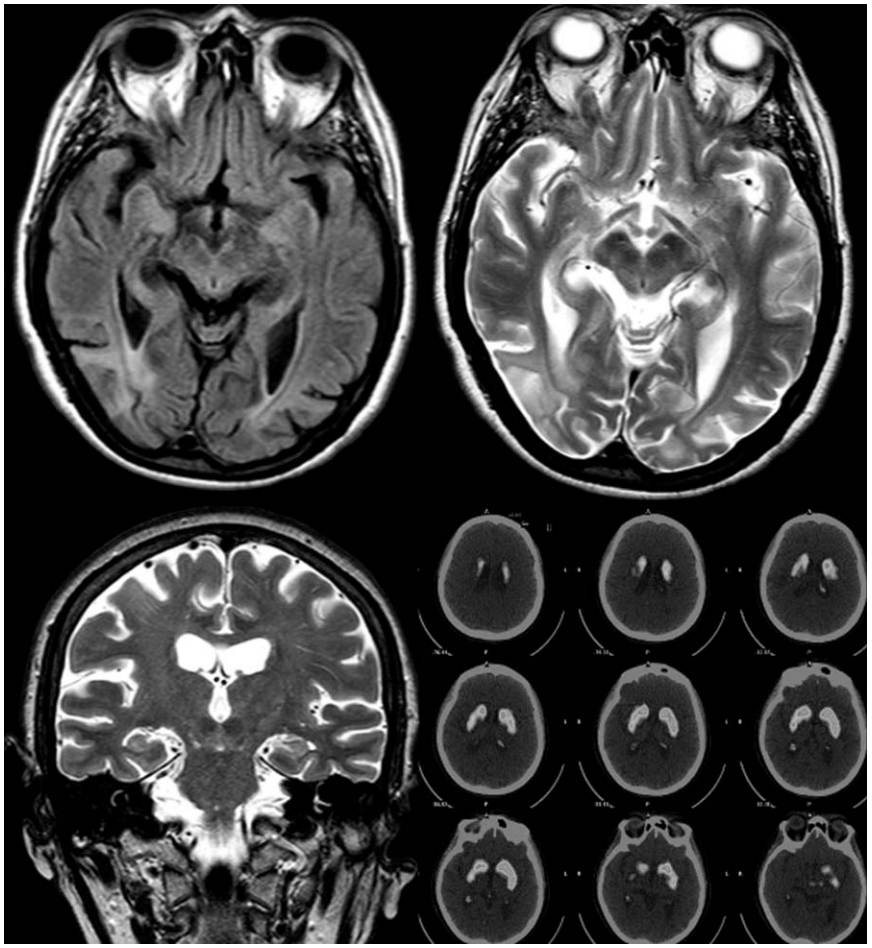

FIG. 1. At the top of the figure, axial MRI scans reveal T2-weighted white matter hyperintensities involving posterior brain areas, expression of ongoing neurodegeneration. The coronal MRI section shows that the temporal lobes are preserved from degeneration relative to the parieto-occipital regions. Quantitative [11C] N-(3-fluoropropyl)-2b-carbonethoxy-3b-(4-iodophenyl) nortropane (FP-CIT) PET analysis detected a marked decreased FP-CIT uptake in the right striatum (right caudate, 3.98 [n.v. 4.97 ± 0.63]; right putamen, 2.98 [n.v. 4.69 ± 0.75]), revealing asymmetrical dysfunction of the nigrostriatal system.

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Encephalitis Lethargica Due to Epstein–Barr Virus Infection

There is circumstantial evidence to suggest that sporadic encephalitis lethargica (EL) might be a postinfectious immunological disorder affecting gray matter, and in some instances it may follow a streptococcal infection.[1] MRI in patients with EL has shown lesions in bilateral substantia nigra compatible with the clinical findings.[1,2] We describe a 20-year-old woman who was 20 weeks' pregnant who 1 week after an upper respiratory tract infection developed parkinsonism,

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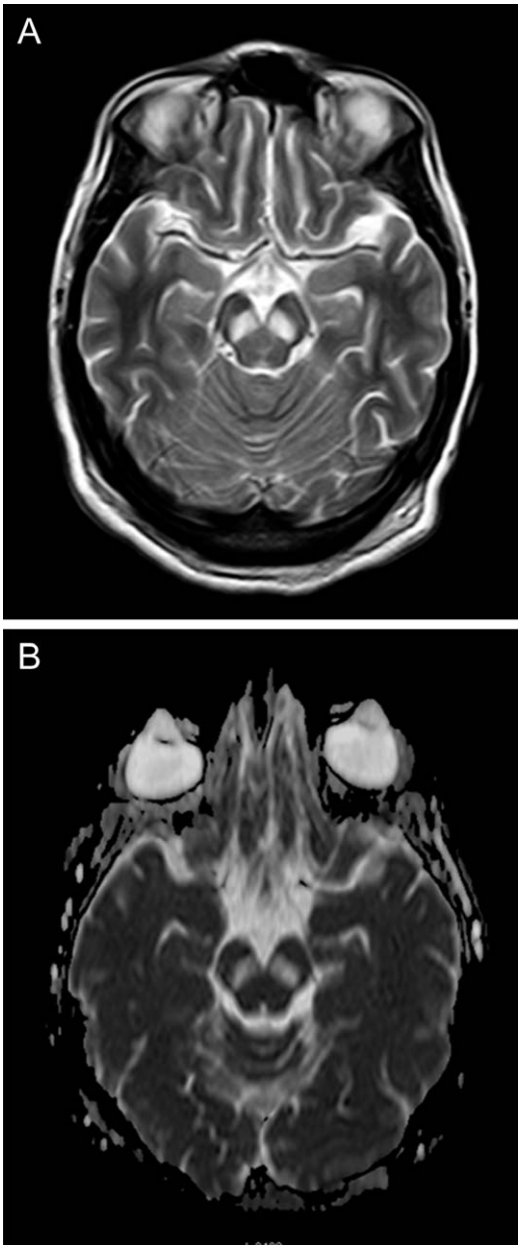

FIG. 1. A: Axial T2-weighted image shows bilateral symmetric hyperintense lesions compromising the pars compacta of the substantia nigra. **B:** Apparent diffusion coefficient demonstrates no restriction, excluding ischemic lesions.

somnolence, lethargy, and autonomic, oculomotor, and neuropsychiatric signs.

The patient developed a sore throat, malaise, headache, fever, and vomiting, and 1 day before admission, she became uncoordinated and unsteady on her feet.

Examination revealed a temperature of 38°C, hypersomnolence, tachycardia, and delirium. The patient was mute and had severe postural and kinetic tremor of the limbs. Three days after admission, she developed lethargy, dysphagia, hyperventilation with irregular, fast, shallow breathing and began to sweat profusely. This was followed a week later by the development of bradykinesia and rigidity. She also had waxy flexibility of the limbs, mutism, gaze-evoked nystagmus, a supranuclear vertical gaze palsy with delayed latency of saccadic eye movements, marked lip protrusion, and severe axial dystonia with spasms.

On admission, laboratory investigation showed neutrophilia (74%). CSF analysis revealed 10 lymphocytes/mm^3, with normal glucose and protein levels. A CAT brain scan on admission showed no abnormalities. T2-weighted MRI images on the third day after admission showed bilateral and symmetric hyperintensities of the pars compacta of the substantia nigra (Fig. 1A), and 3 months later cystic encephalomalacia of the nigra had developed (Fig. 1B). EEG showed disorganized diffuse, intermittent slow-wave activity. Somatosensory, brain stem auditory, and visual-evoked responses were normal.

Repeated serological response to Epstein–Barr virus (EBV) was positive for specific antibodies to viral capside antigen (VCA IgM), and CSF polymerase chain reaction for EBV was positive (Table 1). Three weeks after admission, CSF revealed an IgG level of 8.22 mg/dL, with local synthesis of IgG in the spinal fluid. Thyroid function testing and thyroid antibodies, blood ammonia levels, and wet blood films for acanthocytes and C-reactive protein and anti-streptolysin-O titers were all within the normal range.

The patient remained lethargic for 4 weeks. A normal infant weighting 2500 g was born after 38 weeks of confinement.

One week after onset of parkinsonism, she was given levodopa, which was gradually increased to 750 mg/day. Benefit was noted 2 weeks after starting treatment, measured by the UPDRS motor score over time, with mean values of 78 at the start of treatment versus 60 after 3 months. After 3 months the patient was alert and able to feed herself and walk with assistance, and the oculomotor palsy had improved. After 6 months she was taking levodopa 875 mg/day, and she was able to walk with minimal assistance but had developed motor fluctuations. Despite increasing the dosage of levodopa to 250 mg 4 daily doses, she

Table 1. Serological and CSF findings for EBV encephalitis

Virus test	Day 7	Day 42	Day 180	Normal value
EBV VCA IgM	1.56	1.97	0.3	≤1
EBV VCA IgG	1.45	4.08	1.7	≤1
EBNA IgG	Negative			≤10
EBV CSF PCR	Positive			
Herpes simplex 1 and 2 IgG, IgM	Negative			
Cytomegalovirus IgG, IgM	Negative			
Varicela zoster IgG, IgM	Negative			
Measles IgG, IgM	Negative			
Rubella IgG, IgM; Cox B virus IgG, IgM	Negative			
Culture for enterovirus	Negative			
HS, CMV, VZ, Coxsackie, mycoplasma, ECHO, CSF, PCR	Negative			
Bacterial and mycobacterium	Negative			

VCA, viral capside antigen; EA, early antigen; EBNA, Epstein–Barr virus nuclear antigen; Cox B, Coxsackie; CSF, cerebrospinal fluid; PCR, polymerase chain reaction.

developed increasing wearing-off effects, nocturnal and early-morning akinesia (Video, segment 1), and a severe ''off'' period, with UPDRS motor score values in the ''off'' period of 54 versus 22 in the ''on'' period (Video, segment 2) after 1 year.

Sporadic cases of encephalitis lethargica are uncommon but continue to be reported.[1,3–7] In our patient the diagnosis of recent primary EBV infection was confirmed by CSF PCR and serological detection of the antibodies. The pathogenic mechanism by which EBV induces neurological injury remains incompletely understood. Evidence suggests that an autoimmune or hypersensitivity phenomenon, rather than an active viral replication, is likely to be responsible.[3]

Reversible parkinsonian syndrome associated with anti-neuronal antibodies has been a finding in acute EBV encephalitis.[7] Our case raises the possibility that Von Economo's disease may have been related to a virus such as EBV.[5–7]

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Clinical Features, with Video Documentation, of the Original Familial Lewy Body Parkinsonism Caused By α-Synuclein Triplication (Iowa Kindred)

We previously reported triplication of α-synuclein in a large kindred with autosomal dominant parkinsonism.[1–5] Here we share videotapes of selected cases (see abbreviated pedigree in Fig. 1A).

Case 9-77 (Video Segment 1)

This woman noted insidious, progressive right upper extremity (RUE) resting and activation tremor and stiffness at age 30. She noted parasomnias suggesting REM behavior disorder (RBD) and depression several years prior to motor symptoms. Handwriting became small and tremulous. She also experienced urinary urgency. Examination (age 32) revealed RUE resting and activation tremor and cogwheel rigidity. She was diagnosed with Parkinson's disease (PD) and treated with carbidopa/levodopa with good response, although dyskinesias occurred within 3 years. Subsequently, ropinirole gave some benefit (Video Segment 1). Neuropsychometry (age 32) found no abnormalities. However, by age 41, there was significant reduction in IQ, working memory, executive functioning, visuospatial processing, and psychomotor speed. Donepezil was prescribed with some cognitive improvement. She was bedridden in 12 years. She suffered auditory and visual hallucinations, parasomnias, restless legs symptoms, and intermittent myoclonus. On her last examination (49 years), she exhibited severe bradykinesis and rigidity with contractures. Hypophonia limited mental status testing; however, audible speech content was appropriate. Eye movements remained full, but pursuits were severely saccadic. There was no tremor. Myoclonus was intermittent. She died due to pneumonia at age 49; no postmortem examination was done.

Case 9-60 (Video Segment 2)

This otherwise healthy woman with a history of methamphetamine abuse during her third and fourth decades was fired at age 44 for physical and mental ''slowness.'' She was treated for depression with some benefit, but the motor problems persisted. Within 18 months, she noted activation tremor and symptoms of RBD. By age 46 her cognition and

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

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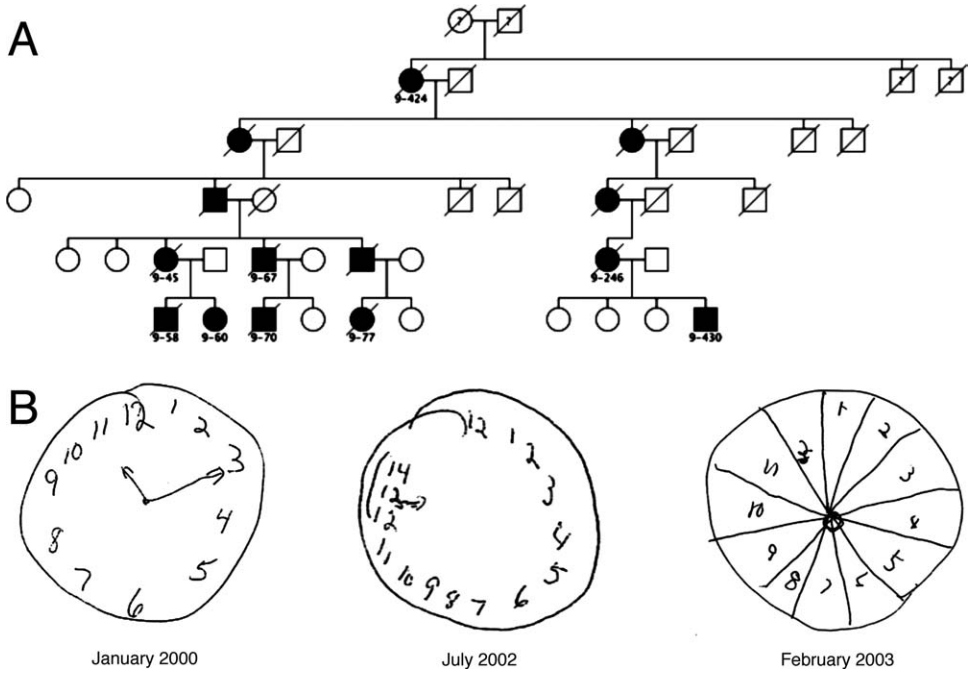

FIG. 1. A: Abridged pedigree. Affected individuals are shown in solid black. **B:** Progressive worsening of case 9-60's constructional apraxia over a 3-year period.

movement would fluctuate over hours/days. Her weight decreased from 130 to 100 pounds over the first 2 years of her illness. She had spontaneous visual and auditory hallucinations and complained of orthostatic dizziness. Carbidopa/levodopa gave moderate benefit in bradykinesis, donepezil improved cognitive fluctuations, clonazepam helped the RBD, and midodrine ameliorated orthostatic hypotension. Nonetheless, confusion mandated 24-hour care. On examination, sitting blood pressure (BP) was 98/67, and pulse (P) was 81; standing BP was 86/60 and P 90. Folstein Mini–Mental Status Examination score was 13/30, with particular difficulty on recall and sequential tasks. She scored 14 on the controlled oral word association test and 16/63 on the Beck Depression Inventory. She had marked constructional difficulties (Fig. 1B). She could not count backwards from 100, 20, or 12. She had anosmia (14/40, University of Pennsylvania Smell Identification Test). There was marked hypophonia, saccadic pursuits, and moderately masked facies. She had difficulty with rapid alternating movements. Gait was shuffling. She needed several corrective steps on the pull test. In the decade since presentation, she has become bedridden, is severely rigid, and is tube-fed. She has no spontaneous vocalizations. She is doubly incontinent and requires full-time care.

Case 9-70 (Video Segment 3)

This man noted the gradual onset of RUE resting and activation tremor at age 24. Tremor was worsened by anxiety and by intravenous cocaine, which he used prior to and during the first year of illness. Within that year, he suffered depression and attempted suicide; by age 34 he was being treated with fluoxetine, with good response. Parkinsonian symptoms progressed, with worsening tremor, rigidity, gait difficulties, and postural instability. Carbidopa/levodopa gave dramatic benefit but was discontinued several years later because of orthostatic hypotension and hallucinosis. At his last examination, at age 39 (Video Segment 3), he had severe bradykinesis and hypophonia; mental status testing was not possible. Eye movements were severely saccadic; there was severe rigidity throughout and no tremor. He could stand and walk with 1-person assistance, showing marked slowness and severe postural instability. The patient was bedridden within the year, requiring tube feeding. The subject succumbed to pneumonia at age 43. Pathological examination was previously described.[6]

Case 9-246 (Video Segment 4)

The subject was diagnosed with Parkinson's disease when 46 years old, with complaints of slowed gait and right shoulder pain.[3] She responded well to carbidopa/levodopa treatment initially. Subsequently motor fluctuations and postural instability developed. She developed "toe walking," cognitive impairment, and orthostatic hypotension and thereafter became wheelchair- and subsequently bed-bound. She succumbed after 6 years. Pathological examination has been previously described.[3]

Summary

This family has autosomal dominant parkinsonism because of α-synuclein triplication. Dopamine-responsive parkinsonism, cognitive difficulties, RBD, and dysautonomia are common. End-stage illness includes contractures, myoclonus, and severe motor and cognitive impairment. Of note, there was presymptomatic amphetamine/cocaine use in 2 of the cases described.

Legends to the Video

Video Segment 1—Case 9-77. This subject has facial hypomimia (lips apart, reduced blinking), with rapid resting

tremor of right arm and adduction tremor of both legs. There is bradykinesia of repetitive finger- and foot tapping bilaterally, also affecting rapid alternating movements, left more than right, which also reveals an activation component of the tremor. When walking, there is a markedly reduced arm swing bilaterally.

Video Segment 2—Case 9-60. This subject exhibits facial hypomimia and fairly symmetric, marked bradykinesis, particularly evident during finger tapping. The clock test is abnormal. Apraxia manifests on testing of rapid alternating movements. When walking, her trunk is bent forward, and arm swing is reduced bilaterally, more so on the left.

Video Segment 3—Case 9-70. This patient, at an advanced stage of disease, has marked facial hypomimia, with the mouth open and markedly reduced eye blinking. Hands are dystonic, more so on the right. He has severe bradykinesia, whereas tremor is now mild.

Video Segment 4—Case 9-246. The subject demonstrates bradykinesis and mask facies. Asymmetric reduced arm swing is noted during gait. Walking premedication (at 52 seconds) demonstrates reduced arm swing and mild scissoring of gait with toe walking. Postmedication dyskinesia is apparent when retesting walking (at 67 seconds). Postural instability is noted. ■

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No Evidence for *THAP1/DYT6* Variants as Disease Modifiers in DYT1 Dystonia

Early-onset generalized dystonia is a rare movement disorder that can cause severe physical disability. The most common mutation in the *DYT1* gene in early-onset dystonia is a 3-bp (GAG) deletion leading to loss of 1 of a pair of glutamic acid residues (ΔE302/303) in the C-terminal region of the encoded protein, torsinA.[1] Penetrance of DYT1 dystonia is only 30%–40%, and interfamilial and intrafamilial phenotypic variability is considerable. This low penetrance can only partially be explained by a nonsynonymous polymorphism in exon 4 of the *DYT1/TOR1A* gene (D216H), with a higher frequency of the H216 allele in nonmanifesting carriers (NMCs) than in manifesting carriers (MCs) (reviewed in Schmidt and Klein[1]). A number of different mutations in the *THAP1* gene have been found to cause DYT6 dystonia, typically manifesting as early-onset generalized or segmental dystonia, frequently with prominent laryngeal involvement.[1] Interestingly, a physical interaction between THAP1 and the *TOR1A/DYT1* promoter has recently been demonstrated in vitro, and this interaction is affected by pathogenic *THAP1* mutations.[2,3] To investigate whether sequence variations in *THAP1* act as genetic modifiers for DYT1 dystonia, we sequenced the coding region and intron/exon junctions of the *THAP1* gene in 40 carriers of the *DYT1* GAG deletion from 22 families: 26 MCs, with phenotypes ranging from mild focal to severe generalized dystonia, and 14 NMCs.

Patients and Methods

Patients and relatives were ascertained from various movement disorder outpatient clinics in Germany (Genetic Network for Hereditary Movement Disorders, GeNeMove), as

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previously described,[4] and at the Section of Clinical and Molecular Neurogenetics at Lubeck University. The study was approved by institutional review boards, and all subjects gave written informed consent. The mean age of NMCs at the time of recruitment, 50.4 years (range, 15–88 years), was considerably higher than that of MCs, 23.7 years (range, 2–52 years). All samples were genotyped as positive for the *DYT1/TOR1A* GAG deletion, followed by direct DNA sequencing of *THAP1* exons 1–3 including intron/exon junctions.

Results

We did not identify any *THAP1* mutations in carriers of the *DYT1* GAG deletion, but did detect 4 previously known polymorphismic variations. Three of these variants, −237,236 GA>TT (found in 2 MCs and 1 NMC), IVS1+126 C/T (5 MCs and 3 NMCs), and IVS3-87 A>G (2 MCs and 2 NMCs), were found in both MCs and NMCs, whereas the fourth variant, IVS1+9 C>A, was identified only in 3 NMCs and not in any MCs.

Discussion

Currently, only 2 genes responsible for primary early-onset dystonia have been identified, *DYT1/TOR1A* and *DYT6/THAP1*. Recent experimental evidence demonstrated a direct physical interaction between the transcription factor THAP1 and the *DYT1/TOR1A* promoter.[2,3] In 1 of these studies,[2] binding of THAP1 to the *DYT1/TOR1A* core promoter region led to transcriptional repression of *DYT1/TOR1A* expression in a model cell culture system. This repression was diminished by DYT6-associated mutations; however, this finding remains to be verified in vivo. These studies suggest a functional link between these 2 monogenic forms of primary dystonia. We therefore hypothesized that mutations or other sequence variations in *THAP1* might influence penetrance of DYT1 dystonia. However, no *THAP1* mutations were identified in our cohort of *DYT1* GAG deletion carriers. One polymorphism that may be associated with dystonia (−237,236 GA>TT)[5] was found at comparable frequencies in DYT1 MCs and NMCs. Another single-nucleotide polymorphism in a conserved region of intron 1, IVS1+9 C>A, was only found in 3 NMCs and not in any MCs. This *THAP1* variant, which is adjacent to the consensus 5′ splice site, has been identified slightly more frequently in patients with late-onset focal dystonia (7 of 1210 and 3 of 388) compared with controls (1 of 600 and 1 of 185).[6,7] However, this apparent association was not statistically significant, and the relevance of these findings needs to be tested in further patient cohorts. In summary, our findings suggest that additional, as-yet-unidentified factors—genetic, epigenetic, or environmental—act to influence and modify penetrance and the phenotype of DYT1 dystonia. These might include as-yet-unanalyzed polymorphisms in the 5′- or 3′-untranslated regions of *THAP1*, which may influence THAP1 expression. ■

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Pathological Findings in a Case of Stiff Person Syndrome with Anti-GAD Antibodies

Stiff person syndrome (SPS) is an immune-mediated disease characterized by muscle stiffness, episodic painful spasms of limbs and trunk, and the presence of anti-GAD antibodies.[1] Anti-GAD antibodies signify multiple autoimmune diseases in addition to SPS. SPS may be a direct consequence of antibody-mediated neuronal dysfunction, but the pathogenesis remains elusive.[2] We present here clinical and postmortem findings from a patient with SPS.

A 69-year-old man was admitted with acute, severe, and painful spasm. He had a background history of hypothyroidism, pernicious anemia, sensory neuronopathy, gait ataxia, and myasthenia gravis (treated with azathioprine). Following a recent hip replacement, the patient developed pain and stiffness in his right leg. He had exquisite hypersensitivity to any tactile stimulation of the muscles of the right lower leg, triggering painful spasms, and markedly increased tone in the right leg. EMG of the gastrocnemius, biceps femoris, and lumbar paraspinals showed continuous motor unit activity at rest with exacerbation by tactile stimulation, supporting a diagnosis of SPS. Anti-GAD antibodies were positive (180 U/mL; normal < 1). An initial benefit from IVIg was not sustained, and he was treated symptomatically with antispasmodics. Over the following years the patient developed treatment-resistant persistent, severe, painful spasms with progression to involve the left leg and waist. During his final admission, 5 years after diagnosis, he developed pulmonary embolus and died. An EMG on this occasion had demonstrated fasciculations and multiple after-discharges, indicative of hyperexcitability and suggestive of Isaac's syndrome (negative voltage-gated antibodies).

Macroscopic and microscopic examination of the brain was normal. Microscopic examination of the spinal cord revealed vacuolation of motor neurons in the caudal segments (T12 to sacral; Fig. 1a), with sparing of motor neurons superior to this. Electron microscopy revealed these vacuoles to be lined by a membrane and contain invaginations that contained cytoplasmic matter (Fig. 1b–d). These then appeared to ''bud off'' from the inner surface of the vacuole into the vacuole itself and degenerate. A number of lipofuscin-containing lysosomes with features of hydropic swelling were observed in the cytoplasm of affected cells, suggesting that the vacuoles may represent hyperswollen lysosomes. There was no significant lymphocytic infiltrate, as has been described in other case reports/series,[3,4] likely because of extended immunosuppressive treatment. Immunohistochemistry: CD68 revealed a microglial reaction in the gray matter; GFAP demonstrated marked gray matter gliosis. There was no associated lymphocytic or neutrophil reaction and no apparent long-tract degeneration. Histology of the dorsal root ganglion revealed neuronal loss with macrophage infiltration and attack of ganglion cells (Fig. 1e). One residual ganglion cell contained a round, hyaline inclusion, similar in appearance to a Lewy body (Fig. 1f). These structures were not observed on immunohistochemistry for p62 or alpha synuclein.

This report provides valuable information on neuropathological findings in SPS. The discrepancy between disease activity and lack of inflammation on pathological examination is of interest. One explanation is that the initial inflammatory component results in permanent damage to the inhibitory GABA-nergic neurones, causing loss of spinal inhibition and resulting in recurrent spasms. If this is true, then early treatment with immunosuppressive medication is more likely to be efficacious.

Prostatic adenocarcinoma discovered at autopsy was irrelevant to this illness because of the positive anti-GAD antibodies and multiple autoimmune diseases. Antiamphiphysin antibodies (seen in paraneoplastic SPS) were negative.

To our knowledge, this is only the second report in the literature to demonstrate vacuolation of spinal cord motor neurons in a patient with SPS and the first to provide EM examination findings of the spinal cord. The previous report referred to a 65-year-old man with SPS where neuropathological examination revealed cytoplasmic vacuoles in the motor neurons in the lumbar spinal cord.[5] The distribution of these abnormal motor neurons (T12 to sacral cord) in the patient reported here suggests it is relevant to the clinical picture of exclusive involvement of the legs and lower part of the trunk with sparing of the arms. This report together with the previous single case report strengthens the pathological characterisation of SPS through the presence of vacuolation in the spinal motor neurones. The relationship between inflammation and vacuolar motor neuron degeneration in SPS remains elusive.

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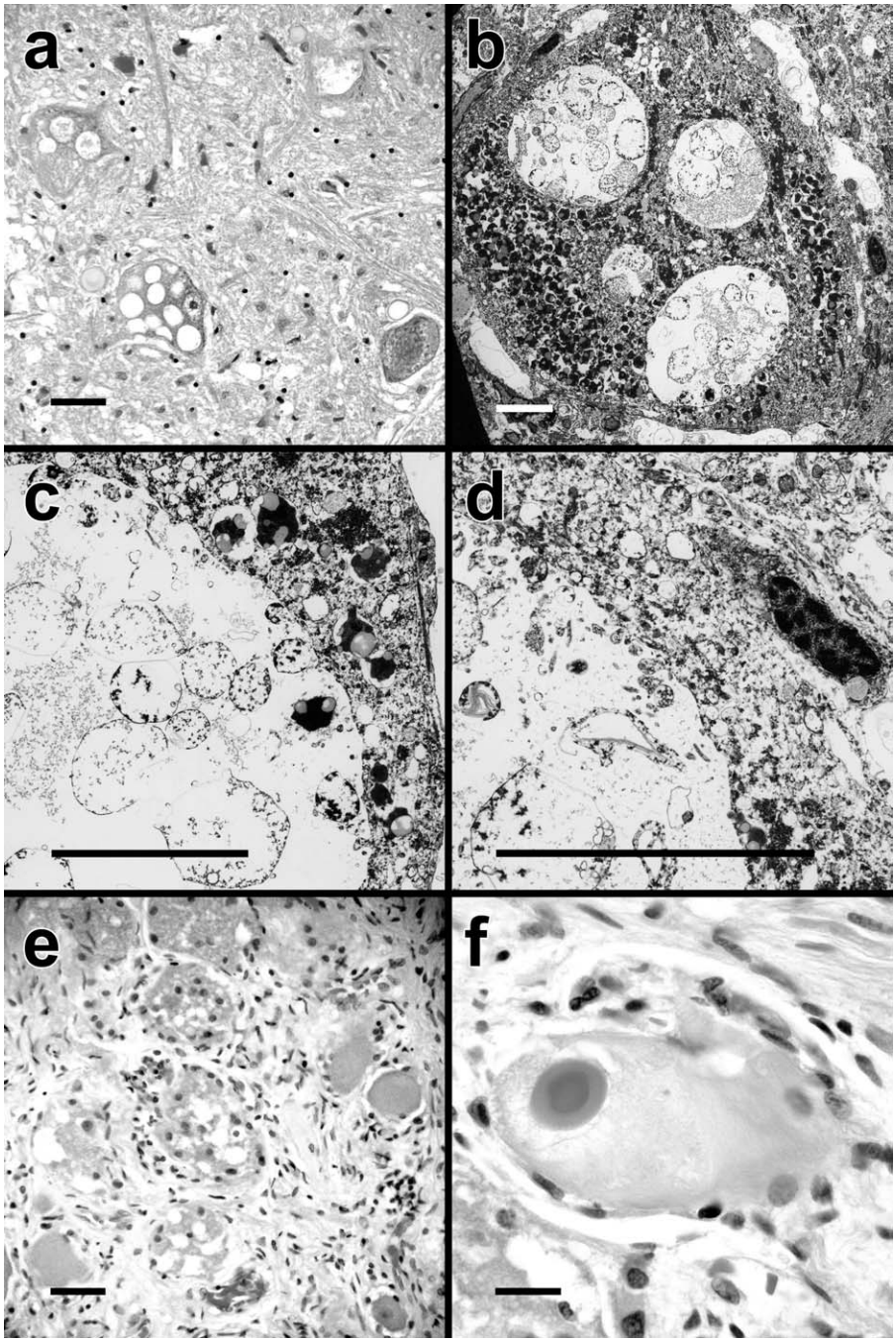

FIG. 1. a: Vacuolation of lower motor neurons on light microscopy. **b:** Electron microscopy with vacuoles and numerous lipofuscin-containing lysosomes at the cell periphery. **c, d:** Electron microscopy of the periphery of vacuoles reveals multiple invaginations containing cytoplasmic contents, membrane-free lipofuscin, and lysosomes with hydropic swelling in the cell cytoplasm. **e:** Light microscopy of the dorsal root ganglion shows a macrophage and microglial infiltrate with neuronal degeneration. **f:** One dorsal root ganglion cell contains a Lewy-like inclusion.
Scale bar: a, 100 μm; b, c, and d, 10 μm; e, 100 μm; f, 10 μm.

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Mutation in 5′ Upstream Region of *GCH*I Gene Causes Familial Dopa-Responsive Dystonia

Dopa-responsive dystonia (DRD) is commonly caused by heterozygous mutations in the guanosine triphosphate (GTP) cyclohydrolase I gene (*GCH*I).[1] In the 5′ upstream region, 3 different mutations have been identified in 2 subjects with DRD.[2,3] One subject had 2 mutations, −39C>T and −132C>T, and another had a single mutation, −22C>T, with no data available on first-degree relatives.[2,3] We report on multiple generations of 1 family with DRD in whom the −22C>T mutation segregates with affected status.

One family of Irish/French-Canadian ethnicity was studied. Ten family members, spanning 3 generations, underwent a neurologic exam and provided blood samples. The local institutional review board approved the study. All participants gave informed consent.

The criterion for definite DRD was definite dystonia and a marked, sustained response to levodopa or a dopamine agonist.[4] The criterion for probable DRD was definite dystonia in a subject who declined a trial of medication. A movement disorders neurologist (N.S.) determined the diagnosis and affected sites as described.[5] Establishment of dystonia status was made prior to genetic testing, which was done blind to clinical designation.

The full *GCH*I gene (exons 1–6) was analyzed by bidirectional sequencing from genomic DNA from every subject. Control samples, consisting of 46 European white samples from the CEPH collection and 7 from the discarded sample collection of the Massachusetts General Hospital Neurogenetics DNA Diagnostic Lab, were utilized.

Six subjects had dystonia (Fig. 1; III-2, III-4, IV-2, IV-5, V-2, and V-3). Four were receiving medical treatment (III-2, III-4, IV-5, and V-2). All 6 affected subjects experienced onset in a foot or leg during childhood. Two displayed involvement of a noncontiguous body region: the neck and right leg in subject III-2 and the neck, right leg, and left hand in subject V-2. Duration of disease varied, from 1 year (V-3) to 54 years (III-2). Subject V-2, with the greatest spread in symptoms, had DRD for 12 years. Subject III-4 did not display any progression, with dystonia remaining in the right foot, and had DRD for 53 years. Of the affected subjects, 3 demonstrated a good response to relatively low therapeutic doses of carbidopa/levodopa (III-2, III-4, and V-2). IV-5 became nauseous on carbidopa/levodopa but displayed a good response to a relatively low therapeutic dose of ropinirole. Subject IV-2 had taken carbidopa/levodopa in the past and saw improvement, but discontinued medication based on personal preference. Subject V-3 had relatively mild symptoms and declined medical treatment. Thus, V-3 was classified as probable DRD, and the other affected subjects (III-2, III-4, IV-2, IV-5, and V-2) were classified as definite DRD.

We demonstrated that the −22C>T mutation in the *GCH*I gene segregates with affected status in multiple generations of a single DRD family. This mutation was not found in 53 control samples (106 normal alleles) or in 214 clinical samples (428 alleles), about which we have no phenotypic information, that have been sequenced in the MGH Neurogenetics DNA Diagnostic Laboratory. This makes it likely that the −22C>T mutation is pathogenic and results in DRD. ■

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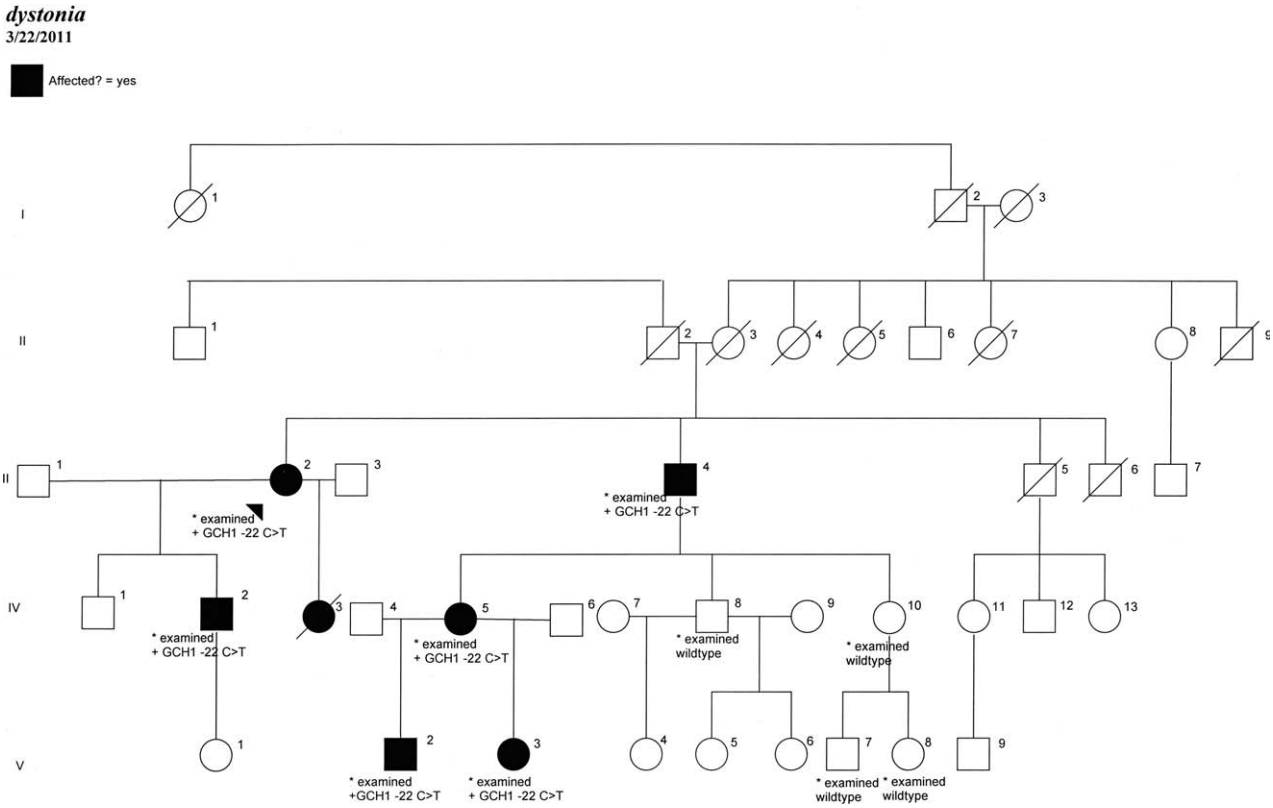

FIG. 1. Pedigree (arrow, proband; shaded symbols, those with dopa-responsive dystonia; clear symbols, unaffected individuals; *those who underwent an exam and provided DNA; +those with the mutation; wild type, those without the mutation).

Ability to Cycle Despite Severe Freezing of Gait in Atypical Parkinsonism in Fahr's Syndrome

The retained ability to cycle despite freezing of gait (FOG) has been reported to be typical of patients with PD,[1,2] and the "bicycle sign" (i.e., the loss of the ability to cycle) has been suggested as a red flag indicative of atypical parkinsonism.[3] However, we present here a patient with Fahr's syndrome and severe FOG, but a remarkably preserved ability to cycle 7 years after disease onset. Fahr's syndrome encompasses a group of neurodegenerative disorders associated with calcification of the basal ganglia, cerebellum, and other brain regions.[4] Parkinsonism with FOG and early falls are part of the clinical phenotype of this disorder.[5]

This 57-year-old patient developed difficulty walking with falls at the age of 53, followed swiftly by stuttering, erectile dysfunction, and urinary urgency. There was no relevant family history. On examination, he had hypomimia, festinant speech, echolalia, and scanning dysarthria. There was bilateral, but asymmetrical, bradykinesia and rigidity, intermittent rest tremor and bilateral postural arm tremor, dysmetria, and dysdiadochokinesia. He had marked FOG and tended to festinate backward on the pull test (see Video, Segment 1). The Mini–Mental State Examination was 25/30. A CT brain scan showed widespread calcification within the basal ganglia and dentate nuclei consistent with Fahr's syndrome. Extensive investigation showed no other abnormalities, and a dopamine transporter (DAT) scan was normal. He was treated with levodopa (L-dopa) with a mild improvement of his symptoms. The patient reported that despite the marked FOG, he

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could get around his local village by cycling with no difficulty (see Video, Segment 2).

Here, we report a patient with atypical parkinsonism and severe FOG who, nonetheless, has a negative bicycle sign, which has been suggested to distinguish patients with PD from atypical parkinsonism. This case suggests that this sign should be used with some caution in this regard. It remains unclear why, in some patients, there is a dissociation between severe difficulty with generating leg movements while walking, manifesting as FOG, and preserved ability to generate leg movements while cycling, although some possible suggestions have been made.[2] For example, the action of cycling might represent a type of an external pacing cue that helps to overcome freezing.[7] Another notable aspect is that the speed of leg movements seems to improve when cycling. This is not simply an improvement related to the "on" state in PD patients, as this was also observed in our patient who had a normal DAT scan and little response to L-dopa. The improvement may be related to "paradoxical kinesia," a brief, sudden period of mobility in response to stress or life-threatening events.[6]

The bicycle sign has been suggested as a new red flag for distinguishing PD from atypical parkinsonism.[3] One issue with the previous report is that the atypical parkinsonian patients, taken together as a group, were significantly older and more impaired in terms of UPDRS, postural instability, and ataxia than PD patients. It is unclear whether patients in the earlier stages of atypical parkinsonian conditions also lose the ability to cycle. In conclusion, here, we demonstrate a patient with atypical parkinsonism and marked FOG resulting from Fahr's syndrome with a perfectly preserved ability to cycle 7 years after disease onset. We suggest that the bicycle sign should be used with caution as a red flag to distinguish PD from atypical parkinsonism.

Legend to the Video

The first part of the video demonstrates the patient with Fahr's syndrome and severe freezing of gait, which improves when using a visual cue stick. The second part of the video shows the patient cycling without any difficulties. ■

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Desferrioxamine Treatment of Aceruloplasminemia: Long-term Follow-up

Aceruloplasminemia (aCp) is an autosomal recessive neurodegenerative disorder characterized by iron deposition in the brain and visceral organs, such as the liver and pancreas. It results from the absence of ceruloplasmin (CP) caused by mutations in the *CP* gene.[1–4] Clinical presentations include diabetes mellitus caused by iron accumulation in islet beta cells, retinal degeneration, and neurological manifestations of movement disorder and cognitive impairment.[1,3,4] Currently, symptomatic treatment is provided to aCp patients.[1–3,5,6] There have been attempts to treat aCp with iron chelation by desferrioxamine, which promotes the excretion of excess and potentially toxic iron in patients with iron overload.[1,2,5,6] However, the effectiveness of this therapy is inconsistent. Whereas some cases reported improvements in clinical features,[1,3,6] some did not respond to treatment.[5] Hence, we evaluated the efficacy of 4-year aCp treatment with desferrioxamine in a previously reported Chinese patient who had a novel homozygous mutation (848 G>C in exon 5) of the *CP* gene.[4]

The 52-year-old female patient was the index patient in our reported Chinese aCp family in 2006.[4] She had a homozygous cG848C mutation in exon 5 of the *CP* gene and undetectable CP. She progressively developed diabetes mellitus, mild anemia, retinal degeneration, and neurological symptoms, particularly hand tremors, mild cervical dystonia, and memory disturbances. Her brain MRI scan showed pronounced hypointensity signals in the bilateral dentate nucleus, red nucleus, substantia nigra, basal ganglia, and

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

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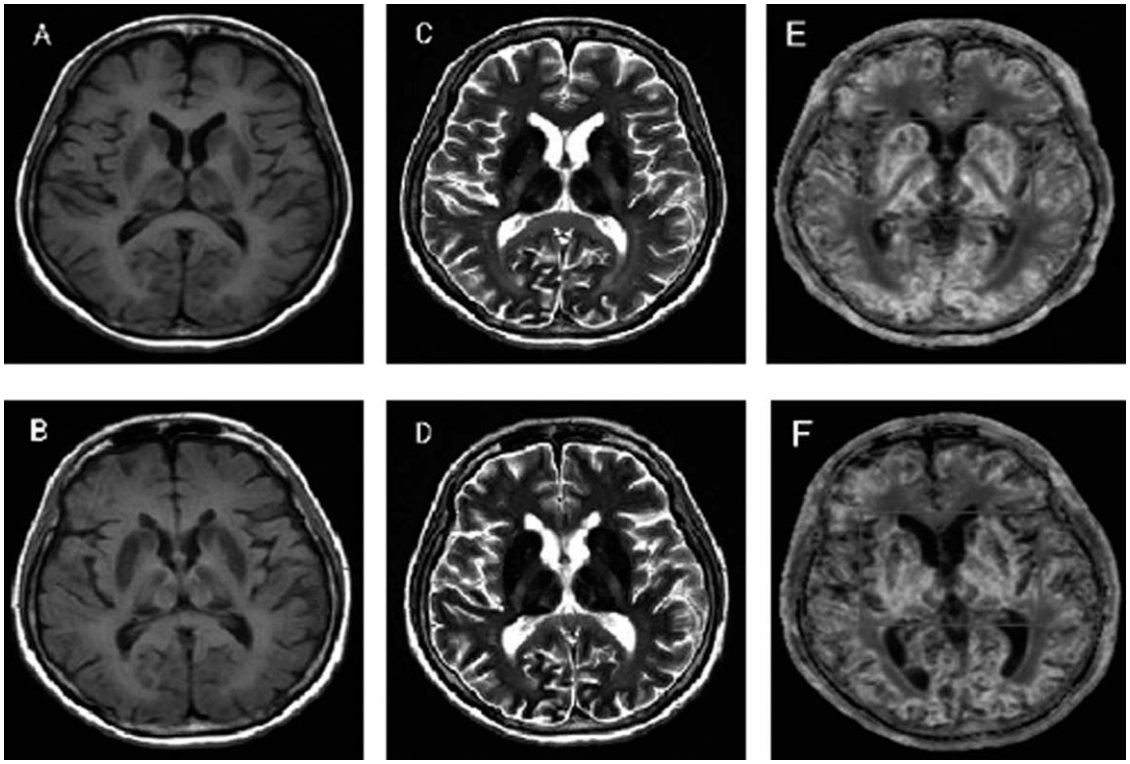

FIG. 1. Brain MRI of the aCp patient treated with desferrioxamine. Pretreatment (**A:** T1; **C:** T2; **E:** R2*); posttreatment (**B:** T1; **D:** T2; **F:** R2*).

Table 1. R2* Values (1/T2*) from Brain ROIs

	Controls (n = 9)				
ROI	Median	Range	Pretreatment	Posttreatment	R2* Reduction (%)
Dentate nucleus	58.13	36.95–67.89	94.87	91.59	3.6
Red nucleus	52.72	29.22–77.45	107.85	102.90	4.6
Substantia nigra	52.86	33.54–83.17	105.39	77.71	26.3
Thalamus	26.06	17.96–35.83	96.65	92.47	4.3
Pallidum	35.27	30.17–47.95	98.41	86.23	12.4
Caudate	26.11	19.17–39.31	93.87	64.93	30.8
Putamen	32.99	28.28–45.23	93.26	79.72	14.5

ROI, region of interest.

thalamus in both T1 and T2 sequences, suggestive of marked iron overload in the brain, when she was first presented to our department at West China Hospital of Sichuan University in 2006 (Fig. 1A,C). The patient accepted treatment with desferrioxamine (500 mg) by intravenous infusion in a 5% glucose solution once a week for 4 years.[4] During the 4-year follow-up (2006–2010), her anemia did not significantly worsen (pretreatment: hemoglobin, 97 g/L; posttreatment: hemoglobin, 91g/L; range, 97–90g/L during the follow-up). Serum ferritin was significantly decreased (pretreatment: 2,000 ng/mL; posttreatment: 1,293 ng/mL). However, her diabetes was not well controlled (fasting glucose: 10.65 mmol/L), and her hand tremors, neck dystonia, and dementia slightly worsened. Furthermore, she developed mild ataxia and rigidity of the limbs (evaluations using the Fahn-Marsden rating scale, UPDRS, and the Brief Ataxia Rating Scale are shown in Supporting Information). Conventional MRI scans in T1 and T2 phases showed no obvious improvements (Fig. 1B,D). After informed consent and local ethics committee approval were obtained, we investigated differences in the regional brain iron levels of the patient using a T2*-weighted gradient echo sequence on a 3.0-T MR scanner (EXCITE; GE, Milwaukee, WI) between a pretreatment scan in 2006 and a posttreatment scan in 2010 (scanning parameter settings as previously reported).[7] The calculated R2* values (R2* = 1/T2*) from different brain regions of interest are shown in Table 1. However, although R2* values decreased by one fifth to one third in the putamen and substantia nigra, the symptoms continued to progress.

Mildly decreased R2* values were detected in the patient 4 years after desferrioxamine treatment, suggesting that iron chelation can reduce abnormal iron deposition in the central nervous system. We suggest that with desferrioxamine treatment, time is necessary for dramatic improvements in iron-

abnormal deposition and clinical symptoms. However, benefit from treatment with desferrioxamine still remains uncertain regarding the result of a single case. More studies are needed.

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Kin-Cohort Analysis of *LRRK2*-G2019S Penetrance in Parkinson's Disease

The G2019S substitution in the leucine-rich repeat kinase 2 (*LRRK2*) gene is the most common pathogenic mutation associated with autosomal, dominant Parkinson's disease (PD). Its penetrance is incomplete and has not been established. Many studies have addressed the issue, as it is important for genetic counseling, but their results have been inconsistent (Fig. 1).

We estimated G2019S penetrance through the kin-cohort analysis, which estimates the cumulative risk of disease in proband relatives according to Mendelian inheritance patterns, regardless of genetic testing results.[1] We applied this method to families identified through the analysis of a large consecutive series of 2,000 patients with PD diagnosed according to UK Parkinson's Disease Brain Bank criteria (60.1% male, all Caucasians of Italian origin, except for 25 patients originating mainly from other European countries). Proband relatives were assumed to be affected by PD when a medical diagnosis of PD and prescription of dopaminergic therapy was reported. Kin-cohort analysis was performed

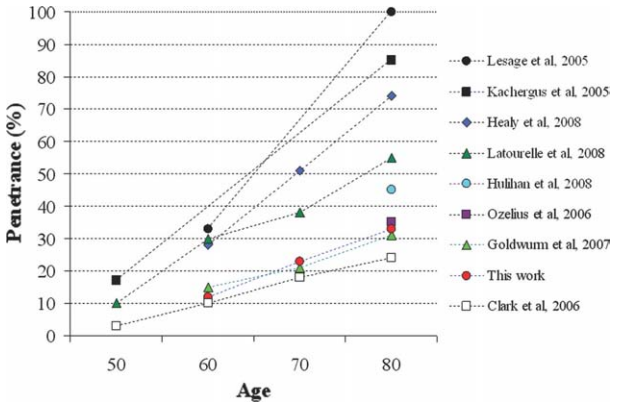

FIG. 1. LRRK2 G2019S penetrance estimates. From Lesage et al., 2005: Penetrance was calculated on two highly selected autosomal dominant families; numbers of subjects (affected and not affected) were not reported; statistical method was not reported; results: age 60 = 33%, age 80 = 100%; CIs were not reported. From Kachergus et al., 2005: Penetrance was calculated on 13 families identified from highly selected autosomal dominant cases; subjects 13 PD probands + 22 relatives (7 with PD, 15 not affected); method: "number of affected mutation carriers within each 5-year age group was divided by the total number of carriers (both affected and nonaffected) within that group" (probands were not excluded); results: age 50 = 17%, age 70 = 85%; CIs were not reported. From Healy et al., 2008: Penetrance was calculated on a multicenter casistic of 133 families, mainly of familial PD cases (see text); subjects: 327 affected and 718 nonaffected (probands were excluded); method: Kaplan-Meier and maximum likelihood; results: age 60 = 28%, age 70 = 51%, age 80 = 74%; CIs were not reported. From Latourelle et al., 2008: Penetrance was calculated on parents of 22 cases identified in a group of selected familial PD; method: product-limit survival estimation; results: age 60 = 30%, age 70 = 38%, age 80 = 55%; CIs were not reported. From Hulihan et al., 2008: Odds ratio was derived from the analysis of 328 PD cases (30% of carriers) and 371 controls (2% of carriers); penetrance was calculated from odds ratio with the assumption of 2% lifetime risk of PD in the general population; results: lifetime risk = 45%; CIs were not reported. From Ozelius et al., 2006: Odds ratio was derived from the analysis of 120 PD cases (18.3% of carriers) and 317 controls (1.3% of carriers); penetrance was calculated from odds ratio with the assumption of 2% lifetime risk of PD in the general population; results: lifetime risk = 35%; CIs were not reported. From Goldwurm et al., 2007: Penetrance was calculated on 36 carrier relatives found in 19 families identified through the analysis of 1,092 unrelated consecutive PD patients; method: Kaplan-Meier; results: age 60 = 15% (CI, 6–35), age 70 = 21% (CI, 11–42); age 80 = 32% (CI, 18–52). In this work: Penetrance was calculated on 24 families identified through the analysis of 2,000 unrelated consecutive PD patients; method: kin-cohort; age 60 = 12% (CI, 1–24), age 70 = 23% (CI, 9–35), age 80 = 33% (CI, 12–61). From Clark et al., 2006: Penetrance was calculated on 28 families identified through the analysis of 504 unrelated PD patients not selected for family history; method: kin-cohort; age 60 = 12%, age 70 = 18%, age 80 = 24% (CI, 13.5–43.7).

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using the open-source statistical computing environment R, its package "kin-cohort," and its function kc.moments.[2]

We found 27 G2019S-carriers; 13 had familial and 14 sporadic PD. Three were not willing to have a detailed reconstruction of their pedigree and were excluded from the study. Kin-cohort analysis of 154 first-degree relatives resulted in a penetrance of 12% (confidence interal [CI] = 1%–24%) at 60 years, 23% (CI = 9%–35%) at 70, and 33% (CI = 12–61%) at 80. Results in 190 second-degree relatives were similar (10%, 10%, and 30%, respectively).

The evaluation of the penetrance of a mutation is very complicated. Ideally, the general population should be tested for the mutation without any selection criteria to verify how many carriers are affected. Unfortunately, this is not feasible when the frequency of the mutation is very low, as is the case of *LRRK2*-G2019S. For this reason, the mutation is sought in selected subjects, in whom the probability of being a carrier is higher, such as PD patients. When one starts from a series of patients and wishes to assess the penetrance in presymptomatic relatives, probands must be excluded. Further, it is essential to avoid biased patient selection. If the study is confined to patients with a positive family history for PD, it selects patients in whom other genetic or environmental factors may increase penetrance. This may account for the almost complete penetrance found in the first trials in families highly selected for linkage studies.[3] Also, subsequent trials in case series with additional familial cases report higher values than those we found.[4,5] In particular, the GenePD study actually started from a series of cases of familial PD.[4] The investigators tried to correct this bias by studying only the parents of subjects recruited as sibling pairs. However, 9 PD-affected relatives of carriers did not carry the *LRRK2*-G2019S themselves, suggesting that other susceptibility factors were still present and might have inflated penetrance.[4] Another study presented the data on G2019S carriers collected by an international consortium of 21 trial sites, including our own.[5] Even in this study, there was an imbalance in favor of familial cases. This is common, because centers tend to perform tests more easily in patients with a positive family history. Further, most sporadic cases were excluded from the analysis. As the investigators acknowledge, this makes the values "most appropriately used for the estimation of the age specific cumulative risks of PD in patients with known family history."[5] Kin cohort analysis is, therefore, important, given the bias and errors of the above-cited studies.

In studies in which penetrance was assessed on the basis of consecutive PD patients and was, therefore, not inflated with familial cases, results were lower, ranging from 24% to 45% (Fig. 1).[6–10] In these studies, the calculation methods were different, but in all cases, probands were identified without knowledge of PD family history, and high-risk families were not specifically selected.

Such penetrance values appear to be more realistic in patients with no or few affected relatives. Should the patients have many affected relatives, this should be borne in mind by the genetic counselor, and the values reported by Healy et al.[5] would appear to be more suitable.

In conclusion, we believe that the lifelong penetrance of *LRRK2*-G2019S mutation usually does not exceed 25% to 35%, unless family history suggests otherwise.

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A Preliminary Study of Finasteride in Tourette Syndrome

The 2 main categories of anti-tic agents employed for Tourette syndrome (TS), antipsychotics and alpha-agonists, are often poorly tolerated because of their serious side effects. We recently reported that finasteride, the 5α-reductase inhibitor approved for benign prostatic hyperplasia and androgenetic alopecia,[1] reduced tic severity and obsessive–compulsive manifestations in an adult male TS patient refractory to standard treatments.[2] To confirm and extend this finding, we tested the therapeutic effects of an 18-week finasteride (5 mg/day) regimen in 10 male adult TS patients (see Supplementary Table 1). The following inclusion criteria were adopted: (1) age between 18 and 45 years at the time of release of informed consent; (2) male sex; (3) TS diagnostic criteria based on the DSM-IV-TR guidelines[3]; (4) no changes in pharmacotherapy (if existent) over the 2 months prior to the beginning of the trial; (5) significant tic-induced distress or impairment, as reported by patients; (6) Yale Global Tic Severity Scale (YGTSS)[4] global score $\geq$ 50 at the beginning of the trial; (7) no significant abnormalities in hematochemical, endocrine, and urinary parameters; (8) lack of cognitive or other neurological impairments; and (9) ability to swallow pills.

The study protocol was approved by the local institutional review board. All patients provided written informed consent. Only 2 individuals had additional tic medications before the trial (aripiprazole and pimozide, one each) and were allowed to maintain them at unmodified doses throughout the study.

Patients were monitored at baseline and after 2, 6, 12, and 18 weeks of treatment, with standard physical and neurological examinations, as well as YGTSS assessment; general well-being, psychiatric functioning, adverse events, and treatment compliance were evaluated through an open-ended interview at each visit. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[5] was used at baseline and in week 18 to evaluate obsessive–compulsive manifestations.

Patients displayed a time-dependent decline in global severity, as well as total, motor, and phonic tics (Fig. 1A–D). Furthermore, the 6 patients with obsessive–compulsive comorbid symptoms displayed significant reduction in Y-BOCS total and compulsion, but not obsession, scores (Fig. 1E–G). No significant differences were observed in body weight, vital signs, or other clinical and laboratory parameters. The majority of subjects reported full therapeutic compliance and no neuropsychiatric, metabolic, or endocrine side effects. Two patients complained of a reduction in libido and occasional difficulty in achieving erection but deemed this untoward effect acceptable and decided not to discontinue the therapy.

These results confirm the therapeutic potential of finasteride for TS male adult patients. The uncontrolled nature of the study and the lack of treatment blinding in the design pose important limits to the value of these results in view of the possibility of placebo effects, as well as ascertainment and observer bias. In consideration of the role of 5α-reductase in the conversion of testosterone into its potent androgenic metabolite, 5α-dihydrotestosterone,[1] our findings may support previous evidence of the role of androgens in TS pathophysiology.[6,7] Future controlled studies are warranted to properly evaluate finasteride's therapeutic effectiveness in adult male TS patients and potentially pave the way for novel, well-tolerated therapies.

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

Antonella Muroni, Silvia Paba, Francesco Marrosu, and Marco Bortolato contributed equally to this article.

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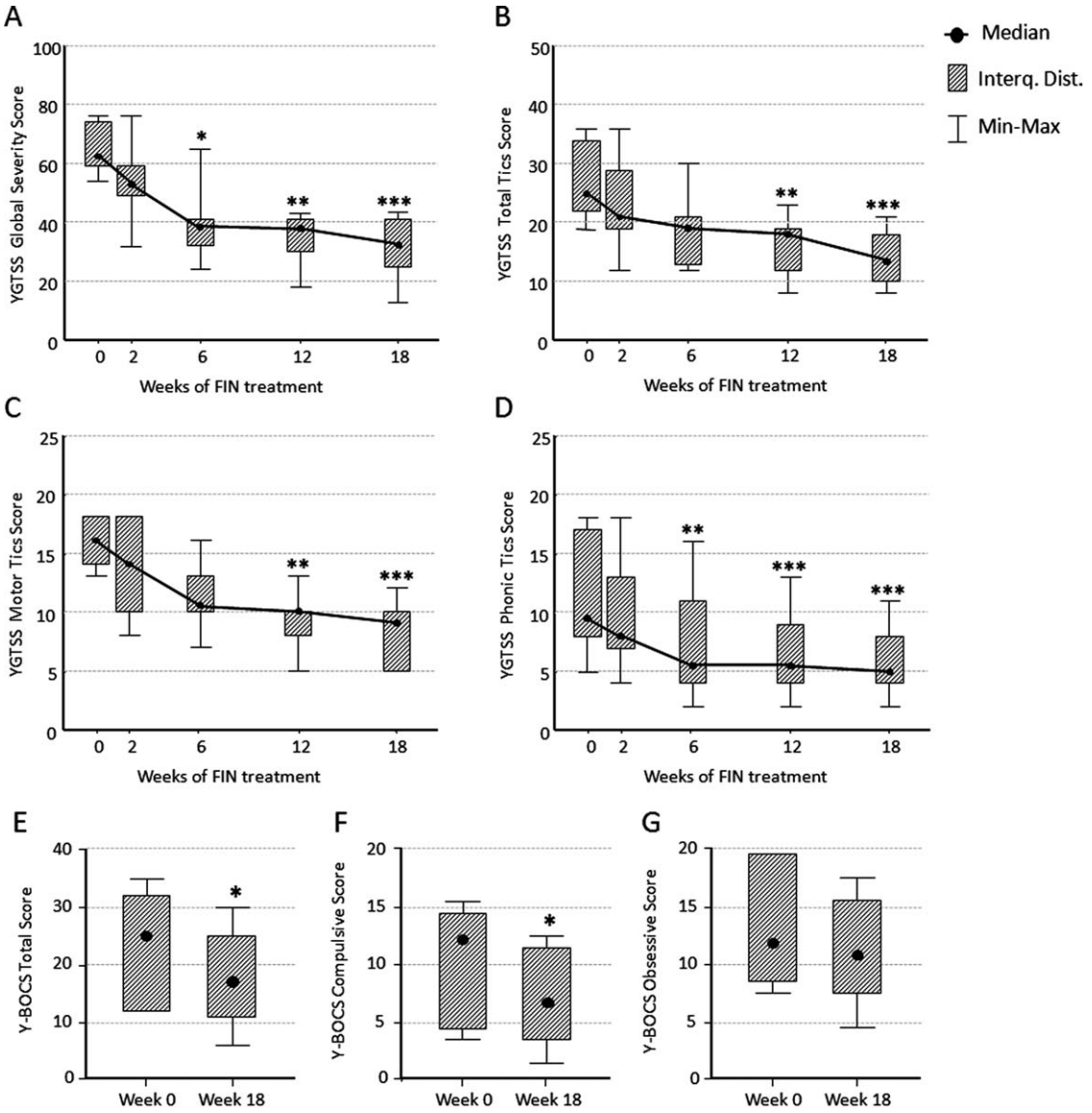

FIG. 1. Effects of finasteride (FIN) on severity of tics and obsessive–compulsive manifestations in patients with Tourette syndrome (n = 10). FIN induced significant reductions in the severity of (**A**) global symptoms ($\chi^2(4) = 31.12$, $P < .0001$), (**B**) total tics ($\chi^2(4) = 34.16$, $P < .0001$), (**C**) motor tics ($\chi^2(4) = 34.16$, $P < .0001$), and (**D**) phonic tics ($\chi^2(4) = 34.62$, $P < .0001$), as assessed by Yale Global Tic Severity Scale (YGTSS) scores. Analyses of Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores in the 6 patients with obsessive–compulsive symptoms revealed a significant reduction in (**E**) total scores ($Z = 2.20$, $P = .028$) and (**F**) compulsion subscale scores ($Z = 2.20$, $P = .028$) but not in (**G**) obsession subscale scores ($Z = 1.83$, $P = .068$, NS), $^{***}P < .001$, $^{**}P < .01$, $^{*}P < .05$ versus baseline scores (after adjustment for multiple comparisons for YGTSS scores). Analyses of YGTSS scores were performed with Friedman's test, followed by the Wilcoxon-Nemenyi-McDonald-Thompson test for post hoc comparisons. Analyses of Y-BOCS scores were performed with the Wilcoxon signed-rank test.