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Brief Reports

Apraxia of Lid Opening Mimicking Ptosis in Compound Heterozygosity for A467T and W748S *POLG1* Mutations

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Abstract: **Patients harboring A467T and W748S *POLG1* mutations present with a broad variety of neurological phenotypes, including cerebellar ataxia, progressive external ophthalmoplegia (PEO), myoclonus, epilepsy, and peripheral neuropathy. With exception of ataxia and myoclonus, movement disorders are not typical features of *POLG1* associated disorders. We report on two affected siblings compound heterozygous for A467T and W748S mutations, one suffering from choreoathetosis and apraxia of lid opening due to focal eyelid dystonia that mimicked progression of ptosis, resulting in functional blindness. So far, focal dystonia has not been reported in *POLG1* mutation carriers, and should be considered when investigating patients with PEO and ptosis. Further studies on *POLG1* mutations in focal dystonia are warranted.** © 2008 Movement Disorder Society

Key words: focal dystonia; blepharospasm; ptosis; POLG; botulinum neurotoxin

Mutations in the polymerase γ gene (*POLG1*), coding for a protein involved in mitochondrial DNA (mtDNA) maintenance, cause a broad variety of autosomal dominant and recessive neurological phenotypes, including progressive external ophthalmoplegia (PEO), ptosis, cerebellar ataxia, epilepsy, dementia, myopathy, myoclonus, peripheral neuropathy, and headache, in some cases accompanied by liver involvement.[1] In *POLG1* associated disorders, relationship between genotype and phenotype is complex, with a considerable overlap of clinical spectrum.[2,3] With exception of ataxia and myoclonus, movement disorders are not typical features of *POLG1* mutations. Recently, Parkinsonism has been associated to *POLG1*, accompanied either by PEO and other characteristic symptoms,[4] or neuropathy alone.[5] One study in Finnish patients with recessive ataxia due to homozygous W748S mutations described involuntary movements, namely athetoid and choreoathetoid movements of extremities and face, and tremor of head and limbs.[6]

Here, we report on two siblings compound heterozygous for A467T and W748S, the most frequent recessive *POLG1* mutations, presenting with a remarkably later onset and longer survival than most patients of the same genotype. One suffered from choreoathetosis and apraxia of lid opening (ALO) due to dystonic activity of eyelid muscles, resulting in functional blindness. So far, dystonia has not been reported in *POLG1* mutation carriers.

SUBJECTS AND METHODS

Subjects

Three sisters, ages 39 (Patient 1), 38, and 37 (Patient 2), the children of nonconsanguineous parents, were normal at birth and through childhood. The oldest developed neurological symptoms at the age of 28, heralded by episodic headache, cognitive decline, and seizures, repeatedly resulting in generalized status epilepticus. When seen first at age 32, Patient 1 presented with marked ataxia, both due to cerebellar affection and sensorimotor peripheral neuropathy, dysarthria, PEO with diplopia, mild bilateral ptosis, epilepsy, moderate cognitive impairment, myoclonus and choreoathetoid movements of the arms and perioral muscles. She had never been treated with neuroleptics. MRI of the brain showed moderate generalized cerebral atrophy, including midbrain and cerebellum. Histology of vastus lateralis muscle revealed mild unspecific myopathological alterations without ragged

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TABLE 1. *Phenotypes, genotypes, and mtDNA copy numbers in blood*

Subjects	Age (years)		Neurological phenotype	*POLG1* genotype	Copy number	*P*
	d. onset	Now				
Mother	Na	64	None	W748S + E1143G/wt	194 ± 31	0.0009
Father	Na	64	None	A467T/wt	287 ± 21	0.26
Daughter (Patient 1)	28	39	Ataxia, neuropathy, PEO, epilepsy, focal dystonia, athetosis, cognitive decline, headache	W748S + E1143G/A467T	104 ± 24	0.000002
Daughter	Na	38	None	W748S + E1143G/wt	244 ± 63	0.15
Daughter (Patient 2)	36	37	Ataxia, neuropathy, PEO	W748S + E1143G/A467T	141 ± 15	0.000014
Controls (n = 15)	48 ± 14		None	wt/wt	323 ± 110	–

Copy numbers are given in mean ± SD.

POLG1 genotype: The two sides of the slash indicate genotyping results of the two chromosomes as determined by PCR-RFLP. The term "wt" in this respect indicates that none of the three *POLG1* mutations (W748S, E1143G, and A467T) were detected.

SD, standard deviation; d. onset, disease onset; na, not applicable; PEO, progressive external ophthalmoplegia; wt, wild type.

red or cytochrome *c* oxidase negative fibers, while biochemical analyses of respiratory chain enzymes and citrate synthase activities were normal (Table 1).

Patient 2 was healthy until the age of 36, when she developed PEO, mild bilateral ptosis, dysarthria, ataxia, and neuropathy. Brain MRI was normal. Examination of muscle tissue was identical to Patient 1.

Mother, father, and the third sister were seen at ages 64, 64, and 38, respectively. Besides obstetric cholestasis in the sister, no liver disease, diabetes, or neurological symptoms became evident.

Genetic Analysis

Total DNA was extracted from muscle tissue in both patients, followed by long-range PCR to test for mtDNA rearrangements. Also, total DNA was extracted from blood in all subjects, at first analyzed for the two most frequent recessive mutations in *POLG1* (A467T, W748S) and the E1143G polymorphism by PCR-RFLP, followed by sequencing.

Copy numbers of the mitochondrial genome were determined in blood leukocytes in all subjects by real-time PCR as described earlier.[7] In all subjects, quadruple experiments were performed, and arithmetic means and standard deviations were calculated. Copy numbers were compared to those of 15 age- and sex-matched healthy controls (f/m: 13/2), using student's *t*-test.

RESULTS

Clinical Course

After initial presentation, Patient 1 was seen at regular intervals, and a slow worsening of diplopia, neuropathy, and ataxia was documented, whereas epilepsy, choreoathetosis, and cognitive function remained stable. Involuntary closing of the eyes due to lowering of the lids also worsened, at first attributed to aggravation of ptosis, resulting in phases of functional blindness at the age of 35. At this time, she started to recline her head and to hold open her eyes with her fingers during conversation or reading attempts, accompanied by voluntary contraction of the frontalis muscle, as sometimes observed in ALO. Although no apparent blepharospasm was observed, and the patient's maneuvers did not function as a sensory trick, we assumed dystonic closing of the eyelids (in contrast to myopathic ptosis), and needle electromyography revealed persistent and dystonic muscle activity of the pretarsal part of the orbicularis oculi muscle. Injections of botulinum neurotoxin A (BoNT/A; Botox®) into both upper eyelids (4 units per side) led to marked improvement with mild residual ptosis only, similar to the initial clinical examination. BoNT/A injections were continued in 3 months intervals, with ongoing success until now. When Patient 2 was seen 1 year after disease onset, there were no involuntary movements of any kind.

Genetic Analysis

Long-range PCR detected multiple mtDNA deletions in skeletal muscle of Patients 1 and 2. Both were compound heterozygous for A467T and W748S *POLG1* mutations. Mother and healthy sister were heterozygous for the W748S mutation, and the father was heterozygous for the A467T mutation. As described before,[3,6] W748S was found together with E1143G in each case, suggesting allelic coupling of both mutations.

MtDNA copy numbers in blood were significantly reduced in both patients compared to controls, even

more obvious in Patient 1 with earlier disease onset and more severe clinical phenotype (reduction of 68% and 56%, respectively). Also, mean copy numbers of the healthy family members were lower when compared with mean values of controls, reaching significance in the mother only.

DISCUSSION

Our study on a family of A467T and W748S *POLG1* mutation carriers, including two affected siblings, extends previous observations on the diversity of clinical spectrum in *POLG1* associated disorders. In Patient 1, diagnosis of ALO due to focal eyelid dystonia was probably delayed, because it accompanied mild ptosis in PEO and mimicked severe paresis of eyelid muscles. Indeed, ALO is known to occur without any obvious spasms of the orbicularis oculi muscle as seen in typical blepharospasm, frequently hampering recognition.[8] Difficulties in separating blepharospasm and ALO from myasthenic or myopathic ptosis were reported before, and in some cases, the underlying disorder was only unmasked by a poor response with severe ptosis after BoNT/A treatment.[9,10] In isolated ALO, BoNT/A was shown to be effective,[11] and our patient suffered no side effects after repeated injections. In ambiguous cases, distinct electromyographic features of the various compounds of the orbicularis oculi muscle in blepharospasm and ALO offer clarification.[12]

Frequently, ALO with and without blepharospasm is associated to neurodegenerative disorders, mostly Parkinson's disease and progressive supranuclear palsy.[8] Focal dystonia was reported in Leigh's syndrome and Leber's hereditary optic neuropathy,[13] but is not a typical feature of mitochondrial disease in adulthood. So far, it was unknown in patients harboring *POLG1* mutations. As a defect of mitochondrial complex I was implicated in the pathogenesis of focal dystonia before,[14] and mitochondrial disease presenting with dystonia as dominant clinical phenotype was reported very recently,[15] our observation justifies further examination of *POLG1* mutations in focal dystonia. In fact, it was shown that *POLG1* mutations can lead to basal ganglia dysfunction, namely parkinsonism, even in the absence of primary clinical features of *POLG1* associated disorders.[5]

Finally, our observations might further elucidate the complex relationship between genotype and phenotype in *POLG1*, and diagnostic procedures. First, our patients had a later disease onset and longer survival time than most A467T and W748S compound heterozygotes reported before, and those of similar course of disease featured a phenotype resembling our affected siblings.[2,3] We hypothesize that, although often severe, a subgroup of compound heterozygotes shows a considerable milder phenotype of later disease onset and longer survival, eventually distinguished by ataxia and adult-onset PEO, probably defined by further, yet unknown, genomic variations. Second, mtDNA content in blood was significantly reduced in both patients compared to age- and sex-matched healthy controls, suggesting that mtDNA depletion is not restricted to liver or muscle tissue in *POLG 1* associated disorders, but may be detected in easily obtainable blood samples as well.

In conclusion, *POLG1* mutations might present with treatable focal dystonia, which should be considered in cases of PEO and ptosis. Further studies on *POLG1* mutations in focal dystonia are warranted.

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GPi-DBS in Huntington's Disease: Results on Motor Function and Cognition in a 72-Year-Old Case

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Video 

Abstract: **Huntington's disease (HD) produces debilitating motor abnormalities that are poorly responsive to medical therapy. Deep brain stimulation (DBS) of the posteroventral globus pallidus internus (GPi) may offer a treatment option for patients with diskinetic phenotype and minimal cognitive impairment, but its role in the management of HD remains unclear and to date only two cases have been reported. We report the outcome of GPi-DBS in a 72-year-old man with HD. Stimulation at 130 Hz caused a rapid amelioration of chorea producing the worsening of bradykinesia, whereas 40 Hz stimulation (maintaining constant the total electrical energy delivered) improved chorea while preserving the ability to walk. At 1-year follow-up, chorea has completely disappeared; however, the patient was unable to stand and walk. The cognitive profile showed a progressive deterioration, with an extension of deficit from the mainly dysexecutive alterations at baseline to a more diffused cognitive deterioration.** © 2008 Movement Disorder Society

Key words: Huntington's disease; deep brain stimulation; Globus pallidus; surgery; therapy

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by progressive cognitive impairment, movement disorders, and psychiatric symptoms. When the movement disorder, particularly the chorea, is disabling, pharmacological treatment is the mainstay of treatment but it is often ineffective. Thus, the following surgical therapies have been introduced: pallidotomy,[1,2] human fetal striatal transplantation,[3] and deep brain stimulation (DBS).[4,5] The preferred target of DBS is the posteroventral globus pallidus internus (GPi) because of the striking effects of pallidal surgery for choreodystonic movements induced by levodopa (L-dopa) in Parkinson's disease (PD),[6] senile chorea,[7] and chorea associated with cerebral palsy.[8]

To date, two HD cases treated with GPi-DBS have been reported.[4,5] Further experience is needed to confirm the efficacy of DBS in HD, to guide the development of patient selection criteria, and to determine the optimal target sites and stimulation parameters. In this report, we describe the use of bilateral GPi-DBS in a HD patient with medically intractable chorea.

METHODS

DBS leads (model 3387; Medtronic) were bilaterally implanted under general anesthesia. Brain magnetic resonance imaging and computed tomography were utilized for targeting procedures. The leads were connected to an implantable pulse generator (IPG) (Kinetra, Medtronic), which was secured in the subcutaneous tissues of the chest.

The effect of the stimulation by means of each of the four electrode contacts was investigated using different settings of stimulation (frequency: 40, 130, and 180 Hz; pulse width: 60, 90, 120, 180, and 210 mcsec; voltage: from 1 to 7 V). The patient was evaluated 15 min after the change of parameters, and after 24 hours when a new set of parameters was tested.

When comparing the different settings we maintained constant the total electrical energy delivered (TEED) determined using the equations proposed by Moro et al.[4] as follows:

$$\mathrm{TEED} = [(\mathrm{voltage} \times \mathrm{pulsewidth} \times \mathrm{frequency})/\mathrm{impedance}]^2 \quad [\mathrm{TEED}^{(1)}],$$

An equation empirically derived from their previous studies on patients affected by PD[9] but believed to be incorrect by Koss et al.[10] who suggested,

$$\mathrm{TEED1sec}\left[(\mathrm{voltage}^2 \times \mathrm{pulsewidth} \times \mathrm{frequency})/\mathrm{impedance}\right]^2 \times 1\ \mathrm{sec} \quad [\mathrm{TEED}^{(2)}].$$

Clinical assessments were prospectively performed using the motor section of the Unified Huntington's Disease Rating Scale[11] and of the Unified Parkinson's Disease Rating Scale[12] (Table 1).

At baseline and at follow-up visits, the patient underwent an extensive neuropsychological examina-

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tion by means of a previously reported standardized battery[13] (Table 2).

RESULTS

The patient is a 72-year-old man with genetically confirmed HD. His motor symptoms began at age 55 and progressed to severe generalized choreathetosis. Within the previous 2 years, he showed weight loss and balance impairment with falls. The introduction of haloperidol induced a marked sedation, whereas tetrabenazine was tolerated only at low doses with only modest benefit (Table 1). Because of the absence of severe psychiatric disorders and neuropsychological deficits (Table 2), the patient was considered eligible for bilateral GPi-DBS. Surgical procedure was well tolerated.

Effect on Motor Function

The patient was discharged from the hospital with IPG left off to allow stabilization of the micropallidotomy effect, which caused only a mild reduction of dyskinesias (Table 1). One month after surgery, monopolar stimulation using ventral contacts seemed to be more efficacious on chorea but it was associated with a severe hypotonia of axial muscles causing flexion of the head and loss of trunk control. Parameters was maintained as follows: right GPi: 2.6 V, 130 Hz, 90 mcsec, contact 2 negative and case positive; left GPi: 2.7 V, 130 Hz, 90 mcsec, contact 6 negative and case positive.

Four months after the surgery, we found that stimulation at 40 Hz significantly improved chorea. Five minutes after the IPG was switched on, limbs chorea improved consistently while mild dyskinesias were still present on the face and shoulders. Chorea gradually reappeared 15 min after the IPG has been switched off. Stimulation at 130 Hz caused further improvement of chorea but also worsening of bradykinesia and a severe disturbance of gait characterized by freezing and start hesitation; the effect of these different frequencies was confirmed in double-blind fashion maintaining constant TEED calculated by means of both the proposed methods (Table 1). Accordingly, stimulation parameters were changed as follows: right GPi: 2.0 V, 40 Hz, 90 mcsec, contact 1 negative and case positive; left GP: 2.0 V, 40 Hz, 90 mcsec, contact 5 negative and case positive.

During the following months, gait and apathy progressively worsened. Despite the complete resolution of chorea and an associated weight gain, which allowed the withdrawal of the medications, the patient's level of independence worsened due to the severe impairment of autonomous gait. The lowering of amplitude of stimulation did not improve the axial impairment. Eleven months after surgery, the stimulation was switched off and, surprisingly, this did not cause the reoccurrence of chorea (Table 1). A 250-mg L-dopa challenge improved the patient's ability to arise

TABLE 1. *Motor function during follow-up visits*

	Month before and after surgery	−6	−1	1	3	4			6	11	12
Oral therapy (mg/day)	Olanzapine					10	10	10	7.5		
	Tetrabenazine		37.5	31.25	37.5	37.5	37.5	37.5	37.5		
	Levodopa									800	800
	Stimulation (frequency)	–	–	Off	On (130)	Off	On (40)	On (130)	On (40)	On (40)	Off
Motor assessment	Chorea (0–28)	17	17	13	16	15	9	9	3	4	4
	Variation compared to baseline (−1 month)			−23.5%	−5.9%	−11.8%	−47.1%	−47.1%	−82.4%	−76.5%	−76.5%
	Dystonia (0–20)	2	4	4	2	2	2	2	1	0	0
	Variation compared to baseline (−1 month)			0.0%	−50.0%	−50.0%	−50.0%	−50.0%	−75.0%	−100.0%	−100.0%
	Bradykinesia/rigidity (0–28)	15	14	11	11	11	11	11	14	6	6
	Variation compared to baseline (−1 month)			−21.4%	−21.4%	−21.4%	−21.4%	−21.4%	0.0%	−57.1%	−57.1%
	Axial symptoms (0–16)	7	6	5	12	14	11	14	14	14	14
	Variation compared to baseline (−1 month)			−16.7%	+100.0%	+133.3%	+83.3%	+133.3%	+150.0%	+133.3%	+133.3%

Chorea score was defined as the sum of UHDRS items 12a–12g (maximum score: 28); dystonia score as the sum of UHDRS items 11a–11e (maximum score: 20); bradykinesia/rigidity score as the sum of the UHDRS items 11, 12, 14, 15 (maximum score: 28); axial symptoms as the sum of UHDRS items 18, 19, 20; and of UPDRS item 27 (arising from chair) (maximum score: 16).

TABLE 2. *Chronic effect on cognition*

Test	Baseline	Month 6	Month 12
MMSE	27 (24.3)	**23 (20.3)**	**22 (19.3)**
Abstract reasoning			
PM'47	**13 (11.4)**	**15 (13.4)**	**11 (9.4)**
Memory			
RAVLT: immediate recall	28 (29.3)	26 (27.3)	**21 (22.3)**
RAVLT: delayed free recall	6 (6.8)	**2 (3.8)**	**0**
RAVLT: delayed recognition (hits/false alarms)	13/**15**	13/**18**	14/**17**
Immediate visual memory	17 (16.2)	15 (14.2)	15 (14.2)
Rey-Osterrieth complex figure: recall	**2.5 (4.25)**	**6.5 (8.25)**	**2 (3.75)**
Digit span: forward–backward	5 vs. 3	7 vs. **2**	5 vs. 3
Corsi's block test: forward–backward	5 vs. 4	NP	5 vs. 3
Language			
Phonological fluency (stimuli: A, F, S)	**19 (12.5)**	**11 (4.5)**	**8 (1.5)**
Semantic fluency (stimuli: furniture, birds)	**7**	**4**	**5**
Nouns naming (30 items)	**26**	**22**	**26**
Verbs naming (28 items)	**22**	**18**	**23**
Visuo-spatial abilities			
Copying drawings	4	4	**2**
Copying drawings with landmarks	18	18	19
Line cancellation	60	**16**	60
MFTC (hits/false alarms)	**7**/1	**3**/2	**2**/1
Rey-Osterrieth complex figure: copy	**17 (17.75)**	**5 (5.75)**	**4 (4.75)**
Tests for apraxia			
Ideomotor praxis	17	18	18
Oro-facial praxis	19	16	18
Executive functions			
Stroop test: interference/time[a]	5 (−3.25)	0 (−8.25)	0 (−8.25)
Stroop test: interference/errors[a]	**30 (29.25)**	**30 (29.25)**	**30 (29.25)**
Temporal rule induction[a]	**17 (19.5)**	**25 (27.5)**	**33 (35.5)**
WCST: number of categories	3	**0**	**0**
WCST: % of errors[a]	**55**[b]	**63**[c]	**68**[c]
WCST: % of perseverative errors[a]	**49**[c]	**44**[c]	**51**[c]
WCST: % of "conceptual level" responses	**36**	**12**	**9**
Frontal assessment battery	**10**	**9**	**3**

Numbers in brackets indicate the corrected scores for age and years of education according to an Italian population-based standardization; scores in bold are below the cut-off of normality.

[a]Reverse scores: lower scores indicate better performances.

[b]Below 10th percentile.

[c]Below 1st percentile.

IVM, immediate visual memory; MFTC, multifeatures targets cancellation; MMSE, mini-mental state examination; NP, not performed; PM'47: Raven's progressive matrices'47; RAVLT, Rey's auditory verbal learning test; ROCF, Rey-Osterrieth complex figure; WCST, Wisconsin card sorting test.

from chair without assistance and slightly the gait, so the patient started chronic therapy with L-dopa (up to 800 mg/die) with a mild improvement of bradykinesia, gait, and apathy (Table 1).

Effect on Cognitive Functions (Table 2)

At baseline evaluation (1 month before surgery), the patient's cognitive profile was characterized mainly by dysexecutive syndrome. On the first follow-up visit, 6 months after surgery, the score of Mini-Mental State Examination worsened as did scores of test for executive functions. Scores of linguistic and memory task were lower as well. On the second follow-up visit, 1 year after surgery, he performed worse on all executive tasks, in comparison with both the baseline and 1st follow-up visits. Scores worsened also on phonological fluency task and on elementary constructional abilities.

DISCUSSION

We have confirmed that bilateral GPi-DBS produces a long-term reduction of chorea due to HD. Despite the benefit, surgery has been related to worsening of gait, apathy, and decline of cognitive function.

In the past, pallidotomy has been associated with only modest palliative functional improvement in dystonic features[1] or worsening of parkinsonism.[2,4] Based on this, it has been suggested that the use of DBS to maximize benefits and minimize potential side effects such as bradykinesia. In the first 8-month-follow up report on the use of GPi-DBS to treat HD chorea, authors reported a dramatic reduction of dyskinesias: stimulations at 40 and 130 Hz (maintaining constant the TEED) were equally effective but the second worsened bradykinesia.[4] According to Koss et al., the equation utilized to calculate the TEED was incorrect and it was not possible to discern whether the observed clinical effects resulted from changes in stimulation frequency or from the overall increase in TEED.[10] We confirmed the findings of Moro et al. by maintaining constant TEED calculated with both the equations proposed. This would suggest that in HD the clinical effect of DBS is frequency-dependent and support the concept that bradykinesia and chorea probably reflect underlying differences in neuronal firing patterns and coding.[14] However, it is difficult to say to what extend TEED reflects the real impact of the stimulation on the neurons and axons for at least two reasons: (1) TEED does not reflect the size and the shape of the electrical field; (2) it is known that voltage is the most critical factor for alteration of cell population activity in the human brain.[9]

The secondly reported HD patient had a 12 months lasting, reversible suppression of his choreathetoid movements after surgery. A trial of reduced frequency to 40 Hz produced a poor control of chorea and required reinstitution of high-frequency stimulation (180 Hz). At 10 months, the patient's glottic function worsened, and concerns of dysphagia and airway protection prompted institutionalization; by 12 months his rigidity also progressed. These side effects were not improved by lowered IPG voltage or by turning the stimulator off.[5] Similar to our case, a delayed worsening of parkinsonism was present and it did not change even after a prolonged period without stimulation.

The pathophysiology of the evolving and delayed worsening of gait and akinesia is difficult to explain. In this single case it is not possible to exclude that it was at least in part related to the evolution of the disease and that also the long-term improvement of chorea was related to its progression toward a parkinsonian phenotype. However, DBS may have actually produced a pallidotomic effect, analogous to the worsening of bradykinesia observed after pallidotomy in HD patients.[2,4] The effect of isolated lesions of GPi in subjects not affected by PD or dystonia has been recently reviewed as follows: the clinical picture is characterized mainly by axial parkinsonism and delayed onset of symptoms after the initial insult.[15] Our patient shares some of these features.

This is the first study systematically assessing the cognitive profile of an HD patient treated with DBS: evaluations showed a progressive deterioration, with an extension of deficit from the mainly dysexecutive alterations at baseline to a more diffused cognitive deterioration. The cause of such worsening is only speculative since it is not possible to discern whether it has been caused by the effect of surgery or by the natural course of the disease. In addition, it is not possible to estimate the real impact of stimulation on cognitive functions since the patient was always assessed in stimulation-on condition.

The outcome of the patient hence reported highlights the important ethical decisions that must be made in treating patients with HD. DBS may aid the symptoms, but will not stem the inexorable deterioration of patients with this disease. In addition, similarly to another case,[5] the functional gain of our patient was negligible. Whether or not DBS should be used on a regular basis in such patients still remains to be determined. Further experience with this population will guide the development of patient selection criteria, define the optimal sites and stimulation parameters for DBS, and elucidate the electrophysiological changes in HD.

LEGENDS TO THE VIDEO

Segment 1. The patient, 6 months before surgery, presents severe chorea of facial muscles, trunk, and limbs. The patient is able to stand up without assistance and to walk for a few meters. Chorea of the lower limbs and impairment of postural stability (as revealed by the retropulsion pull test) destabilize him during walking.

Segment 2. Three months after surgery, Gpi-DBS at 180 Hz provides a reduction of dyskinesias, especially of the lower limbs. Stimulation of ventral contacts causes head drop.

Segment 3. Four months after surgery. Fifteen minutes after the IPG has been switched off chorea reappears.

Segment 4. Four months after surgery. Gpi-DBS at 40 Hz provides a reduction of chorea and an improvement of axial symptoms: the patient is able to walk with unilateral assistance.

Segment 5. Nine months after surgery. Limbs chorea has disappeared while facial grimaces are still pres-

ent. Despite the use of 40 Hz stimulation, the patient cannot arise from chair and walk due to a severe start hesitation.

Segment 6. Nine months after surgery. Fifteen minutes after the IPG has been switched off chorea reappears only with very mild dyskinesias of upper limbs, the patient is able to arise from chair, and gait impairment is improved.

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Deep Brain Stimulation in Parkinson's Disease Following Fetal Nigral Transplantation

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Video 

Abstract: **OFF-period dyskinesias have been reported as a consequence of fetal nigral transplantation for Parkinson's disease. This type of dyskinesias may appear in patients even in the prolonged absence of antiparkinson medication and be aggravated by levodopa. Therefore, pharmacological therapeutic approaches in these patients are limited. Here we report two patients with bilateral fetal nigral grafts in the caudate and putamen subjected to deep brain stimulation (DBS) of the globus pallidus internus (GPi) or subthalamic nucleus (STN). Clinical assessment was performed according to UPDRS and the clinical dyskinesia rating scale. In both patients, we found significant improvement in OFF-period symptoms as well as levodopa-induced dyskinesias. However, only GPi-DBS led to a significant reduction of OFF-period dyskinesias whereas STN-DBS did not influence dyskinesias unrelated to external dopaminergic application. These findings, based on two case reports, highlight the pivotal role of the GPi in mediating dyskinesia-related neural activity within the basal ganglia loop.** © 2008 Movement Disorder Society

Key words: Parkinson's disease; neural transplantation; deep brain stimulation; dyskinesias

This article includes supplementary video clips, available online at http://www.interscience.wiley.com/jpages/0885-3185/suppmat

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TABLE 1. *Characteristics of patients at baseline and following fetal nigral grafting and deep brain stimulation*

	Patient 1	Patient 2
Before transplantation		
UPDRS III		
Med OFF	74	49
Med ON	24	14
Dyskinesias (CDRS)		
Med OFF	0	0
Med ON	2	3
Dyskinesias (UPDRS IV)		
Item 32	0	0
Item 33	0	0
Medication (mg/d)	Levodopa: 1,400	Levodopa: 250 Pergolide: 0.5 Deprenyl: 10
LEDD (mg)	1,400 mg	400 mg
Before DBS		
Follow-up period after transplantation	8 yr	8 yr
UPDRS III		
Med OFF	44	30
Med ON	34	14.5
Dyskinesias (CDRS)		
Med OFF	10	6
Med ON	15	10
Dyskinesias (UPDRS IV)		
Item 32	3	4
Item 33	3	3
Medication (mg/d)	Levodopa: 500	Levodopa: 100 Amantadine: 200
LEDD (mg)	500 mg	100 mg
Following DBS		
Follow-up period	3 yr	2 yr
UPDRS III	50	28
Stim OFF Med OFF		
Stim ON Med OFF	33	11
Dyskinesias (CDRS)		
Stim ON Med OFF	10	2
Stim ON Med ON	–[a]	4
Dyskinesias (UPDRS IV)		
Item 32	1	0
Item 33	2	0
Medication (mg/d)	–	–
LEDD (mg)	0	0
Stereotactic coordinates (x, y, z) relative to midACPC	R: 11.4, −2.1, −2.2 L:−11.2, −2.1, −3.0	R: 21.3, 4.5, −3.6 L: −20.5, 1.9, −2.4

[a]After STN-DBS, patient 1 refused assessment in the medication ON condition.

UPDRS III, unified Parkinson's disease rating scale part III (max 108); CDRS, clinical dyskinesia rating scale (max 28); DBS, deep brain stimulation; LEDD, levodopa equivalent daily dosage.

Since the 1980's, intrastriatal transplantation of human fetal nigral neurones has been used as an experimental therapy to restore baseline dopamine synthesis in PD. The grafted dopamine neurones can reinnervate the degenerated striatum, release dopamine, and become functionally integrated into patients' neural circuitries.[1] Whereas open trials have reported clinical beneficial effects, two double-blind studies failed to show significant improvement of motor symptoms compared to sham-surgery.[2,3] Additionally, a significant number of transplanted patients developed severe OFF-period dyskinesias ("runaway dyskinesias") that persisted even after withdrawal of levodopa (L-dopa) medication. Because of the dyskinetic states which are usually aggravated by dopaminergic medication, pharmacological approaches are limited and DBS might be an alternative therapeutic option. Here we report the long-term outcome in two patients with persistent OFF-period dyskinesias after grafting, who later underwent DBS of the subthalamic nucleus (STN-DBS) or globus pallidus internus (GPi-DBS).

CASE REPORTS

Patient 1

The 53-year-old man (PD since 14 years, baseline characteristics in Table 1) was selected for simultaneous bilateral grafting of fetal nigral cells (5 trajectories into putamen, 2 into the head of the caudate nucleus). The tissue preparation, neurosurgical procedure, and postoperative management have been described elsewhere.[1] Long-term dopaminergic graft survival was demonstrated by [^{18}F]fluorodopa PET and *N*-(3-iodopropen-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl)tropane SPECT.[1,4]

The transplantation initially resulted in amelioration of OFF-period symptoms. Subsequently, he developed disabling OFF-period dyskinesias (Clinical dyskinesia rating scale [CDRS] 10/28) particularly on the left body side with involuntary arm elevation, continuous eye rubbing and head scratching (Videotape). Because of aggravation of dyskinetic states by L-dopa (CDRS 15/28), the use of dopaminergic medication had to be limited with the consequence of progressive decline in severity of OFF-phase symptoms (Table 1) and return of hypokinetic fluctuations which could not be controlled by various therapeutic approaches.

Because of prominent OFF-phase symptoms and hypokinetic fluctuations, 8 years after transplantation, the patient was selected for STN-DBS. As a result of STN-DBS, the patient experienced a permanent functional ON-state with sufficient mobility (Unified Parkinson's disease rating scale [UPRDS] total 58/220, UPDRS III 33/108 in the L-dopa test, Table 1). Dopaminergic medication was completely withdrawn. The adjustment of stimulation parameters, however, was difficult due to a very low threshold for stimulation-induced dyskinesias that resembled the previous L-dopa-induced peak-dose dyskinesias. Despite different pharmacological and programming measures, we were unable to completely abolish dyskinesias throughout the day (Videotape). Three years after surgery, however, the overall severity and duration of dyskinesias has improved compared to the state before STN-DBS (3 years post-DBS UPDRS IV item 32 [duration]: 1/4 and

33 [disability]: 2/4), while the benefit on OFF period symptoms was sustained.

Patient 2

The 41-year-old man (PD since 12 years, baseline characteristics in Table 1) was treated by staged bilateral neural transplantation with the second graft (right striatum) 6 months after the first graft. Cell preparation, surgical procedure, immunosuppression, and demonstration of long-term graft survival were identical to patient 1.[1]

Following transplantation, he experienced considerable reduction of OFF-phase symptoms in the medication OFF condition, which was stable for 8 years (Table 1). One year following transplantation, however, disabling OFF-period dyskinesias gradually occurred with continuous choreoathetoid movements in arms and fingers (CDRS 6/28, Videotape). Additionally, he was suffering from severe L-dopa-induced dyskinesias (CDRS 10/28). Despite reduction of LEDD to 100 mg and antidyskinetic therapy with amantadine he continued to have dyskinesias throughout the day (UPDRS IV item 32: 4/4), which were rated as severely disabling (UPDRS IV item 33: 3/4) (Table 1).

Because of the prominent hyperkinesias but relatively few OFF-period symptoms, 8 years after bilateral grafting, the patient was selected for bilateral GPi-DBS. GPi-DBS significantly reduced dyskinesias (CDRS 2/28 in the formal assessment, Videotape). In contrast, the patient reported complete reduction of dyskinesias during the day (item 32 und 33 0/4). Because OFF-period symptoms were concomitantly improved (UPDRS III 11/108 in the formal assessment), all dopaminergic medication could be stopped.

DISCUSSION

These two case reports demonstrate that disease- and treatment-related complications following fetal nigral grafting in PD can be effectively treated by DBS. In patient 1, STN-DBS primarily improved OFF-period symptoms, which reduced the necessity for additional dopaminergic drug therapy. The effect on dyskinesias, however, was not immediate. In fact, this patient became very sensitive to stimulation-induced dyskinesias and continued to exhibit fluctuating choreoathetoid dyskinesias with stable stimulation parameters even after complete withdrawal of any dopaminergic drug-therapy. These "OFF-period" dyskinesias resembled clinically the peak-dose dyskinesias before surgery and were probably the result of an interaction between STN-DBS and diurnal fluctuations in the release of dopamine from the fetal graft. The failure to reduce OFF-period dyskinesias in our patient contrasts with a previous report[5] that found marked reduction of off-period dyskinesias by STN-DBS. However, in this abstract, the stereotactic position of the stimulation contacts has not been specified and therefore the beneficial effect may not be attributed to stimulation of the STN proper but rather the adjacent subthalamic area. Following this notion, a previous study reported significant reduction of L-dopa-induced dyskinesias through STN-DBS, most probably due to stimulation of the subthalamic area.[6] A recent computational model affirmed the clinical finding that stimulation contacts positioned in the dorsal portion of the STN simultaneously influence GPi fibers of passage within the subthalamic area and therefore potentially reduce dyskinesias.[7]

In patient 2, GPi-DBS significantly improved both OFF-period dyskinesias and L-dopa-induced dyskinesias and reduced the severity of OFF-motor signs. The beneficial effect of GPi-DBS on OFF-period dyskinesias in our patient parallels the outcome of a previously reported single case observation.[8]

The etiology of OFF-period dyskinesias following striatal fetal nigral grafting is still unclear. The development of dyskinesias after transplantation is probably not associated with dopaminergic overgrowth or excessive dopamine release from the grafts. Accordingly, [^{18}F] PET studies in PD patients with postgrafting dyskinesias have not provided evidence for dopaminergic overgrowth.[4] Favored hypotheses rather involve patchy and uneven dopaminergic innervation resulting in dopamine overflow from reinnervated into nonreinnervated striatal regions and activation of supersensitive dopamine receptors. Inflammatory reactions around the grafts may further promote dyskinesias. Eventually, unfavorable composition of the graft with respect to the predominant type of dopaminergic neurones from the substantia nigra or ventral tegmental area may play a role.[9]

The pathophysiological sequelae of unregulated intrastriatal dopamine release following fetal nigral grafting on the direct and indirect basal ganglia pathway have not been specifically investigated. However, experimental studies on L-dopa-induced dyskinesias have highlighted the crucial role of D1 dopamine receptor-mediated transmission at the level of the direct pathway from the striatum to the GPi.[10] Increased sensitivity of D1 dopamine receptors have recently been identified as a prominent risk factor for dyskinesias.[11] Consequently, in animal and human studies, alterations of the direct pathway due to L-dopa-induced dyskinesias led to fundamental changes in the electrophysio-

logical properties of the GPi with reduced GPi firing rates and abnormal bursting discharge.[12] Modulation of the pathological activity within the GPi by means of DBS immediately reduces dyskinesias irrespective of the medication state.[13] In contrast, intervening within the STN probably does not directly ameliorate L-dopa-induced dyskinesias but rather exerts its antidyskinetic influence by postoperative reduction of dopaminergic medication.[13] The superior effect of GPi-DBS compared to STN-DBS in reducing OFF-period dyskinesias, unrelated to external dopamine application, supports this concept assigning a pivotal role to the direct pathway in mediating dyskinesia-related neural activity. Alternatively or complementary to the proposed systemic effects on neural activity within the basal ganglia loop, differential effects of STN-DBS versus GPi-DBS[14] on striatal dopamine release may impact the different outcomes in our patients. However, in contrast to the results of aforementioned animal studies, a PET study in PD patients with STN-DBS failed to detect any significant change in the extracellular striatal concentration of dopamine.[15]

In conclusion, we showed that following fetal nigral grafting patients can benefit from additional neuromodulation therapy. The choice of target may need to be tailored to the individual clinical symptomatology. STN-DBS in our patient led to marked improvement in hypokinetic fluctuations but was less effective in reducing OFF-period dyskinesias. In patients with prominent OFF-period dyskinesias after fetal nigral transplantation, GPi-DBS may be the better option because of its immediate antidyskinetic effect. However, the small number of patients enrolled and some shortcoming in trying all possible stimulation parameters (patient 1) may limit the conclusions that can be drawn from our data.

LEGENDS TO THE VIDEO

Segment 1. ("Patient 1/Before STN-DBS/Medication OFF") The patient from case report 1 was videotaped 8 years following fetal nigral grafting and 2 months before implantation of bilateral subthalamic leads for deep brain stimulation. In the medication off condition, the patient presents with marked limb hypokinesia and, simultaneously, intermittent off-period dyskinesias with involuntary arm elevation, continuous eye rubbing and head scratching.

Segment 2. ("Patient 1/Following STN-DBS/Medication OFF/ Stimulation ON"). Three years following subthalamic deep brain stimulation, the patient continues to show off-period dyskinesias.

Segment 3. ("Patient 2/Before GPi-DBS/Medication OFF"). The patient from case report 2 was videotaped 8 years following fetal nigral grafting and 3 months before implantation of bilateral leads within the globus pallidus internus for deep brain stimulation. In the medication off condition, the patient shows limb hypokinesia with intermittent dyskinesias, accentuated in the right hand and fingers.

Segment 4. ("Patient 2/Following GPi-DBS/Medication OFF/Stimulation on"). Two years following pallidal deep brain stimulation, severity of dyskinesias in the medication off condition is reduced. Despite complete cessation of dopaminergic medication, off-period symptoms are sufficiently alleviated by deep brain stimulation.

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Levodopa Therapy in a Lesch-Nyhan Disease Patient: Pathological, Biochemical, Neuroimaging, and Therapeutic Remarks

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Video 

Abstract: **Lesch-Nyhan disease (LND) is a hereditary disorder of purine metabolism causing severe neurobehavioral disturbances in which an abnormal central nervous system dopaminergic function has been implied. However, levodopa treatment has rarely been used, and reports describe heterogeneous responses. We report an LND patient with low dopamine metabolite values in cerebrospinal fluid for whom early levodopa/carbidopa therapy was begun with a notable clinical improvement. We propose that very early treatment of LND patients with levodopa may improve their neurological symptoms and may contribute to a better outcome.** © 2008 Movement Disorder Society

Key words: cerebrospinal fluid; dopamine; Lesch-Nyhan disease; lumbar puncture; monoamines; neurotransmitter

Lesch-Nyhan disease (LND) is a hereditary disorder caused by deficient activity of the enzyme hypoxanthine-guanine phosphoribosyl tranferase (HPRT), biochemically characterized by hyperuricemia.[1] The clinical features associated with LND include those related directly to the hyperuricemia (gout, nephrolithiasis, arthritis, etc.), neurobehavioral manifestations indicative of central nervous system (CNS) disturbances, and other clinical signs (hyperemesis, anemia, etc.).[1] Delayed motor development, dystonia, choreoathetosis, dysarthria, hypotonia, pyramidal signs, and aggressive and/or self-injurious behavior have been described as the most characteristic neurobehavioral manifestations.[2] The exact pathophysiological mechanism by which the impaired purine metabolism causes these neurobehavioral disturbances remains unclear, but abnormal central monoamine metabolism may play a role. In particular, several lines of evidence suggest that LND is associated with an abnormal CNS dopaminergic function. However, only a few studies have reported treatment protocols using substitutive levodopa, and they describe very heterogeneous responses to therapy.

We report the case of a child affected with LND presenting low dopamine (DA) metabolite values in cerebrospinal fluid (CSF). Treatment with L-dopa/carbidopa was started during the early stages of his neurodevelopment.

CLINICAL REPORT

The patient is a boy, the second child of healthy nonconsanguineous parents. Pregnancy, delivery, and neonatal period were uneventful. From the first days of his life, a lack of spontaneous movements and poor head control were present. Clinical examination at 4 months revealed marked hypertonia of the extremities, brisk deep reflexes, bilateral Babinski's sign, and trunkal hypotonia with no abnormal movements. Head circumference and ocular pursuit were appropriate. Brain MRI disclosed slight signs of cortical atrophy. Blood cell count, glucose, transaminases, CK, creatinine, uric acid, ammonia, lactate, pyruvate, plasma amino acids, urine organic acids, and uric acid were normal. Ocular examination, evoked auditive potentials, nerve conduction, and electromyography were also normal. At the age of 10 months, he developed tremor and marked dystonic movements of the hands and the mouth (Video 1). Serum urate was elevated (484 μmol/L [normal range: 100–330 μmol/L)], and in 24 hours urine, the urinary uric acid/creatinine ratio was in the upper normal limit (2.1 mmol/mol creatinine; normal range: 0.2–2 mmol/mol creatinine). HPRT activity was requested. At the same time, due to the presence of dyskinetic movements, a lumbar puncture was performed, showing low levels of homovanillic acid

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TABLE 1. *Biogenic amine and pterine concentrations in CSF before treatment and follow-up*

	Before treatment	After L-dopa therapy (L-dopa plus carbidopa and folinic acid, 6 mg/kg/day)
Age	10 mo	3 yr 4 mo
HVA	322 nmol/L (344–906 nmol/L)	366 nmol/L (304–658 nmol/L)
MHPG	52 nmol/L (20–80 nmol/L)	49 nmol/L (22–54 nmol/L)
5-HIAA	327 nmol/L (170–490 nmol/L)	192 nmol/L (106–316 nmol/L)
Neopterin	11 nmol/L (8–43 nmol/L)	13 nmol/L (7–55 nmol/L)
Biopterin	21 nmol/L (8–54 nmol/L)	24 nmol/L (10–52 nmol/L)

HVA: homovanillic acid; 5-HIAA: 5-hydroxyindoleacetic acid; MHPH: 3-methoxy-4-hydroxyphenylglycol.

Numbers in brackets represent the age-related controls values.[3]

(HVA) in CSF compared to age normal range[3] (Table 1). Treatment with L-dopa/carbidopa (1/0.25 proportion) was gradually introduced (up to 3 mg/kg/day), resulting in moderate improvement. At the age of 1 year and 6 months, the patient showed better head control, and he started picking up objects; dyskinetic movements were still present, while peripheral hypertonia and brisk deep tendon reflexes decreased notably (Video 2). The low CSF HVA concentration together with the clinical improvement led us to hypothesize a primary neurotransmitter synthesis defect, but tyrosine hydroxylase gene study showed no mutations. When uric acid metabolism was assessed again, the patient presented a serum urate value of 463 μmol/L (normal range: 100–330 μmol/L), urinary uric acid/creatinine ratio at 2.32 mmol/mol creatinine (normal range: 0.2–2 mmol/mol creatinine), and markedly elevated renal excretion of xanthine and hypoxanthine. HPRT activity in hemolisate was undetectable, and adenine phosphoribosyltransferase activity was elevated (59 nmol/hour/mg hemoglobin; normal range: 19–38 nmol/hour/mg hemoglobin). Molecular analysis disclosed a 5-bp deletion in HPRT exon 3, corresponding to position 261–265 of HPRT mRNA, associated with a 12-bp insertion in position 261. This mutation has not been previously reported, and it predicted a change in HPRT protein with a frameshift after Gly58 and a stop codon in position 74. The child has presented a moderate progressive improvement to date (3 years of age). Therapy with L-dopa/carbidopa (up to 6 mg/kg/day) and folinic acid (to avoid cerebral folate deficiency) has not been withdrawn. Head control has been fully attained, tremor has completely disappeared, the quality of movements is notably more precise, and the patient sits without support. Dystonic movements are still present although less pronouncedly than baseline conditions (Video 3). He is able to transfer objects between hands and do pincer grasping. Comprehension has always seemed to be preserved. He never presented self-injurious behavior. The CSF HVA concentration is now in the normal range (Table 1).

DISCUSSION

We describe the case of a child affected with LND presenting clinical signs of impaired CNS dopaminergic function. The notable tremor, the marked dystonia developed during early infancy, and the obvious sustained response to L-dopa led us to investigate a primary dopaminergic defect. However, some clinical characteristics such as the absence of oculogyric crisis and the preservation of facial gesticulation did not fit into a primary dopaminergic defect picture.

It has been suggested that LND may be associated with abnormal dopaminergic function, including neuropathological, biochemical, and neuroimaging studies. While no morphological abnormalities in the CNS of LND patients have been reported, direct measurement of neurotransmitters in brain tissue has shown that DA and HVA are significantly lower in the limbic and striatal regions of deceased LND patients.[4,5] Moreover, pathological studies have shown increased dopamine D2-receptor immunoreactivity in putamen, and, less evidently in the caudate nucleus.[5] As a result of recent findings, a theory of postsynaptic DA supersensitivity owing to a decreased presynaptic DA activity, has been formulated.[5] Interestingly, when the substantia nigra was explored, DA levels turned out to be not significantly lower than in controls,[4] and tyrosine hydroxilase neurons and fibers were not decreased.[4] These findings suggest that the DA terminals are reduced and damaged due to a developmental or a degenerative process, finally resulting in impaired activity in the striatum.

Moreover, evidence of dopaminergic function abnormalities also comes from positron emission tomography images, which show an abnormally reduced number of dopaminergic nerve terminals and cell bodies involving all dopaminergic pathways, but especially in the putamen.[6,7]

The role of neurotransmitters in brain development has recently been documented.[8] Interestingly, the early dopaminergic input from the midbrain may play an important role in the development of the basal ganglia and cerebral cortex.[9] Furthermore, brain development has to be completed during the first months of life, when axonal and dendritic branching is ongoing and synaptogenesis is just beginning. DA disturbances in

these neurodevelopmental periods may be crucial for further CNS function.

CSF dopamine metabolite analysis has previously been examined to assess the functioning of the CNS dopamine pathway in LND[10–13] by measuring the end product of DA: HVA. These studies were performed some time ago (during the 70s and the 80s) and sometimes their results were not adequately evaluated.[11] Obtained HVA values must be properly compared to age-related control ranges, so as to permit an accurate interpretation of the results (the concentration of brain neurotransmitters is inversely correlated with age).[3] The patient described above initially presented slightly decreased levels of CSF HVA compared to age-related controls (Table 1). Silverstein et al. described age-related changes of HVA in CSF, and their results showed that the deficiencies of HVA increased from infancy to adolescence.[13] Perhaps our patient's young age obscured DA deficiency. Nonetheless, biochemical response to L-dopa treatment was remarkable, and second sample HVA values were higher, and inside the normal range. However, the notably clinical improvement described could have been developmental and/or due to L-dopa therapy. Their respective contributions are difficult to evaluate, owing to the heterogeneity of LND.

Among the previously reported L-dopa treated patients, some failed to improve, while some even presented intolerable side effects.[10–13] An important limitation in the evaluation of the therapies used in the preceding reports was the different ages at which treatment was started. It is likely that delayed L-dopa treatments do not help to recover the previously damaged nerve terminals. Furthermore, due to the already decreased presynaptic DA activity, these patients may present a postsynaptic DA supersensitivity[5] that would account for the lack of effectiveness and even for the presence of side effects, like Watts et al. reported.[14] Some time before, Mizuno et al. had described 4 patients with no CSF examination treated at different unreported ages, but they did not evaluate the impact on movement disturbances.[15] Jankovich et al. performed pretreatment CSF analysis, but L-dopa doses and therapy duration were not detailed, age at beginning of the treatment was very variable, and their clinical results were mixed.[12]

Our clinical observation points out the need to develop neurological therapies for HPRT-deficient patients, among which L-dopa may be promising. However, no general conclusions can be obtained from a single case report, due to LND heterogeneity. In any case, we found that early L-dopa treatment is advisable to enable good response and to optimize neurological outcome. CSF neurotransmitter analysis may be a useful biochemical aid to select LND patients for L-dopa therapy and monitor their treatment. Further studies, clinical observations, and double-blind trials are needed to establish the usefulness of L-dopa in patients with LND.

LEGENDS TO THE VIDEO

Video 1. Frequent dyskinetic movements of the mouth and the extremities. Absence of voluntary grasping. No head control. Explosive uncoordinated movements.

Video 2. Better head control. Able to pick up objects. Fine motor movements have improved.

Video 3. Head control is fully reached. Dystonic movements are clearly improved. Able to transfer objects between hands, put rings in a bar, and do pincer grasping.

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Therapy-Refractory Tourette Syndrome: Beneficial Outcome with Globus Pallidus Internus Deep Brain Stimulation

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Abstract: **We report on a female patient with Tourette syndrome (TS) and a 12-month follow-up after chronic deep brain stimulation in the globus pallidus internus which resulted in excellent remission of motor and vocal tics.** © 2008 Movement Disorder Society

Key words: Tourette syndrome; deep brain stimulation; globus pallidus internus

Tourette syndrome (TS) is a chronic and, in severe cases, debilitating disorder characterized by motor and vocal tics and additionally accompanied by features of obsessive–compulsive disorder and self-injurious behavior. Although the pathophysiological mechanisms are yet unknown and the involvement of infection and inflammation has been discussed,[1] several studies have shown the influence of the dopaminergic system, as antipsychotic agents are successful in the treatment of TS mostly as an antagonist,[2] but also partly as an agonist of dopamine.[3] Functional and neuroimaging studies emphasize abnormally functioning dopaminergic striato-cortical circuits. To affect these loops in TS-patients, refractory to medical treatment, the strategy of deep brain stimulation (DBS) has been replaced: introduced by Vandewalle.[4] In general, stimulation targets are the thalamus,[5,6] the anterior internal capsule,[7] the nucleus accumbens[8] and the Gpi[9–11] (case series by Servello is added), or combined approaches.[12]

Here, we report on a female patient with TS and a 12-month follow-up study after chronic DBS of the Gpi.

CASE REPORT

The 44-year-old female patient has been suffering from TS since childhood. When she was 5-year-old she first developed vocal tics (squealing in church), followed by motor tics like blinking, bouncing, and touching. After delivery of her son at the age of 20, the symptoms worsened and the patient showed self-mutilation with biting, beating as well as grunting, and screaming. At this time, she also showed compulsive behavior for cleanliness. During the course of disease, the patient regularly developed a depressive mood and agitation proportional to the extent of tics. The intensity of her condition finally led to three suicide attempts, social isolation, and disability.

For the last 17 years, the patient was continuously treated as inpatient and outpatient of our clinic and the diagnosis of TS was established according to the criteria of DSM-IV.

Conventional medication attempts with a range of antipsychotics over many years did not have any substantial effect. Ultimately, the combination of aripiprazole and tiapride (together with monthly outpatient electroconvulsive therapy (ECT) over the last 5 years) has led to a partial suppression of tics. The rationale for ECT was derived from case reports where a substantial improvement of tics[13,14] was demonstrated.

Previous therapies with α-2-adrenoreceptor agonists, dopamine agonists and opioid agonists, as well as alternative treatments like antibiotics, immunoglobulins, and plasmapheresis (already described as possibly effective in single reports[15]) only resulted in a temporary improvement of the tics.

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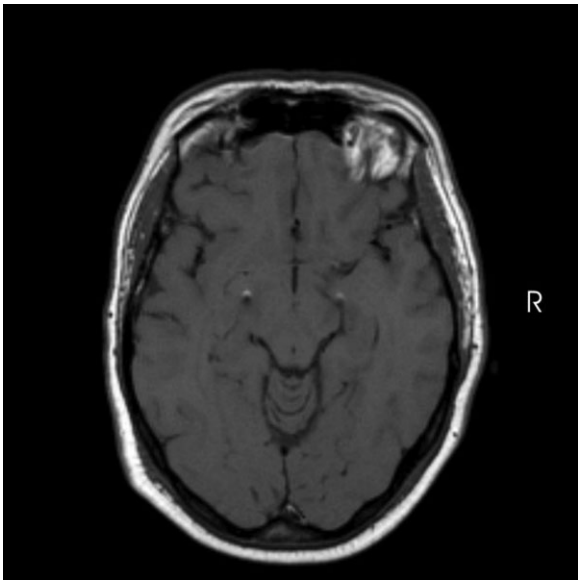

FIG. 1. Axial MRI of the patient's brain showing the tip of the electrodes 6 mm below the level of the anterior and posterior commissures. On the right, the optic tract can be seen on which the electrode tip projects.

Before stereotactic intervention, primary symptoms were severe grinding of her teeth, beating her hips, as well as persistent grunting and quacking.

After informed consent, electrode implantation (DBS 3389, Medtronic) for bilateral Gpi-stimulation was performed under propofol anesthesia with MRI-guided stereotaxy using a modified Leksel/Lerch system. The coordinates of the stereotactic target point were as follows: 3 mm anterior to the AC-PC midpoint, 4 mm below the AC-PC plane, and 20 mm lateral to the intercommisural line. Before the implantatation, three microelectrodes were inserted on each side simultaneously in order to confirm the single-cell activity typical for Gpi and to prove the appropriate distance to the internal capsule by macroelectrode stimulation. A postoperative MRI showed both electrode tips on top of the optic tracts (right electrode 18 mm lateral, 1 mm anterior, 7 mm below midcommissural point; left electrode 19 mm lateral, 1 mm anterior and 5 mm below). On the right side, electrode contact 2 was chosen for chronic stimulation because the deeper contacts caused visual symptoms. On the left side, electrode contact 1 was chosen (Fig. 1). After 5 days, during which the electrode lead had been externalized and further test stimulations had shown no unwanted effects, implantation of the pulse-generators (Soletra, Medtronic) was performed. Initially, standard settings also used in Gpi-DBS for dystonia were chosen (monopolar stimulation, amplitude 2.5 V, pulse width 120 μS, and frequency 130 pps) and slowly increased to 3.2 V at discharge. Stimulation parameters were further increased 3 months after stimulation (3.5 V, 150 μS, 145 pps), 4 months after implantation (3.5 V, 180 μS, 145 pps), and at 12 months after the implantation (4.2 V, 210 μS, 145 pps). Under this setting, the current applied was 94 μA on each side.

A decrease in tic frequency and intensity was noted during the first week after the start of the continuous stimulation and tics almost disappeared after 6 weeks of stimulation. Aripiprazole and tiapride were discontinued. Clinical outcome was assessed using the Yale Global Tic Severity Scale (YGTSS), the Verbal Learning Memory Test (VLMT), and the Stroop-Test. The neuropsychological testing before and after the intervention revealed an identical performance profile. The YGTSS score dropped from 83 preoperatively to 28 after 6 weeks and to 10 after 12 months (see Table 1). These 10 points did not result from either motor or phonic score, but from minimal impairment in job functioning.

During the follow-up period of 12 months, the patient did not show tics. For the last 17 years, she never had tic-free periods exceeding 3 weeks.

In the first few months after intervention, the patient made frequent visits to our clinic as outpatient complaining of depressive moods, vertigo, and stomach aches. At that time, the patient emphasized having difficulties adjusting to the new situation, the absent necessity of being an inpatient and recognizing that the illness had been a big part of her life. We supported her with regular outpatient appointments and centered psychotherapeutic interventions. At present, the patient is stabilized and has begun to engage in previously neglected activities such as horseback riding.

DISCUSSION

We demonstrate full remission of tic symptoms after Gpi-DBS in a patient suffering from intractable TS

TABLE 1. *Follow-up of Yale Global Tic Severity Scale*

	Preoperative		+6 wk		+12 mo	
	Motor	Vocal	Motor	Vocal	Motor	Vocal
Number	4	2	2	1	0	0
Frequency	4	3	2	2	0	0
Intensity	4	3	2	2	0	0
Complexity	3	3	2	2	0	0
Interference	4	3	2	1	0	0
Aggravation	50		10		10	
Total score	83		28		10	

with a follow-up period of 12 months. This long-time effectiveness might after all eliminate a placebo effect as the patient was receptive to other invasive treatments in her medical history only temporarily. The cause of therapeutic effects is supposed to be due to a regulation ("override") of a possibly disturbed inhibitory output from the basal ganglia to the thalamus. A disturbed Gpi-outflow could lead to a disinhibition of excitatory thalamus neurons and consequently to thalamo-cortical hyperactivity.[16] A just published case series with 18 TS patients and successful DBS of the thalamus[6] represents the first publication on a bigger cohort; even when taking this into account, there still is no consensus for the best stimulation target. (Again, Servello's report is discussed.)

Although most patients with chronic TS are used to a temporary waxing and waning course of illness or an amelioration of symptoms after medical treatment, the relatively prompt recovery after surgical intervention was problematic for our patient. Psychological interventions are imperative in order to help patients to cope with their "new life," that is without the symptoms previously dominating their lives.

As demonstrated in patients with Gpi implants for dystonia,[17] a low rate of side effects and a good clinical efficacy with this target has been established; therefore, we consider Gpi-DBS as also very promising for the treatment of TS.

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Novel, Complex Interruptions of the GAA Repeat in Small, Expanded Alleles of Two Affected Siblings with Late-Onset Friedreich Ataxia

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Abstract: **Friedreich ataxia (FA) is an autosomal recessive disorder associated with expanded GAA repeats in intron 1 of the *FRDA* gene. Two siblings presented with a mild form of FA at >60 years of age. Both had a large expansion (>600 repeats) and a small expansion (120 repeats) by long-range PCR. Sequence analysis of the small allele revealed multiple, complex interruptions in the GAA repeat. These 2 patients presented later than predicted from their allele size alone, when compared with a large cohort of FA patients. Accounting for the interruptions in the GAA repeat, though, did not make the age of onset consistent with that noted in other patients. Three additional patients with late onset FA and small expanded alleles also exhibited interrupted GAA repeats that were not associated with inappropriately late onset. Our observations suggest that interrupted GAA repeats do not clearly impact the age of onset in FA.** © 2008 Movement Disorder Society

Key words: dorsal column; ataxia; triplet repeat; spasticity.

Friedreich ataxia (FA) is an autosomal recessive disorder characterized by progressive ataxia and onset usually before the age of 25 years.[1] Most patients have expanded GAA repeats in intron 1 of the *FRDA* gene. Normal alleles contain 5 to 33 repeats, while premutation alleles contain 34 to 65 uninterrupted GAA repeats. Disease-causing alleles contain 66 to 1,700 repeats, with the majority of alleles having 600 to 1,200 repeats. Long stretches of GAA repeats assume a novel DNA structure that interferes with transcription, resulting in decreased expression of the gene product (frataxin).[2] Age of symptom onset correlates with the size of the smaller expansion.[3] Late onset (26–39 years) and very late onset (>40 years) cases represent atypical presentations of FA.[4] Almost all patients, even with the shortest (<100) GAA repeats, have some symptoms by age 40.

In the present work, we present two siblings with onset at >60 years of age with a mild form of the disease. Both had a large expansion (~600–1,000 repeats) and a small expansion (~120 repeats) as determined by long-range PCR. In a previously reported similar family, the mild phenotype was explained by the presence of interruptions in the GAA repeats.[5] Such interruptions might prevent further expansion by reducing slippage during replication, blocking the formation of the DNA structure that reduces transcription of the frataxin allele, thus leading to improved frataxin expression and less severe disease.[2] In the present work, we identified further patients with interrupted repeats and late onset FA and compared their presentation to that noted in a large cohort of patients with FA.

METHODS

Genomic DNA was extracted from whole blood using the PureGene DNA extraction kit (Gentra Systems) according to the manufacturer's protocol. The region of interest in intron 1 of the *FRDA* gene was amplified using the Expand Long Template PCR System (Roche) using primers GAA-F and GAA-R,[6] with the following thermal profile: 92°C for 2 minutes; 10 cycles of 92°C for 20 seconds, 62°C for 30 seconds, 68°C for 4 minutes; 15 cycles of 92°C for 20 seconds, 62°C for 30 seconds, 68°C for 4 minutes with a 20-second extension per cycle, followed by 1 cycle at 68°C for 7 minutes. PCR products were electrophoresed on a 1% agarose gel, and allele sizes were estimated relative to a 500-bp ladder. The shorter expanded alleles were then excised and gel purified using the Qiaquik Gel Extraction Kit (Qiagen) according to the manufacturer's protocol. The extracted product was then reamplified to obtain a large quantity of template for analysis. Products from the second round of PCR were sequenced using the Big Dye Terminator v1.1 sequencing kit. Sequences were analyzed on an automated DNA sequencer (ABI 3100).

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PATIENTS

Patient 1A

This patient presented at age 61 with increasing clumsiness and gradual development of difficulty standing on one foot. There was no family history of neurologic disorder, and the patient was not of known Acadian descent. On examination, he was diffusely hyperreflexic, particularly in the lower extremities; a Babinski sign was not observed. Diminished vibratory sensation was present to the ankles bilaterally. TSH, B12, folate, and vitamin E levels were normal. Antigliadin and Lyme titers were negative; RPR was nonreactive; electromyography revealed absent sural sensory potentials but intact motor nerve function. Lumbar puncture and MRI imaging of brain, cervical spine and thoracic spine revealed no abnormalities. A genetic test for FA (performed 12 years later) found GAA repeat lengths of 1,034 and 127; these alleles were sized as 1,047 and 114 in a second test. He had a normal EKG, stress test, and electrolyte panel.

Patient 1B

This patient presented at age 74 with unsteady gait that had been slowly progressive for 6 years. She noted mild difficulty with her hands. She had one brother with FA (Patient 1A) but no other family history of movement disorder. On examination, she had hyperactive reflexes and mildly increased tone in her upper extremities but normal lower extremity reflexes. She had decreased vibratory sensation in her feet but otherwise intact sensation, strength, and speech. Mild right-sided dysmetria was present. She had square wave jerks in primary position, with hypometric saccades. MRI of the head and cervical spine revealed mild cerebellar and occipital lobe atrophy with a chronic right posterior thalamic lacunar infarct and mild cervical spinal cord compression. Molecular analysis of her frataxin gene revealed GAA repeat lengths of 1,005 and 104.

Patient 2

This patient presented with progressive difficulty with balance and coordination at age 41. On initial examination at age 48, proprioception was normal and reflexes were 2+ in the arms and legs. Over the next 9 years, he developed dysarthria, dysmetria, diminished proprioception in the arms and legs, spasticity and diffuse hyperreflexia with clonus and extensor plantar responses. MRI of the brain revealed mild vermian atrophy. Genetic testing of the *FRDA* gene revealed GAA repeat lengths of 115 and 1,025.

Patient 3

This is a 45-year-old man with progressive ataxia for 4 years. This was associated with mild dysarthria and dyscoordination of the hands. He had a brother with a similar syndrome, and examination revealed normal mental status and cranial nerves. He had mild pseudo-athetosis of the hands with arms extended and decreased vibratory sensation. He was mildly dysmetric with a wide-based gait and Romberg's sign. Deep tendon reflexes were absent, and he had extensor plantar responses. Sensory nerve action potentials were absent, and an MRI scan of the brain was normal. *FRDA* gene analysis revealed GAA repeat lengths of 150 and 1,025. Similar results were found in his brother.

Patient 4

This is a 48-year-old woman who presented at age 34 with progressive ataxia. This slowly worsened over the next 14 years, and she developed difficulty with coordination of her hands. On examination, she had moderate dysmetria of her arms and a wide-based gait; reflexes were present but not hyperactive. Sensory examination revealed vibratory sensory loss with sparing of other modalities. Mental status and cranial nerves were normal. Sensory nerve action potentials were reduced. MRI of the brain was unremarkable. Commercial DNA testing for *FRDA* expansions revealed expansions of 290 and 950.

Patient 5

This patient presented at 48 years, after 10 years of variable hand and leg clumsiness, gait difficulty, and slurred speech. On examination, she had nystagmus,

TABLE 1. *Interrupted GAA repeat sequences from FA patients*

Patient 1A and 1B	(GAA)>72+ (GAGAA) + (GAAAA) + (GAA) 20+ (GAAAA) + (GAA) + (GAGGAA) 4 + (GAA)12
Patient 2	(GAA)>89 +(GAGAA)+(GAA)4+(GAGAA) +(GAA)4+(GAAAA) +(GAA)13
Patient 3	(GAA)>78+(GAAAA)+(GAA)17+(GAAAA) +(GAA) +(GAGGAA)5 +(GAA)12
Patient 4	(GAA)>103+ (GAAAGAA) + (GAA) 15
Patient 5	(GAA)>130+ (AAA)

The number of GAA repeats plus the location and the sequence of repeat interruptions are indicated. The number of GAA repeats at the 5′ end represents a minimum repeat number since sequence analysis did not reach the 5′ nonrepeat sequence. Interruptions clustered in the 3′ end of the repeat sequence and were followed by short GAA repeats in all of the patients except No. 5. Interruptions are designated to be consistent with those previously identified (GAGGAA, Ref. 7; GAAAGAA, Ref. 8; GAAAA, Ref. 9).

TABLE 2. *Repeat lengths and age of onset for patients 1–5*

Patients	Age of onset	Total estimated repeat length	Maximum length of GAA repeats
1A	63	120	74
1B	75	120	74
2	41	115	89
3	41	150	108
4	34	290	274
5	38	290	289

Patient repeat lengths as identified by PCR estimate and maximum number based on sequencing.

dysarthria, and severe dysmetria. Reflexes were absent except for the triceps jerks. Proprioception and vibratory sensation were decreased, and her gait was wide based. MRI of the brain was normal. Analysis of her *FRDA* gene revealed GAA repeat expansions of 290 and 850.

RESULTS

Based on previous reports suggesting small interruptions in the GAA repeat in some patients with very late onset of FA, we sequenced the GAA repeat region in a series of patients (Table 1). In sibling Patients 1A and 1B, identical interruptions were identified in the GAA repeat. The longest uninterrupted repeat was 72 bases. In other patients with short GAA repeats, similar interruptions in the 3′ end of the GAA repeat were found in three of four, but the interruptions were less complex. One patient had only a single AAA sequence at the 3′ end of the GAA repeat.[7–9]

We then correlated age of onset with presence or absence of interruptions (Table 2, Fig. 1). Two of 5 patients (Patients 1A and 1B) with interruptions presented later than that expected based on the correlation of total GAA repeat length with age of onset from a large American cohort,[10] but 3 patients (Patients 2, 3, and 4) had an age of onset similar to or only slightly later than that predicted based on the overall cohort (see Fig. 1). The patient with the isolated AAA at the 3′ end of an interrupted repeat (Patient 5) presented slightly later than the expected age. Similarly, the total maximal uninterrupted length did not correlate substantially better with age of onset. This suggests that the presence of interruptions does not significantly affect age of onset.

DISCUSSION

In this work, a variety of small expanded alleles of the *FRDA* gene had an altered sequence compared with the normal sequence. GAA repeats in small expanded alleles were interrupted in 5 of 6 patients analyzed with late to very late onset FA. A sixth patient had an AAA expansion at the end of the sequence. All observed interruptions in the GAA repeats were localized to the 3′ end of the repeat sequence and were preceded by ≥72 uninterrupted GAA repeats.

The age of onset of FA correlates moderately ($r = 0.60$) with the length of the GAA repeat sequence as defined by long-range PCR.[10] Although the correlation is lower in the group of patients with GAA repeat lengths shorter than 400, the presence of interruptions did not clearly influence the age of onset in a simple manner. In the group of patients we identified with GAA interruptions, patients with identified interruptions did not consistently have later age of onset than others in the cohort. Although, in this study (and in those reported previously), the initially identified siblings with interruptions present later than expected, other patients with interruptions did not. Analysis of the age of onset in patients with identified interruptions using the longest uninterrupted stretch of GAA repeat did not substantially change the relation of age of onset to the typical age of onset based on the entire cohort. Thus, our data here provide no evidence for an effect of interrupted repeats in FA.

Still, it is possible that interrupted repeats alter the clinical features of FA. Interruption of the GAA repeat

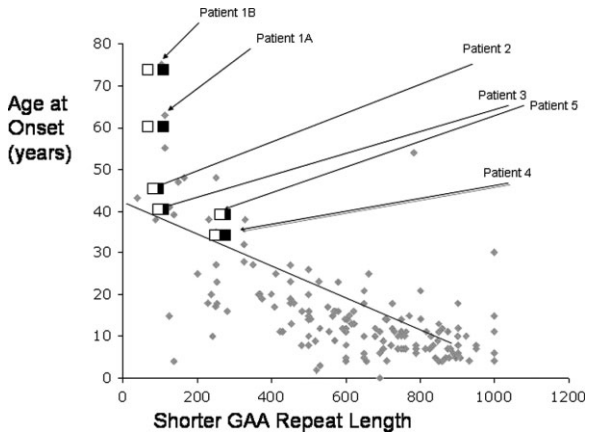

FIG. 1. Correlation of age of onset versus total repeat length and the maximum length of uninterrupted GAA repeats. Age of onset and GAA repeat length were plotted for a large American cohort (diamonds) and each of the 6 patients in the present study (filled square, estimated repeat length; open square, maximum possible uninterrupted GAA repeat length). The age of onset from Patients 1A and 1B remained greater than that predicted based on their repeat length. Patients 2 and 5 had a slightly later age of onset than expected. Patients 3 and 4 still plotted near the line. Patient 5 had no interruptions, while Patients 1 to 4 had interrupted repeats.

(with a change of a single GAA to a GGA) remedies the defect in transcription and blocks formation of triplex structures in vitro. In other disorders, the presence of interruptions in repeat sequences has been suggested to modify the expression of disease severity.[11–14] We identified only one patient without a significant interruption, showing that in late-onset patients the frequency of interruptions may be quite high. If we examined further patients with late-onset disease as well as patients with short repeats and earlier onset, it might be possible to uncover a modest effect of repeat interruptions with disease features.

In addition, we have analyzed the data at present using simple approaches. Conceivably, features beyond the simple size of uninterrupted repeat (such as interruption structure and complexity) might play a crucial role. Alternatively, specific phenotypic features might be altered by the presence of interruptions. In addition to having a less progressive course, patients with late onset FA frequently retain reflexes (as noted for Patients 1A and 1B here). Still, our data overall are most consistent with the possibility that repeat interruptions do not substantially influence the age of onset of FA.

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On the Structure of Motor Symptoms of Parkinson's Disease

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Abstract: **This study aims to investigate the structure of the motor symptoms of Parkinson's disease (PD), as measured by the Motor Section of the Unified Parkinson's Disease Rating Scale (UPDRS). The dimensionality of the Motor Section of the UPDRS was studied using structural equation modeling. The UPDRS measures were obtained from 405 patients with PD [237 men (39 "off", 170 "on", 28 unknown) and 168 women (21 "off", 140 "on", 7 unknown)]. The ordinal character of UPDRS scores and sample size substantiated the use of robust diagonally weighted least squares model estimation. It was shown that the Motor Section of the UPDRS incorporates five main latent symptom factors (rigidity, tremor, bradykinesia of the extremities, axial/gait bradykinesia, speech/hypomimia) plus two additional factors for laterality, which account for asymmetry of tremor, rigidity and bradykinesia of the extremities. Tremor seems to be an independent symptom factor of PD. Other latent variables are substantially correlated.** © 2008 Movement Disorder Society

Key words: Parkinson's disease; structural equation modeling; dimensionality; Motor Section of the UPDRS

The identification of symptom groups of neurological syndromes such as the combination of hypokinesia, rigidity, resting tremor, and postural abnormalities in Parkinson's disease (PD) is important because knowledge about the co-occurrence of symptoms may help to define disease phenotypes and provide clues for differential diagnosis. The number of symptom groups (dimensionality) can be inferred through statistical analysis of measurements used for impairment evaluation. Within the Motor Section of the Unified Parkinson's Disease Rating Scale (UPDRS), main motor symptoms of PD (tremor, rigidity and bradykinesia) and axial symptoms (speech, posture, postural stability and gait) define symptom groups which are in practice evaluated regarding their respective severity. This paper discusses the dimensionality of the Motor Section of the UPDRS and the structure of motor symptoms of PD within the framework of structural equation modeling (SEM) using confirmatory factor analysis.

In previous studies on dimensionality assessment of the Motor Section of the UPDRS,[1–4] between three and six factors were found with percentages of explained total scale variance ranging between 59% and 78%. All these studies used exploratory factor analysis (EFA) methods, principal component analysis included. Such procedures rely on strong assumptions concerning either the distribution of observed variables, their level of measurement, or the number of observations. Principal component analysis requires a continuous measurement level[5,6]; maximum likelihood estimation in EFA requires continuous measurement levels and either normally distributed item responses or a large number of observations which may compensate for small degrees of nonnormality.[7,8] Given the ordinal distributional properties of the items in the Motor Section of the UPDRS, previous conclusions on dimensionality may not be trustworthy because the validity of assumptions of EFA modeling is lacking.

Instead of EFA, we used confirmatory factor analysis (CFA) within a SEM framework to perform a statistical test and to evaluate a number of plausible factor models for the structure of symptoms underlying the Motor Section of the UPDRS. Some SEM estimators are designed for ordinal measurements and thus, in principle, suited for analyzing that structure.

PATIENTS AND METHODS

Sample

The study includes 405 consecutive patients (237 men, 168 women, mean age 61, range 35–80 years) with PD diagnosed according to current clinical criteria.[9] Each patient was evaluated by one member of a group of certified neurologists, movement disorder specialists who routinely use the UPDRS. Sixty patients were examined in defined "off" state, and 310 patients in defined "on" state. For 35 patients, the motor state during evaluation was not specified.

This data consists of two subsamples. The first subsample of size N = 147 [96 men (38 "off", 30 "on", 28 unknown) and 51 women (15 "off", 29 "on", 7

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unknown)] was obtained at the Movement Disorder Centre, Charles University, Prague, Czech Republic. The second of size N = 258 [141 men (1 "off", 140 "on") and 117 women (6 "off", 111 "on")] was acquired at the University Medical Centre Groningen in The Netherlands.

Methods

For analyzing the latent structure of the 27 items of the Motor Section of the UPDRS, the LISREL program[10] was used. If the level of measurement is ordinal and sample size relatively small, as in our case, Jöreskog and Sörbom[11] recommend analyzing the matrix of estimated polychoric correlations of the observed variables along with the estimated matrix of asymptotic covariances of those estimated correlations, and to apply robust diagonally weighted least squares (DWLS) model estimation. The polychoric correlations and the asymptotic covariance matrix were computed using the PRELIS program.[12]

A number of theoretically meaningful models were compared. For the "final" model described here, the path diagram with standardized parameter estimates, the matrix of estimated polychoric correlations, goodness-of-fit statistics and indices, a summary of estimated standard errors of the parameter estimates, and the fitted residual matrix are reported; for details see Ref. 13.

RESULTS

The "final" model of the Motor Section of the UPDRS is shown in Figure 1. A number of theoretically plausible models were tested and compared before the model in Figure 1 was chosen as a most plausible one.[13] Following that conclusion, based on both model estimates and theoretical PD background considerations, the Motor Section of the UPDRS consists of seven factors. Five of them are substantive, each reflecting a PD motor symptom—tremor, rigidity (Rig), bradykinesia of the extremities (Brad), axial/gait bradykinesia (BBrad), and speech/hypomimia (Face). Two additional factors (Left and Right) reflect the asymmetry of tremor, rigidity, and bradykinesia of the extremities.

Although some fitted residuals (see Table 1) remained high, the fit statistics and indices suggest that this model need not to be rejected. Generally, the values of comparative fit index (CFI) and goodness of fit index (GFI) suggest a very acceptable fit, whereas root mean square error of approximation (RMSEA), standardized root mean square residual (SRMR), and normed fit index (NFI) indicate slightly less, but still acceptable model fit (see the values below Fig. 1). Values in the matrix of residual correlations are ranging from −0.40 to 0.34 (median of absolute value 0.04, standard deviation 0.07). The highest fitted residuals are those between action tremor items (right hand and left hand; 0.34), and surprisingly, between item action tremor—left hand and item Tremor—right lower extremity (−0.40). Values of factor loadings range from 0.11 to 0.92 (median 0.64, standard deviation 0.19); see Figure 1. The lowest factor loading (0.11) is for item tremor—right lower extremity as an indicator for latent factor Right; although the corresponding parameter test statistic is nonsignificant (standard error 0.17), it is theoretically meaningful to keep this parameter free. In general, values of estimated standard errors of the parameter estimates ranged from 0.02 to 0.17 (median 0.07, standard deviation 0.04). The estimated composite reliability of our model (by stratified coefficient alpha[14]) equals 0.94.

The four factors of rigidity, bradykinesia of the extremities, speech/hypomimia, and axial/gait bradykinesia are correlated, which is meaningful from a theoretical point of view. The correlations range between 0.54 and 0.85 (see Fig. 1) indicating rather substantial relationships among these symptom factors. Tremor, however, seems to be a PD symptom occurring independently of other motor PD symptom factors.

Goodness-of-Fit Statistics and Indices

- Sample size: 405
- Degrees of freedom: 300
- Satorra-Bentler's scaled χ^2 statistic: 899.33 (P = 0.0)
- Root mean square error of approximation (RMSEA): 0.070
- 90% confidence interval for RMSEA: 0.065, 0.076
- Normed fit index (NFI): 0.96
- Comparative fit index (CFI): 0.97
- Standardized root mean square residual (SRMR): 0.077
- Goodness of fit index (GFI): 0.99
- Fitted residuals: range [−0.40, 0.34], median 0.04, standard deviation 0.07.

DISCUSSION

In this study, the structure of motor symptoms of PD was investigated by applying confirmatory factor analysis models to the Motor Section of the UPDRS.

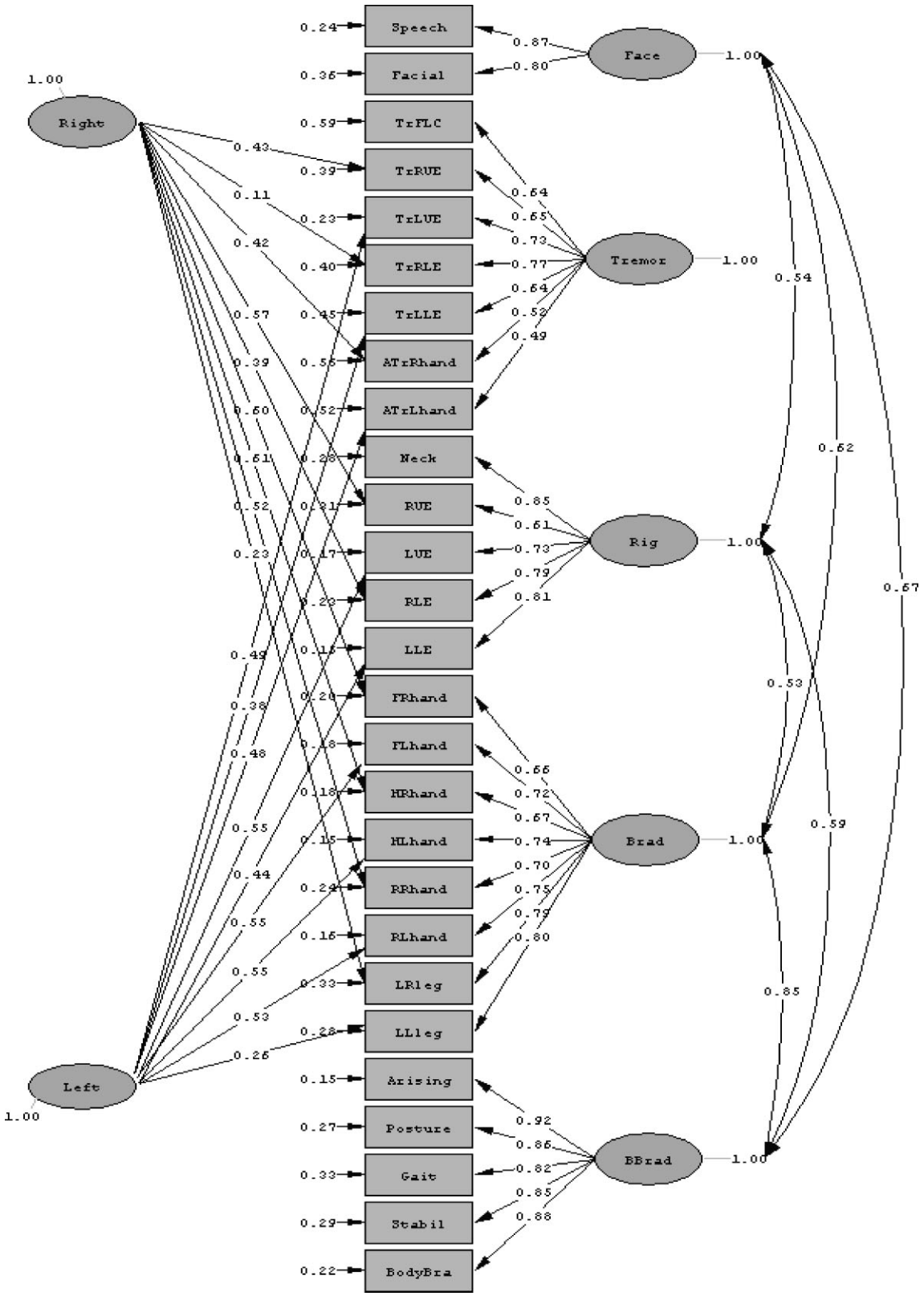

FIG. 1. Path diagram of the seven-factor model of the MS UPDRS showing estimates of completely standardized parameter estimates.

TABLE 1. *Polychoric correlations (below diagonal) and fitted residuals (above diagonal) of the Motor Section of the UPDRS*

	Speech	Facial	Lipschin	TrRUE	TrLUE	TrRLE	TrLLE	ATrRhand	ATrLhand	Rigidity	RUE	LUE	RLE	LLE	FRhand	FLhand	HRhand	HLhand	RRhand	RLhand	LRleg	LLleg	Arising	Posture	Gait	Stabil	BodyBra
Speech		0.00	0.04	−0.05	−0.05	−0.19	−0.27	−0.03	−0.02	−0.05	−0.06	−0.09	−0.01	−0.06	0.03	−0.01	0.01	−0.03	0.04	0.02	0.06	0.02	0.00	0.05	−0.03	0.00	0.00
Facial	0.70		0.19	−0.06	0.07	−0.01	−0.08	0.02	0.09	0.06	0.10	0.07	0.02	0.02	−0.04	0.00	−0.07	−0.05	−0.02	0.00	−0.04	0.02	−0.01	0.02	−0.06	−0.05	0.05
Lipschin	0.04	0.19		0.02	0.11	−0.04	−0.04	−0.21	−0.05	0.20	0.00	0.07	0.02	−0.03	0.08	0.21	0.10	0.15	0.15	0.23	0.08	0.01	0.06	0.22	0.15	0.09	0.25
TrRUE	−0.05	−0.06	0.43		0.04	0.10	−0.24	0.04	0.19	0.06	0.07	−0.01	0.01	−0.09	−0.06	−0.07	−0.07	−0.07	−0.02	−0.08	0.02	−0.13	−0.05	−0.07	0.01	−0.06	0.03
TrLUE	−0.06	0.07	0.57	0.52		−0.14	0.04	−0.13	0.00	0.13	0.00	0.05	0.05	0.02	−0.03	−0.04	−0.04	−0.07	−0.02	0.00	0.04	0.04	0.12	0.02	0.11	0.06	0.11
TrRLE	−0.19	−0.01	0.46	0.65	0.42		0.19	−0.08	−0.40	0.09	0.11	0.00	0.14	0.03	−0.07	−0.04	−0.12	−0.18	−0.03	−0.12	−0.02	−0.06	−0.03	−0.11	−0.05	−0.02	−0.01
TrLLE	−0.27	−0.08	0.37	0.18	0.69	0.68		−0.29	−0.05	0.04	−0.12	0.02	−0.07	0.10	−0.11	−0.01	−0.20	−0.12	−0.11	−0.02	0.01	0.06	−0.01	−0.01	0.03	−0.03	0.03
ATrRhand	−0.03	0.02	0.12	0.55	0.25	0.37	0.04		0.34	0.15	0.11	0.09	0.03	0.00	−0.10	−0.04	−0.07	0.03	−0.03	−0.04	0.01	−0.06	0.07	0.00	0.01	0.04	0.06
ATrLhand	−0.02	0.09	0.26	0.13	0.60	−0.02	0.45	0.60		0.19	−0.02	0.08	0.01	0.02	−0.05	−0.06	0.01	−0.01	0.01	−0.01	0.00	0.02	0.13	0.15	0.14	0.11	0.16
Rigidity	0.35	0.42	0.20	0.06	0.13	0.09	0.05	0.15	0.19		0.01	−0.03	−0.05	−0.09	0.16	0.08	0.08	0.03	0.09	0.06	0.01	0.02	−0.06	−0.01	−0.01	−0.04	0.02
RUE	0.23	0.36	0.00	0.32	0.01	0.17	−0.12	0.35	−0.02	0.53		0.09	0.05	−0.04	−0.04	−0.01	−0.07	−0.06	−0.02	−0.05	−0.02	−0.08	−0.08	−0.01	0.01	−0.03	0.04
LUE	0.25	0.38	0.07	−0.01	0.32	0.00	0.23	0.09	0.34	0.59	0.53		−0.06	−0.01	0.01	0.00	0.01	−0.03	0.01	0.00	−0.07	0.00	0.00	0.04	0.03	0.00	0.08
RLE	0.36	0.36	0.02	0.18	0.05	0.18	−0.07	0.19	0.01	0.61	0.75	0.52		0.09	−0.03	0.00	−0.07	−0.03	−0.02	−0.03	0.02	0.00	−0.07	−0.02	0.00	−0.08	0.02
LLE	0.32	0.37	−0.03	−0.09	0.23	0.03	0.26	0.00	0.23	0.60	0.46	0.82	0.73		−0.03	0.01	−0.04	−0.03	−0.03	0.00	−0.02	0.06	−0.03	0.03	0.04	−0.03	0.04
FRhand	0.38	0.28	0.08	0.20	−0.03	−0.01	−0.11	0.16	−0.05	0.46	0.51	0.27	0.48	0.26		0.11	0.05	−0.04	−0.01	−0.09	−0.02	−0.14	−0.06	−0.04	−0.01	0.00	0.05
FLhand	0.38	0.35	0.21	−0.07	0.23	−0.04	0.20	−0.04	0.21	0.41	0.22	0.58	0.30	0.56	0.59		−0.01	0.02	−0.05	−0.01	−0.12	−0.01	−0.03	−0.04	−0.07	−0.01	0.06
HRhand	0.37	0.26	0.10	0.19	−0.04	−0.05	−0.20	0.19	0.01	0.38	0.49	0.27	0.44	0.25	0.85	0.47		0.10	0.02	−0.05	−0.01	−0.15	−0.02	−0.01	0.00	−0.03	0.06
HLhand	0.37	0.32	0.15	−0.07	0.20	−0.18	0.09	0.03	0.26	0.37	0.18	0.56	0.28	0.53	0.45	0.86	0.59		−0.03	0.01	−0.10	−0.04	−0.01	0.01	−0.01	−0.01	0.06
RRhand	0.42	0.33	0.15	0.20	−0.02	0.03	−0.11	0.19	0.01	0.41	0.51	0.28	0.48	0.27	0.77	0.46	0.80	0.49		0.06	0.03	−0.10	−0.01	−0.03	0.01	−0.03	0.04
RLhand	0.42	0.38	0.23	−0.08	0.26	−0.12	0.18	−0.04	0.25	0.40	0.20	0.58	0.29	0.55	0.40	0.82	0.45	0.86	0.58		−0.09	0.00	0.04	0.01	−0.02	0.00	0.04
LRleg	0.48	0.35	0.08	0.12	0.04	0.00	0.01	0.10	0.00	0.37	0.37	0.24	0.44	0.32	0.63	0.45	0.65	0.49	0.71	0.50		0.13	0.04	−0.05	−0.05	0.00	−0.04
LLleg	0.46	0.42	0.02	−0.13	0.17	−0.06	0.16	−0.06	0.15	0.39	0.18	0.46	0.34	0.53	0.39	0.72	0.39	0.70	0.46	0.74	0.77		0.06	−0.03	−0.05	0.03	−0.03
Arising	0.54	0.49	0.06	−0.05	0.12	−0.03	−0.01	0.08	0.13	0.40	0.25	0.40	0.36	0.40	0.45	0.54	0.50	0.57	0.54	0.63	0.65	0.69		−0.01	0.03	0.05	−0.11
Posture	0.55	0.48	0.22	−0.07	0.02	−0.11	−0.01	0.00	0.15	0.42	0.30	0.40	0.37	0.44	0.43	0.48	0.47	0.54	0.48	0.55	0.52	0.55	0.78		0.05	0.02	−0.03
Gait	0.45	0.38	0.15	0.01	0.11	−0.05	0.03	0.01	0.14	0.40	0.31	0.38	0.38	0.43	0.45	0.43	0.47	0.51	0.50	0.50	0.50	0.51	0.79	0.75		0.02	−0.03
Stabil	0.49	0.41	0.09	−0.06	0.06	−0.02	−0.03	0.04	0.12	0.38	0.27	0.36	0.31	0.37	0.47	0.51	0.45	0.52	0.47	0.54	0.57	0.61	0.83	0.75	0.72		−0.07
BodyBra	0.51	0.52	0.25	0.03	0.11	−0.01	0.03	0.06	0.16	0.46	0.36	0.46	0.43	0.46	0.54	0.60	0.56	0.61	0.57	0.60	0.56	0.58	0.70	0.73	0.69	0.68	

The models were estimated using the DWLS estimator, mainly because of the ordinal measurement level of the items and the relatively small sample size.

Several studies[1–4,15] assessed the construct validity and the dimensionality of the Motor Section of the UPDRS through EFA. As discussed earlier, neither EFA nor some of the CFA estimators are the most appropriate scaling techniques, because the assumptions of the underlying statistical model may easily be violated. In previous dimensionality studies of the UPDRS, sample sizes $N < 300$ were often used.[1–3,15] In addition, measurement of the UPDRS is obviously of ordinal rather than continuous type, which may pose problems when using regular maximum likelihood estimation and PCA.[6] To our knowledge, the only study where the measurement level of the UPDRS data was respected is one by Kroonenberg et al.[16] However, their study primarily focused on the differences in the structure of PD motor signs for "on" and "off" patients; the results appeared to depend on the motor state of the patient. Their model did not fit our data, which might be due to a different scoring practice, a problem that might also account for different validity and reliability results of the UPDRS across countries.

The two factors of laterality (Left and Right) reflect the asymmetry of occurrence of tremor, rigidity, and bradykinesia of the extremities. In a clinical cohort it has been shown that initial PD symptoms start more frequently on the right-sided extremities than on the left.[17] In some EFA studies, side-sensitivity of bradykinesia of the extremities was mentioned before,[2,3] as well as that of action/postural tremor.[1] To our knowledge, side-sensitivity of rigidity and rest tremor, however, has not been previously reported.

The high correlations among the factors rigidity, bradykinesia of the extremities, axial/gait bradykinesia, and speech/hypomimia can be indicators of co-occurrence of these PD symptoms. For most patients in common PD populations, however, the main symptoms co-occur whereas isolated tremor may only be present in very early stages of PD. Further, the relative independence of tremor from rigidity and bradykinesia can be viewed as an indicator of the lack of substantive relationship between tremor and PD disability, a finding consistent with other reports.[18,19]

Since a number of theoretically meaningful models were compared, implying a partly exploratory result, future cross-validation is necessary to challenge our "final" factor structure of the Motor Section of the UPDRS. It should also be realized that larger sample sizes would make model estimation results, especially when considering the ordinal character of item responses, more reliable and final conclusions more valid.

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Psychogenic Propriospinal Myoclonus

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Video 

Abstract: **We report a case of probable psychogenic propriospinal myoclonus (PSM) in a patient who developed a sudden onset of disabling axial flexor myoclonus following a cosmetic surgical procedure. The electrophysiological findings were consistent with previous reports of PSM. Spontaneous remissions and disappearance of the jerks, sustained for 2 years, following removal of superficial surgical screws support the diagnosis of a psychogenic movement disorder.** © 2008 Movement Disorder Society

Key words: psychogenic; myoclonus; propriospinal myoclonus

Propriospinal myoclonus (PSM) is a form of spinal myoclonus characterized by involvement of muscles innervated from different segments of the spinal cord, and sequentially activated via propriospinal pathways.[1] Characteristic electrophysiological findings of slow conduction and selective recruitment of truncal and proximal limb muscles help differentiate PSM from spinal segmental myoclonus.[2] PSM has been documented secondary to intrinsic and extrinsic spinal cord lesions, and in other cases, no clear etiology has been identified. Recently the characteristic electrophysiological findings have been reported in a group of eight healthy volunteers simulating the typical axial flexor jerks of PSM.[3] The differentiation between voluntary and involuntary movements of this nature is further blurred by our report of a patient with probable psychogenic PSM.

CASE REPORT

This 65-year-old woman fell after tripping over a concrete block on the pavement, causing disfiguring soft tissue injuries above her right orbit. Apart from migraine, there were no other medical problems at the time, and no psychiatric history. There was no documented injury or pain in the neck or back following the fall, and at that time, she was neurologically normal. Legal action relating to the circumstances of the incident was initiated. A reconstructive right blepharoplasty was performed for right sided pseudoptosis. She subsequently developed a right frontal headache. The cosmetic results of the surgery were insufficient and it was revised by browplasty that required the placement of three surgical screws into the right frontal bone, including one that penetrated the frontal air sinus. The surgery was complicated by chronic pain around the operational site that was partially relieved by neck massage. Eighteen months after the fall, and following massage of the neck she developed disabling paroxysms of axial, flexor jerks that were most severe when lying supine. There was a suggestion of associated left-sided weakness at onset, but this resolved and MRI and angiogram were normal. At first the jerks occurred several times per day, but rapidly increased in frequency, with bouts of continuous jerking lasting for up to 1 hour, causing significant disability. There was positive, action myoclonus with coexistent stimulus sensitive myoclonus of variable latency, which diminished with distraction. Increasingly her mobility became affected by jerking and unsteady gait. There were periods of complete remission lasting up to several months. Jerking was exacerbated by anxiety, but no other precipitants were identified. Spinal cord and brain MRI were normal except for a few scattered deep white matter ischemic changes. Psychiatric evaluation did not identify features of somatization, depression, or malingering. She incompletely responded to piracetam 16 g per day, clonazepam 4 mg per day, sodium valproate 2 g per day, and baclofen. Three surgical screws used in the blepharoplasty were removed 4

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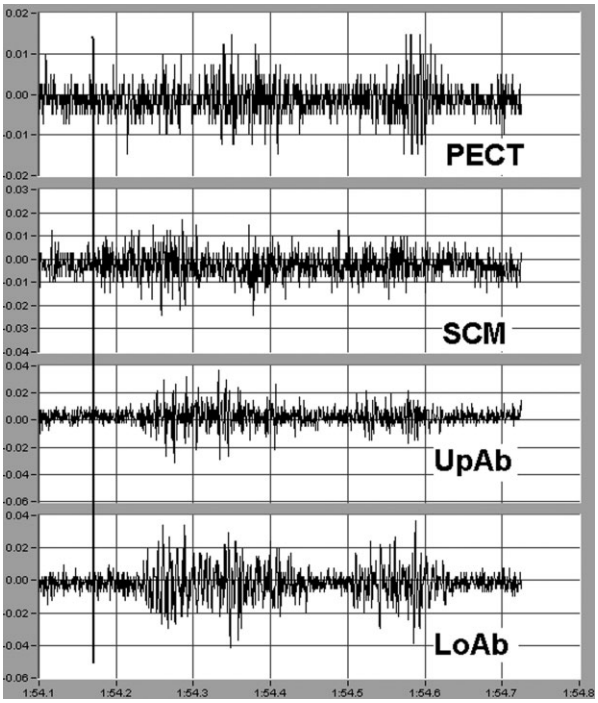

FIG. 1. 0.7 seconds epoch of order of activation study, demonstrating surface EMG bursts in pectoralis (pect), followed by sternomastoid (SCM) and upper (UpAb) and lower abdominal muscles (LoAb). Solid line—onset of jerk.

years after surgery, at the patient's insistence, and the axial jerks coincidentally resolved completely. She returned to normal function and was symptom free at follow-up 2 years later.

Electrophysiological Investigations

Two years after the onset of jerking, routine EEG was normal. Median nerve sensory evoked potentials were normal. A jerk locked back averaged EEG did not show pre-movement cortical potentials. An order of activation study showed variable muscle activation, but the most frequent pattern of activation was caudal, from pectoral to abdominal muscles, with propagation estimated at 9 to 15 m/s. (see Figure 1) EMG burst length was between 50 and 150 milliseconds.

DISCUSSION

This patient had some clinical and electrophysiological findings consistent with previous reports of PSM, as well as features not usually reported to be associated, such as gait unsteadiness and axial jerks while standing. Unusually for PSM there were periods of spontaneous remission and no identifiable pathological lesion to account for the myoclonus. The sudden onset, contemporaneous legal proceedings related to the injury, the associated anxiety and spontaneous, complete remission are supportive of a psychogenic etiology.[4]

The electrophysiological findings reported in PSM include fixed patterns of muscle activation, slow spinal cord conduction (5–15 m/s), EMG burst duration less than 1,000 ms and synchronous activation of agonist and antagonist muscles (reviewed in Ref. 3). In our case, the short EMG burst duration and slow conduction was consistent with these reports. In a number of similar cases, with electrophysiological characteristics of "organic" PSM, the possibility of psychogenic etiology has been raised.[3,5] Healthy volunteers simulating PSM have electrophysiological recordings that are also similar, except for long EMG burst durations.[3] The findings in the present study support these authors' contention that electrophysiological parameters alone are insufficient to identify "organic" PSM. To our knowledge, remissions have not been reported in PSM, and are said to count against the diagnosis.[6]

The patient felt certain that the surgical screws caused the myoclonic jerks, but we were unable to identify a biological mechanism to account for this. Psychogenic PSM is the most likely diagnosis, and removal of the perceived precipitant was curative in this case. The clinical and imaging findings together with the long follow-up in this patient effectively exclude any other diagnostic possibilities.

A psychogenic etiology should be considered when patients develop axial flexor jerks that occur when lying and standing without identifiable central nervous system lesions, even in the presence of suggestive electrophysiological findings. Spontaneous remissions may differentiate psychogenic and organic PSM.

LEGENDS TO THE VIDEO

The patient is shown lying supine with bursts of spontaneous axial jerks occurring at rest without stimulation.

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Potassium Channel Blocker 4-Aminopyridine is Effective in Interictal Cerebellar Symptoms in Episodic Ataxia Type 2—A Video Case Report

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Video 

Abstract: **Episodic ataxia type 2 (EA2) is an autosomal-dominant hereditary disorder clinically characterized by recurrent attacks of vertigo, imbalance and ataxia. Studies have shown that 4-aminopyridine (4-AP) is capable to prevent these attacks. However, there are no reports whether 4-AP is able to attenuate interictal cerebellar ataxia. Using the scale for assessment and rating of ataxia (SARA), we examined the efficacy of 4-AP on interictal ataxia in a 63-year-old female patient who suffered from EA2 since the age of 57. EA2 was diagnosed based on clinical criteria and not genetically proven. When treatment with 4-AP was paused the patient was suffering from marked gait and stance ataxia. After re-initiation of treatment with 5 mg 4-AP t.i.d., there was pronounced improvement in gait and stance ataxia. Within 24 hours SARA score lowered from 8.5 to 4.5 points. We conclude that 4-AP may be beneficial for interictal cerebellar ataxia in late onset EA2.** © 2008 Movement Disorder Society

Key words: episodic ataxia type 2; 4-aminopyridine; interictal ataxia; SARA; video case report

Episodic ataxia type 2 (EA2) is a rare autosomal-dominant hereditary disorder caused by mutations of the calcium channel gene *CACNA1A* on chromosome 19p13.[1] This gene codes for the CaV2.1 subunit of the P/Q-type calcium channel, which is expressed throughout the nervous system but mainly in cerebellar Purkinje cells. EA2 usually starts before the age of 20, however, some patients reveal first symptoms beyond the age of 50. Affected patients suffer from recurrent attacks of vertigo, imbalance and ataxia, which may last for several hours up to days and can often be provoked by physical exertion, emotional stress and consumption of caffeine or alcohol. Most patients show central ocular motor disturbances between these attacks such as gaze-holding deficits, downbeat nystagmus, saccadic eye pursuit movements and impaired visual suppression of the vestibulo-ocular reflex.[2] Interictal cerebellar symptoms are a common condition in the course of the disease[1] and can be so marked that patients become wheelchair-bound. Because EA2 is allelic with familial hemiplegic migraine type 1, half of the patients suffer from migraine headaches. In the majority of cases, there is a positive family history for the disease.[2]

Acetazolamide (ACTZ) is the drug of first choice for treatment of EA2 and prevents or attenuates the attacks in ~50 to 75% of all patients. However, many patients stop treatment with ACTZ in the long run due to adverse effects, such as nephrolithiasis, hyperhydrosis, paresthesia, muscle stiffness, and gastrointestinal disturbance, or because of a loss of efficacy. So far, treatment options for these patients are limited. 4-Aminopyridine (4-AP), a potassium channel blocker, has recently shown to be capable to prevent or markedly attenuate attacks of ataxia in patients in whom treatment with ACTZ had failed.[3] However, there are so far no reports whether 4-AP is able to attenuate interictal progressive cerebellar ataxia that is often a key clinical feature in elderly EA2 patients.

CASE REPORT

We examined a 63-year-old female patient who contacted our Movement Disorder Outpatient Clinic in May 2004. In 2000, at the age of 57, she started to suffer from attacks with vertigo, nausea, and vomiting that were sometimes accompanied by dysarthria and headaches. These attacks initially lasted for about 30 min but prolonged within subsequent years. Additionally, she had problems with visual fixation of objects and often had the impression that her visual image was rolling away. Consumption of coffee or alcoholic beverages led to deterioration of symptoms. In 2006, the attacks completely ceased and interictal gait ataxia became the main clinical problem making her incapable of walking or standing without support. In the past, the patient had suffered from migraine headaches. The mother of the patient also suffered from vertigo

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and headaches, a half-sister complained about chronic headaches.

Clinical examination revealed central oculomotor deficits such as spontaneous nystagmus to the left as well as downbeat nystagmus at gaze to the left, saccadic pursuit movements and impaired visual suppression of the vestibular-ocular reflex. Additionally, we observed dysmetria during the nose–finger test and heel–shin slide as well as marked stance and gait ataxia. Magnetic resonance imaging showed decent atrophy of the upper vermis of the cerebellum but no further pathology, electroencephalography was normal. Tumor screening including serum tumor markers was negative; analysis of cerebrospinal fluid did not show any abnormalities. Vestibular dysfunction was excluded as possible reason for vertigo by otorhinolaryngologic examination that demonstrated regular function of both vestibular organs. There was no sign for baroreceptor or orthostatic dysfunction during autonomic testing including metronomic breathing, Valsalva maneuver and passive orthostasis on the tilt table. Since the patient did not undergo genetic testing, EA2 was diagnosed clinically based on the medical history and the typical clinical findings mentioned above.

Treatment was initiated with ACTZ in December 2003 but had to be ceased due to tinnitus and paresthesia of hands and feet. During treatment with ACTZ the patient had been able to fixate objects better than before, whereas ataxia remained unchanged. Starting from July 2006, we administered 5 mg 4-AP t.i.d. (provided by Synopharm, Germany), which was well tolerated without any adverse effects but initially did not seem to have any subjective benefit for the patient. After 4-AP had been withdrawn due to suspected lack of efficacy after only 14 days of treatment and without further clinical evaluation, the patient returned within 1 week and reported about a distinct worsening of gait and stance ataxia making her unable to walk unassisted. After re-initiation of 4-AP, symptoms markedly improved and are now stable over 1 year.

Evaluations

After informed consent for videotaping had been given, the patient was asked to pause treatment with 4-AP for 24 hours and after that was videotaped and rated according to the recently validated scale for the assessment and rating of ataxia (SARA).[4] The patient was then given a single dose of 5 mg 4-AP and videotaped and rated again as soon as she realized improvement of her symptoms. A final evaluation was done after the patient had taken 3 $\times$ 5 mg 4-AP over 24 hours. All evaluations were done in exact order as provided by SARA. The videotapes were reviewed by a movement disorder expert (A.S.) who was blinded for the treatment. Scores were given according to the SARA criteria based on a common judgment of the expert and the observer who had videotaped the patient (M.L.). ECG was performed before and during treatment to exclude clinically relevant prolongation of QT_C time, which was calculated using Bazett's correction: $QT_c = \overline{QT}\ (\text{milliseconds})/\sqrt{\overline{RR}}\ (\text{seconds})$. QT_C time was within normal range measuring 429 milliseconds before and 414 milliseconds during treatment with 5 mg 4-AP t.i.d.

After 24 hours withdrawal of 4-AP, the patient was suffering from marked gait and stance ataxia (Video), minimal speech disturbance, slight dysmetria during finger chase with the left hand, tremor during the nose-finger test on both sides and a slightly abnormal heel–shin slide. Because of gait ataxia she preferred to use a walker in order to avoid falls. Total SARA score without 4-AP was 8.5 points. One hour after intake of a single dose of 5 mg 4-AP, the patient noticed a slight relief of her symptoms that could only be objectified during the nose–finger test (SARA subscore decreased from 1.0 to 0.5 points) where she had less tremor of her right hand (total SARA score: 8.0 points).

On the next day, after completing her regular daily treatment with 5 mg 4-AP t.i.d., the patient returned to our outpatient clinic without her walker. Gait had markedly stabilized, so she was even able to do some steps of tandem walking (Video). Stance ataxia also had improved (SARA subscore decreased from 2.0 to 1.0 points), the patient was now capable of standing with her feet in tandem position for more than 10 seconds (Video). Furthermore, there was improvement in finger chase, nose–finger test and heel–shin slide. Total SARA score after treatment with 4-AP t.i.d. had lowered to 4.5 points.

DISCUSSION

Our report confirms previous observations that 4-AP treatment offers an option for EA2 patients in whom ACTZ failed to relieve symptoms. Although 4-AP in previous studies has shown to be effective in preventing or attenuating ataxia attacks,[3] our report for the first time suggests that 4-AP may also be beneficial for patients with late onset of EA2 in whom interictal cerebellar ataxia has become the key clinical feature.

Because of the CACNA1A mutation, current density from Cav2.1 channels in EA2 is reduced, which may lead to a general reduction in Purkinje cell firing rates and a loss of inhibition at deep cerebellar nuclei.[5] Ani-

mal studies in guinea pigs have demonstrated that 4-AP is able to increase the excitability of Purkinje cells by reducing the duration of the slowly depolarizing potential and thus latency to the firing of Ca^{2+} spikes in response to intracellular current pulses.[6] Thus, it may be assumed that the beneficial effects of 4-AP are due to its capability to restore overall Purkinje cell excitability and thereby inhibitory effects of Purkinje cells on deep cerebellar nuclei.[5]

Our patient reported symptomatic relief 1 hour after the ingestion of 5 mg 4-AP, which is in keeping with pharmacokinetic studies that found maximal plasma concentrations 1.0–1.2 hours after intake.[7] However, improvement at that time point was only visible during the finger–nose test and was much more marked after 4-AP had been taken three times a day. This observation may indicate that neuronal circuits affected by EA2 need time to adjust to 4-AP before symptomatic effects can be measured. The initial lack of subjective benefit after the first administration of 4-AP might as well have been due to the short duration of initial treatment since therapy with 4-AP supported by regular gait and balance training now shows a long-lasting effect over 1 year.

Future treatment trials are warranted to evaluate and compare the therapeutic effects of ACTZ and 4-AP. These trials should examine the efficacy of both drugs on attacks as well as on interictal ataxia in order to identify the best treatment for patients of various ages and different disease stages.

LEGENDS TO THE VIDEO

Full Video

Time	Content
00:00:00–00:00:23	Patient during normal gait, half-turn and attempt of tandem walking after 24-hr withdrawal of 4-AP
00:00:24–00:00:44	Patient during normal gait, half-turn, and attempt of tandem walking 1 hr after a single dose of 5 mg 4-AP
00:00:45–00:01:01	Patient during normal gait, half-turn, and attempt of tandem walking after treatment with 3 × 5 mg 4-AP per day
00:01:02–00:01:47	Patient during normal stance, stance with feet together and tandem stance after 24-hr withdrawal of 4-AP
00:01:48–00:02:29	Patient during normal stance, stance with feet together and tandem stance 1 hr after a single dose of 5 mg 4-AP
00:02:30–00:03:06	Patient during normal stance, stance with feet together and tandem stance after treatment with 3 × 5 mg 4-AP per day

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Dexmedetomidine and Arousal Affect Subthalamic Neurons

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Abstract: **Stereotactic neurosurgeons hesitate to employ sedation in cases requiring microelectrode recording (MER). We report our experience with dexmedetomidine during MER of subthalamic nucleus (STN). Eleven Parkinsonian patients received dexmedetomidine during deep brain stimulation surgery. Seven received continuous IV infusions during MER in the STN. The bispectral index (BIS) was used to estimate the level of consciousness. The quality of MER was evaluated as a function of BIS, clinical arousal, and dexmedetomidine dose. MER during wakefulness (BIS > 80; 0.1 to 0.4 mcg/kg/hr dexmedetomidine) was similar to the unmedicated state. Subthalamic MER was reduced when the patient was asleep or unarousable (BIS < 80). Anxiolysis persisted for hours. Arousal affects STN neurons. Dexmedetomidine "cooperative sedation," from which the patient is easily aroused, provides interpretable STN MER and prolonged anxiolysis. We suggest dexmedetomidine infusions without a loading dose, a relatively low infusion rate, and discontinuation after completion of the bur holes.** © 2008 Movement Disorder Society

Key words: dexmedetomidine; deep brain stimulation; subthalamic nucleus; microelectrode recording

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has proven effective for treating the motor symptoms of Parkinson's disease (PD). The STN is relatively small and deep,[1] mandating some form of intraoperative localization. For this reason, localizing microelectrode recording (MER) and test stimulation have become routine. Traditionally, MER and intraoperative testing require an awake, cooperative patient.[2,3] Patients fear awake surgical procedures, but many stereotactic neurosurgeons remain hesitant to employ sedation for fear of suppressing symptoms or attenuating localizing signals.

Sedation during MER-guided DBS surgery poses a real challenge as even small doses of sedatives can affect the quality of MER[4] or suppress PD symptoms.[5] Patient comfort would no doubt be maximized by general anesthesia, but probably at the expense of precise electrode positioning and clinical efficacy. Maltete et al. reported generally successful DBS implants with general anesthesia in 15 Parkinson's disease patients, but motor score improvements postoperatively were lower in the anesthetized group.[6] Hertel et al. recently reported decreased background of STN MER in a setting of carefully titrated general anesthesia.[7]

Dexmedetomidine (*Precedex*) is an attractive sedative for use in neurosurgical procedures, because of its minimal respiratory depressant effects, hemodynamic stabilizing properties, and rapid onset and offset. Initially approved for ICU sedation, this α-2 agonist affects receptors primarily in the locus ceruleus with minimal effects on cerebral cortex.[8] This results in a unique "cooperative sedation" where patients may "fall asleep" but are easily aroused.[9]

A recent report suggests that patient cooperation, PD symptoms, and the quality of MER were unaffected by continuous sedation with dexmedetomidine during DBS implant surgery in 11 cases.[10] An extensive positive experience with dexmedetomidine sedation during DBS surgery has been reported at Rush University, but the effects on MER of STN neurons have not yet been published.[9]

Stefani et al. found that spontaneous sleep can have a profound impact on the discharge of STN neurons.[11] This suggests that behavioral arousal could play a clinically relevant role in MER localization. Because patients may "fall asleep" even with low doses of dexmedetomidine, sleep/waking state may be a factor related to anxiolysis rather than frank sedation.

In an effort to reduce discomfort and anxiety in our patients during DBS procedures, we utilize intravenous dexmedetomidine for sedation. Here, we report our observations of the effects of dexmedetomidine on STN MER.

METHODS

We reviewed operative, anesthetic, and MER records from 11 consecutive cases of patients with Parkinson's

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disease who underwent STN DBS electrode implantation during intravenous dexmedetomidine sedation.

Surgery

Parkinson medications were held on the day of surgery, and a Leksell stereotactic frame was placed using local anesthesia. Direct targeting was based on T2 and MP-RAGE volumetric MR.[12] The patient was placed in a semirecumbent position with the frame locked to the operating table. Blood pressure was monitored by an automatic cuff. Spontaneous respiration was monitored along with O_2 saturation.

Sedation

Sedation was provided with continuous infusion of intravenous dexmedetomidine, which usually started at 0.7 mcg/(kg hr) and titrated down based on clinical response. In several patients, an initial loading dose of 1 mcg/kg was administered over 20 min. Level of consciousness was assessed by the neurosurgeon and anesthesiologist using observation and verbal questioning. The bispectral index (BIS) helped to estimate the level of cortical arousal[13]:

BIS = 80 to 100 suggests awake and alert,

BIS = 60 to 80 varying levels of sedation, and

BIS = 40 to 60 general anesthesia.

Sedation was titrated to patient comfort and was transiently increased during bur hole placement. No other drugs with sedative properties were administered.

Microelectrode Recording

MER was initiated 25-mm above the target and recorded on an A*lpha Omega* system. Sample recordings were saved every 0.5-mm during the trajectory. We did not test for motor driving of neurons. Following satisfactory MER and intraoperative macrostimulation testing, the DBS electrode was anchored in position and confirmed with fluoroscopy.

Postoperative

Patients recovered in the postanesthesia care unit and on the neurosurgical ward. A localizing MRI was obtained the day following surgery. Baseline Parkinson's medications were resumed, and most patients were discharged on the second postoperative day.

RESULTS

Eleven Parkinsonian patients underwent MER-guided STN DBS with intravenous dexmedetomidine. All were men, average age 62.3 years, mean disease duration 10.1 years. Eight patients underwent bilateral and three underwent unilateral surgery.

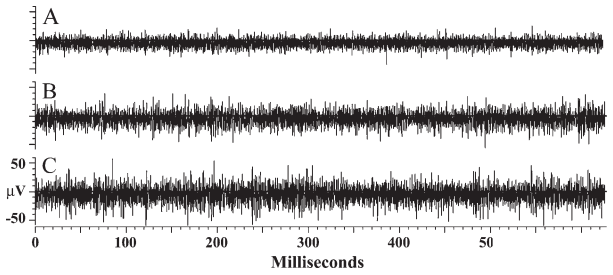

FIG. 1. Axial MRI of the patient's brain showing the tip of the electrodes 6 mm below the level of the anterior and posterior commissures. On the right, the optic tract can be seen on which the electrode tip projects.

Microelectrode recordings were successful for all placements. The mean number of electrode trajectories per side was 1.5 (range 1–4). The mean trajectory length through the subthalamic nucleus was 4.4 mm (range 2.5–6 mm). In 4 patients, dexmedetomidine sedation was discontinued following bur hole placement, the most noxious part of the procedure. The other 7 patients received intravenous dexmedetomidine during microelectrode recording in the subthalamic nucleus.

Subthalamic MER signals equivalent to the nonsedated state were obtained when dexmedetomidine was titrated to an easily arousable level of consciousness (BIS $>$ 80). Suppression of subthalamic neuronal discharge occurred with higher infusion rates and sedation levels where the patient was unarousable (BIS $<$ 80) (Figs. 1 and 2). All patients were sufficiently alert and cooperative for macrostimulation testing following microelectrode recording.

Following dexmedetomidine administration, and up to at least several hours after discontinuation, we observed a prolonged anxiolytic effect. It was relatively common for these patients to lapse into easily arousable sleep during the later stages of the operation. In some patients we observed a clear step-change increase in MER activity in the STN upon behavioral arousal from sleep, consistent with the report by Stefani et al.[11]

DISCUSSION

Eleven Parkinsonian patients received dexmedetomidine sedation during DBS surgery, and localizing unit activity was recorded from STN in every case. MER of STN was obtained during continuous infusion in 7 of these patients. Low level infusions of dexmedetomidine [$\sim$0.1 mcg/(kg hr)] did not substantially suppress

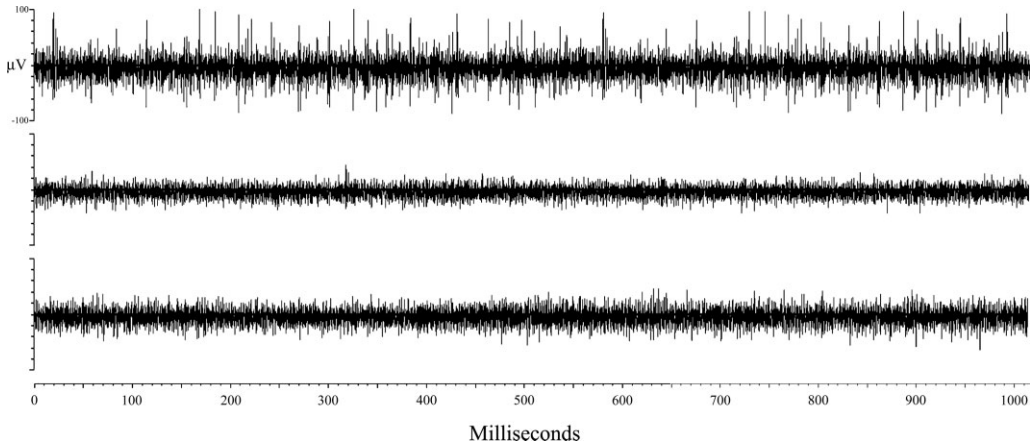

FIG. 2. Deep sedation suppresses STN neuronal activity. All traces were recorded from the same microelectrode position. Upper trace: STN MER signals. Patient is awake with BIS = 95. Middle trace: MER signals following an IV bolus of dexmedetomidine [1 μg/kg load over 10 min, then 0.5 μg/(kg hr)]. Patient becomes unarousable with BIS = 70. Lower trace: MER signals 20 min after stopping dexmedetomidine infusion. Patient awakens with some return of baseline background activity, BIS = 95.

STN neuronal discharges, but higher rates [~0.5 mcg/(kg hr)] resulted in a deeper sedation (lower BIS levels) and suppressed neuronal firing in the STN (see Fig. 1).

The clinical OR setting of these recordings imposed some constraints on analysis of neuronal activity. High-amplitude single-cell activity is lost over time at a given position of the microelectrode. MER across different medication or arousal conditions typically required 10 min or more, longer than we could reliably hold the activity of discriminable single units.

The so-called background multiple cell activity is more stable over time, and may be a marker of pharmacologic modulation.[7] We were able to obtain continuous MER of the STN during relatively rapid changes from sleep to waking, and on one occasion before and after a bolus infusion of dexmedetomidine (see Fig. 2). We could not obtain MER activity during the transition from medicated to nonmedicated, or from wakefulness to sleep because these are not rapid events. There is thus an inevitable confounding of the effect of time with the effect of the manipulation, particularly of drug levels. We hope that future research may provide more details of the effects of arousal versus pharmacologic effects on STN neurons.

Rozet et al. reported that patient comfort was improved with intravenous dexmedetomidine and MER of the subthalamic nucleus was possible. We agree. However, we observed that subthalamic neuronal firing varied with the dose of intravenous dexmedetomidine and the patient's level of behavioral arousal.

Intravenous dexmedetomidine was highly successful in alleviating anxiety during all stages of DBS surgery and particularly for placement of the bur holes. The terminal elimination half-life of dexmedetomidine is recognized as 2 hours, but we observed prolonged, clinically effective anxiolysis even when the infusion was discontinued several hours earlier. We did not observe a benefit with continuous infusion of dexmedetomidine after placement of the bur holes.

There were no apparent complications from the medication. Mild hypotension has been reported with loading doses, and our practice has evolved to utilize dexmedetomidine infusions without a loading dose, maintain a relatively low infusion rate, and discontinue the infusion immediately after the completion of the bur holes. The need for hypotensive agents to maintain normotension during electrode placement appeared to be reduced in these patients. Vasopressors were not required in any of the cases in our series.

Our experience indicates that dexmedetomidine can be used safely to sedate patients with Parkinson's disease during DBS placement without significant effect on the intraoperative localizing value of MER. Steady-state infusion rates of 0.1 to 0.4 mcg/(kg /hr) seem appropriate, with infusion rates titrated to maintain BIS values above 80, discontinuation after placement of bur holes, and the patient kept awake and alert during MER.

CONCLUSIONS

1. STN MER activity may vary with behavioral arousal.
2. Intravenous infusion of dexmedetomidine titrated to easy arousability will allow quality STN MER in the awake and alert patient.

3. Higher doses of dexmedetomidine which produce deep sedation (BIS $\leq$ 80 and patient unarousable) will suppress STN MER signals.

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