*Movement Disorders*

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Letters to the Editor Related to New Topics

# Sustained Dopaminergic Response of Parkinsonism and Depression in POLG-Associated Parkinsonism

Parkinsonism with1,2 or without3 chronic progressive oph- thalmoplegia (CPEO) can be caused by mutations in the mitochondrial DNA polymerase g (*POLG*). *POLG*-associated Parkinsonism (POLG-P) is at least partially responsive to lev- odopa,1,2 but predictors of dopamine-response have not been reported. Of the plethora of different syndromes associated with *POLG*-mutations, depression and anxiety present com- mon major therapeutic problems.4 Patients with idiopathic Parkinson’s disease (IPD) frequently show improvement not only of motor symptoms but also of depression and anxiety after initiation of treatment with levodopa or dopamine ago- nists. Here, we present a patient with POLG-P whose Parkin- sonism and depression showed sustained excellent response to dopaminergic treatment.

A 55-year-old woman of Croatian origin presented with a 3-year history of slowly progressive facial masking, hypo- phonia, symmetric cogwheeling of the wrists, shufﬂing gait, marked bradykinesia, and positive pull test, yielding 47/108 points in the UPDRS motor score. Bilateral ptosis, incom- plete CPEO, and exercise intolerance had been present for 10 years and had led to the previous misdiagnosis of myas- thenia gravis. Severe depression, indicated by 43/63 points on the Beck Depression Inventory, had been noted for 3 years. Family history on the paternal side was positive for CPEO and ptosis, and both sons of the patient, aged 28 and 25 years, were suffering from ptosis, depression, and anxiety but had no extrapyramidal movement abnormalities. Two consecutive subcutaneous injections of apomorphine mark- edly reduced UPDRS motor scores from 47 to 27 points (243%) on 2.5 mg apomorphine and from 55 to 26 points

(253%) on 5 mg apomorphine (Supporting Table 1). The injections also lead to a rapid and marked amelioration of depressed mood. A long-term medication was initiated with extended release formulations of ropinirole (6 mg/d) and lev- odopa (100 mg/d).

At 10 months follow-up, the patient presented with a sus- tained improvement of Parkinsonism and mood as evidenced by a decrease down to 20 points in the UPDRS motor score (257%) and to 4 points on the Beck Depression Inventory (291%) (Testing was done by an examiner blind to the results of the apomorphine tests; for details see Supporting Tables 1 and 2).

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

Potential conﬂict of interest: Nothing to report.

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123I-FP-CIT-DATScan demonstrated a severe symmetric reduction of nigrostriatal dopamine transporters similar to advanced IPD (Fig. 1B) and ruled out a depression-induced ‘‘pseudo-Parkinsonism.’’ In addition, transcranial sonography (performed by an examiner blind to the history and clinical examination of the patient) revealed a hyperechogenic sub- stantia nigra and a hypoechogenic raphe (Fig 1D), thus resembling the characteristic sonography midbrain ﬁndings of IPD with depression.5 Because of the suggestive phenotype and family history, a genetic analysis of the *POLG* gene was initiated, revealing a heterozygous Tyr955Cys mutation, which is known to present, interalia, as POLG-P with autoso- mal dominant inheritance.1

Our ﬁndings present close similarities between IPD and POLG-P: in contrast to other atypical Parkinson diseases like MSA-P or PSP-P, both entities feature predominant degeneration of nigro-striatal dopaminergic neurons, respond well not only to levodopa but also to dopamine agonists and display hyperechogenicity of the substantia nigra.

These similarities are particularly interesting as increased levels of mtDNA deletion and respiratory chain deﬁciency have been found in substantia nigra neurons of IPD patients,6 thus suggesting mitochondrial dysfunction as part of the com- plex pathogenetic pathway of substantia nigra degeneration in IPD. As *POLG* mutations lead to elevated levels of oxida- tive stress and mtDNA damage,7 patients harboring these mutations might be at particular risk for IPD-like substantia nigra degeneration.

Antidepressant effects of levodopa and dopamine agonists, especially of D4/D5 agonists like ropinirole, have been shown consistently in patients with IPD.8 Almost complete remission of depression in our patient might be partially attributed to her dramatic motor improvement but it is likely that speciﬁc dopaminergic effects like in IPD are also involved. Future studies are warranted to test whether depres- sion in *POLG*-patients without Parkinsonism is also associ- ated with a hypoechogenic raphe and responds to dopaminer- gic treatment as well.

In conclusion, the large beneﬁt from dopaminergic therapy emphasizes the need to identify motor and nonmotor parkin- sonian features also in the large majority of those *POLG*- patients that present with a multifaceted phenotype. More- over, differentiating POLG-P from other forms of atypical Parkinsonism is of great importance because of the potential excellent response to dopaminergic medication. Transcranial sonography and apopmorphine testing could serve as inex- pensive, easily available tests for facilitating a differential diagnosis and to predict treatment response of both motor and nonmotor symptoms.

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### 243

*244 LETTERS TO THE EDITOR*

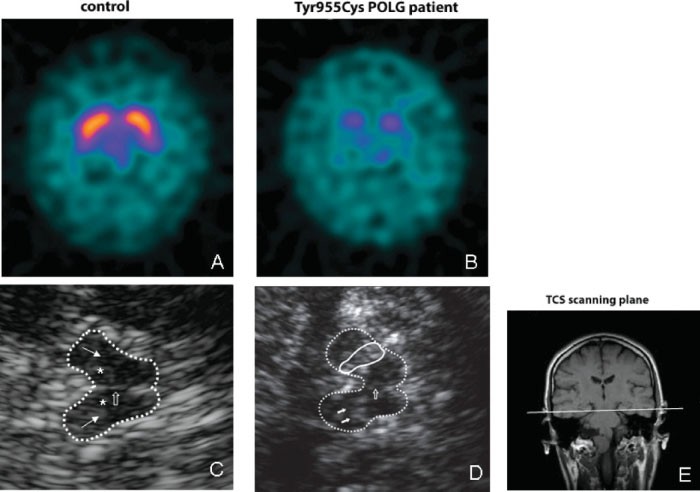
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FIG. 1. Nigrostriatal and midbrain pathology in POLG-associated Parkinsonism visualized by DATScan and transcranial sonography (TCS). A and B: Compared with a healthy control (A) transaxial 123I-FP-CIT-SPECT images of the *POLG* patient (B) show markedly reduced dopamine transporter levels in the putamen and, to a lesser extent, in the caudate. C–E: TCS of the midbrain in the mesencephalic scanning plane (exempla- rily depicted in E) demonstrates an enlarged area of hyperechogenicity (line ipsilateral to the probe, white arrows contralateral side) at the ana- tomical site of the SN within the hypoechogenic butterﬂy-shaped mesencephalic brainstem (dotted lines) in the *POLG* patient (D). In a control only small dots of hyperechogenicity are visible at this site (white arrows) (C). The midline raphe (unﬁlled arrow) is interrupted in the patient (D) whereas it is continuous in the control person (C). (\*) red nucleus. [Color ﬁgure can be viewed in the online issue, which is available at [www.](http://www/) interscience.wiley.com.]

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*Movement Disorders, Vol. 25, No. 2, 2010*

### LETTERS TO THE EDITOR 245

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## References

1. Luoma P, Melberg A, Rinne JO, et al. Parkinsonism, premature menopause, and mitochondrial DNA polymerase gamma muta- tions: clinical and molecular genetic study. Lancet 2004;364:875– 882.
2. Invernizzi F, Varanese S, Thomas A, Carrara F, Onofrj M, Zeviani M. Two novel POLG1 mutations in a patient with progres- sive external ophthalmoplegia, levodopa-responsive pseudo-ortho- static tremor and parkinsonism. Neuromuscul Disord 2008;18:460– 464.
3. Davidzon G, Greene P, Mancuso M, et al. Early-onset familial par- kinsonism due to POLG mutations. Ann Neurol 2006;59:859–862.
4. Schulte C, Synofzik M, Gasser T, Scho¨ls L. Ataxia with ophthalmo- plegia or sensory neuropathy is frequently caused by POLG muta- tions. Neurology 2009;73:898–900.
5. Walter U, Hoeppner J, Prudente-Morrissey L, Horowski S, Herpertz SC, Benecke R. Parkinson’s disease-like midbrain sonography abnormalities are frequent in depressive disorders. Brain 2007;130 (Part 7):1799–1807.
6. Bender A, Krishnan KJ, Morris CM, et al. High levels of mitochon- drial DNA deletions in substantia nigra neurons in aging and Parkin- son disease. Nat Genet 2006;38:515–517.
7. Graziewicz MA, Bienstock RJ, Copeland WC. The DNA polymerase gamma Y955C disease variant associated with PEO and parkinson- ism mediates the incorporation and translesion synthesis opposite 7,8-dihydro-8-oxo-2’-deoxyguanosine. Hum Mol Genet 2007;16: 2729-2739.
8. Rektorova I, Balaz M, Svatova J, et al. Effects of ropinirole on non- motor symptoms of Parkinson disease: a prospective multicenter study. Clin Neuropharmacol 2008;31:261-266.

# Novel *PANK2* Gene Mutations in Korean Patient with Pantothenate Kinase-Associated Neurodegeneration Presenting Unilateral Dystonic Tremor

Video 

Pantothenate kinase-associated neurodegeneration (PKAN [MIM 234200]) is a rare autosomal recessive disorder with iron accumulation in the basal ganglia, due to mutations in the pantothenate kinase 2 (*PANK2*) gene on chromosome 20p13.1 The phenotype of PKAN is widely variable and overlaps with a wide spectrum of disorders characterized by neurodegeneration with brain iron accumulation, formerly known as Hallervorden-Spatz syndrome.2

A 55-year-old Korean man visited our movement disorder clinic due to tremulous movement in the right arm and hand. He was healthy until his late thirties, but he felt unpleasant movements on the right hand while doing ﬁne actions, and then he had slowly progressive difﬁculty in writing and manip- ulation with right hand for 7 years. There was no history of drug exposure, trauma or other medical problems, but family history was positive for his brother, who had similar symptoms. Initial neurological examination revealed the postural and kinetic tremulous movements in the right arm and hand (video, segment 1). He had no problem in the left upper and both lower extremities, and his gait and balance were normal. There was no other focal neurologic sign. He did not have any cognitive or psychiatric problems like depression or obsessive–compulsive disorder. The score of minimental sta-

tus examination was 30.

Initial routine blood tests including thyroid and parathyroid hormone test, peripheral blood smear test, and gene studies for Huntington‘s disease and torsion dystonia (*DYT1* gene) were not remarkable. Cervical spine magnetic resonance images (MRI) was normal. Brain T2-weighted ﬂuid-attenu- ated inversion recovery (FLAIR) MRI showed symmetrical low signal intensity in the pallidum with a slight anterome- dial core of high signal intensity, as the so-called ‘‘eye-of- the-tiger’’ sign (Fig. 1A). Although he had unilateral symp- toms in the right upper extremity, there was no difference in size and intensity between bilateral brain lesions. Further- more, brain perfusion single photon emission computed to- mography (SPECT) showed no signiﬁcant perfusion asymme- try in this patient (Fig. 1B).

Genetic studies of the *PANK2* gene (GenBank ID: NM\_153638.2) examined by DNA sequence analyses revealed the two heterozygous mutations. One mutation was 1-bp nucleotide deletion of C and insertion of TT in exon 3 (c.1153delCinsTT), resulting in frame shift and generation of a premature stop codon (p.Leu385PhefsX11; Fig. 2A). Another mutation was a single nucleotide substitution (c.1319G>C) in exon 4, which was predicted to replace arginine residue at codon 440 with proline (p.Arg440Pro; Fig. 2B).

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*Movement Disorders, Vol. 25, No. 2, 2010*

### 246 LETTERS TO THE EDITOR

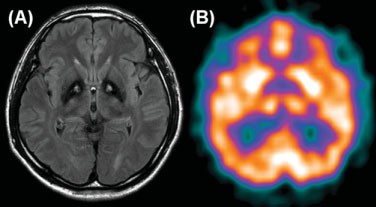
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FIG. 1. Bilateral hypointensity with central region of hyperintensity in the medial globus pallidus, or the so-called ‘‘eye-of-the-tiger’’ sign in the T2-weighted FLAIR MRI (A). Brain perfusion SPECT showed no signiﬁcant perfusion asymmetry (B).

His dystonic tremor in the right arm did not respond to anticholinergics, beta-blockers and muscle relaxants, but had a partial response to the additional levodopa/carbidopa (250/ 25 mg three times a day) treatment (video, segment 2). Dur- ing medical treatment, his disability had been in stationary state over the following 3 years and was restricted to his right arm and hand.

For now, we report a Korean patient with PKAN present- ing atypical phenotype that included late-onset, levodopa-re- sponsive dystonic tremor in the mainly unilateral upper ex- tremity, and identiﬁed two novel compound heterozygous mutations in exon 3 (Leu385PhefsX11) and exon 4 (Arg440Pro) of the *PANK2* gene. To our knowledge, these two mutations have not been reported previously. Although we recommended further genetic study for his brother with similar neurologic symptoms and other asymptomatic family members, they denied the further genetic studies.

To date, numerous mutations underlying PKAN have been reported; patients with nonsense mutations show typical phe- notype while those with missense mutations tend to show atypical clinical manifestations.2–4 In one latest report about atypical PKAN, there are many differences of phenotype between two siblings with same genotype.5

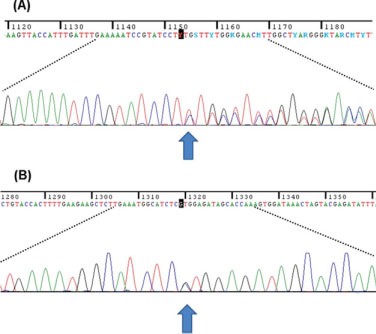
Similar to our patient, some reports about PKAN have pre- sented focal or unilateral phenotype at early stage. However, many of those cases had progressed within several years, and then eventually had been aggravated, presenting multi-focal variable motor symptoms.6–8 These clinical courses are dif- ferent from that of our patient, whose disability had been in stationary state over 7 years and was steadily restricted to his right arm and hand. Interestingly, our case showed an unilat- eral dystonic tremor even though his brain MRI revealed symmetrical ‘‘eye-of-the-tiger’’ sign in the basal ganglia. Fur- thermore, in contrast with our expectation, his brain perfusion SPECT showed no signiﬁcant perfusion asymmetry.

Because one reported case and our case have showed some improvement by levodopa treatment,6 it should be con- sidered levodopa treatment to patients with the late-onset atypical PKAN presenting dystonic symptoms.

## Legends to the Video

Segment 1. The patient shows unilateral tremulous move- ments in right upper extremity and intermittent pronating

FIG. 2. Sequence analysis of the patient showed two novel muta- tions; they included a deletion/insertion and frame-shift mutation (c.1153delCinsTT; p.Leu385PhefsX11) in exon 3 (A) and a missense mutation (c.1319G>C; p.Arg440Pro) in exon 4 (B).

contractions while raising his arm straightly. He was unable to write legibly and draw the spiral of Archimedes with the right hand, but could do well the same task with the left hand.

Segment 2. His dystonia and dystonic tremor in the right arm had partially improved after additional levodopa/carbi- dopa treatment.

Author Roles: WT Yoon: Execution of project and writ- ing ﬁrst draft of manuscript; WY Lee: Conception, organiza- tion of the project, and manuscript review; HY Shin: Manu- script review and critique; ST Lee: Execution of gene study; CS Ki: Manuscript review and critique.

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## References

1. Zhou B, Westaway SK, Levinson B, Johnson MA, Gitschier J, Hayﬂick SJ. A novel pantothenate kinase gene (*PANK2*) is de- fective in Hallervorden-Spatz syndrome. Nat genet 2001;28:345– 349.

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*Movement Disorders, Vol. 25, No. 2, 2010*

### LETTERS TO THE EDITOR 247

1. Hartig MB, Hortnagel K, Garavaglia B, et al. Genotypic and phenotypic spectrum of *PANK2* mutations in patients with neuro- degeneration with brain iron accumulation. Ann Neurol 2006;59: 248–256.
2. Hayﬂick SJ, Westaway SK, Levinson B, et al. Genetic, clinical, and radiographic delineation of Hallervorden-Spatz syndrome. N Engl J Med 2003;348:33–40.
3. Pellecchia MT, Valente EM, Cif L, et al. The diverse phenotype and genotype of pantothenate kinase-associated neurodegenera- tion. Neurology 2005;64:1810–1812.
4. Wu YR, Chen CM, Chao CY, Lyu RK, Lee-Chen GJ. Pantothe- nate kinase-associated neurodegeneration in two Taiwanese sib- lings: identiﬁcation of a novel *PANK2* gene mutation. Mov Dis- ord 2009;24:940–941.
5. Yamashita S, Maeda Y, Ohmori H, et al. Pantothenate kinase-asso- ciated neurodegeneration initially presenting as postural tremor alone in a Japanese family with homozygous N245S substitutions in the pantothenate kinase gene. J Neurol Sci 2004;225:129–133.
6. Antonini A, Goldwurm S, Benti R, et al. Genetic, clinical, and imaging characterization of one patient with late-onset, slowly progressive, pantothenate kinase-associated neurodegeneration. Mov Disord 2006;21:417–418.
7. Chung SJ, Lee JH, Lee MC, Yoo HW, Kim GH. Focal hand dystonia in a patient with *PANK2* mutation. Mov Disord 2008;23: 466–468.

# Backpack Treatment for Camptocormia

Video 

Camptocormia, also called bent spine syndrome, is an extreme ﬂexion of the trunk during walking that resolves in the supine position. Treatment attempts for this disabling condition are often unsuccessful. We describe a case of markedly improved camptocormia with the simple interven- tion of wearing a backpack.

A 69-year-old man with Parkinson’s disease (PD) pre- sented with progressive camptocormia for the prior 1.5 years. He had been diagnosed with PD 5 years earlier after the onset of left upper extremity resting tremor, shoulder pain, and bradykinesia. He had no discomfort when seated or supine, but with walking, he developed dramatic thoracolum- bar ﬂexion associated with pain in the lower abdomen and back. The camptocormia was worse in the evenings; he reported ﬂexion approaching 908 at night compared with only slight ﬂexion in the mornings. The severity of camptocormia was unrelated to PD medication dosing, although his other PD motor symptoms responded well to dopaminergic ther- apy. It was exacerbated by carrying weight in front of him. It was alleviated by using a walker and with pressure on his lower back, a possible sensory trick. Magnetic resonance imaging (MRI) of the brain was unremarkable and MRIs of thoracic and lumbar spine were notable for mild degenerative changes. Botulinum toxin A injections to the rectus abdomi- nis muscles ﬁrst with 180 units and later with 360 units were ineffective. Muscle relaxants were also ineffective. Addi- tional levodopa improved his PD symptoms and produced mild dyskinesias but did not improve the camptocormia.

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Neurologic exam, performed while PD medications were active, revealed normal muscle tone throughout, mild asym- metric bradykinesia, absence of tremor, and mild choreiform dyskinesias. He had mild age-appropriate thoracic kyphosis while seated and standing, but otherwise no abnormal ante- rior or lateral ﬂexion. He was examined in the morning, a time when he reported his truncal ﬂexion was relatively mild. After walking for about 30 s, he had onset of thoracolumbar ﬂexion that progressed for another 30 s to reach a maximum of ,408. This degree of ﬂexion was intolerably painful, caused him to stop walking and forced his trunk upright. He would then resume walking and the pattern would repeat. The rectus abdominis muscles were palpably tight during ﬂexion. The camptocormia was completely relieved when wearing a low-slung backpack weighing ,6 kg (video) and returned upon removal. It was also improved by using a wheeled walker or by pressing his back against the hallway handrail. He found the backpack less cumbersome and embarrassing than using a walker.

In follow-up clinic visits, he reported a consistent immedi- ate beneﬁt each time a backpack was worn. The beneﬁt was sustained, without decrement, for long durations (hours) and was terminated only by removal of the backpack. However, prolonged use of a backpack was limited by discomfort from the backpack itself. Changing to a smaller size backpack, titrating the weight it contained, and adjusting it to hang lower partially alleviated this discomfort.

Camptocormia is associated with heterogeneous etiologies including parkinsonism, primary and secondary dystonias, spinal deformities, neuromuscular disorders, psychogenic causes, and others.1 Among PD patients, camptocormia has a reported prevalence of 7%2 and is associated with greater discomfort and disability.3 It has features of a truncal kineso- genic dystonia. Many patients have palpable contraction of the rectus abdominis, improvement with sensory tricks, and a diurnal pattern of exacerbation.1,4 Like other axial manifesta- tions of PD, it responds poorly to levodopa.1,4 Other treat- ments including muscle-relaxants, botulinum toxin, and deep brain stimulation have been attempted but are unsatisfactory in many cases.1,5 Thoracolumbar orthoses have been tried but some are poorly tolerated and others, while beneﬁcial, require custom design and inpatient rehabilitation training.6

We speculate that the backpack may have acted as a coun- terweight to help correct posture as well as stimulated a sensory trick. To our knowledge, backpack therapy has not previously been reported in camptocormia, and we suggest it as an inexpensive, noninvasive option for this disabling condition.

## Legends to the Video

Segment 1. The patient is shown walking down a hallway with camptocormia building up gradually over about 60 s. A backpack is then worn, which resolves the camptocormia. The camptocormia is also relieved when using a walker or when standing with his back against a handrail. Thoracolum- bar ﬂexion is absent when supine on the examination table. The video is intentionally mute to avoid distracting back- ground noise.

Author Roles: Brooke Gerton was involved in the Clinical observations, writing of ﬁrst draft, manuscript review, and cri- tique. Brett Theeler was involved in the Clinical observations,

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*Movement Disorders, Vol. 25, No. 2, 2010*

### 248 LETTERS TO THE EDITOR

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## References

1. Azher SN, Jankovic J. Camptocormia: pathogenesis, classiﬁcation, and response to therapy. Neurology 2005;65:355–359.
2. Tiple D, Fabbrini G, Colosimo C, et al. Camptocormia in Parkin- son disease: an epidemiological and clinical study. J Neurol Neu- rosurg Psychiatry 2009;80:145–148.
3. Bloch F, Houeto JL, Tezenas du Montcel S, et al. Parkinson’s dis- ease with camptocormia. J neurol neurosurg psychiatry 2006;77: 1223–1228.
4. Djaldetti R, Mosberg-Galili R, Sroka H, Merims D, Melamed E. Camptocormia (bent spine) in patients with Parkinson’s disease— characterization and possible pathogenesis of an unusual phenom- enon. Mov Disord 1999;14:443–447.
5. Melamed E, Djaldetti R. Camptocormia in Parkinson’s disease. J neurol 2006;253 (Suppl 7):VII14–VII16.
6. de Seze MP, Creuze A, de Seze M, Mazaux JM. An orthosis and physiotherapy programme for camptocormia: a prospective case study. J Rehabil Med 2008;40:761–765.

# Deep Brain Stimulation in a Patient with Isolated Mixed Tremor



Isolated mixed tremors are characterized by the presence of postural and resting tremor in the absence of other neuro- logic signs, such as, bradykinesia or rigidity.1 A recent study has demonstrated that about half of the patients with isolated mixed tremor and intact nigrostriatal pathway at baseline developed Parkinson’s disease (PD) 2 years later, whereas

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*Movement Disorders, Vol. 25, No. 2, 2010*

the remaining patients continued to present only mixed tremor at a 2-year follow-up.1 It is still unknown, however, whether these latter patients will develop PD over time or will remain consistent with a diagnosis of ET with resting tremor. Deep brain stimulation (DBS) of the ventral interme- diate thalamic nucleus (Vim) is an effective treatment option for ET patients with medication-resistant tremors.2 Here we describe a patient with disabling isolated mixed tremor and intact nigrostriatal pathway, resistant to pharmacologic treat- ment, who beneﬁted from surgery.

A 57-year-old woman had a 1-year history of tremor affecting her arms, legs, trunk, and head with increasing dis- ability in the last 5 months. Her tremor was present at rest, in the maintenance of posture and on standing. Secondary causes of tremor were excluded. There was no familial his- tory of neurological disorders. When she was ﬁrst admitted to our clinic, her neurological examination showed head and trunk tremor along with a moderate resting and postural tremor in the four limbs, predominant on the right side, and severe legs tremor during standing. Electrophysiological stud- ies revealed involvement of agonist-antagonist distal muscles of upper and lower limbs at a frequency of 4 to 5 Hz, at rest and in the maintenance of posture (Fig. 1A) On standing, a rhythmic legs tremor at a frequency of 5 Hz, synchronous in proximal muscles and asynchronous in distal muscles was recorded (Fig. 1C). MRI scan of the brain was normal. [123I]- FP-CIT SPECT revealed integrity of the nigrostriatal dopami- nergic system. The patient had received various treatments (clonazepam, propranolol, primidone, etc.) in adequate dos- age but these did not result in any signiﬁcant improvement. She complained of increased disability for daily life activities and was assessed for surgery. At the clinical follow-up (18 months after baseline evaluation), the patient showed asym- metric postural and resting tremor of the upper and lower limbs, and marked tremor of the trunk and lower limbs on standing position. A second [123I]-FP-CIT SPECT performed 18 months after the ﬁrst examination was normal. Both pre- and post-operatively Fahn–Tolosa–Marin Tremor Rating Scale was performed (see Table 1). After written consent was obtained, she underwent monopolar bilateral microelec- trode guided Vim-DBS after the usual preoperative CT-MRI localization of the target coordinate. The Vim coordinates were 4 mm posterior to the mid commissural point, 3 mm above, and 13 mm lateral to the commissural plane with active contacts 1 and 5. The patient remained conscious. The DBS setting had a frequency of 130 Hz, a pulse width of 250 ls, and a amplitude of 1 mA.

Post-operatively, the beneﬁt was rapidly evident with marked improvement of tremor of head, trunk, and limbs. Comparison of pre- and post-operative video segments depicts the improvement quite clearly. In on-stimulation con- dition, resting and postural tremor completely disappeared in distal muscles of upper and lower limbs (Fig. 1B). On stand- ing, only an asynchronous tremor was recorded in the distal muscles of the legs with substantially (more than 50% of baseline) decreased amplitude (Fig. 1D). At the follow-up visit, 12 months after surgery, DBS was still effective and the patient showed no tremor in her four limbs, trunk, and head. Her quality of life substantially improved and she remained off medication.

The Vim nucleus is the primary surgical target for the treatment of tremor.3 The beneﬁcial effect of Vim DBS on

### LETTERS TO THE EDITOR 249

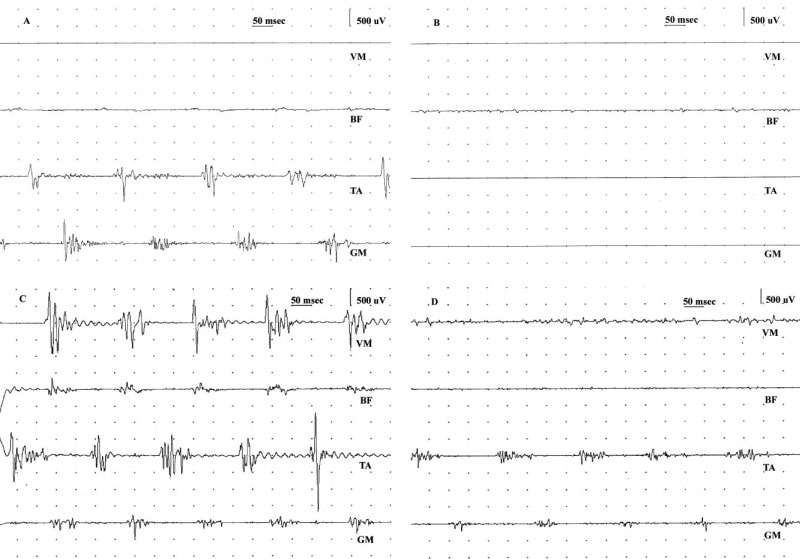
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FIG. 1. EMG recording of leg muscles in a patient with isolated mixed tremor. At rest: at the pre-operative evaluation, rhythmic and asynchro- nous 4 to 5 Hz EMG activity involving TA and GM (A); in on-stimulation condition, tremor completely disappeared in distal muscles (B). On standing, at the pre-operative evaluation, a rhythmic 5 Hz tremor developed in all leg muscles, synchronous in VM and BF, asynchronous in TA and GM (C); in on-stimulation condition, EMG amplitude decreased in TA and GM, whereas tremor disappeared in VM and BF muscles (D). VM, vastus medialis muscle; BF, biceps femoris muscle; TA, tibialis anterior muscle; GM, medial gastrocnemius muscle.

ET has been well-documented. Several studies have demon- strated that about 80% of patients experience signiﬁcant over- all tremor relief.4–6 No report of Vim DBS procedure in patients with isolated mixed tremor and intact dopaminergic nigrostriatal system has been documented until now. Interest- ingly, in our patient, Vim DBS produced the clinical disap- pearance not only of the axial tremors along with the postural tremor of the limbs but also of the resting tremor.

In conclusion, we described the ﬁrst reported patient with isolated mixed tremor refractory to medications, who was suc- cessfully treated with Vim DBS. This case suggests that Vim

TABLE 1. *Fahn–Tolosa–Marin tremor rating scale (FTMTRS) before and after DBS*

|  |  |  |  |
| --- | --- | --- | --- |
| FTMTRS | Section A | Section B | Section C |
| Pre-operative | 28 | 15 | 17 |
| Post-operative | 2 | 1 | 0 |
| Follow-upa | 2 | 1 | 0 |

aEvaluation performed after a 12-months period of follow-up.

DBS may be an effective target for the treatment of patients with isolated mixed tremors and intact nigrostriatal system.

## Legends to the Video

Segment 1. Preoperative video clip of the patient showing marked tremor of head, trunk, and lower limbs on standing position. Asymmetric postural and resting tremor of the upper and the lower limbs are also depicted in the video.

Segment 2. Postoperative, stimulator off, video clip show- ing tremor of head, trunk, and lower limbs on standing posi- tion with markedly asymmetrical postural tremor of upper and lower limbs.

Segment 3. Postoperative, stimulator on, video clip: head, trunk, and lower limbs tremor on standing along with resting and postural tremor of the upper and lower limbs completely disappeared.

Segment 4. At the follow-up visit, 12 months after sur- gery, stimulator off, video clip showed tremor of head, trunk, and four limbs, predominant on the right side.

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*Movement Disorders, Vol. 25, No. 2, 2010*

### 250 LETTERS TO THE EDITOR

Segment 5. At the follow-up visit, 12 months after sur- gery, stimulator on: patient showed no tremor in her four limbs, trunk, and head.

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Author Roles: S. Paglionico: Organization and execution of research project, writing of the ﬁrst draft, review and cri- tique of the manuscript; G. Arabia: Execution of research pro- ject, review and critique of the manuscript; A. Lavano: Orga- nization of research project, review and critique of the manu- script; M. D. Rose: Review and critique of the manuscript; D. Pirritano Organization of research project, review and critique of the manuscript; A. Quattrone: Conception and organization of research project, review and critique of the manuscript.

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## References

1. Ceravolo R, Antonini A, Volterrani D, et al. Predictive value of nigrostriatal dysfunction in isolated tremor: a clinical and SPECT study. Mov Disord 2008;21:2049–2054.
2. Lyons KE, Pahwa R. Deep brain stimulation and tremor. Neuro- therapeutics 2008;5:331–338.
3. Starr PA, Vitek JL, Bakay RA. Deep brain stimulation for move- ment disorders. Neurosurg Clin N Am 1998;9:381–402.
4. Benabid AL, Pollak P, Gervason C, et al. Long-term suppression of tremor by chronic stimulation of the ventral intermediate tha- lamic nucleus. Lancet 1991;337:403–406.
5. Ondo W, Jankovic J, Schwartz K, et al. Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson’s disease tremor. Neurology 1998;51:1063–1069.
6. Koller WC, Lyons KE, Wilkinson SB, Troster AI, Pahwa R. Long-term safety and efﬁcacy of unilateral deep brain stimulation of the thalamus in essential tremor. Mov Disord 2001;16:464–468.

# Epileptic Lingual Myoclonus Associated with Cavernoma

Video 

Episodic lingual movements have been reported in associa- tion with chronic epilepsy, head trauma, and brainstem ische-

Potential conﬂict of interest: Nothing to report.

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*Movement Disorders, Vol. 25, No. 2, 2010*

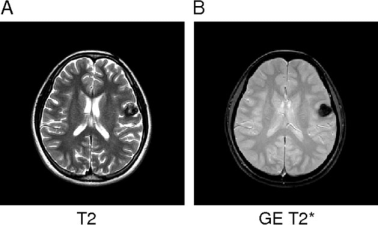
mia.1–3 Cavernous angioma (cavernoma) is a highly epilepto- genic type of vascular malformation in the central nervous system, causing mainly focal epileptic seizures with or with- out secondary generalization in about a half of all patients with cavernoma.4 Antiepileptic agents can adequately control seizures in 60% of cavernoma patients. This report describes a case of left frontal cavernoma presenting as epileptic lin- gual myoclonus.

A 16-year-old girl with no history of neuroleptic drug use experienced sudden onset of episodic involuntary tongue movements for 2 days. The episodes occurred about ten times per day, and each lasted less than 30 sec. The episodes were characterized by involuntarily opening of her mouth, which would immediately reopen whenever she tried to close it. She videotaped her tongue movements by cell phone. Most of the episodes showed isolated tongue involvement and were char- acterized by repetitive contractions of the entire tongue at a frequency of about 5 Hz (video). Two worst episodes involved severe tongue contractions with right facial numbness and twitching. Although she remained alert during the episodes, her impaired tongue movements prevented her from speaking and swallowing normally. Her general physical examination was unremarkable. Neurological examination revealed no cra- nial nerve dysfunction, limb weakness, or somatic or cortical sensory loss. Her deep tendon reﬂexes were normal, and the plantar reﬂexes were ﬂexor bilaterally. Her tandem gait was normal, and no other cerebellar signs were noted.

Brain magnetic resonance imaging (MRI) disclosed a 1.4 3 1.2 3 1.1 cm mixed inhomogenous signal intensity nodu- lar lesion with popcorn appearance over the left side poste- rior frontal region (Fig. 1). This nodular lesion was character- ized by peripheral hyposignal intensity on T2-weighted imag- ing and with a blooming effect on gradient-echo T2\* imaging. Postcontrast T1-weighted imaging revealed minimal enhancement. These imaging ﬁndings suggested cavernous angioma. Interictal electroencephalography (EEG) showed transient synchronized sharp waves over bilateral frontal regions with the right side predominance. She responded very well to treatment with topiramate 25 mg twice daily with complete resolution of the events. She opted to discon- tinue the topiramate after 6 months and 20-month follow-up revealed no further episodes of abnormal tongue movement.

Various involuntary tongue movements described in the literature include fasciculations, tremor, myoclonus, dyskine- sia, dystonic spasm, and undulating hyperkinesias.2,5,6 Iso- lated lingual myoclonus is very rare. It usually presents con- tinuously rather than episodically and has been reported in association with head trauma, encephalitis, and Arnold-Chiari malformation.7 The patient in the current case presented with episodic lingual myoclonus with repetitive, tongue contrac- tions with occasional facial involvement, which suggested a seizure disorder. Brain MRI revealed a cavernoma over the left posterior frontal region, which corresponds to the tongue motor area of the motor cortex. Interictal EEG also revealed transient synchronized sharp waves over bilateral frontal regions. The involuntary tongue movements responded well to antiepileptic treatment. The above clinical features indi- cated an epileptic origin. Due to bilateral innervation of the tongue muscle, a unilateral hemispheric lesion can cause lin- gual myoclonus. A case of episodic lingual myoclonus reported earlier revealed no evidence of pathology.8 EEG in that case revealed no concomitant abnormalities. Paroxysmal

### LETTERS TO THE EDITOR 251

ception, Organization; Manuscript: Review and Critique; Chieh- Hsun Lee: Research project: Conception; Manuscript: Review and Critique.

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FIG. 1. T2WI of brain MRI showing mixed signal intensity nodular lesion with peripheral hypointensity and with popcorn appearance over the left posterior frontal region (A). A ‘‘blooming effect’’ with gradient-echo sequences is visible (B).

rhythmic wavelike tongue movements have also been reported in three children with chronic epilepsy.1 Their tongue movements varied in frequency (2, 6, and 3 Hz) and involved the middle and posterior parts of the tongue. The movements occurred mainly during sleep and responded poorly to medication. These episodes were accompanied by desynchronization of the EEG. The authors in that case attributed the paroxysmal lingual movements to an unusual form of subcortical seizures.

In summary, the tongue movements in this patient with ep- ileptic lingual myoclonus associated with a cavernoma were effectively controlled by a 6-month course of an anticonvulsant drug. At 20-month follow-up, no recurrence was noted. Lingual myoclonus is a rare presentation of frontal cavernoma.

## Legends to the Video

Segment 1. showing episodic involuntary muscle twitch- ing (frequency ,5 Hz) involving the entire tongue muscle.

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## References

1. Jabbari B, Coker SB. Paroxysmal, rhythmic lingual movements and chronic epilepsy. Neurology 1981;31:1364–1367.
2. Li JY, Lee CH. Episodic tongue hyperkinesias and alternating limb movements associated with basilar artery ischemia. Mov Dis- ord 2009;24:1249–1251.
3. Keane JR. Galloping tongue: post-traumatic, episodic, rhythmic movements. Neurology 1984;34:251–252.
4. Jin K, Nakasato N, Shamoto H, Kanno A, Itoyama Y, Tominaga

T. Neuromagnetic localization of spike sources in perilesional, contralateral mirror, and ipsilateral remote areas in patients with cavernoma. Epilepsia 2007;48:2160–2166.

1. Edwards M, Schott G, Bhatia K. Episodic focal lingual dystonic spasms. Mov Disord 2003;18:836–837.
2. Kim SJ, Lee WY, Kim BJ, et al. Isolated tongue tremor after re- moval of cerebellar pilocytic astrocytoma: functional analysis with SPECT study. Mov Disord 2007;22:1825–1828.
3. Postert T, Amoiridis G, Pohlau D, Hoffmann V, Przuntek H. Epi- sodic undulating hyperkinesias of the tongue associated with brainstem ischemia. Mov Disord 1997;12:619–621.
4. Bettoni L, Bortone E, Chiusi M, Tortorella R, Zanferrari C, Mancia D. Isolated episodic lingual myoclonus. Eur Neurol 1999;41:118–119.

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