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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 exter- nal 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* muta- tion 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 *g* gene (*POLG1*), coding for a protein involved in mitochondrial DNA (mtDNA) maintenance, cause a broad variety of autosomal domi-

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nant and recessive neurological phenotypes, including progressive external ophthalmoplegia (PEO), ptosis, cer- ebellar ataxia, epilepsy, dementia, myopathy, myoclonus, peripheral neuropathy, and headache, in some cases accompanied by liver involvement.1 In *POLG1* associ- ated disorders, relationship between genotype and pheno- type 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 character- istic symptoms,4 or neuropathy alone.5 One study in Fin- nish 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 heterozy- gous 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, dysto- nia 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 epi- lepticus. 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 chor- eoathetoid movements of the arms and perioral muscles. She had never been treated with neuroleptics. MRI of the brain showed moderate generalized cere- bral 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*

Age (years)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Subjects | d. onset | Now | Neurological phenotype | *POLG1* genotype | Copy number | *P* |
| Mother | Na | 64 | None | W748S *1* E1143G/wt | 194 *6* 31 | 0.0009 |
| Father | Na | 64 | None | A467T/wt | 287 *6* 21 | 0.26 |
| Daughter (Patient 1) | 28 | 39 | Ataxia, neuropathy, | W748S *1* E1143G/A467T | 104 *6* 24 | 0.000002 |
|  |  |  | PEO, epilepsy, focal |  |  |  |
| Daughter | Na | 38 | dystonia, athetosis,  cognitive decline, headache None | W748S *1* E1143G/wt | 244 *6* 63 | 0.15 |
| Daughter (Patient 2) | 36 | 37 | Ataxia, neuropathy, PEO | W748S *1* E1143G/A467T | 141 *6* 15 | 0.000014 |
| Controls (*n 5* 15) | 48 *6* 14 |  | None | wt/wt | 323 *6* 110 | – |

Copy numbers are given in mean *6* 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 bio- chemical analyses of respiratory chain enzymes and ci- trate 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 cholesta- sis in the sister, no liver disease, diabetes, or neurolog- ical 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 polymor- phism 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, quadru- ple 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 regu- lar intervals, and a slow worsening of diplopia, neurop- athy, and ataxia was documented, whereas epilepsy,

choreoathetosis, and cognitive function remained sta- ble. 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 vol- untary contraction of the frontalis muscle, as some- times observed in ALO. Although no apparent blephar- ospasm 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 neu- rotoxin A (BoNT/A; Botox1) 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 com- pound 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

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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 com- pared with mean values of controls, reaching signiﬁ- cance in the mother only.

## DISCUSSION

Our study on a family of A467T and W748S *POLG1* mutation carriers, including two affected sib- lings, extends previous observations on the diversity of clinical spectrum in *POLG1* associated disorders. In Patient 1, diagnosis of ALO due to focal eyelid dysto- nia was probably delayed, because it accompanied mild ptosis in PEO and mimicked severe paresis of eyelid muscles. Indeed, ALO is known to occur with- out 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 disor- der 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 Par- kinson’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 mito- chondrial disease presenting with dystonia as dominant clinical phenotype was reported very recently,15 our ob- servation justiﬁes further examination of *POLG1* muta- tions 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 fea- tures 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 hetero- zygotes 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 con- siderable 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 com- pared to age- and sex-matched healthy controls, suggest- ing 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* *1289*

# 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 posteroven- tral 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 fol- low-up, chorea has completely disappeared; however, the patient was unable to stand and walk. The cognitive pro- ﬁle showed a progressive deterioration, with an extension of deﬁcit from the mainly dysexecutive alterations at base- line 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 psychi- atric symptoms. When the movement disorder, particu- larly the chorea, is disabling, pharmacological treatment is the mainstay of treatment but it is often ineffective. Thus, the following surgical therapies have been intro- duced: pallidotomy,1,2 human fetal striatal transplanta-

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

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tion,3 and deep brain stimulation (DBS).4,5 The pre- ferred target of DBS is the posteroventral globus pal- lidus internus (GPi) because of the striking effects of pallidal surgery for choreodystonic movements induced by levodopa (L-dopa) in Parkinson’s disease (PD),6 se- nile 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 con- ﬁrm the efﬁcacy of DBS in HD, to guide the develop- ment 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 subcu- taneous tissues of the chest.

The effect of the stimulation by means of each of the four electrode contacts was investigated using dif- ferent 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 main- tained constant the total electrical energy delivered (TEED) determined using the equations proposed by Moro et al.4 as follows:

TEED¼½ðvoltage *3*pulsewidth*3*frequencyÞ=

impedance] ½TEED ];

2 ð1Þ

An equation empirically derived from their previous studies on patients affected by PD9 but believed to be incorrect by Koss et al.10 who suggested,

TEED1sec[ðvoltage2 *3* pulsewidth *3* frequencyÞ=

impedance] *3* 1 sec ½TEED ]:

2 ð2Þ

Clinical assessments were prospectively performed using the motor section of the Uniﬁed Huntington’s Disease Rating Scale11 and of the Uniﬁed Parkinson’s Disease Rating Scale12 (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 battery13 (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 tetra- benazine 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 tol- erated.

Effect on Motor Function

The patient was discharged from the hospital with IPG left off to allow stabilization of the micropallidot- omy effect, which caused only a mild reduction of dys- kinesias (Table 1). One month after surgery, monopo- lar 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 stimu- lation 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 meth- ods (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 pro- gressively 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 stimula- tion 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

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

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Month before and after surgery | *2*6 | *2*1 | 1 | 3 | 4 |  |  | 6 | 11 | 12 |
| Oral therapy | Olanzapine |  |  |  |  | 10 | 10 | 10 | 7.5 |  |  |
| (mg/day) | 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 | | | | *2*23.5% | *2*5.9% | *2*11.8% | *2*47.1% | *2*47.1% | *2*82.4% | *2*76.5% | *2*76.5% |
| baseline (*2*1 month) | |  |  |  |  |  |  |  |  |  |  |
| Dystonia (0–20) | | 2 | 4 | 4 | 2 | 2 | 2 | 2 | 1 | 0 | 0 |
| Variation compared to  baseline (*2*1 month) | |  |  | 0.0% | *2*50.0% | *2*50.0% | *2*50.0% | *2*50.0% | *2*75.0% | *2*100.0% | *2*100.0% |
| Bradykinesia/rigidity (0–28) | | 15 | 14 | 11 | 11 | 11 | 11 | 11 | 14 | 6 | 6 |
| Variation compared to  baseline (*2*1 month) | |  |  | *2*21.4% | *2*21.4% | *2*21.4% | *2*21.4% | *2*21.4% | 0.0% | *2*57.1% | *2*57.1% |
| Axial symptoms (0–16) | | 7 | 6 | 5 | 12 | 14 | 11 | 14 | 14 | 14 | 14 |
| Variation compared to baseline (*2*1 month) | |  |  | *2*16.7% | *1*100.0% | *1*133.3% | *1*83.3% | *1*133.3% | *1*150.0% | *1*133.3% | *1*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).

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|  |  |  |  |
| --- | --- | --- | --- |
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| 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 |  |  |  |

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.

|  |  |  |  |
| --- | --- | --- | --- |
| Ideomotor praxis | 17 | 18 | 18 |
| Oro-facial praxis | 19 | 16 | 18 |
| Executive functions  Stroop test: interference/timea | 5 (*2*3.25) | 0 (*2*8.25) | 0 (*2*8.25) |
| Stroop test: interference/errorsa | 30 (29.25) | 30 (29.25) | 30 (29.25) |
| Temporal rule inductiona | 17 (19.5) | 25 (27.5) | 33 (35.5) |
| WCST: number of categories | 3 | 0 | 0 |
| WCST: % of errorsa | 55b | 63c | 68c |
| WCST: % of perseverative errorsa | 49c | 44c | 51c |
| WCST: % of ‘‘conceptual level’’ responses | 36 | 12 | 9 |
| Frontal assessment battery | 10 | 9 | 3 |

aReverse scores: lower scores indicate better performances.

bBelow 10th percentile.

cBelow 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 execu- tive 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 execu- tive tasks, in comparison with both the baseline and 1st follow-up visits. Scores worsened also on phono- logical 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.

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In the past, pallidotomy has been associated with only modest palliative functional improvement in dys- tonic features1 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 wors- ened bradykinesia.4 According to Koss et al., the equa- tion 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 pro- posed. 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 pro- tection 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 worsen- ing 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 parkin- sonian phenotype. However, DBS may have actually produced a pallidotomic effect, analogous to the wor- sening 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 alter- ations at baseline to a more diffused cognitive deterio- ration. 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 deter- mined. 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 assis- tance 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 improve- ment of axial symptoms: the patient is able to walk with unilateral assistance.

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

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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

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*Abstract:* OFF-period dyskinesias have been reported as a

consequence of fetal nigral transplantation for Parkin- son’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 fe- tal nigral grafts in the caudate and putamen subjected to deep brain stimulation (DBS) of the globus pallidus inter- nus (GPi) or subthalamic nucleus (STN). Clinical assess- ment was performed according to UPDRS and the clinical dyskinesia rating scale. In both patients, we found signiﬁ- cant 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

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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  UPDRS III | 8 yr | 8 yr |
| Med OFF | 44 | 30 |
| Med ON  Dyskinesias (CDRS) | 34 | 14.5 |
| Med OFF | 10 | 6 |
| Med ON  Dyskinesias (UPDRS IV) | 15 | 10 |
| 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

persisted even after withdrawal of levodopa (L-dopa) medication. Because of the dyskinetic states which are usually aggravated by dopaminergic medication, phar- macological 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 under- went 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 tis- sue preparation, neurosurgical procedure, and postopera- tive management have been described elsewhere.1 Long- term dopaminergic graft survival was demonstrated by [18F]ﬂuorodopa PET and *N*-(3-iodopropen-2-yl)-2*b*-car- bomethoxy-3*b*-(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

Stereotactic coordinates (*x*, *y*, *z*) relative to midACPC

R: 11.4, *2*2.1, *2*2.2 R: 21.3, 4.5, *2*3.6

L:*2*11.2, *2*2.1, *2*3.0 L: *2*20.5, 1.9, *2*2.4

of hypokinetic ﬂuctuations which could not be con-

trolled by various therapeutic approaches.

Because of prominent OFF-phase symptoms and

aAfter 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 exper- imental 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 signiﬁ- cant number of transplanted patients developed severe OFF-period dyskinesias (‘‘runaway dyskinesias’’) that

hypokinetic ﬂuctuations, 8 years after transplantation, the patient was selected for STN-DBS. As a result of STN-DBS, the patient experienced a permanent func- tional ON-state with sufﬁcient mobility (Uniﬁed Par- kinson’s disease rating scale [UPRDS] total 58/220, UPDRS III 33/108 in the L-dopa test, Table 1). Dopa- minergic 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

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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 bilat- eral neural transplantation with the second graft (right striatum) 6 months after the ﬁrst graft. Cell prepara- tion, surgical procedure, immunosuppression, and dem- onstration of long-term graft survival were identical to patient 1.1

Following transplantation, he experienced consider- able reduction of OFF-phase symptoms in the medica- tion 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 contin- ued to have dyskinesias throughout the day (UPDRS IV item 32: 4/4), which were rated as severely dis- abling (UPDRS IV item 33: 3/4) (Table 1).

Because of the prominent hyperkinesias but rela- tively few OFF-period symptoms, 8 years after bilat- eral 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 assess- ment), 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 dyskine- sias 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 report5 that found marked reduction of off-period dyski- nesias 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 pas- sage within the subthalamic area and therefore poten- tially reduce dyskinesias.7

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

The etiology of OFF-period dyskinesias following striatal fetal nigral grafting is still unclear. The devel- opment of dyskinesias after transplantation is probably not associated with dopaminergic overgrowth or exces- sive dopamine release from the grafts. Accordingly, [18F] PET studies in PD patients with postgrafting dys- kinesias have not provided evidence for dopaminergic overgrowth.4 Favored hypotheses rather involve patchy and uneven dopaminergic innervation resulting in do- pamine overﬂow from reinnervated into nonreinner- vated 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 path- way have not been speciﬁcally investigated. However, experimental studies on L-dopa-induced dyskinesias have highlighted the crucial role of D1 dopamine re- ceptor-mediated transmission at the level of the direct pathway from the striatum to the GPi.10 Increased sen- sitivity 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 dyskine- sias led to fundamental changes in the electrophysio-

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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 com- pared to STN-DBS in reducing OFF-period dyskine- sias, unrelated to external dopamine application, sup- ports this concept assigning a pivotal role to the direct pathway in mediating dyskinesia-related neural activ- ity. Alternatively or complementary to the proposed systemic effects on neural activity within the basal ganglia loop, differential effects of STN-DBS versus GPi-DBS14 on striatal dopamine release may impact the different outcomes in our patients. However, in contrast to the results of aforementioned animal stud- ies, 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 neuromodu- lation therapy. The choice of target may need to be tai- lored to the individual clinical symptomatology. STN- DBS in our patient led to marked improvement in hypo- kinetic 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 imme- diate 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/Medica- tion OFF’’) The patient from case report 1 was video- taped 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 hypo- kinesia and, simultaneously, intermittent off-period dyskinesias with involuntary arm elevation, continuous eye rubbing and head scratching.

Segment 2. (‘‘Patient 1/Following STN-DBS/Medi- cation OFF/ Stimulation ON’’). Three years following subthalamic deep brain stimulation, the patient contin- ues 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 hypo- kinesia with intermittent dyskinesias, accentuated in the right hand and ﬁngers.

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

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*L-DOPA TREATMENT IN LESCH-NYHAN DISEASE* *1297*

# 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 dis- order of purine metabolism causing severe neurobehavio- ral 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 cerebro- spinal 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 hypoxan- thine-guanine phosphoribosyl tranferase (HPRT), bio-

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chemically characterized by hyperuricemia.1 The clini- cal features associated with LND include those related directly to the hyperuricemia (gout, nephrolithiasis, ar- thritis, etc.), neurobehavioral manifestations indicative of central nervous system (CNS) disturbances, and other clinical signs (hyperemesis, anemia, etc.).1 De- layed 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 neurobeha- vioral disturbances remains unclear, but abnormal cen- tral monoamine metabolism may play a role. In parti- cular, several lines of evidence suggest that LND is associated with an abnormal CNS dopaminergic func- tion. However, only a few studies have reported treat- ment 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/carbi- dopa was started during the early stages of his neuro- development.

## 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 trun- kal hypotonia with no abnormal movements. Head cir- cumference 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 conduc- tion, 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 lmol/L [normal range: 100–330 lmol/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 per- formed, showing low levels of homovanillic acid

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

After L-dopa therapy (L-dopa plus carbidopa and folinic acid,

ditions (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).

Before treatment 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 range3 (Table 1). Treatment with L-dopa/carbidopa (1/0.25 propor- tion) 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 con- trol, and he started picking up objects; dyskinetic movements were still present, while peripheral hyper- tonia 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 lmol/L (normal range: 100–330 lmol/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 phosphor- ibosyltransferase activity was elevated (59 nmol/hour/ mg hemoglobin; normal range: 19–38 nmol/hour/mg hemoglobin). Molecular analysis disclosed a 5-bp dele- tion 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 posi- tion 74. The child has presented a moderate progres- sive 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 con-

## DISCUSSION

We describe the case of a child affected with LND presenting clinical signs of impaired CNS dopaminer- gic function. The notable tremor, the marked dystonia developed during early infancy, and the obvious sus- tained response to L-dopa led us to investigate a pri- mary 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 neuro- pathological, 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 sig- niﬁcantly lower than in controls,4 and tyrosine hydroxi- lase 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 abnor- malities also comes from positron emission tomogra- phy images, which show an abnormally reduced num- ber 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 im- portant 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

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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 LND10–13 by measuring the end product of DA: HVA. These studies were performed some time ago (during the 70s and the 80s) and some- times 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 sec- ond sample HVA values were higher, and inside the normal range. However, the notably clinical improve- ment 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 pre- sented intolerable side effects.10–13 An important limi- tation in the evaluation of the therapies used in the preceding reports was the different ages at which treat- ment was started. It is likely that delayed L-dopa treat- ments 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 supersensitivity5 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. per- formed pretreatment CSF analysis, but L-dopa doses and therapy duration were not detailed, age at begin- ning of the treatment was very variable, and their clini- cal 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 moni- tor their treatment. Further studies, clinical observations, and double-blind trials are needed to establish the useful- ness 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 grasp- ing. No head control. Explosive uncoordinated move- ments.

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 pin- cer 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

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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 an- tipsychotic 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 tar- gets are the thalamus,5,6 the anterior internal capsule,7 the nucleus accumbens8 and the Gpi9–11 (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 inten- sity 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 sub- stantial effect. Ultimately, the combination of aripipra- zole 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 sub- stantial improvement of tics13,14 was demonstrated.

Previous therapies with *a*-2-adrenoreceptor agonists, dopamine agonists and opioid agonists, as well as al- ternative treatments like antibiotics, immunoglobulins, and plasmapheresis (already described as possibly effective in single reports15) only resulted in a tempo- rary improvement of the tics.

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*TOURETTE SYNDROME AND DEEP BRAIN STIMULATION* *1301*

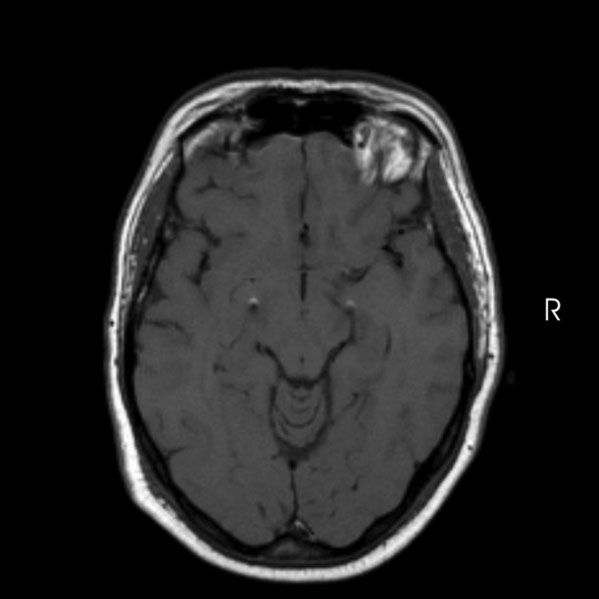


FIG. 1. Axial MRI of the patient’s brain showing the tip of the elec- trodes 6 mm below the level of the anterior and posterior commis- sures. On the right, the optic tract can be seen on which the electrode tip projects.

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 per- formed under propofol anesthesia with MRI-guided ster- eotaxy using a modiﬁed Leksel/Lerch system. The coor- dinates 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 lat- eral, 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). Af- ter 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 lS, 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 lS, 145

pps), 4 months after implantation (3.5 V, 180 lS, 145 pps), and at 12 months after the implantation (4.2 V, 210 lS, 145 pps). Under this setting, the current applied was 94 lA 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 discon- tinued. Clinical outcome was assessed using the Yale Global Tic Severity Scale (YGTSS), the Verbal Learn- ing Memory Test (VLMT), and the Stroop-Test. The neuropsychological testing before and after the inter- vention revealed an identical performance proﬁle. The YGTSS score dropped from 83 preoperatively to 28 af- ter 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 com- plaining of depressive moods, vertigo, and stomach aches. At that time, the patient emphasized having dif- ﬁculties 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 | | | | *1*6 wk | | | *1*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 |  |

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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 treat- ments in her medical history only temporarily. The cause of therapeutic effects is supposed to be due to a regulation (‘‘override’’) of a possibly disturbed inhibi- tory output from the basal ganglia to the thalamus. A disturbed Gpi-outﬂow could lead to a disinhibition of excitatory thalamus neurons and consequently to tha- lamo-cortical hyperactivity.16 A just published case se- ries with 18 TS patients and successful DBS of the thalamus6 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 inter- ventions are imperative in order to help patients to cope with their ‘‘new life,’’ that is without the symp- toms previously dominating their lives.

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

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*INTERRUPTIONS IN GAA REPEATS IN FRIEDREICH ATAXIA* *1303*

# 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 expan- sion (>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 addi- tional patients with late onset FA and small expanded al- leles also exhibited interrupted GAA repeats that were not associated with inappropriately late onset. Our obser- vations 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 dis- order 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 premuta-

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tion 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 transcrip- tion, 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 dis- ease. 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 pres- ence of interruptions in the GAA repeats.5 Such inter- ruptions might prevent further expansion by reducing slippage during replication, blocking the formation of the DNA structure that reduces transcription of the fra- taxin allele, thus leading to improved frataxin expres- sion 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.

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## METHODS

Genomic DNA was extracted from whole blood using the PureGene DNA extraction kit (Gentra Sys- tems) 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 Sys- tem (Roche) using primers GAA-F and GAA-R,6 with the following thermal proﬁle: 928C for 2 minutes; 10 cycles of 928C for 20 seconds, 628C for 30 seconds, 688C for 4 minutes; 15 cycles of 928C for 20 seconds, 628C for 30 seconds, 688C for 4 minutes with a 20-second extension per cycle, followed by 1 cycle at 688C for 7 minutes. PCR products were electropho- resed on a 1% agarose gel, and allele sizes were esti- mated relative to a 500-bp ladder. The shorter expanded alleles were then excised and gel puriﬁed using the Qiaquik Gel Extraction Kit (Qiagen) accord- ing to the manufacturer’s protocol. The extracted prod- uct 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 clum- siness and gradual development of difﬁculty standing on one foot. There was no family history of neurologic dis- order, 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 pres- ent to the ankles bilaterally. TSH, B12, folate, and vita- min 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 move- ment disorder. On examination, she had hyperactive reﬂexes and mildly increased tone in her upper extrem- ities 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 pri- mary position, with hypometric saccades. MRI of the head and cervical spine revealed mild cerebellar and occipital lobe atrophy with a chronic right posterior tha- lamic lacunar infarct and mild cervical spinal cord com- pression. Molecular analysis of her frataxin gene

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 ten- don 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 ex- amination 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. Com- mercial 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*

revealed GAA repeat lengths of 1,005 and 104.

Patient 1A and 1B

(GAA)>72*1* (GAGAA) *1* (GAAAA)

*1* (GAA) 20*1* (GAAAA) *1* (GAA)

*1* (GAGGAA) 4 *1* (GAA)12

Patient 2

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

Patient 2 (GAA)>89 *1*(GAGAA)*1*(GAA)4*1*(GAGAA)

*1*(GAA)4*1*(GAAAA) *1*(GAA)13

Patient 3 (GAA)>78*1*(GAAAA)*1*(GAA)17*1*(GAAAA)

*1*(GAA) *1*(GAGGAA)5 *1*(GAA)12

Patient 4 (GAA)>103*1* (GAAAGAA) *1* (GAA) 15

Patient 5 (GAA)>130*1* (AAA)

The number of GAA repeats plus the location and the sequence of repeat interruptions are indicated. The number of GAA repeats at the 50 end represents a minimum repeat number since sequence analysis did not reach the 50 nonrepeat sequence. Interruptions clustered in the 30 end of the repeat sequence and were followed by short GAA repeats in all of the patients except No. 5. Interruptions are desig- nated to be consistent with those previously identiﬁed (GAGGAA, Ref. 7; GAAAGAA, Ref. 8; GAAAA, Ref. 9).

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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 vibra- tory 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 interrup- tions 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 30 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 30 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 pre- sented 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

30 end of an interrupted repeat (Patient 5) presented

slightly later than the expected age. Similarly, the total maximal uninterrupted length did not correlate substan- tially 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 an- alyzed 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 local- ized to the 30 end of the repeat sequence and were pre- ceded by ‡72 uninterrupted GAA repeats.

The age of onset of FA correlates moderately (*r 5* 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 interrup- tions 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 sib- lings 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

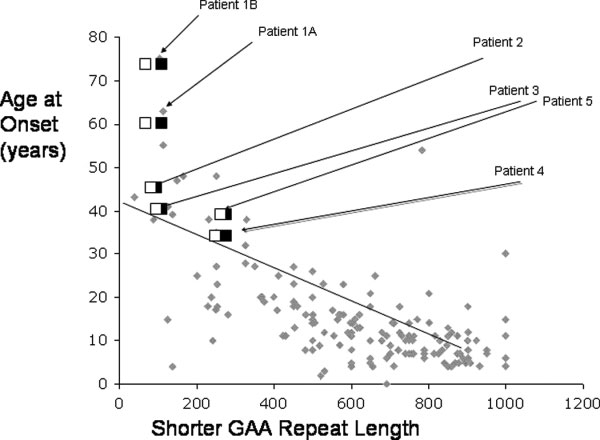


FIG. 1. Correlation of age of onset versus total repeat length and the maximum length of uninterrupted GAA repeats. Age of onset and GAA repeat length were plotted for a large American cohort (dia- monds) and each of the 6 patients in the present study (ﬁlled square, estimated repeat length; open square, maximum possible uninter- rupted 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 interrup- tions, while Patients 1 to 4 had interrupted repeats.

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(with a change of a single GAA to a GGA) remedies the defect in transcription and blocks formation of tri- plex 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 inter- ruption, showing that in late-onset patients the fre- quency of interruptions may be quite high. If we exam- ined 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 inter- ruptions 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 inter- ruption 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 inter- ruptions do not substantially inﬂuence the age of onset of FA.

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*STRUCTURE OF MOTOR SYMPTOMS OF PARKINSON’S DISEASE* *1307*

# 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 mod- eling; dimensionality; Motor Section of the UPDRS

The identiﬁcation of symptom groups of neurologi- cal syndromes such as the combination of hypokinesia, rigidity, resting tremor, and postural abnormalities in Parkinson’s disease (PD) is important because knowl- edge about the co-occurrence of symptoms may help to deﬁne disease phenotypes and provide clues for dif- ferential diagnosis. The number of symptom groups (dimensionality) can be inferred through statistical analysis of measurements used for impairment evalua- tion. Within the Motor Section of the Uniﬁed Parkin-

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son’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 pa- per discusses the dimensionality of the Motor Section of the UPDRS and the structure of motor symptoms of PD within the framework of structural equation model- ing (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. Princi- pal component analysis requires a continuous measure- ment level5,6; maximum likelihood estimation in EFA requires continuous measurement levels and either nor- mally 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 analy- sis (CFA) within a SEM framework to perform a sta- tistical test and to evaluate a number of plausible fac- tor models for the structure of symptoms underlying the Motor Section of the UPDRS. Some SEM estima- tors 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 crite- ria.9 Each patient was evaluated by one member of a group of certiﬁed neurologists, movement disorder spe- cialists 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 sub- sample of size N *5* 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 *5* 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 pro- gram10 was used. If the level of measurement is ordi- nal and sample size relatively small, as in our case, Jo¨reskog and So¨rbom11 recommend analyzing the ma- trix 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, good- ness-of-ﬁt statistics and indices, a summary of esti- mated 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 theoreti- cally 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 con- sists 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) re- mained high, the ﬁt statistics and indices suggest that this model need not to be rejected. Generally, the val- ues of comparative ﬁt index (CFI) and goodness of ﬁt index (GFI) suggest a very acceptable ﬁt, whereas root mean square error of approximation (RMSEA), stand- ardized root mean square residual (SRMR), and

normed ﬁt index (NFI) indicate slightly less, but still acceptable model ﬁt (see the values below Fig. 1). Val- ues in the matrix of residual correlations are ranging from *2*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 ex- tremity (*2*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 parame- ter 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 (me- dian 0.07, standard deviation 0.04). The estimated composite reliability of our model (by stratiﬁed coefﬁ- cient alpha14) equals 0.94.

The four factors of rigidity, bradykinesia of the extremities, speech/hypomimia, and axial/gait brady- kinesia 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 fac- tors. 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 v2 statistic: 899.33 (*P 5*

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 [*2*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.

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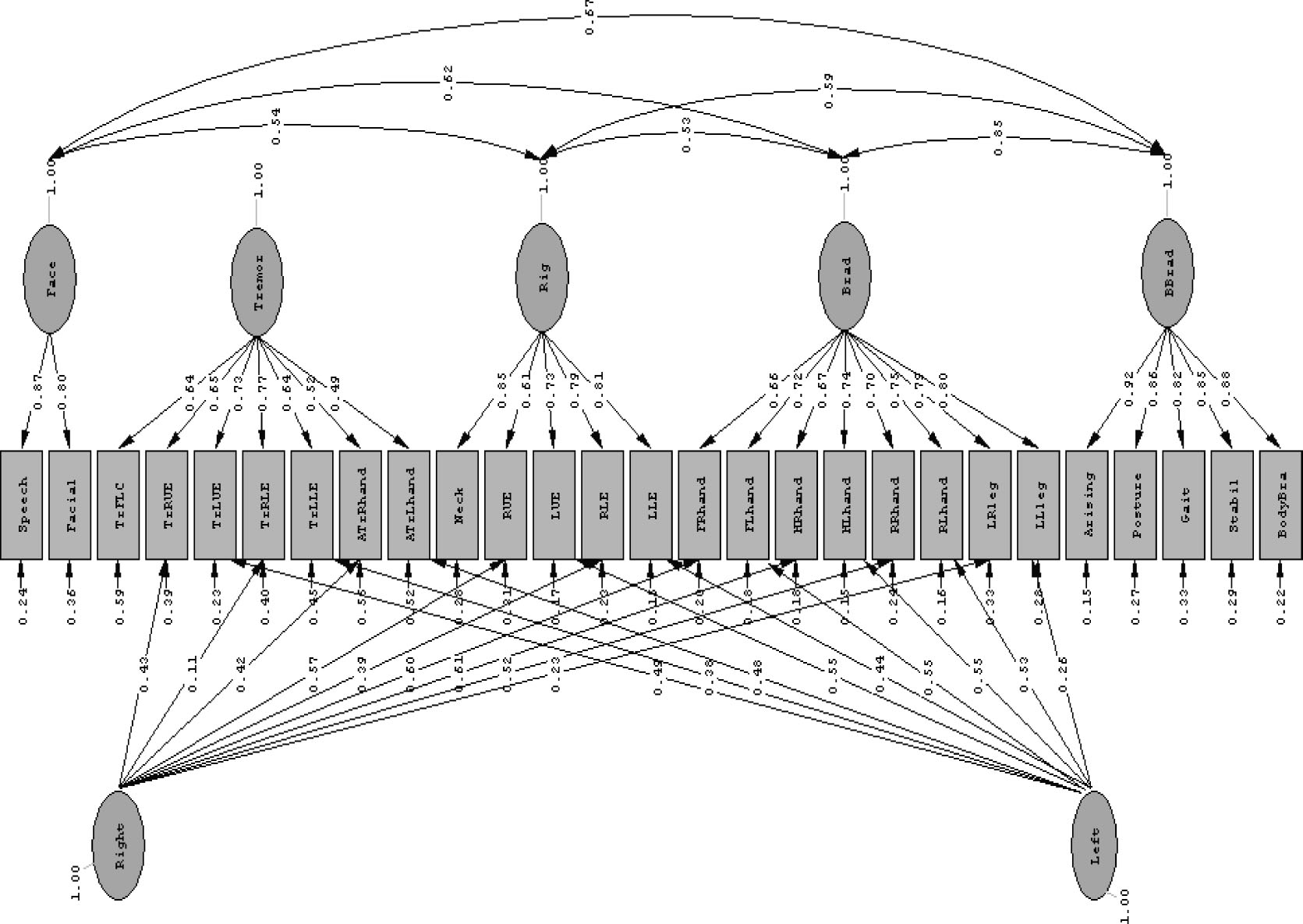
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*1309*

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

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|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Rigidity | 0.35 | 0.42 | 0.20 | 0.06 | 0.13 0.09 0.05 0.15 0.19 0.01*2*0.03*2*0.05*2*0.09 0.16 0.08 0.08 0.03 0.09 0.06 0.01 0.02 *2*0.06 *2*0.01 *2*0.01*2*0.04 0.02 |
| RUE | 0.23 | 0.36 | 0.00 | 0.32 | 0.01 0.17 *2*0.12 0.35 *2*0.02 0.53 0.09 0.05*2*0.04 *2*0.04 *2*0.01 *2*0.07 *2*0.06 *2*0.02 *2*0.05 *2*0.02*2*0.08 *2*0.08 *2*0.01 0.01*2*0.03 0.04 |

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

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Speech 0.00 0.04 *2*0.05 *2*0.05 *2*0.19 *2*0.27 *2*0.03 *2*0.02 *2*0.05 *2*0.06*2*0.09*2*0.01*2*0.06 0.03 *2*0.01 | | | | | | | | | | | 0.01 | *2*0.03 | 0.04 | 0.02 0.06 | 0.02 0.00 0.05 *2*0.03 0.00 | 0.00 |
| Facial 0.70 0.19 *2*0.06 0.07 *2*0.01 *2*0.08 0.02 0.09 0.06 0.10 0.07 0.02 0.02 *2*0.04 0.00 | | | | | | | | | | | *2*0.07 | *2*0.05 | *2*0.02 | 0.00 *2*0.04 | 0.02 *2*0.01 0.02 *2*0.06*2*0.05 | 0.05 |
| Lipschin | 0.04 0.19 |  | 0.02 | 0.11 *2*0.04 *2*0.04 | *2*0.21 | *2*0.05 | 0.20 | 0.00 0.07 | 0.02*2*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 | *2*0.05 *2*0.06 | 0.43 |  | 0.04 0.10 *2*0.24 | 0.04 | 0.19 | 0.06 | 0.07*2*0.01 | 0.01*2*0.09 *2*0.06 | *2*0.07 | *2*0.07 | *2*0.07 | *2*0.02 | *2*0.08 0.02*2*0.13 *2*0.05 *2*0.07 0.01*2*0.06 0.03 | | |

|  |  |
| --- | --- |
|  |  |
|  |  |
| 0.11 0.06 | 0.11 |

Speech Facial LipschinTrRUETrLUETrRLETrLLEATrRhandATrLhandRigidity RUE LUE RLE LLE FRhandFLhand HRhandHLhandRRhandRLhand LRleg LLleg ArisingPosture Gait Stabil BodyBra

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| TrLUE | *2*0.06 0.07 | 0.57 | 0.52 |  | *2*0.14 | 0.04 | *2*0.13 | 0.00 | 0.13 | 0.00 | 0.05 | 0.05 | 0.02 *2*0.03 | *2*0.04 | *2*0.04 | *2*0.07 | *2*0.02 0.00 0.04 0.04 0.12 0.02 | | | | |
| TrRLE | *2*0.19 *2*0.01 | 0.46 | 0.65 | 0.42 |  | 0.19 | *2*0.08 | *2*0.40 | 0.09 | 0.11 | 0.00 | 0.14 | 0.03 *2*0.07 | *2*0.04 | *2*0.12 | *2*0.18 | *2*0.03 *2*0.12 *2*0.02*2*0.06 *2*0.03 *2*0.11 *2*0.05*2*0.02 *2*0.01 | | | | |
| TrLLE *2*0.27 *2*0.08 0.37 | | | 0.18 | 0.69 | 0.68 |  | *2*0.29 | *2*0.05 | 0.04 *2*0.12 | | 0.02*2*0.07 | | 0.10 *2*0.11 | *2*0.01 | *2*0.20 | *2*0.12 | *2*0.11 | *2*0.02 | 0.01 0.06 *2*0.01 *2*0.01 | 0.03*2*0.03 | 0.03 |
| ATrRhand *2*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 *2*0.10 | *2*0.04 | *2*0.07 | 0.03 | *2*0.03 | *2*0.04 | 0.01*2*0.06 0.07 0.00 | 0.01 0.04 | 0.06 |
| ATrLhand *2*0.02 0.09 0.26 0.13 0.60 *2*0.02 0.45 0.60 0.19 *2*0.02 0.08 0.01 0.02 *2*0.05 *2*0.06 0.01 *2*0.01 0.01 *2*0.01 0.00 0.02 0.13 0.15 0.14 0.11 0.16 | | | | | | | | | | | | | | | | | | | | | |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| LUE | 0.25 | 0.38 | 0.07 | *2*0.01 | 0.32 | 0.00 0.23 | | 0.09 | 0.34 | 0.59 | 0.53 |  | *2*0.06*2*0.01 0.01 | | | 0.00 | 0.01 | *2*0.03 | 0.01 | 0.00 *2*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 *2*0.07 | | 0.19 | 0.01 | 0.61 | 0.75 | 0.52 | 0.09 *2*0.03 | | | 0.00 | *2*0.07 | *2*0.03 | *2*0.02 | *2*0.03 0.02 | | 0.00 *2*0.07 *2*0.02 | | | 0.00*2*0.08 | | 0.02 |
| LLE | 0.32 | 0.37 | *2*0.03 | *2*0.09 | 0.23 | 0.03 0.26 | | 0.00 | 0.23 | 0.60 | 0.46 | 0.82 | 0.73 | *2*0.03 | | 0.01 | *2*0.04 | *2*0.03 | *2*0.03 | 0.00 *2*0.02 | | 0.06 *2*0.03 0.03 | | | 0.04*2*0.03 | | 0.04 |
| FRhand | 0.38 | 0.28 | 0.08 | 0.20 *2*0.03 *2*0.01 *2*0.11 | | | | 0.16 | *2*0.05 | 0.46 | 0.51 | 0.27 | 0.48 | 0.26 |  | 0.11 | 0.05 | *2*0.04 | *2*0.01 | *2*0.09 *2*0.02*2*0.14 *2*0.06 *2*0.04 *2*0.01 0.00 | | | | | | | 0.05 |
| FLhand | 0.38 | 0.35 | 0.21 | *2*0.07 0.23 *2*0.04 0.20 | | | | *2*0.04 | 0.21 | 0.41 | 0.22 | 0.58 | 0.30 | 0.56 | 0.59 |  | *2*0.01 | 0.02 | *2*0.05 | *2*0.01 *2*0.12*2*0.01 *2*0.03 *2*0.04 *2*0.07*2*0.01 | | | | | | | 0.06 |
| HRhand | 0.37 | 0.26 | 0.10 | 0.19 *2*0.04 *2*0.05 *2*0.20 | | | | 0.19 | 0.01 | 0.38 | 0.49 | 0.27 | 0.44 | 0.25 | 0.85 | 0.47 |  | 0.10 | 0.02 | *2*0.05 *2*0.01*2*0.15 *2*0.02 *2*0.01 0.00*2*0.03 | | | | | | | 0.06 |
| HLhand | 0.37 | 0.32 | 0.15 | *2*0.07 0.20 *2*0.18 0.09 | | | | 0.03 | 0.26 | 0.37 | 0.18 | 0.56 | 0.28 | 0.53 | 0.45 | 0.86 | 0.59 |  | *2*0.03 | 0.01 *2*0.10*2*0.04 *2*0.01 0.01 *2*0.01*2*0.01 | | | | | | | 0.06 |
| RRhand | 0.42 | 0.33 | 0.15 | 0.20 *2*0.02 0.03 *2*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*2*0.10 *2*0.01 *2*0.03 0.01*2*0.03 | | | | | | | 0.04 |
| RLhand | 0.42 | 0.38 | 0.23 | *2*0.08 | 0.26 *2*0.12 | | 0.18 | *2*0.04 | 0.25 | 0.40 | 0.20 | 0.58 | 0.29 | 0.55 | 0.40 | 0.82 | 0.45 | 0.86 | 0.58 |  | *2*0.09 | 0.00 | 0.04 | 0.01 | *2*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 | *2*0.05 | *2*0.05 | 0.00 | *2*0.04 |
| LLleg | 0.46 | 0.42 | 0.02 | *2*0.13 | 0.17 *2*0.06 | | 0.16 | *2*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 | *2*0.03 | *2*0.05 | 0.03 | *2*0.03 |
| Arising | 0.54 | 0.49 | 0.06 | *2*0.05 | 0.12 *2*0.03 | | *2*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 |  | *2*0.01 | 0.03 | 0.05 | *2*0.11 |
| Posture | 0.55 | 0.48 | 0.22 | *2*0.07 | 0.02 *2*0.11 | | *2*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 | *2*0.03 |
| Gait | 0.45 | 0.38 | 0.15 | 0.01 | 0.11 *2*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 | *2*0.03 |
| Stabil | 0.49 | 0.41 | 0.09 | *2*0.06 | 0.06 *2*0.02 | | *2*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 |  | *2*0.07 |
| BodyBra | 0.51 | 0.52 | 0.25 | 0.03 | 0.11 *2*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 |  |

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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 studies1–4,15 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 assump- tions 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 likeli- hood 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 bradyki- nesia of the extremities was mentioned before,2,3 as well as that of action/postural tremor.1 To our knowl- edge, side-sensitivity of rigidity and rest tremor, how- ever, has not been previously reported.

The high correlations among the factors rigidity, bra- dykinesia of the extremities, axial/gait bradykinesia, and speech/hypomimia can be indicators of co-occur- rence 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 inde- pendence of tremor from rigidity and bradykinesia can be viewed as an indicator of the lack of substantive relationship between tremor and PD disability, a ﬁnd- ing 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 pro- priospinal 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 sur- gical screws support the diagnosis of a psychogenic move- ment 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 in- nervated from different segments of the spinal cord, and sequentially activated via propriospinal pathways.1 Char- acteristic electrophysiological ﬁndings of slow conduc- tion and selective recruitment of truncal and proximal

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

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limb muscles help differentiate PSM from spinal seg- mental myoclonus.2 PSM has been documented second- ary 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 move- ments 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 mi- graine, there were no other medical problems at the time, and no psychiatric history. There was no docu- mented 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 inci- dent was initiated. A reconstructive right blepharoplasty was performed for right sided pseudoptosis. She subse- quently developed a right frontal headache. The cos- metic 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, includ- ing 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. Eight- een 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 contin- uous jerking lasting for up to 1 hour, causing signiﬁcant disability. There was positive, action myoclonus with coexistent stimulus sensitive myoclonus of variable la- tency, 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 anxi- ety, but no other precipitants were identiﬁed. Spinal cord and brain MRI were normal except for a few scat- tered 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 sur- gical screws used in the blepharoplasty were removed 4

*PSYCHOGENIC PROPRIOSPINAL MYOCLONUS* *1313*

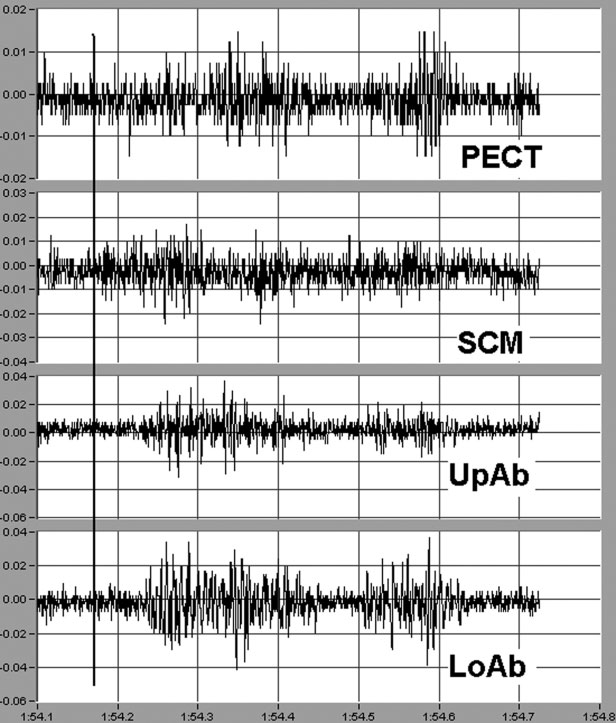


FIG. 1. 0.7 seconds epoch of order of activation study, demonstrat- ing surface EMG bursts in pectoralis (pect), followed by sternomas- toid (SCM) and upper (UpAb) and lower abdominal muscles (LoAb). Solid line—onset of jerk.

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 electrophysiologi- cal 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, contempo- raneous legal proceedings related to the injury, the asso- ciated 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 antag- onist 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 elec- trophysiological characteristics of ‘‘organic’’ PSM, the possibility of psychogenic etiology has been raised.3,5 Healthy volunteers simulating PSM have electrophysiolog- ical recordings that are also similar, except for long EMG burst durations.3 The ﬁndings in the present study support these authors’ contention that electrophysiological parame- ters 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 re- moval 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 elec- trophysiological ﬁndings. Spontaneous remissions may differentiate psychogenic and organic PSM.

## LEGENDS TO THE VIDEO

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

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# Potassium Channel Blocker

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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 pre- vent 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; in- terictal 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 through- out the nervous system but mainly in cerebellar Purkinje

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

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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 sev- eral 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 pur- suit movements and impaired visual suppression of the vestibulo-ocular reﬂex.2 Interictal cerebellar symptoms are a common condition in the course of the disease1 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 mi- graine 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, hyper- hydrosis, paresthesia, muscle stiffness, and gastroin- testinal disturbance, or because of a loss of efﬁcacy. So far, treatment options for these patients are lim- ited. 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.

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## CASE REPORT

We examined a 63-year-old female patient who con- tacted our Movement Disorder Outpatient Clinic in May 2004. In 2000, at the age of 57, she started to suf- fer 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. Addition- ally, 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 bev- erages led to deterioration of symptoms. In 2006, the attacks completely ceased and interictal gait ataxia became the main clinical problem making her in- capable 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

*4-AMINOPYRIDINE IN EPISODIC ATAXIA TYPE 2* *1315*

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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, sacca- dic 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 at- rophy 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 ex- cluded as possible reason for vertigo by otorhinolar- yngologic examination that demonstrated regular func- tion of both vestibular organs. There was no sign for baroreceptor or orthostatic dysfunction during auto- nomic testing including metronomic breathing, Val- salva 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 paresthe- sia 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. (pro- vided by Synopharm, Germany), which was well toler- ated without any adverse effects but initially did not seem to have any subjective beneﬁt for the patient. Af- ter 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 unas- sisted. 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 video- taped and rated again as soon as she realized improve- ment of her symptoms. A ﬁnal evaluation was done af- ter the patient had taken 3 *3* 5 mg 4-AP over 24

hours. All evaluations were done in exact order as pro- vided 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 treat- ment to exclude clinically relevant prolongation of QTC time, which was calculated using Bazett’s correction: QTc ¼ QT ðmillisecondsÞ= RR ðsecondsÞ. QTC time was within normal range measuring 429 milliseconds before and 414 milliseconds during treat- ment 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 with- out 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).

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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 mark- edly stabilized, so she was even able to do some steps of tandem walking (Video). Stance ataxia also had im- proved (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 prevent- ing 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 cer- ebellar 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-

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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 Ca2*1* 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.

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Full Video

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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 *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 *3* 5 mg 4-AP per day

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*DEXMEDETOMIDINE, AROUSAL, SEDATION, AND STN NEURONS* *1317*

# 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 Par- kinsonian 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, clini- cal arousal, and dexmedetomidine dose. MER during wakefulness (BIS > 80; 0.1 to 0.4 mcg/kg/hr dexmedeto- midine) was similar to the unmedicated state. Subthala- mic MER was reduced when the patient was asleep or unarousable (BIS < 80). Anxiolysis persisted for hours. Arousal affects STN neurons. Dexmedetomidine ‘‘coopera- tive sedation,’’ from which the patient is easily aroused, provides interpretable STN MER and prolonged anxioly- sis. We suggest dexmedetomidine infusions without a load- ing dose, a relatively low infusion rate, and discontinua- tion 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 nu- cleus (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 intra-

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This work was presented in poster format at the American Society of Stereotactic and Functional Neurosurgeons in Boston, Massachu- setts, June 2006.

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operative 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 attenuat- ing localizing signals.

Sedation during MER-guided DBS surgery poses a real challenge as even small doses of sedatives can affect the quality of MER4 or suppress PD symptoms.5 Patient comfort would no doubt be maximized by gen- eral 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 set- ting of carefully titrated general anesthesia.7

Dexmedetomidine (*Precedex*) is an attractive seda-

tive for use in neurosurgical procedures, because of its minimal respiratory depressant effects, hemodynamic stabilizing properties, and rapid onset and offset. Ini- tially approved for ICU sedation, this *a*-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 posi- tive 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 dex- medetomidine, 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 ob- servations 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 implanta- tion during intravenous dexmedetomidine sedation.

Surgery

Parkinson medications were held on the day of sur- gery, 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 moni- tored along with O2 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 con- sciousness was assessed by the neurosurgeon and anes- thesiologist using observation and verbal questioning. The bispectral index (BIS) helped to estimate the level of cortical arousal13:

BIS *5* 80 to 100 suggests awake and alert, BIS *5* 60 to 80 varying levels of sedation, and BIS *5* 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 record- ings were saved every 0.5-mm during the trajectory. We did not test for motor driving of neurons. Follow- ing satisfactory MER and intraoperative macrostimula- tion testing, the DBS electrode was anchored in posi- tion 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 Parkin- son’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

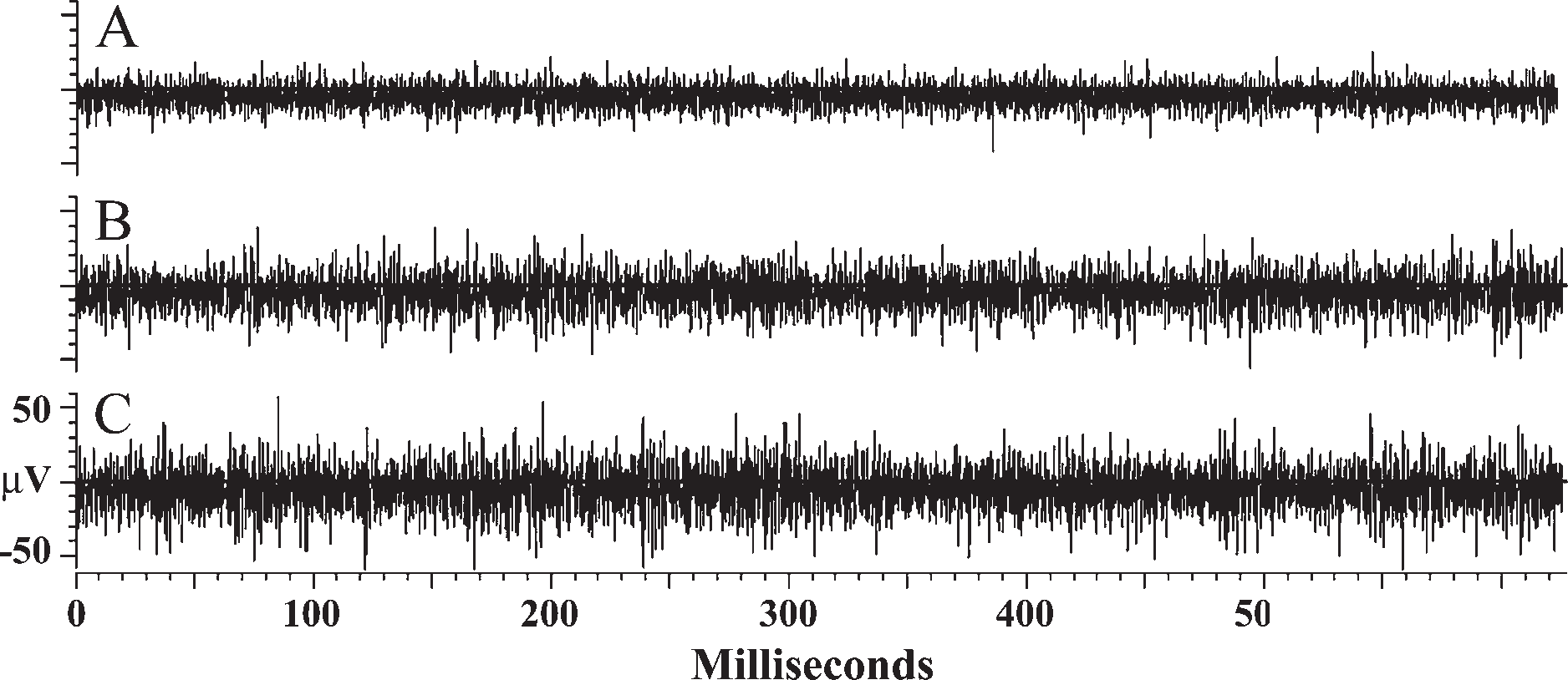


FIG. 1. Axial MRI of the patient’s brain showing the tip of the elec- trodes 6 mm below the level of the anterior and posterior commis- sures. On the right, the optic tract can be seen on which the electrode tip projects.

duration 10.1 years. Eight patients underwent bilateral and three underwent unilateral surgery.

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 place- ment, 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 nonse- dated state were obtained when dexmedetomidine was titrated to an easily arousable level of consciousness (BIS > 80). Suppression of subthalamic neuronal dis- charge 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 rela- tively 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 dexmedetomi- dine 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 dexmedetomi- dine [~0.1 mcg/(kg hr)] did not substantially suppress

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*DEXMEDETOMIDINE, AROUSAL, SEDATION, AND STN NEURONS* *1319*

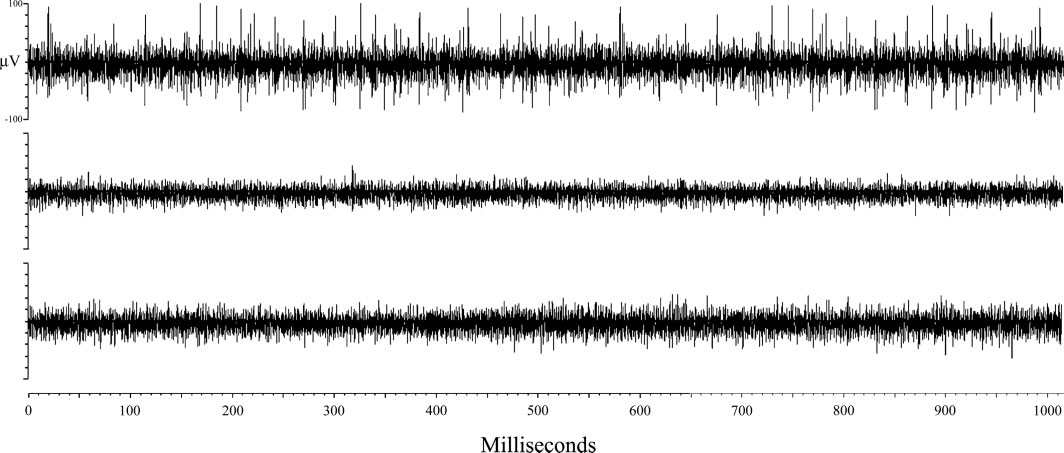
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FIG. 2. Deep sedation suppresses STN neuronal activity. All traces were recorded from the same microelectrode position. Upper trace: STN MER signals. Patient is awake with BIS *5* 95. Middle trace: MER signals following an IV bolus of dexmedetomidine [1 lg/kg load over 10 min, then 0.5 lg/(kg hr)]. Patient becomes unarousable with BIS *5* 70. Lower trace: MER signals 20 min after stopping dexmedetomidine infusion. Patient awakens with some return of baseline background activity, BIS *5* 95.

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

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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 phar- macologic modulation.7 We were able to obtain contin- uous 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 pharmaco- logic 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 dexmede- tomidine 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 dis- ease 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.

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

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