Movement Disorders
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Letters to the Editor Related to New Topics

Retina Thickness in Parkinson's Disease and Essential Tremor

Visual symptoms, particularly impaired foveal vision, are common among the nonmotor phenomena in Parkinson's disease (PD). Experimental evidence from humans and monkeys shows that there are dopaminergic cells in the retina, including the amacrine subtype A18 with D1 and D2 receptors, and interplexiform cells.

Postmortem studies have shown that PD eyes have lower dopamine content,[1] compared with healthy controls. Likewise, a loss in the sensitivity to contrast and color vision, altered visual evoked potential, and electroretinographic measurements have been observed, indicating foveal retinal ganglion cells damage in PD.[2]

Quantitative morphology of gross retinal histology in humans can be measured in vivo using time domain *Optical Coherence Tomography* (*OCT*). In PD a thinning of the peripapillary retinal nerve fiber layer, which represents axons of the ganglion cells, and macula have been shown, supporting the hypothesis that dopaminergic deficit in the retina can cause structural changes.[2–5] However, the usefulness of measuring foveal thickness by *OCT* as a diagnostic tool to differentiate PD from other tremor disease, such as essential tremor (ET) remains unknown. Therefore, the main purpose of this pilot study was to measure foveal thickness in patients with PD, and to compare it against a normal population and patients with ET.

We designed a cross-sectional pilot study that included a consecutive sample of outpatients diagnosed with idiopathic PD in accordance with the UK Parkinson's Disease Society brain bank, and ET based on clinical criteria. Patients with any coexisting ocular disease were excluded. This study was approved by the Ethics Committee of the General Yagüe Hospital, Burgos (Spain), and all patients signed the informed consent before being enrolled. Control subjects were matched for age ($\pm$ 5 years) and gender to PD patients. Demographic and PD/ET laterality data were collected. *OCT* was acquired through a dilated pupil by an experienced operator using the *OCT3* (Carl Zeiss Meditec, Dublin, Calif), with axial resolution of $\leq$ 10 μm. The macular thickness map analysis and the center foveal thickness was automatically determined by the *OCT3* software.[6] Images were considered to be of good quality if the signal-to-noise ratio was greater than 30dB or had more than 95% sweeps accepted.

Data analysis was performed from an exploratory point of view using the statistical package *SPSS program* (*SPSS 17*; SPSS, Chicago). Only descriptive analysis was used, owing to the small sample size. Data were summarized as mean $\pm$ standard deviation, and median (range). To maintain independence of all observations, right eye [RE] versus left eye [LE] were analyzed for each patient.

Fifty-two eyes from 9 patients with PD (5 men and 4 women) with a mean age of 64.1 + 12 years and disease duration of 8.4 $\pm$ 1.9 years, 8 patients with ET (4 men and 4 women) with a mean age of 67.8 $\pm$ 4.8 years and disease duration of 23.7 $\pm$ 18.3 years, and 9 controls were included. The mean foveal thickness was thinner in the PD group compared with the ET group and controls (Table 1). For the PD and ET groups, the mean foveal thickness was also thinner in the contra lateral eye of the most affected side (Table 1).

In this pilot study, based on the *OCT* imaging, the fovea was thinner in the PD group compared with the ET group and controls. Interestingly, whereas interocular macular symmetry has been found in the normal population,[7] we found that the foveal thickness was asymmetric and thinner in the eye contralateral to the side more affected by tremor and parkinsonism in the ET and PD groups, respectively. Hajee et al, also found the correlation between thinning in the left and the right eye of the same was not perfect.[7] Hence, this interocular foveal asymmetry should be considered in interpretation. Except that for ET, although mild tremor asymmetry has been documented as a fundamental characteristic of ET, there is no published information regarding foveal thickness in patients with ET. The similar asymmetry finding in ET is difficult to understand, and we cannot obviously explain it based on our preliminary data. However, abnormal OCT measures have also been found in other neurodegenerative diseases, such as Alzheimer's disease, multiple sclerosis, and spinocerebellar ataxias, most likely related to the loss of retinal ganglion cells and axons.[8] Therefore, further studies are required to establish whether OCT measures contribute for a sensitive and specific diagnosis of PD and to differentiate it from other conditions. We recognize our results cannot be compared with prior *OCT* reports in PD because of the different imaging map protocol and equipment. We are also aware that because of the small sample size used, these results need to be repeated in larger cohorts to ensure reproducibility.

With regards to technical feasibility, the OCT compared with other expensive ones, such as the single photon emission computed tomography (SPECT) studies using 123I-FP-CIT (DAT scan), is widely available, fast, as it only takes a few minutes to perform, and relatively inexpensive. Based on our preliminary data, and in accordance with other authors,[2–5] we believe that foveal thickness measured by the OCT could be a promising, feasible biomarker of PD, by quantifying the morphological changes of retinal dopaminergic neurons.

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TABLE 1. *Clinical characteristics and Retina thickness*

	Total retina thickness (μm) mean (SD) [Range]	Right eye/left eye retina thickness (μm) median range)
Controls (n = 9)	218.9 (15.3) [189-238]	221 (194–235)/221 (182–252)
Parkinson's disease	202.2 (27.8) [154-227.5]	207 (117–248)/214 (148–257)
Right PD (n = 5)	203.4 (28.7) [154-227]	214 (154–248)/207 (148–257)
Left PD (n = 4)	200.7 (30.7) [155-229]	202 (117–222)/219 193–232)
Essential tremor	207.3 (27.3) [174-5-242.5]	220 (177–228)/196 (152–257)
Right ET (n = 3)	198.6 (13.8) [186-213.5]	220 (220–224)/169 (152–207)
Left ET (n = 5)	212.6 (28.2) [174.5-242-5]	220 (177–228)/226 (172–257)

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Acute Renal Failure in Patients with Bilateral Deep Brain Stimulation

The management of Parkinson's disease is mainly pharmacological with levodopa but in recent years, surgery [deep brain stimulation of the subthalamic nucleus (STN-DBS)] has been revitalized for the treatment of patients with uncontrollable motor complications.[1]

A large proportion of patients suffering from Parkinson's disease presents with urinary dysfunction described as urgency, increased frequency or incontinence as predominant symptoms[2,3] and also STN-DBS has proven to improve urinary function.[4] Data from experimental urodynamic measures in men and animal models have demonstrated a significant influence of STN-DBS on urinary bladder function.[5,6] In these studies, the main effect of STN-DBS appeared to be a normalization of urodynamic parameters but there is no data reported about kidney function in these patients.[7] Despite its clinical efficacy, the manifold physiological consequences of STN-DBS are to date poorly understood.

Acute renal failure (ARF) defined as an abrupt or rapid decline in renal filtration function and creatinine clearance (CC) is used to estimate the glomerular filtration rate (GFR). The CC test compares the level of creatinine in urine with the creatinine level in the blood, usually based on measurements of a 24-hour urine sample. GFR has never been studied in Parkinson patients with normal preoperative renal function immediately after STN-DBS. Here, we report a decline in renal filtration function after STN-DBS.

Nineteen patients (15 men and four women) with a mean (±SD) age of 63 ± 7 years at the time of surgery and a mean duration of disease of 16 ± 9 years were selected for implantation of electrodes in the STN. The selection criteria were clinically diagnosed Parkinson's disease, severe levodopa-related motor complications despite optimal adjustment of antiparkinsonian medication, an age under 70 years, no

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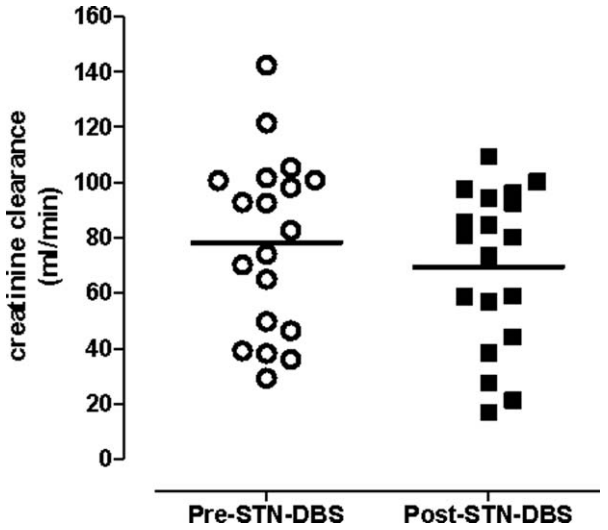

FIG. 1. Creatinine clearance before and after STN-DBS.

surgical contraindications, and no dementia or major ongoing psychiatric illness. Electrodes were implanted bilaterally under local anesthesia as described previously.[8]

Patients were evaluated preoperatively (1 week after surgery) and postoperatively (1 week after surgery). Evaluations included (1) the Unified Parkinson's Disease Rating Scale (UPDRS) parts III (motor); (2) mean dose of levodopa; (3) all medical manifestations; (4) 24 hours urine; (5) urine ionogram and biochemistry (6) blood ionogram; and (7) CC.

CC and fractional excretion of sodium, potassium, and phosphate were calculated as previously reported (5). Urea was measured by an enzymatic test and creatinine by the Jaffé method. Ion-selective electrodes performed the quantifications of sodium and potassium in urine samples. Phosphate was determined by a direct photometric method. All assays were performed by Cobas Mira Plus analyser (ABX Diagnostics, Geneva, Switzerland). Urine and plasma osmolality were determined by means of an osmometer (model 3 MO, Advanced Instruments). Wilcoxon signed rank test and Spearman test were used for statistical analysis.

After surgery, DBS-STN produced a statistically and clinically significant reduction in mean Unified Parkison's Disease Rating Scale (UPDRS) motor scores. UPRSS-III was significantly improved after DBS-STN ($P < 0.005$): 52 ± 8.3 before surgery and 16.5 ± 8.4, 1 week after surgery. As well as a major amelioration in therapy-related complications, with a reduction in mean levodopa dosage (mg/day): from 1,118 ± 496 before surgery to 653 ± 447 after surgery.

Mean estimated GFR, calculated by CC (mL/min) declined significantly ($P < 0.005$) after STN-DBS, from 78.2 ± 31.1 to 69.3 ± 27.9 (Fig. 1). Moreover, three patients without preoperative renal insufficiency (RI) (CC < 90 mL/min) developed acute RI postoperatively: stage 2 RI in two patients; and stage 3 RI in one patient. Three patients with preoperative RI exacerbated: stage 2 into stage 3 in one patient; and stage 3 into stage 4 in two patients.

Mean urinary volume in mL/day were similar preoperatively (1,601 ± 562) and postoperatively (1,521 ± 583). No changes were observed in urine and blood ionogram before and after surgery (Table 1).

STN-DBS has been shown to ameliorate bladder dysfunction (increases bladder capacity) in patients with Parkinson's disease, by modulation of sensory processing.[9] It appears to be a normalization of urodynamic parameters, but there is no data reported about kidney function in these patients.

In our patients kidney function was altered immediately after surgery. A decline in filtration function developed after STN-DBS and some patients without preoperative RI developed acute RI postoperatively. In these patients no urinary retention occurred, urinary volume was similar before and after surgery. No preoperative hemodynamic complications, as dehydration occurred; like other series, neurostimulator implantation anesthetic technique is not associated with major hemodynamic adverse effects.[10]

A recent study of experimentally induced ARF showed that there is a close interaction between the kidney and the central nervous system.[11] Sympathetic influence in kidney functions is under control of brainstem biogenic amine cell groups and hypothalamic nuclei.[12,13] It cannot be excluded that there may be regional effects of DBS-STN on hypothalamic centers, depending on the exact location of the contacts in the STN area.

Effect of DBS-STN in hypothalamic centers remains a valid hypothesis which could explain an altered kidney function immediately after surgery, but further investigations are required to explore this possible mechanism. With these preliminary results the authors suggest that it is necessary to evaluate CC before and after surgery for early orientation of patients with RI.

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TABLE 1. *Urine and blood ionogram before and after surgery*

Parkinson patient experimental conditions	STN-DBS before	STN-DBS after
24 hours urine volume (mL)	1,601 ± 562	1,521 ± 583
Glomerular filtration rate (mL/min)	78.2 ± 31.1*	69.3 ± 27.9*
Blood ionogram		
Sodium (mEq/L)	139 ± 2.2	136 ± 2.1
Potassium (mEq/L)	4.1 ± 0.1	4.0 ± 0.1
Chloride (mEq/L)	105 ± 4.6	108 ± 4.9
Blood biochemistry		
Urea (g/L)	0.43 ± 0.1	0.44 ± 0.1
Creatinine (mg/L)	10.3 ± 1.9	10.3 ± 1.8
Urine ionogram		
Sodium (mmmol/L)	109 ± 40	123 ± 67
Potassium (mmmol/L)	33.7 ± 11.3	33.7 ± 10.4
Calcium (mg/dL)	8.2 ± 4.2	7.7 ± 4.3
Phosporum (mg/dL)	59.8 ± 26.1	55.1 ± 27.9
Uric acid (mg/dL)	6.4 ± 5.3	10.3 ± 7.6
Urine biochemistry		
Urea (mg/dL)	1,821 ± 691.6	1,669 ± 631.2
Creatinine (mg/dL)	76.39 ± 36	72.0 ± 35

*$P < 0.0001$.

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ADEM Presenting as a Movement Disorder

Video 

Acute disseminated encephalomyelitis (ADEM) is a demyelinating disease of the central nervous system characterized by multifocal neurological deficits and encephalopathy.[1] We report a patient with ADEM who presented with a movement disorder.

A 44-year-old woman was admitted with choreiform movements. Her medications included sodium valproate 400 mg thrice daily for migraine and phenelzine 30 mg twice daily for schizoaffective disorder. The patient had developed involuntary movements in her left leg 3 days following an upper respiratory tract infection. The movements progressed to involve both upper and lower limbs. Phenelzine was ceased with no improvement. Examination revealed choreiform movements affecting the upper limb and lower limb, particularly on the left. The movements were continuous, with intermittent brief jerks (See Video 1).

CT brain was unremarkable. Blood glucose was normal. The creatine kinase (CK) was elevated at 9882 μmol/L, decreasing to 835 μmol/L by day 5. Sodium valproate level was 106 μmol/L (therapeutic range 350–700 μmol/L). The ASOT was elevated at 473 IU/mL, and increased to 837 IU/mL after 2 weeks. Anti-DNAse B titre remained negative.

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

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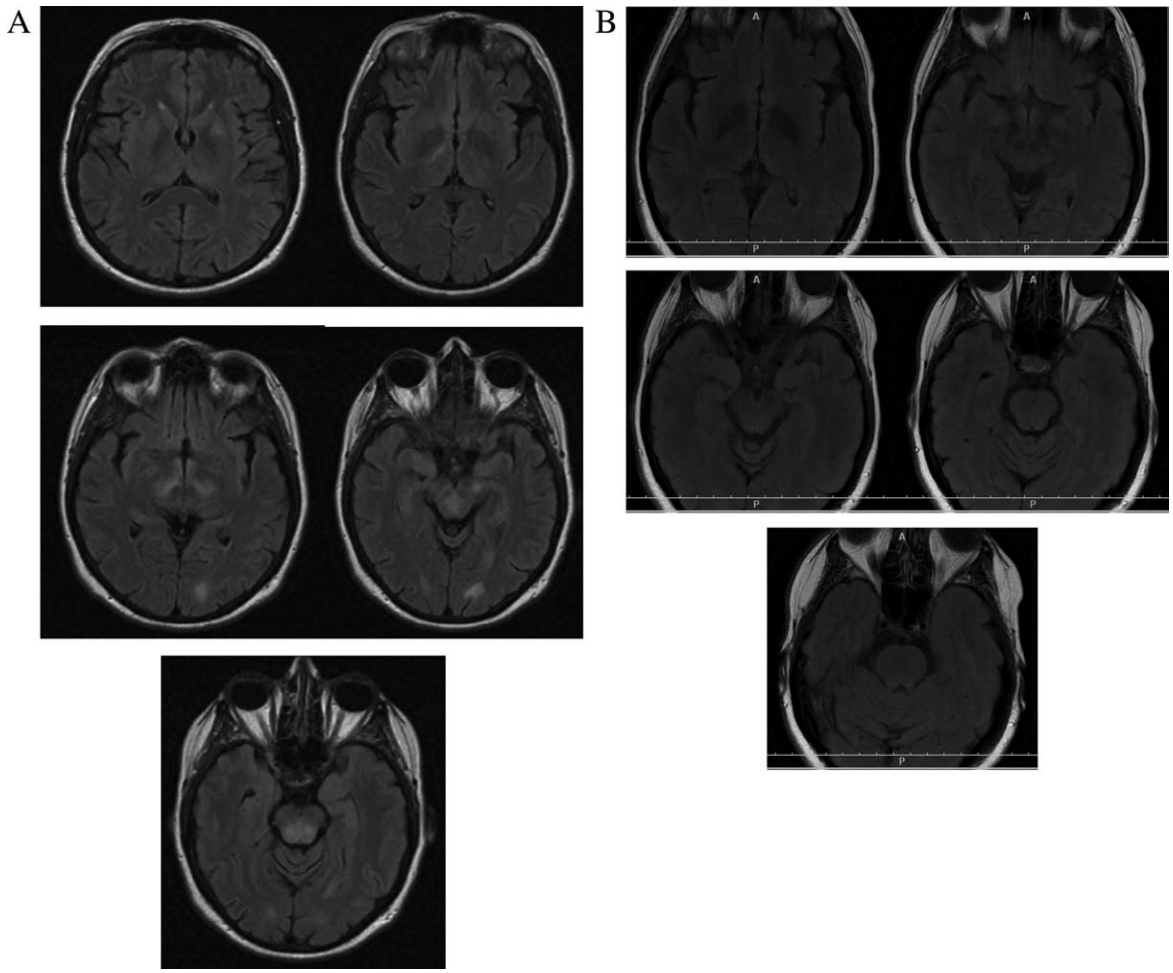

FIG. 1 (**A**) Axial fluid-attenuated inversion recovery (FLAIR) MRI brain. Multiple foci of hyperintenstiy in the subthalamic regions, brainstem, cerebellum (not shown), left occipital white matter, and left lentiform nucleus. (**B**) Repeat axial fluid-attenuated inversion recovery (FLAIR) MRI brain three months after onset, showing resolution of lesions.

The patient was commenced on benzylpenicillin and clonazepam. Phenelzine was recommenced. Her movement disorder improved within a few days and resolved over the following several days. On the 5th day, the patient developed a fever and left-sided 6th nerve palsy. The cerebrospinal fluid (CSF) showed normal protein and glucose and one mononuclear cell. Oligoclonal bands were not present. MRI brain revealed multiple nonenhancing foci of hyperintensity in the subthalamic regions bilaterally, brainstem, cerebellum, left lentiform nucleus, and left occipital white matter (Fig. 1A).

The patient then deteriorated with delirium, ataxia, nystagmus, a left Horner's syndrome and bilateral sixth nerve palsies. Repeat cerebral MRI showed progression of the previous findings, with patchy areas of enhancement. Methylprednisone was commenced. Repeat CSF examination 2 days later showed 12 mononuclear cells, but remained otherwise normal.

Tests for HIV, *Borrelia burgdorferi*, *B. henselae*, *B. pertussis*, EBV, CMV, Mycoplasma, Toxoplasmosis, Cryptococcal antigen, Q fever, Barmah Forest, HSV 1 and 2, Influenza A and B, Flavivirus, Ross River, HHV 6, VZ, measles, and Rickettsia serology were negative. Testing for metabolic diseases, as well as autoimmune markers including anti-GQ1b IgG antibodies were negative.

By day 17, the patient gradually improved, and was discharged to rehabilitation.

At 3-month follow-up, the patient had experienced complete resolution of her symptoms and MRI changes (Fig. 1B).

The clinical and radiological findings in our patient were consistent with ADEM. Although lesions in ADEM typically enhance with gadolinium, Schwarz et al. reported patchy enhancement in 24% of cases, with no enhancement in 4%.[1] Similarly, although CSF oligoclonal bands were negative, the reported percentage in ADEM varies from 0 to 58% in contrast to multiple sclerosis where oligoclonal bands are detected in 90–95% of cases.[2] This lower percentage may be explained by polyclonal, rather than oligoclonal activation in ADEM in response to an antigenic challenge.

It is likely that the bilateral subthalamic lesions and possibly also the left lentiform nucleus lesion resulted in the development of chorea in our patient.

The finding of an elevated ASOT raises the possibility of Sydenham's chorea, but in the setting of a persistently negative anti-DNAse B is insufficient evidence to support a recent streptococcal infection. A normal value for anti-streptococcal antibody is difficult to define, owing to disparities due to age, geography, and seasonal variation.[3]

Reports of choreiform movements associated with sodium valproate have been described.[4] However our patient improved despite continuation of this medication. We have found one report of chorea associated with monoamine oxidase inhibitors.[5] However, the patient also improved despite recommencement and maintenance of her monoamine oxidase inhibitor. An adverse reaction to this medication, such as serotonin syndrome, is therefore also unlikely. The elevation in CK is presumably related to muscle damage in the setting of intense and prolonged involuntary movements.

Intravenous immunoglobulin has been used for treatment of steroid-resistant ADEM with success in a few cases, however it is unclear whether the improvement was co-incidental with the self-limiting nature of the disease.[6] Reports regarding the effectiveness of plasmapheresis have been inconsistent.[7]

In conclusion, we describe an adult patient who presented with an involuntary movement disorder and subsequently went on to develop a typical clinical course and radiological findings consistent with ADEM.

Legend to the Video

Video clip of initial examination showing choreiform movements affecting upper limbs and lower limbs, particularly on the left.

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Pet Findings in Reversible Improvement of Olfactory Dysfunction After STN Stimulation in a Parkinson's Disease Patient

Olfactory dysfunction (OD) is one of the earliest nonmotor symptoms of Idiopathic Parkinson's disease (PD).[1] Hyposmia in PD is generally bilateral and remains unaffected by parkinsonian medication.[1] Despite of its high occurrence, little is really known about the mechanisms of olfactory loss.[2] Most hypotheses raised to explain this phenomenon involve neurodegenerative processes of olfactory structures.[3] The authors report a case and the fluorodeoxyglucose (FDG)-PET findings of a patient who underwent bilateral deep brain stimulation of the subthalamic nucleus (STN-DBS) and subsequently developed a great improvement in motor symptoms paralleled by an impressive recovery of olfaction after surgery.

A 51-year-old man with advanced PD, severe motor fluctuations, and incapacitating levodopa-induced dyskinesias underwent bilateral STN-DBS. He presented early onset of PD symptoms (35 years-old). Eight years ago, he started complaining of severe loss of olfaction discrimination (he seldom perceived very intense and unpleasant fragrances) and loss of libido. His motor scores on the UPDRS part III in ON medication were 35 and 74 in OFF medication condition. Chronic monopolar stimulation was applied on the contacts corresponding to the STN (two distal contacts on each side as the cathodes—1.7 V (right), 2.0 V (left), pulse width 210 μs, and frequency of 130 Hz). At five months on postoperative follow-up, the patient had experienced improvement in the UPDRS part III score (16 ONmed/ONstim vs. 39 OFFmed/ONstim). During a routine visit, the patient spontaneously reported marked improvement in his olfactory function. Olfaction was assessed using the brief smell identification test (12-items, B-SIT).[4] He recognized the odor of eight of twelve substances, score considered normal olfaction for someone his age, according to the Doty's values.[1]

Six months after surgery, under informed consent, the patient underwent FDG-PET scan study, in the ONstim/ONmed vs. the OFFstim/ONmed conditions. The first study was performed with the stimulator ON and under routine medication (best functional condition). The radiotracer was injected at rest, in a dark and quiet room during odor exposi-

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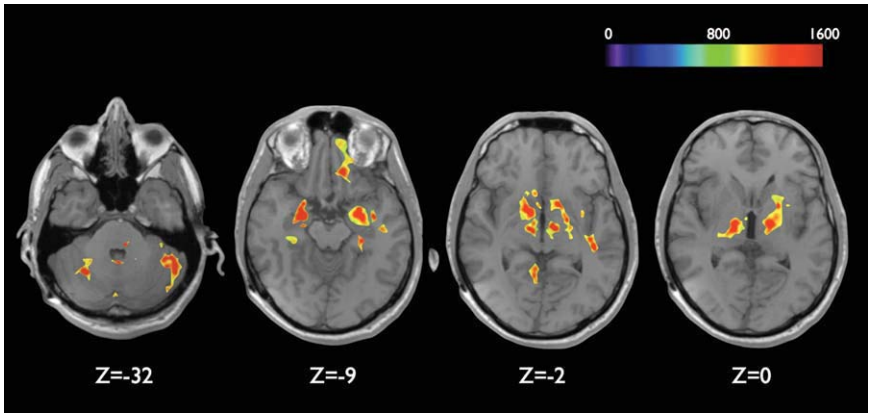

FIG. 1. Results of regional brain activation related to the olfactory paradigm during bilateral STN stimulation. Images corresponding to "on" and "off" conditions were compared through computerized voxel-based image subtraction (Matlab®/ImageJ®), fused onto the MRI (Osirix®) and plotted into the Tailarach atlas (Brainsight®). The image shows in red and yellow the greater activation areas (thalamus, striatum, nucleus accumbens and amygdaloid complex bilaterally, and the left gyrus rectus). At the bottom "Z" shows the brain slice distance from the AC–PC line (coordinates of Talairach Atlas). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

tion to one of the substances (B-SIT). The second PET study was performed under the same conditions, but the stimulator had been turned off for seven days. At this time, the patient experienced return of hyposmia, as he observed and reported spontaneously. The OD at this point corresponded to the identification of 2/12 fragrances in B-SIT. The results of PET images revealed significant metabolic activation of thalamus, striatum, nucleus accumbens, and amygdaloid complex bilaterally as well as the left gyrus rectus. The tissue around the electrode also revealed metabolic activation, from deep STN extending to ventral thalamus (Fig. 1).

Previous reports have stated that odor discrimination improves after STN-DBS in PD patients, while olfactory detection threshold does not. These results suggest that STN-DBS might modulate cognitive processing of olfactory information.[5] The return to hyposmia after the stimulation was turned off, favors the hypothesis that functional changes in striatum-thalamus-cortical networks, rather than irreversible degeneration of olfactory structures only, are responsible for OD observed in PD patients. The progressive neuronal loss throughout the brain generates dysfunction in the chronometry of circuits of the basal ganglia affecting different systems interpreted clinically as various symptoms of PD. Once the hyper activation of STN is reversed by the onset of local electrical stimulation, its influence spreads out to other neural circuits correcting dysfunctions of modulatory neurotransmitters, which in turn is related to the temporary improvement of motor and nonmotor symptoms. Although data in previous studies[6] suggest that the motor effect obtained by dopaminergic medication and by STN stimulation shares the same activated brain areas, this is not likely to happen with olfactory function because dopaminergic reposition has no effect on hyposmia.[1]

In line with previous reports, PET signs of motor improvement, attenuation of the Parkinson disease related pattern (PDRP)[6] was expressed, except for a residual hypermetabolism in left striatum observed in the present study. Although a remarkable motor improvement was observed in this patient, the expected abolition of PDRP was not fully expressed. This apparent inconsistency may be related to individual variability in a single subject analysis or it may suggest the participation of left striatum in the olfactory information-processing network in this patient. Also, a substantial increase in metabolism in the vicinity of the subthalamic target site extending rostrally into the ventral thalamus was observed. Since the FDG hypermetabolism was highly coincident with the location of electrodes, this component is probably related to the direct effects of electrical stimulation of STN, inhibiting depolarization on the cell membrane.[6] The electrode trajectory performed in this patient includes the motor anterior ventralis oralis nucleus of thalamus/posterior ventralis oralis nucleus of thalamus (VoA/VoP), as observed in the postoperative MRI, the upper contact is located within the ventral portion of thalamus. Besides the activation of amygdaloid complex, hippocampus, orbitofrontal cortex, striatum, thalamus, midbrain, and cerebellum related to olfactory stimulation in PD patients, as shown by Westermann et al.,[7] also observed in this case, there was additional activation of bilateral nucleus accumbens and left gyrus rectus. Although further studies are required for more robust conclusions, the present findings suggest that the activated areas may mediate the odor discrimination improvement after bilateral STN-DBS. The stimulation of thalamic region in this case might also have activated thalamic nuclei related to olfactory function [e.g., nucleus parataenialis of thalamus (Pt)]. The connections of the Pt nucleus arise from the secondary olfactory centers through stria medullaris of thalamus.[8] The activation of this nucleus could influence the olfactory circuitry at distant sites once reports of olfactory sensation were observed by direct electrical stimulation of this region.[9]

These preliminary observations suggest that OD in PD may rather be a circuitry dysfunction and not only a neurodegenerative process in olfactory structures; a dysfunction of cognitive processing involved in odor discrimination might explain this phenomenon. There are multiple levels of integration of olfactory information and the STN-DBS seems to influence the circuit involving the primary olfactory areas, limbic areas as the ventral striatum and basal frontal cortex.

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Familial Nonkinesigenic Paroxysmal Dyskinesia and Intracranial Calcifications: A New Syndrome?

Paroxysmal nonkinesigenic dyskinesia (PNKD) refers to a clinical syndrome characterized by attacks of involuntary movements, including dystonia, chorea, athetosis, or ballism, occurring at rest.[1,2] PNKD is associated to a wide range of aetiologies, for example, autoimmune, vascular, traumatic, infective, and endocrine disorders.[1] However, most cases of PNKD are idiopathic and neuroimaging is usually unremarkable.[1,2] We report a PNKD family whose computed tomography (CT) scan revealed intracranial calcifications.

This four-generation family includes 5 (one deceased) patients (Table 1; Fig. 1). The proband (*individual IV:2*) is 7-year-old girl who experienced at age of 9 months a first attack of dystonic posture of the head with concomitant ballistic and choreic movements of upper and lower extremities. This event lasted 30 minutes, without alteration of consciousness, and was followed by prompt recovery. One month later, the girl experienced a similar episode precipitated by fever and resolving spontaneously. Neurological examination between attacks was normal. Laboratory investigations (serum and urine copper, calcium, phosphorus, vitamin D, ceruloplasmin, ferritin, transferrin, serum iron, thyroid, parathyroid, and adrenocorticotropic hormones, anti-transglutaminase antibodies, serum lipoproteins and lipid profile, lactate, pyruvate, amino acids, and urine organic acids) were normal. Brain magnetic resonance imaging (MRI) was unremarkable. Mutations in *MR-1* (myofibrillogenesis regulator 1)[3] and *SLC2A1* (Glut-1)[4] genes were excluded, as well as and family linkage to chromosome 14q[5] (lod score $< -2; \Theta = 0$). In the following years, the girl continued to experience similar episodes at the frequency of about one per year. In one occa-

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TABLE 1. *Clinical features of the PNKD patients*

Pt ID/age/sex	Age of onset	Precipitating factors	Body regions involved (duration)	Neurological examination	Intracranial calcifications distribution	Frequency of the attacks/Outcome
I:2/82/M	70 years	Fever	Head (15′)	Normal	ND[a]	Single episode
II:3/70/F	4 years	Fasting, emotional stress	Head, limbs (15–20′)	Postural, kinetic tremor	Basal ganglia, cerebellum	Yearly/Spontaneous remission at 30 years
III:2/39/M	4 years	Emotional stress	Head, limbs, and trunk (20–30′)	Normal	Basal ganglia, cerebral white matter	Yearly/Spontaneous remission at 33 years
III:3/37/M	6 years	Fever, emotional stress	Head, limbs (20–30′)	Normal	Basal ganglia	Yearly/Persist
IV:2/7/F	9 months	Fever	Head, limbs (5–30′)	Normal	Absent	Sporadic/Persist

[a]ND: Not done.

sion, ictal electroencephalography (EEG) recording excluded the epileptic nature of the event. At the age of 7 years, a new CT scan was unremarkable.

Individual III:2 is a 39-year-old man suffering from recurrent attacks of choreic-dystonic postures involving the head, limbs, and trunk from 4 years of life, precipitated by emotional stress. At age 33 years, brain CT and MRI revealed basal ganglia and cerebral white matter calcifications. Extensive laboratory screening and neurological examination were unremarkable. No further attacks were reported during the last 6 years.

Individual III:3 is a 37-year-old man experiencing yearly attacks of sudden-onset dystonia and choreic movements of the head and limbs from age 6 to 30 years, related to physical or emotional stress. Neurological examination was unremarkable. Laboratory investigations and EEG were normal. Brain CT at age 30 years showed basal ganglia calcifications.

Individual II:3 is a 70-year-old woman presenting her first attack choreic-dystonic postures involving the head and the four limbs at the age of 4 years. Subsequently, these manifestations occurred regularly at the frequency of one per year in association with fasting or stress. Laboratory investigations and neurological examination were normal. At the age of 65 years, brain CT revealed basal ganglia and cerebellar calcifications. The patient still experiences yearly episodes and, in the last few years, developed postural and kinetic tremor, responding to alcohol intake.

Individual I:2 experienced a single episode of choreic-dystonic postures of the head at the age of 75 years, precipitated by fever and lasting about 20 minutes.

This family shows typical clinical features of PNKD.[1,2] All patients showed a typical pattern and duration of the episodes, not activated by movement, and showed normal neurological status between attacks except for the oldest living individual (II:3) who developed late-onset postural and kinetic tremor, responding to alcohol intake. Individual I:1 who experienced a single attack at age 75 years related to febrile illness, was considered as probably affected, considering the transitory nature of his manifestation and the fact that fever was a precipitating factor also in other affected members, as reported in PNKD.[6] The course of the disease was relatively benign and affected individuals achieved spontaneous remission or continued to have about yearly episodes without treatment. Mutations in *MR-1*, the only gene associated with familial PNKD,[3,7] were excluded.

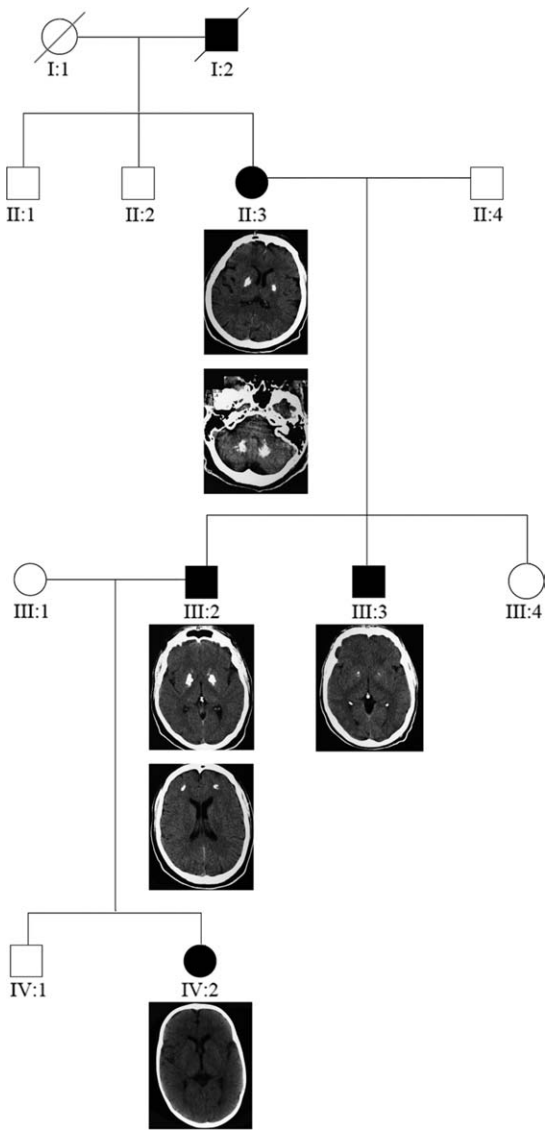

FIG. 1. Pedigree and CT scans of affected family members. See the text for details.

Indeed, the most distinctive feature in our family was the finding of symmetrical intracranial calcifications, primarily affecting the basal ganglia, which has been previously reported in few isolated cases.[8–11] Hereditary brain calcinosis may be found in several different conditions,[12] for example, disorders of parathyroid hormone or calcium regulation, mitochondrial diseases, and defects of organic or amino acid metabolism. However, all these aetiologies were ruled out in our family. Linkage to 14q, described in families with Fahr disease and neurological symptoms,[5] was excluded, confirming that this condition is genetically heterogeneous.[13,14] Moreover, the pathogenetic role of calcifications remains unclear as the youngest patient showed unremarkable neuroimaging despite full phenotypical presentation. Identification of further families could shed light on the pathogenesis of PNKD.

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Dramatic Response of Facial Stereotype/Tic to Tetrabenazine in the First Reported Cases of Neuroferritinopathy in the United States

Video 

Neuroferritinopathy is a rare neurodegenerative disease associated with brain iron deposition caused by mutations in gene encoding the ferritin light polypeptide (FTL). A 460dupA FTL was first identified in patients in northern England.[1] Since then several different mutations of FLT were identified in Japanese and French, and French–Canadian/

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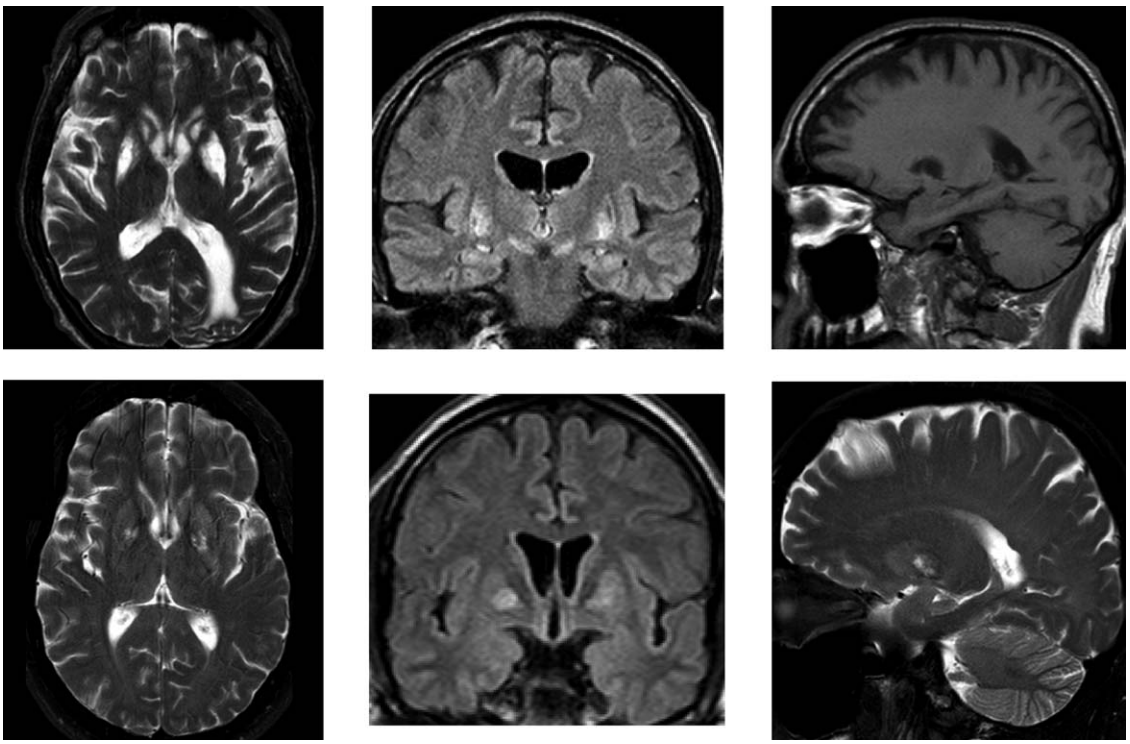

FIG. 1. Top row of MRIs (various sequences) of the father, age 74, and bottom role shows MRIs of son, age 49.

Dutch,[2–6] but the original mutation, which accounts for the majority of documented cases, has not been reported outside the United Kingdom. We report the first cases of neuroferritinopathy in North America, and the first cases showing the 460dupA FTL mutation originating from outside the United Kingdom, in an American family of German ancestry. One patient presented with oral tics/stereotypies most phenotypically similar to those seen in frontotemporal dementia or Tourette's. These completely resolved with low-dose tetrabenazine (TBZ). His father who demonstrated facial and appendicular chorea, marked bulbar dysfunction, ataxia, and dementia, also improved with TBZ.

A 49-year-old right-handed man presented with a 2-year history of varied involuntary facial movements including asymmetric facial grimacing, symmetric lip pursing, tongue biting and teeth clicking, paranasal contractions, touching his mouth with his hand, and vocalizations including throat clearing, coughing, and a "TZ" sound. These were partially suppressible but there was no clear urge to move. These movements worsened while on escitalopram, despite improvement of mood. No other exacerbating or alleviating factors were noted. His other subjective complaints were of mild worsening of balance, mild decreased dexterity manifest only while typing, and general fatigue. Past medical and social histories were unrevealing. The patient's father is affected and is presented below. His paternal grandfather was diagnosed with Huntington's disease and "bulbar palsy" and had chorea. Two of the grandfather's brothers were diagnosed with Parkinson's disease but we have no actual clinical descriptions.

Formal neurological examination was largely normal. MMSE was 29/30. Cranial nerves were intact. Motor testing showed normal strength, bulk and tone, and a trace action tremor. Sensory, cerebellar, and gait examinations were normal. Reflexes were modestly depressed throughout. The patient had frequent mouth touching, right facial grimacing, and finger rubbing, which was partially suppressible (Supporting Information Video Segment 1). Patients provided informed consent for the videos.

Ferritin was 22 μg/mL and iron binding percentage was 28%, a lower than typical ferritin: iron binding ratio. Thyroid test and electrolytes were normal. Acanthocyte smear, Huntington's testing, ceruloplasmin, and chorein (*VPS13A*) testing were normal. EMG/NCV was normal. Brain MRI showed T2 and FLAIR lesions in the globus pallidus and to a lesser extent in the cerebelli (Fig. 1).

The patient was placed on TBZ, which was eventually maintained on 37.5 mg/day (25 mg in A.M. and 12.5 mg in P.M.) resulting in complete cessation of the movements. After 6 months, he reported some subjective worsening in balance without falls. TBZ withdrawal did not alter the balance complaint but did result in recrudescence of the same movements within 24 hours. The TBZ was reinstituted at the same dose without any other adverse events.

The father of Case 1 first appreciated involuntary movements of the hand around age 50. Upon presentation to us at age 69, he had oral and appendicular movements, a 4-year history of progressive dysarthria and dysphagia, marked sialorrhea, a 2-year history of gait and balance difficulty with several falls, and recent mild cognitive slowing. Examination showed a MMSE of 29/30. Cranial nerves showed guttural, more than lingual or labial dysarthria, and hypomimia, but were otherwise normal. Strength was normal but there were

some fasciculations and distal atrophy. Sensory examination showed decreased distal vibration and proprioception. Gait was modestly wide based and unsteady but not parkinsonian. Reflexes were normal with downgoing toes and positive "frontal release signs." The involuntary movements were complex and best described as a mix of stereotype (mouth and hands) and chorea, with oral movements most prominent (Supporting Information Video Segment 2, age 74).

Over the next 6 years, the dysphagia/dysarthria, gait, and cognition gradually progressed. At age 75, he was anarthric, unable to volitionally move the tongue despite lack of peripheral involvement per EMG, and wheelchair bound. Unrevealing evaluations were similar to Case 1 but also showed normal CSF studies, including a normal 14-3-3 protein, and a normal ataxia panel including dentatorubral-pallidoluysian atrophy. MRI showed T2 lesions throughout the striatum and globus pallidus (Fig. 1). TBZ did help the chorea and stereotype but was poorly tolerated at higher doses due to sedation and parkinsonism. TBZ withdrawal on several occasions resulted in increased movements. He remains on 25 mg/day with continued benefit.

We report the first cases of neuroferritinopathy in the United States. The mutation was identical to the original one, which until now was isolated only in cases originating in the United Kingdom. The family denies any known ancestry from that area. On examination, the father appears to have a "classic" phenotype of chorea, prominently in the lower face, with later onset of gait disorder and dementia. However, we feel that the phenomenology of the son is best described as tics, or possibly stereotype, potentially expanding the phenotype of neuroferritinopathy. He had a complete resolution of symptoms on TBZ, whereas his father had fair control of the chorea movements, but was limited by side effects.

Legends to the Video

Segment 1. Patient showing facial stereotype/tics.
Segment 2. Patient showing constant facial stereotype, diffuse slow chorea, and mild ataxia.

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Complex Hyperkinetic Movement Disorders Associated with *POLG* Mutations

Video 

Patients presenting with complex hyperkinetic movement disorders remain a major diagnostic challenge due to difficulties in clinical classification and an increasing number of associated monogenetic diseases.[1]

Mutations in the mitochondrial DNA polymerase gamma (*POLG*) have been described to cause a broad variety of phenotypes,[2] but chorea, dystonia, and myoclonus have only

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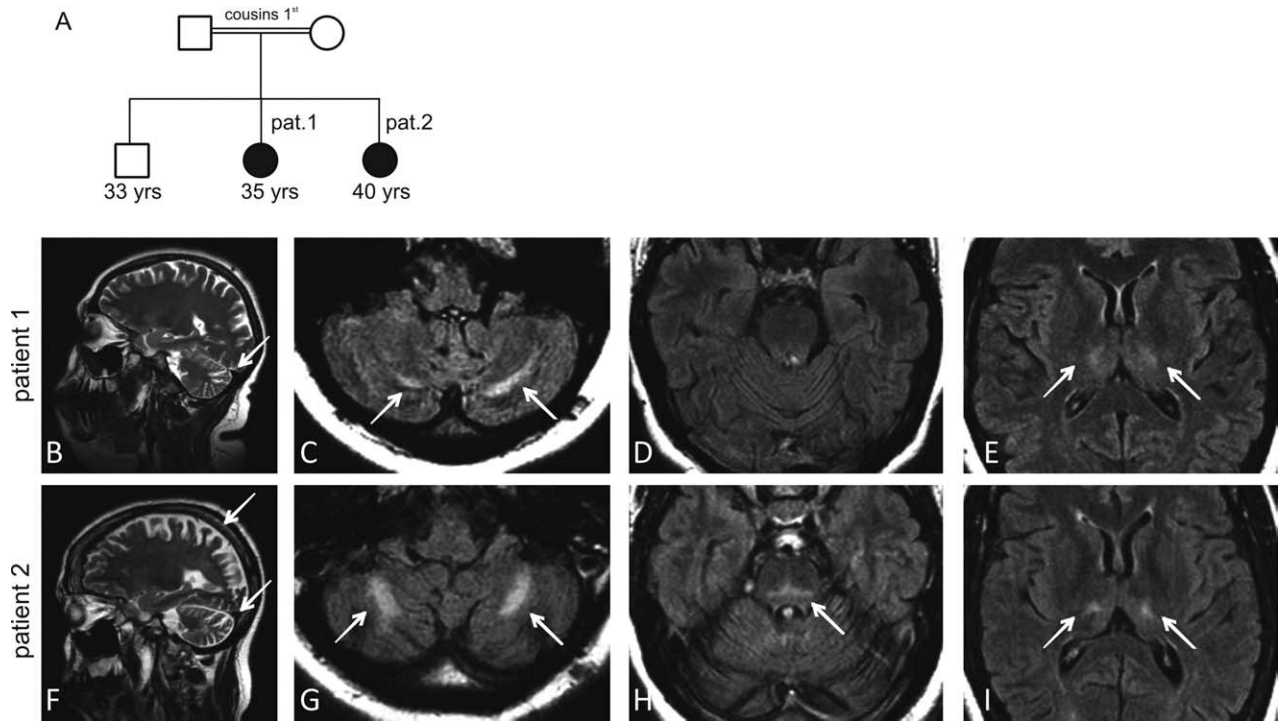

FIG. 1. Pedigree and characteristic MRI findings in two patients with a homozygous W748S *POLG* mutation. Two affected Sicilian siblings of consanguineous parents (**A**) were investigated by magnetic resonance imaging. MR T2 weighted images in Patient 1 (**B–E**) reveal an enlarged cerebellar primary fissure (B), beginning bilateral hyperintense lesions in the cerebellar white matter (C), and the thalamus (E). The brain stem and pons appeared normal in Patient 1 (D). T2 weighted images in Patient 2 (**F–I**) show cerebellar and parieto-occipital atrophy (F) and, like in Patient 1 and similar to other POLG patients,[5] symmetric hyperintense lesions in the cerebellar white matter (G) and the thalamus (I) and, additionally, in the pons (H). Magnetic resonance spectroscopy of the cerebellar white matter lesions revealed normal levels of choline and creatine, but reduced levels of *N*-acetyl aspartate, indicating chronic neuronal loss (not shown).

been mentioned as parts of a plethora of *POLG*-associated symptoms,[2,3] not as the only presenting symptom. Here we report on two siblings from a consanguineous Sicilian family with a homozygous *POLG* mutation. The index patient presented with a complex hyperkinetic movement disorder as initial symptom, whereas other common *POLG*-associated symptoms did not evolve until three years later.

The index patient (Patient 1) underwent uncomplicated surgery of a right-sided carpal tunnel syndrome at 32 years of age. Two weeks later, she developed complex regional pain syndrome of the operated limb with severe pain and allodynia. Another two weeks later, dystonic posturing of the right hand with rapid jerky wrist and finger movements manifested. These jerks consisted of a complex mixture of phasic dystonic wrist flexions and small amplitude finger movements (polymini-myoclonus). In addition, continuous jerky movements of her feet at rest were observed (Supporting Information Video, Segment 1), which were presumably preexisting but unrecognized by the patient herself. These movements were unpatterned and similar to limb movements seen in patients with benign hereditary chorea.[1,4] EEG and SEP recordings showed no cortical correlates of the limb jerks but temporo-parietal focal slowing and intermittent temporal sharp-slow waves. As the forceful wrist and finger movements triggered pain attacks, injections to wrist and finger extensors and flexors were given with a total dose of 800 U botulinum neurotoxin A (BoNTA); (Dysport, Ipsen Pharma). Injections dramatically reduced movement-induced pain attacks and were repeated every 3-month since then (Supporting Information Video, Segment 2). Severe depression with recurrent anxiety attacks necessitated admission to the local psychiatric hospital. Secondary generalized seizures and premature amenorrhoea started at the age of 33 years. Comprehensive neuropsychological testing revealed below-average cognitive capacities. At the age of 35 years, she started to develop sensory neuropathy, mild external ophthalmoplegia, and subtle gait ataxia, yet without leading to incapacitations in daily life (Supporting Information Video, Segment 3) (for MRI images, see Fig. 1).

Patient 2, the index patient's sister, manifested with slowly progressive cognitive deficits during primary school, leading to severe cognitive deficits at the age of 40. At age 13 years, epileptic seizures, recurrent headaches, and mild personality changes started. The movement disorder was similar to her sister's: action-triggered myoclonus started at the left arm at age 14 years and generalized afterwards, whereas dystonic ulnar deviation of the right hand with flexion of the fingers III–V was first noticed at age 20 years. Since then, she also developed progressive cerebellar ataxia and became wheel-chair bound at the age of 31. At the last examination (age 40 years) incomplete chronic progressive external ophthalmoplegia (PEO); (Supporting Information Video, Segment 5) and severe axonal sensorimotor neuropathy were detected. As her phenotype suggested mitochondrial recessive ataxia syndrome (MIRAS),[6]

genetic analysis of the *POLG* gene was initiated, revealing a homozygous W748S mutation in both patients. Genotyping of intragenic single nucleotide polymorphism (SNPs) rs2072267, rs2307433, rs2246900, rs2302084, and rs2307438 showed a homozygous "C-Insertion-G-C-G" haplotype, which is identical to the haplotype common in North European W748S mutation carriers[6] and thus suggests a relation between an ancient founder from North Europe and these Sicilian patients.

Our findings demonstrate that *POLG* mutations should be considered in the workup of progressive complex hyperkinetic movement disorders. As of yet, hyperkinetic movements like myoclonus and chorea have been mentioned in *POLG* patients mainly as part of a plethora of *POLG*-associated symptoms.[2,3] As shown in Patient 1, complex hyperkinetic movements presenting with myoclonus, dystonia, and possibly also choreic elements may be the only feature seen for several years. This finding moreover demonstrates that not only apraxia of eye lid opening[7] and dystonic toe curling,[8] but also upper limb dystonia is part of the spectrum of *POLG*-associated dystonia.

Interestingly, the disease course in Patient 1 shows that cerebellar ataxia, sensory neuropathy, and/or PEO are not necessarily presenting or early features of autosomal-recessive-*POLG* (AR-*POLG)* mutations. A family history with consanguineous marriage and/or recessive inheritance (like in our pedigree) or *POLG*-characteristic features in the disease course (like in Patient 1) may support the decision for *POLG* sequencing in undiagnosed patients with hyperkinetic movement disorders.

Legends to the Video

Patient 1

Segment 1. At the age of 33 years, Patient 1 showed dystonia of both arms, with predominant dystonic ulnar deviation of the right upper limb with jerky wrist and finger movements, which had started four weeks after carpal tunnel surgery induced CRPS. Distal finger movements have smaller amplitudes characteristic of polymini-myoclonus. Also her feet show unpatterend jerky movements, which may be classified as myoclonus but are also similar to limb movements in benign hereditary chorea.[1,4]

Segment 2. Botulinum toxin treatment of extensor and flexor muscles of the right forearm markedly reduced hyperkinetic movements. The main therapeutic goal remained pain reduction. Apart from the botulinum toxin effect, also intermittent mirror movements can be observed in this segment.

Segment 3. At the age of 35 years, external ophthalmoplegia, slowing of voluntary saccades and gait ataxia started. Also, a reduced arm swing on the right side was first noticed.

Patient 2

Segment 4. At the age of 40 years, Patient 2 displayed dystonic ulnar deviation of the left upper limb with distal predominance. She showed intermittent facial and jaw opening dystonia. At rest, she had marked postural instability caused by trunk ataxia, which is aggravated by motor actions like e.g. lifting the upper limbs.

Segment 5. In Patient 2 severe dysarthria, incomplete horizontal and vertical external ophthalmoplegia and ataxia were observed as clinical features of MIRAS. Patient 2 was only able to stand assisted for a few seconds.

Author Roles: Synofzik was involved in the Research project: Conception, Organization, Execution; Manuscript: Writing of the first draft. Schüle was involved in the Research project: Execution; Manuscript: Review and Critique. Schulte was involved in the Research project: Execution; Manuscript: Review and Critique. Lindig was involved in the Research project: Execution; Manuscript: Review and Critique. Krüger was involved in the Research project: Execution; Manuscript: Review and Critique. Schöls was involved in the Research project: Organization; Manuscript: Review and Critique. Asmus was involved in the Research project: Conception, Organization, Execution; Manuscript: Writing of the first draft.

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Neuroleptic Malignant Syndrome with Aripiprazole in Huntington's Disease

The atypical antipsychotic drug aripiprazole is a partial dopamine D2 and serotonin 5-HT_{1A} receptor agonist and an antagonist at serotonin 5-HT_{2A} receptors. It is a promising agent for patients with schizophrenia but also for those with Huntington's disease (HD), who may suffer from psychosis, aggression, cognitive decline, and movement disorder. Recent reports[1,2] and clinical observations suggest that aripiprazole improves chorea and functional disability with an effect comparable with tetrabenazine but with less sedation and better tolerability. Thus, aripiprazole may be an attractive treatment option in HD, in particular for patients with psychosis and chorea or those not responding to other chorea treatments. In schizophrenia, however, aripiprazole was associated with neuroleptic malignant syndrome (NMS).[3,4] Patients with HD may have an increased risk for developing NMS although the occurrence of NMS in HD is rarely reported.[5] Here, we present a case of MNS in a HD patient treated with aripiprazole.

The patient, a 55-year-old retired engineering technician, presented with increasingly severe behavioral disorders including irritability and violent behavior. Unequivocal motor signs of HD (chorea) had been observed for the first time 10 years before. The father and brother of the patients had died of HD. The clinical diagnosis of HD was confirmed with molecular genetic testing (CAG repeat expansion with 43 triplets). An MRI scan of the brain at the time of diagnosis showed normal cerebral morphology. Recent MRI scans revealed HD typical morphological alterations (symmetric atrophy of the striatum and widening of the lateral ventricles). Subsequently, the patient developed severe chorea of arms and legs, head and trunk together with moderate cognitive impairment. He lost 25 kg of weight because of chorea-induced difficulties with eating. On admission, he presented with severe dysarthria, generalized chorea, slowing of saccadic eye movements, severely unsteady gait and postural instability. Cognitive deficits comprised several domains including attention, memory, and executive functions.

Initially, the patient had been treated for chorea with perphenazine and tiapride; because of increasingly aggressive behavior, risperidone was initiated and considered effective over 4 years. Sertraline was added to treat depressive symptoms. Upon admission, the patient was treated with risperidone (3 mg/d), sertraline (50 mg/d), and tiapride (700 mg/d). Trimipramine (50 mg) and melperone (50 mg) had been tried unsuccessfully to ameliorate insomnia. We considered a connection between risperidone and aggravated agitation and restlessness in terms of an extrapyramidal side effect. Withdrawing risperidone, we added aripiprazole (10 mg) to tiapride and melperone to treat the patient's aggressive behavior because aripiprazole is known to reduce aggressive symptoms in other psychiatric disorders.[6] Within 2 days, the patient attracted attention because of apathy, muscular rigidity, and fever together with tachycardia and tachypnea. Peak creatine kinase levels were 33980 U/L, leucocytosis reached levels of 19.5 G/L. Upon immediate withdrawal of all dopamine antagonists (tiapride, melperone, aripiprazole), parenteral hydration and treatment with diuretics, clinical symptoms, and laboratory abnormalities resolved within 2 weeks. Because of recurrent symptoms of chorea, irritability, and disturbed sleep, we initiated tetrabenazine (up to 112.5 mg) and quetiapine (50 mg) together with sertraline (150 mg) and mirtazapine (45 mg), resulting in adequate symptom control without recurrence of NMS.

To the best of our knowledge, this is the first report of NMS in HD with aripiprazole treatment. The application of conventional clinical doses of aripiprazole, such as in our case, leads to a nearly complete saturation of D2-like dopamine receptors.[7] High dopamine D2 receptor affinity has been suggested as one of the bases of NMS, particularly of note when adding aripiprazole to other dopamine-receptor antagonists[3] as in our case. Blocking striatal and hypothalamic dopamine transmission may have contributed to muscular rigidity and dysfunctional thermoregulation.[7] Although a polypharmacologic cause of NMS has to be considered in our patient, the proportionally low affinity of tiapride and melperone to D2-like dopamine receptors suggests that aripiprazole may have been the main culprit. In conclusion, when using aripiprazole in HD one needs to be aware of the risk for NMS, in particular, if patients take other dopamine-receptor antagonists.

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Electrophysiological Evaluation of Thalamic DBS for Orthostatic Tremor

Orthostatic tremor (OT) is characterized by high-frequency muscle discharges of the leg when standing.[1] Pharmacological treatment offers a limited improvement but a benefit with thalamic stimulation was recently published.[2,3] We report new electrophysiological evidence in a case of OT with DBS in the ventral intermediate nucleus of the thalamus (Vim). A 68-year-old woman had both legs shaking during standing and was unable to maintain balance during bipedestation. Surface EMG showed a 12 to 18 Hz tremor in the lower limbs when standing. Treatment with propranolol, gabapentin, clonazepam, primidone, or ropirinole was unsuccessful and DBS was offered. The patient signed a written consent. The surgical procedure was similar to that done in Parkinson patients.[4] The lateral aspect of the Vim was determined by MRI/CT imaging and neuronal recordings and bilateral electrodes were implanted (DBS model 3389, Medtronic, Minneapolis, MN). All drugs were withdrawn after surgery. One year after DBS implantation (bipolar, 185 Hz, 90 μs) the patient could stand up normally without any help or leg trembling. Nevertheless, when the patient walked still remained a degree of postural instability although not appreciable by her. For gait analysis (STEP 32; Demitalia, Torino, Italy), the patient walked along a corridor several times. We studied the tibialis anterior, gastronimius, rectus femoris, biceps femoris, and paraspinal of both sides. The analysis was with the stimulator OFF and ON and with the eyes opened and closed. Tremor amplitude diminished significantly in all muscles studied ($P < 0.01$) with ON stimulation but the frequency remained the same. Tremor started before the patient reached

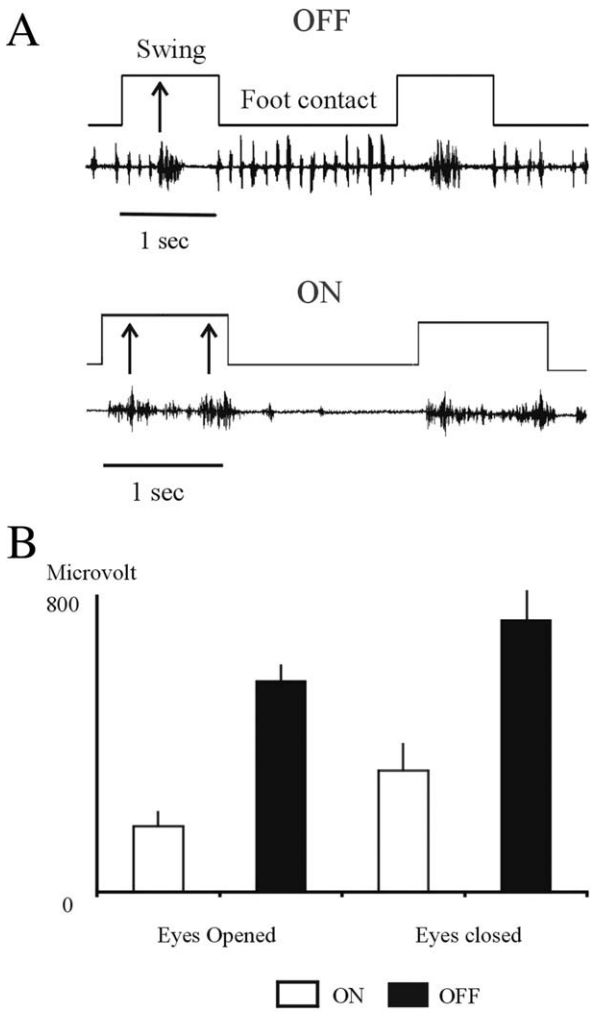

FIG. 1. **A**: Right foot step cycle during OFF (above) and ON stimulation (below). During OFF stimulation, the anterior tibialis is activated just once along the swing phase (arrow). The contraction of the muscle is vigorous in amplitude and occurred in the middle of the phase. During foot contact, the muscle shows several bursts with a frequency similar to OT. However, during ON stimulation, the same muscle is activated twice along the swing phase and is almost silence during foot contact. **B**: EMG tremor amplitude of the right anterior tibialis during OFF and ON stimulation and with the eyes opened and closed (the patient was standing). With the eyes closed, the amplitude of the tremor was higher ($P < 0.01$) than with the eyes opened during OFF and ON stimulation (1 second calculated).

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orthostatism during OFF but had a delay of 500 to 1,000 ms during ON stimulation. The parameters of the step cycle were normal with OFF and ON stimulation. However, during OFF stimulation, the tibialis anterior contracted in the middle of the swing phase and showed a 12-Hz tremor activity during foot contact. On the contrary, during ON stimulation, the muscle produced two sets of contractions for each swing phase and was silent during foot contact both activities considered normal (Fig. 1A). A significant difference of tremor amplitude was found with the eyes closed compared with the eyes opened in OFF and ON stimulation (Fig. 1B).

Our results confirm the validity of Vim DBS for drug refractory OT.[2,3] The reduction in the amplitude of tremor indicates a role of the Vim in the genesis of OT but the lack of effect in the frequency suggests other generators. The greater amplitude of the patient tremor with the eyes closed compared with the eyes opened in OFF and ON stimulation points to the involvement of somatosensory inputs and may explain the degree of postural instability. At this respect, Wu et al.[5] discarded the possible effect of vestibular afferents and suggested the posterior fossa as the origin of tremor. Another factor influencing the stability when walking during OFF stimulation may be the tremor frequency found during the phase of contact and the irregular activation of the tibialis anterior during the phase of swing.

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