

L E T T E R S : N E W O B S E R V A T I O N S

Reversible Parkinsonism Due to Involvement of Substantia Nigra in Epstein-Barr Virus Encephalitis

Although the prevalence of Epstein-Barr Virus (EBV) infection in general population is high, it is uncommon that EBV infection causes Parkinsonism, especially injuring sub- stantia nigra directly. We report a case of reversible Parkin- sonism due to involvement of substantia nigra in EBV- related encephalitis.

Case Report

A 24-year-old female teacher presented with fever, head- ache, and vomiting. Then an akinetic-rigid syndrome with tremor developed several days later. There was no family or personal history of movement disorders or other neurologi- cal or psychiatric diseases. Exposure to toxic substances or illicit drugs was denied. The cerebrospinal ﬂuid (CSF) exami- nation showed normal chlorine and glucose content, but there were 50 white blood cells per cubic millimetre and slightly elevated protein content. CSF culture did not grow any organisms. Immunoglobulin M (IgM) levels of anti- EBV–viral capsid antigen (VCA) were remarkably increased in serum and CSF. IgG levels of anti-EBV-VCA were increased in serum but not detectable in CSF. Anti–Epstein- Barr nuclear antigen (EBNA) antibodies were not detectable in either serum or CSF. Magnetic resonance imaging (MRI) showed bilateral substantia nigra lesions on admission. After a 2-month treatment with Madopar, the patient recovered completely without any sequelae. Madopar was slowly tapered off and withdrawn. A repeated MRI after 3 months showed resolution of the lesions (Fig. 1).

Discussion

This patient ﬁrst presented with fever, headache, and vom- iting, followed by an akinetic-rigid syndrome with tremor developing several days later. Clinical, historical, and investi- gative data ruled out iatrogenic, toxic, genetic, and other secondary causes. Although no virus has been isolated from our patient, we believe that she had postencephalitic Parkin- sonism, as suggested by a history and serologic and CSF evidence. The MRI showed isolated involvement of the sub-

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stantia nigra and no lesions or signs of demyelination else- where in the brain; thus, it was conﬁrmed that damage to the substantia nigra alone could produce clinical features of PD. Although several viruses are known to cause Par- kinsonism,1 it is uncommon that a virus could have pro- duced lesions predominantly in the substantia nigra and have caused reversible Parkinsonism. Such selective lesions have demonstrated with toxins such as 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine (MPTP).2 However, the current study demonstrates the capability of a virus to do so. Hsieh et al.3 reported the case of a boy who presented with reversible Parkinsonism as the major symptom of EBV encephalitis. Brain single-photon emission computed tomography (SPECT) showed diminished perfusion in the region of the right caudate nucleus and no abnormalities in substantia nigra. Roselli et al.4 also reported a case of reversible Parkinsonism associated with EBV encephalitis and antineuronal antibodies detected in a human neuro- blastoma cell line, which suggests that an autoimmune mechanism may play an important pathophysiological role. However, MRI showed no abnormalities in substan- tia nigra in these 2 cases, which was different from our case. Our observation indicates a direct acute neurotropic effect of EBV on nigral dopaminergic cells. The patient showed a substantial response in the acute phase to dopa- minergic medication. During the treatment, this patient did not develop L-dopa–related dyskinesias or wearing off. We will follow this patient to observe whether she devel- ops PD later.

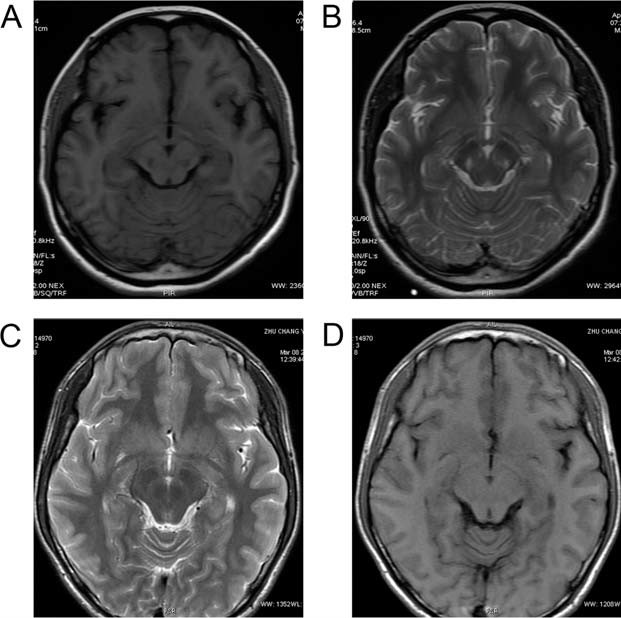


FIG. 1. MRI showed symmetric (A) hypointensity signal on T1- weighted imaging and (B) hyperintensity signal on T2-weighted imag- ing in bilateral substantia nigra on admission. A repeated MRI after 3 months showed resolution of the lesions on (C) T2-weighted imaging and (D) T1-weighted imaging.

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In conclusion, our report indicates that EBV infection can injure substantia nigra directly and cause reversible Par- kinsonism. Nevertheless, given the high prevalence of EBV infection in the general population, EBV testing can be worthwhile in acute-onset movement disorders, especially those manifesting with Parkinsonism.

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## The New Bradykinesia Akinesia Incoordination (BRAIN) Test: Preliminary Data from an Online Test of Upper Limb Movement

The Bradykinesia Akinesia Incoordination (BRAIN) test is computer software based on the alternate ﬁnger tap test.1–3 It detects motor features of Parkinson’s disease (PD) and corre- lates with the ‘‘gold standard’’ Uniﬁed Parkinson’s Disease Rating Scale (UPDRS).2,3 Users alternately tap 2 keys, 15 cm apart on a standard U.S. or U.K. computer keyboard, as fast and accurately as possible, for 60 seconds. The original ver- sion ran in MS-DOS and testing was performed observed, under experimental conditions.2,3 We have produced a new online version of the BRAIN test, written in JavaScript, that can be self-administered in all mainstream Internet browsers. Data are stored in a secure online database.

Nineteen PD patients (UK Brain Bank Criteria) from the Movement Disorder Clinic at the Royal London Hospital consented to participate. Age (mean 67 years), disease dura-

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tion (mean 9.7 years), hand dominance (17 right-handed), medication (16 on L-dopa, 2 on dopamine agonist monother- apy, 1 newly-diagnosed), motor ﬂuctuations (present in 10) and *on/off* status (10 tested while *on*) were recorded. Patients followed on-screen instructions and were not assisted. Both hands were tested for each patient (total tests

¼ 38). Patients were examined according to the motor sec- tion of the UPDRS. Full ethical approval was granted. Statis- tics were performed in GraphPad Prism V5 for Windows. Descriptive statistics and normality testing were performed for all variables. Logarithmic transformations were made where necessary to normalize the data.

The BRAIN test reports 4 variables: kinesia score (KS), number of alternating key taps in 60 seconds; akinesia time (AT), mean dwell time on each key in milliseconds (ms); dysmetria score (DS), weighted index using the number of incorrectly hit keys corrected for speed; and arrhythmia score (AS), variance of the time interval between keystrokes. Our preliminary results give the following means (with 25th and 75th percentiles) for PD patients (n ¼ 38 tests): KS 91.6 taps (73.5, 110.8); AT 169 ms (86, 237); DS 2.88 (2.39,

3.34); and AS 4.45 (4.17, 4.79).

In the previous version of the BRAIN test, the variable that correlated best with the UPDRS was KS. Using 2-tailed Pearson’s tests and linear regression on the current data, sig- niﬁcant correlations were seen between UPDRS and KS, and component UPDRS scores and KS (Fig. 1A–E). These corre- lations are comparable to those seen with the previous, observed version of the BRAIN test.2

KS scores were analyzed for number of taps in the ﬁrst 30 seconds and last 30 seconds of the timed minute, in test runs that had low DS scores (ie, most accurate, n ¼ 14). There was no difference in the mean number of taps (43.6 and

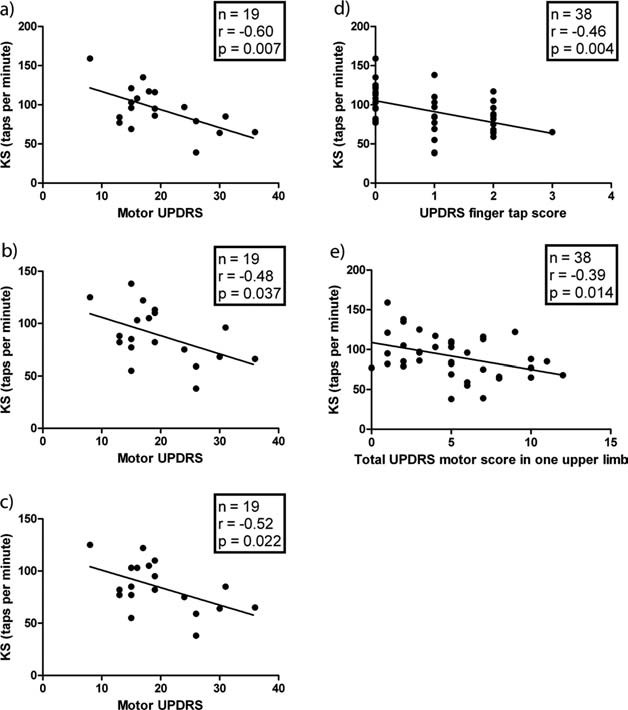


FIG. 1. Correlation between total UPDRS motor score and KS in dom- inant hand (A), nondominant hand (B) and most affected hand (C). Correlation between finger tapping score and KS (D) and total UPDRS motor score in 1 upper limb and KS (E).

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44.0 taps, respectively, paired *t* test, *P* ¼ 0.74). This obser- vation supports the future use of a 30-second test.

The BRAIN test is a quick and now widely available objec- tive test of upper limb movement, making it an attractive option for use in the outpatient clinic and in clinical drug tri- als. We are validating this online test to conﬁrm the normal range of the 4 variables in PD and matched controls, and to evaluate whether AT, DS, and AS correlate with disease sever- ity scales. We will also further develop the BRAIN test to op- erate with other language-dependant keyboard layouts (non- U.S., non-U.K.) to enable more widespread use. The BRAIN test can be found at [http://www.predictpd.com/token.](http://www.predictpd.com/token)

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## Glucocerebrosidase Gene Mutations Are Associated with Parkinson’s Disease in Russia

Mutations in the gene encoding glucocerebrosidase (*GBA*), the enzyme deﬁcient in the lysosomal storage disor- der Gaucher disease (GD), have been associated with Par-

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kinson’s disease (PD) in different ethnic populations.1,2 To date, almost 300 mutations have been identiﬁed in the *GBA* gene, of which the N370S, L444P mutations are the most common.1 At the same time the N370S and L444P variants are the most frequent mutations in the *GBA* gene among GD patients in Russia, accounting for 45% and 23% of the mutant alleles, respectively.3 *GBA* mutation frequency among PD patients in Russia has not yet been investigated.

Here we examined a possible association of L444P, N370S mutations with PD in Russia. The study was approved by the local ethics committee. The data set was composed of 330 unrelated PD cases (mean age, 63.8 6 9.8

years) and 240 controls (mean age, 67.7 6 8.8 years). All subjects were residents of the northwestern region of Russia. One hundred patients had familial PD (mean age, 62.7 6 10.3 years). Eighty-ﬁve patients had early-onset PD (::;50 years old): mean age, 55.5 6 11.1 years; mean age of onset,

43.6 6 5.8 years. To screen N370S, L444P mutations in patients and controls, pair primers and corresponding restriction enzymes were used as previously described.4 All found mutations were veriﬁed by direct sequencing of PCR products. Mutation frequencies in patients and controls were compared using chi-square adjustment. Odds ratios with 95% conﬁdence intervals were calculated to test the associa- tion between the *GBA* mutations and PD.

The distributions and association of *GBA* mutations in patients and controls are shown in Table 1. Heterozygous *GBA* mutations were detected in 9 PD patients (2.7%) and 1 subject in the control group (0.4%); *P* ¼ .038. The L444P mutation was more common in our sample of PD patients than the N370S, as was previously shown for other non-Jew- ish cohorts.1 Inversely, the N370S mutation dominated among GD patients in Russia.3 To date, several studies have reported full *GBA* sequencing, estimating the odds ratio for carrying a *GBA* mutation in a subject with PD as 5.43 (95% CI, 3.89–7.57),2 which is compatible with the sixfold increase of PD in L444P, N370S carriers revealed in our study.

Most published studies speciﬁcally investigated sporadic PD. In our study we showed the increased frequency of the L444P mutation in familial PD. The association of *GBA* var- iants with familial PD was also reported in the PROGENI study.5 It was established earlier that parkinsonism associ- ated with a *GBA* mutation appears to phenotypically resem- ble sporadic PD, but an early disease onset was reported.1 In our study the frequency of the L444P mutation in patients with early-onset (::;50 years old) PD was the highest among the studied groups.

In summary, we have demonstrated that *GBA* L444P, N370S mutations are found in Russian PD patients at the same frequencies as mutations in the *LRRK2* gene.6,7 Our data indicate that the *GBA* L444P, N370S mutations are genetic susceptibility factors for Parkinson’s disease in Russia.

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### Table 1. Distributions and association of L444P, N370S *GBA* mutations in patients and controls

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *GBA* mutations | All PD patients (n ¼ 330) | Early onset—before 50 years old (n ¼ 85) | Family history (n ¼ 100) | Controls (n ¼ 240) |
| L444P  N370S | 6 (1.8%)  3 (0.9%) | 5 (5.9%)  14.9 (2.9–77.0), *P* ¼ .001a  0 | 3 (3.0%)  7.4 (0.4–156.9), *P* ¼ .044a  0 | 1 (0.5%)  0 |
| L444P þ N370S | 9 (2.7%) | — | — | — |

6.7 (1.05–42.4), *P* ¼ .038a

aOdds ratio (95% conﬁdence interval), *P* value.

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## A Stimulus-Sensitive Tic Disorder Characterized by Echophenomena and Coprolalia

The coexistence of echopraxia, echolalia, coprolalia and force obedience were ﬁrst studied by George Beard and la- beled as the ‘‘Jumping Frenchmen’’ of Maine.1 Similar but culturally distinct phenomenon was later described from Siberia (miryachit)2 and in Malayian women (latah).3 Gilles de la Tourette4 described ‘‘maladie des tics convulsifs’’ and considered this new disorder to be similar in causation to the culturally determined startle syndromes. More recent studies have distanced these disorders from Gilles de la Tourette syn- drome despite the publication of some cases with stimulus- induced tics5 and considered them to be factitious, psycho- genic, or psychotic in origin.6 It was later proposed that there is a universal tendency to exaggerated startle in some individ- uals, which may be more or less exaggerated.7

Our patient was a 41-year-old man from Istanbul, whose symptoms began at the age of 8 years shortly after a rat had jumped onto him. Following this frightening episode, he reacted with tic-like grimaces, neck turning to the left, and the utterance of a single stereotyped obscenity every time he looked at an animal, someone uttered the name of a furry animal, or someone used the word furry in conversation. He also developed severe echopraxia, which he could only brieﬂy suppress voluntarily and at the expense of chest pain. He involuntarily concentrates on the gestures of the person he talks to, rather than the content of the conversation. He cannot watch television because he becomes extremely ex- hausted by echopraxia. There were no spontaneously occur- ring tics and no forced obedience.

He completed primary school with difﬁculty and experi- enced great stress during military service. He was married, but divorced due to his imitation behaviors. He was a

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security guard at night to avoid social contact, but was then offered a well-paid job by a rich employer to entertain clients with his antics. He refused treatment despite having a myo- cardial infarction after pronounced teasing by his neighbors. He had never received psychotropic medication including neuroleptics. There is no family history for tics, Tourette’s syndrome, or any other psychiatric and neurologic disorder.

The neurological examination was normal, except he dis- played echopraxia, echolalia, and coprolalia (see Video). He displayed a short startle response upon auditory or tactile stim- ulus, and after the startle he imitated behavior, shouting or clapping, or touching the person who touched him in the ﬁrst place. He had severe obsessive-compulsive disorder, depression, claustrophobia, and nyctophobia; but there was no evidence of schizophrenia and he had rational insight into his behavior.

We described this patient as ‘‘huylu’’ of Turkey (which means tetchy). We believe that he has a neuropsychiatric dis- order akin to culturally related startle syndromes and stimu- lus-induced tics. Because of the striking imitation behavior and echophenomena, stimulus sensitivity to animals domi- nating the clinical picture, and the lack of abnormal move- ments spontaneously, under situations of stress or boredom, we think this condition is not a variant of Gilles de la Tour- ette syndrome, but much more closely linked to latah and Jumping Frenchmen.

# Video Legend

Video: The patient displayed echopraxia, echolalia, and coprolalia upon stimuli given by our staff. In segment 1, the patient tries to duplicate every movement made by our staff. In segment 2, the television is turned on, and the patient ﬁrst shows an attempt to imitate what he sees; however, he can- not duplicate many movements and shows signs of anxiety and avoids looking at the screen. In segment 3, the patient immediately repeats the name of a furry animal pronounced by the doctor, and then swears a few times. He uses the same swearing words each time, and turns his head to the left with mouthing and anxiety.

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## Generalized Dystonia, Athetosis, and Parkinsonism Associated with *FOXG1* Mutation

FOXG1 haploinsufﬁciency is a rare cause of complex de- velopmental encephalopathy due to de novo intragenic mutations of the Forkhead box G1 (*FOXG1*) gene, large deletions encompassing the gene, or disruption of *cis*-regula- tory elements.1 The typical FOXG1 syndrome, a key differ- ential diagnosis of Rett syndrome, is one of early-onset severe encephalopathy with microcephaly, and hand and tongue stereotypies. Less than 10% of the FOXG1 patients are able to walk.1 Mixed hyperkinetic, early-onset, move- ment disorders are also a hallmark of the syndrome. They are characterized by various combinations of chorea, dysto- nia, and athetosis. Clinical spectrum and disease’s course in adulthood are poorly known.1–3

A 38-year-old female had no familial history of neurologic or psychiatric disorder. Pregnancy, delivery, and perinatal period were normal. She had severe psychomotor retardation from age 3 months. Microcephaly was noted from age 11 months (-2 standard deviations [SD]) and gradually wors- ened. She walked at age 5 years and never acquired lan- guage. Social interactions were very poor. She had pharmacoresponsive epilepsy with tonic-clonic seizures and stereotypies since childhood. Around the age of 30 years, according to the mother, although the date of onset could not be veriﬁed, she developed dyskinetic movement disorders with gradual worsening of walking difﬁculties. At age 38, she was treated with valproate (for 20 years) and lamotri- gine (for 2 years) for epilepsy. She had microcephaly (head circumference -3.5 SD), and convergent strabismus. She had stereotypies with frequent rubbing/twiddling hand move- ments and occasional episodes of trunk rocking (see Video). She also had generalized dystonia with predominant cranio- facial involvement, athetoid movements of the 4 limbs, and akinetic-rigid parkinsonism without tremor (see Video). There was no manifestation of vegetative dysfunction. At the last follow-up at age 41 years, the patient could still walk unaided. Brain magnetic resonance imaging (MRI) showed simpliﬁed gyral pattern and reduced white matter volume (Fig. 1). Dopamine transporter imaging with 123I-FP-CIT (DaTSCAN) showed a moderate asymmetrical reduction in striatal uptake predominating in putamina. Array compara- tive genomic hybridization found no chromosomal abnor- mality and sequencing of the *MECP2* gene was normal. Molecular studies identiﬁed a new mutation c.610C>T in

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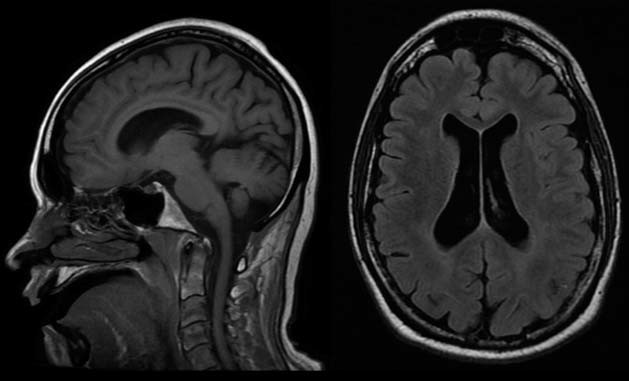


FIG. 1. Axial and parasagittal brain MRI showing frontal hypogenesis, simplified gyral pattern, and globally reduced white matter volume. MRI, magnetic resonance imaging.

*FOXG1*, resulting in the p.Leu204Phe change at the amino acid level.

The *FOXG1* mutation was absent in her mother but its de novo origin could not be ascertained, because of the father’s death. However, its causative role is highly proba- ble: (1) it lies in the functionally critical DNA-binding fork- head domain of the protein; (2) it involves a residue highly conserved in different species; and (3) it was never found in 200 control females.

Four adult FOXG1 patients have been previously reported (aged 18–31 years).1–3 None of them had been able to walk and there is no detailed information on the characteristics and course of their movement disorders. Our patient is the oldest reported FOXG1 case, which conﬁrms that prolonged survival into adulthood is possible. She has original pheno- typic characteristics: (1) she was able to walk, accounting for a rare ‘‘mild’’ phenotype of the disorder; (2) dystonia and athetoid movements started later in life than in other reported FOXG1 patients1–5; (3) she had late-onset a kinetic-rigid parkinsonism similar to what has been reported in patients with Rett syndrome.6 Antiepileptic drugs might have contributed to the movement disorders, but the absence of a temporal link between drugs intake and their develop- ment, and the DaTSCAN abnormalities do not favor this hy- pothesis. Although we cannot exclude a co-occurrence of early-onset Parkinson’s disease and FOXG1 syndrome, our ﬁndings, based on this single case, suggest that dysfunction of the nigrostriatal pathway can result from *FOXG1* muta- tions. A similar alteration has been evidenced in RTT patients.7

This report further expands the clinical spectrum of *FOXG1* mutations. It also emphasizes the diagnostic value of movement disorders including dystonia, athetosis, and/or parkinsonism associated with stereotypies, in adult patients with early-onset encephalopathy and microcephaly.

# Legends to the Video

Video: Mixed movement disorders due to FOXG1 syndrome.

Segment 1. The patient is able to walk unaided. Note the dystonic posture of the 4 limbs (distal more than proximal).

Segment 2. The dystonic posture of the upper limbs inter- feres with voluntary movements. Note the athetoid move- ments of the hands and feet.

Segment 3. Note the severe orofacial involvement with mobile dystonia.

Segment 4. Rubbing and twiddling hand stereotypies.

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L E T T E R S : N E W O B S E R V A T I O N S

## Dystonia in Mitochondrial Spinocerebellar Ataxia and Epilepsy Syndrome Associated with Novel Recessive POLG Mutations

Mutations in the polymerase c (POLG) gene cause a growing spectrum of autosomal dominant and recessive phenotypes. Chorea, myoclonus, ataxia, and parkinsonism can be observed; dystonia has been rarely described.1 We present a girl with mitochondrial spinocerebellar ataxia and epilepsy (MSCAE)2 who developed dystonia and is com- pound heterozygote for a novel combination of POLG mutations.

Our patient presented elsewhere at age 15 years with gen- eralized epilepsy and mild long-standing learning difﬁculties requiring special education. While taking valproate, she developed acute liver failure. A mitochondrial disorder was suspected in light of an older brother with infantile-onset seizures and developmental delay who died at age 18 months from valproate-associated liver failure. Laboratory investigations, including muscle biopsy for respiratory chain enzymes and mitochondrial DNA analysis, were normal. Nuclear DNA genetic analysis revealed compound hetero- zygosity for POLG gene mutation, p.W748S, and pT914P variant. At 16 years, she developed migraines, right-sided epilepsia partialis continua, myoclonic arm jerks, a pancere- bellar syndrome, and progressive cognitive impairment. At 18 years, she noted episodic involuntary right foot in-turn- ing. She developed head, left neck, and left shoulder tremor at age 20 and was referred to our service for treatment.

Examination revealed mild external ophthalmoplegia, sacca- dic pursuit, writhing tongue movements, dysarthria, bilateral dysdiadochokinesis and dysmetria, and poor heel-toe walking. A mild left laterocollis, tremor of the left neck, and a ‘‘no-no’’ head tremor improved with a sensory trick. She had myoclonic and choreic ﬁnger and arm movements, dystonic posturing of hands and feet while walking, and striatal toes, more evident on the right. She had features of mild peripheral neuropathy. Plantar responses were ﬂexor (see Video).

Brain MRI at age 15 (Fig. 1A,B) was compared to age 20 (Fig. 1C,D), which showed persistent thalamic and dentate nuclei T2 hyperintensity and increased signal change in the cerebellar hemispheres. Nerve conduction studies conﬁrmed mild sensory axonal peripheral neuropathy. Surface electro- myography of the left sternocleidomastoid (Fig. 1E) showed a rhythmic 5- to 6-Hz tremor without EEG correlate; back-

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averaging was not performed. The tremor responded to bot- ulinum toxin injections.

Mutations in the POLG gene are an uncommon, but im- portant, cause of movement disorders. Our case demon- strates typical features of MSCAE: adolescent-onset ataxia, myoclonus, migraine, epilepsy, and neuropathy. External ophthalmoplegia and ptosis are reported in MSCAE and other POLG mutations, but tend to occur later.3 Severe liver disease can occur secondary to valproate treatment.4 Our patient’s tremor and cerebellar signs are possibly explained by cerebellar and thalamic involvement seen on MRI. How- ever, the pathophysiology-MRI correlate of dystonia is not clear; it is also possible that other normal-appearing tissue is involved.

Our case demonstrates two novel features: ﬁrst, cervical and limb dystonia, which should be added to the clinical spectrum of POLG1 mutations, and, second, the combina- tion of T419P and W748S mutations, which has been reported in 2 patients with Alpers,5 but not in MSCAE, thereby expanding the MSCAE genotype.

Our case highlights that POLG1 mutations can present relatively late and reminds neurologists to consider

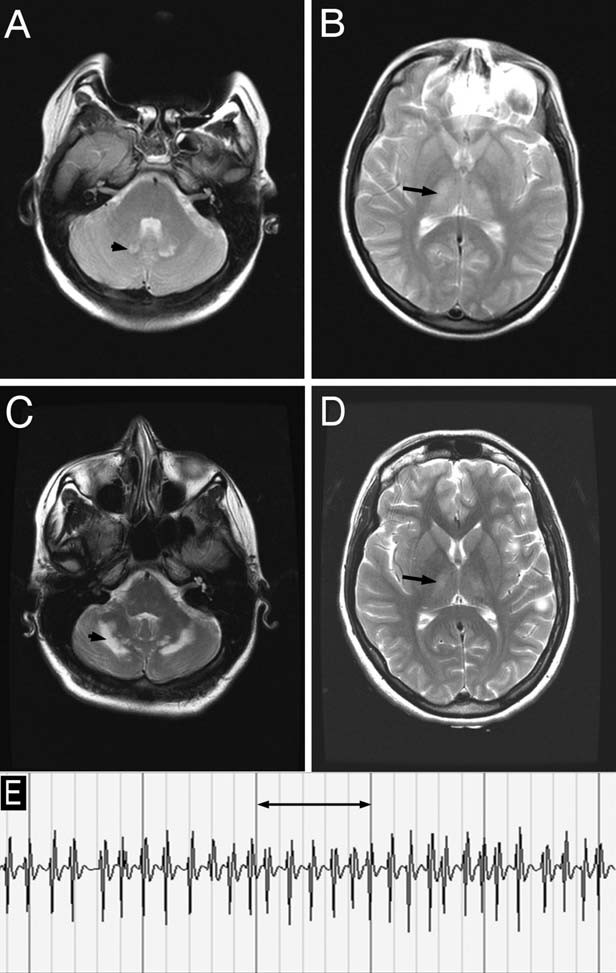


FIG. 1. Axial brain MRI revealing bilateral T2 hyperintense signal in the thalami (arrows) and dentate nuclei (arrowheads) at age 15 years (A, B) and more extensive signal change in the cerebellar hemispheres at age 20 (C, D). Left sternocleidomastoid surface electromyography demonstrating 5- to 6-Hz frequency tremor (E). Double-headed arrow represents 1 second.

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mitochondrial disease in the differential diagnosis of hepatocerebral disorder. Particularly, it emphasizes that POLG1 mutations are associated with movement disor- der, epilepsy, and life-threatening valproate-associated liver failure. Neurologists should be ever mindful of the potential consequences of valproate prescription in this scenario.

# Legend to the Video

The video was taken at age 20 years. Segment 1 demonstrates components of the patient’s pancerebellar syndrome, including dysarthria, dysmetria, and dysdiado- chokinesis. Also visible is her ‘‘no-no’’ head tremor. During ﬁnger-to-nose testing, choreic and myoclonic move- ments are evident in both arms. Segment 2 demonstrates tongue dystonia, further distal arm chorea and myoclonus, and ataxic gait with hand and foot dystonic posturing and striatal toes, more evident on the right. Segment 3 high- lights her left torticollis accompanied by head, neck, and shoulder tremor.

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L E T T E R S : N E W O B S E R V A T I O N S

## Changing to Interleaving Stimulation Might Improve Dystonia in Cases Not Responding to Pallidal Stimulation

For the treatment of medication-refractory dystonia, bilat- eral pallidal deep brain stimulation (GPi-DBS) has proven to be an efﬁcient option. On average, 40%–55% improvement on dystonia rating scales (DRS) can be achieved according to the results of multicenter trials1–3 lasting for years.4 How- ever, a considerable portion (10%–25%)1–3 of the patients experience minimal alleviation despite of good electrode placement. These patients can be regarded as nonresponders to GPi-DBS, deﬁned as having either limited improvement (<25% on DRS) or worsening. In addition to adjusting the amplitude, frequency, or pulse width of stimulation, the elec- trode conﬁguration from the commonly applied single monopolar stimulation mode (1 contact on the electrode is negative) can be changed to either double monopolar stimu- lation (2—usually adjacent—negative contacts on the elec- trode are stimulated with the same amplitude and pulse- width values) or bipolar stimulation mode (1 contact on the electrode is positive) in case of unsatisfactory outcome.5 Although these techniques had been utilized in multicenter trials, nonresponsiveness to GPi-DBS did occur.2 In the pres- ent case series, we report that the recently introduced inter- leaving stimulation mode is superior to single or double monopolar stimulation in 4 patients.

Of 42 consecutive patients with dystonia who underwent GPi-DBS implantation at University of Pe´cs,6 4 patients had limited response 6–12 months after implantation. They received Activa RC generator (Medtronic, Minneapo- lis, MN), which was programmed according to the guid- ance of the German multicenter trial1: Brieﬂy, those contacts were chosen for single monopolar stimulation where the largest acute reduction of dystonic hyperkinesia was achieved or phosphenes were elicited or the postopera- tive brain scans suggested the most optimal position. We applied stable frequency (130 Hz) and pulse width (120 ls) values, whereas amplitude was programmed to the sub- maximal value (0.5 V below the threshold of inducing acute adverse effects). Because the beneﬁcial effects of GPi- DBS may have a protracted appearance, these settings remained unchanged for 6–9 months. In these 4 cases we detected <25% improvement on DRS; therefore, we switched to the monopolar stimulation of an adjacent con- tact using its submaximal amplitude value without further beneﬁt. Subsequently, double monopolar stimulation mode was also tried without any improvements. Finally, we

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This retrospective study was approved by the Regional Ethical Board of the University of Pe´ cs.

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L E T T E R S : N E W O B S E R V A T I O N S

### Table 1. Characteristics of the patients, the applied stimulation parameters and the severity of dystonia

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ID | Age | Sex | Dystonia | Disease duration | Preop DRS | Single monopolar stimulation | DRS during single monopolar stimulation | Double monopolar stimulation | Interleaving stimulation | DRS during interleaving stimulation |
| 1 | 28 | M | Young, | 23 y | 43 | L: Cþ0-, 2.4 V, 130 Hz, | 37 | L: Cþ0-1-, 2.4 V, | L1: Cþ0-, 2.4 V, | 17 |
|  |  |  | rim, segm |  |  | 120 ls  R: Cþ8-, 2.1 V, 130 Hz, |  | 130 Hz, 120 ls R: Cþ8-9-, 2.1 V, | 125 Hz, 120 ls L2: Cþ1-, 3.1 V, |  |
|  |  |  |  |  |  | 120 ls |  | 130 Hz, 120 ls | 125 Hz, 120 ls R1: Cþ8-, 2.1 V, |  |
|  |  |  |  |  |  |  |  |  | 125 Hz, 120 ls R2: Cþ9-, 3.3 V, |  |
| 2 | 16 | F | Young, | 13 y | 40 | L: Cþ0-, 2.0 V, 130 Hz, | 33 | L: Cþ0-1-, 2.0 V, | 125 Hz, 120 ls L1: Cþ0-, 2.0 V, | 9 |
|  |  |  | rim, gen |  |  | 120 ls  R: Cþ8-, 2.15 V, |  | 130 Hz, 120 ls | 125 Hz, 120 ls |  |
|  |  |  |  |  |  | 130 Hz, 120 ls |  | R: Cþ8-9-, 2.15 V, 130 Hz, 120 ls | L2: Cþ1-, 3.3 V, 125 Hz, 120 ls R1: Cþ8-, 2.15 V, |  |
|  |  |  |  |  |  |  |  |  | 125 Hz, 120 ls R2: Cþ9-, 3.45 V, |  |
| 3 | 28 | M | Young, | 12 y | 36 | L: Cþ1-, 2.0 V, | 30 | L: Cþ1-2-, 2.0 V, | 125 Hz, 120 ls  L1: Cþ1-, 2.0 V, | 11.5 |
|  |  |  | rim, segm |  |  | 130 Hz, 120 ls R: Cþ8-, 1.8 V, |  | 130 Hz, 120 ls | 125 Hz, 120 ls |  |
|  |  |  |  |  |  | 130 Hz, 120 ls |  | R: Cþ8-9-, 1.8 V, 130 Hz, 120 ls | L2: Cþ2-, 3.3 V, 125 Hz, 120 ls  R1: Cþ8-, 1.8 V, |  |
|  |  |  |  |  |  |  |  |  | 125 Hz, 120 ls R2: Cþ9-, 3.3 V, |  |
| 4 | 52 | M | Adult, | 10 y | 28 | L: Cþ0-, 2.1 V, | 26 | L: Cþ0-1-, 2.1 V, | 125 Hz, 120 ls L1: Cþ0-, 2.1 V, | 8.5 |
|  |  |  | rim, segm |  |  | 130 Hz, 120 ls R: Cþ8-, 2.3 V, |  | 130 Hz, 120 ls R: Cþ8-9-, 2.3 V, | 125 Hz, 120 ls L2: Cþ1-, 3.4 V, |  |
|  |  |  |  |  |  | 130 Hz, 120 ls |  | 130 Hz, 120 ls | 125 Hz, 120 ls R1: Cþ8-, 2.3 V, |  |
|  |  |  |  |  |  |  |  |  | 125 Hz, 120 ls  R2: Cþ9-, 3.2 V, |  |
|  |  |  |  |  |  |  |  |  | 125 Hz, 120 ls |  |

*Single monopolar stimulation* refers to the unipolar stimulation mode, which was initiated immediately after the primary testing, applying only 1 negative contact on the electrode, whereas the case was positive.

*DRS during single monopolar stimulation:* severity of dystonia assessed by DRS 6–9 months after initiating single monopolar stimulation.

*Double monopolar stimulation:* negative contact of standard stimulation mode and the adjacent (usually the more proximal) contact were programmed to negative and stimulated with the same pulse width, amplitude, and frequency.

*Interleaving stimulation:* negative contacts of double monopolar stimulation were stimulated with different (their submaximal) amplitude values.

*DRS during interleaving stimulation:* severity of dystonia assessed by DRS 2–3 months after the initiation of interleaving stimulation.

Adult, adult onset; C, case; DRS, Burke-Fahn-Marsden Dystonia Rating Scale; gen, generalized; L, left electrode; prim, primary; R, right electrode; segm, segmental; Young, young onset.

applied an interleaving stimulation mode: The contacts of the double monopolar stimulation mode remained nega- tive, but they were stimulated by different (their individual submaximal) amplitude values. (Table 1). The use of this interleaving stimulation resulted in further prompt and considerable improvement without any permanent side effects.

# Conclusions

Most GPI-DBS trials applied a Kinetra generator (Med- tronic, Minneapolis, MN), enabling double monopolar stim- ulation, where both negative contacts were stimulated with the same pulse-width and amplitude values. In these cases,

the lowest threshold for eliciting side effects limited the am- plitude of the common stimulation of both negative con- tacts. However, the recently introduced interleaving mode allows the independent stimulation of 2 contacts with differ- ent pulse-width and amplitude values. Therefore, each con- tact can be stimulated by its individual submaximal amplitude, producing different (presumably larger and more conical) electrical spreading and tissue activation. To our knowledge, this is the ﬁrst case series describing the beneﬁ- cial effects of interleaving stimulation mode in dystonia. This is consistent with its previously demonstrated usefulness for subthalamic stimulation,7 which warrants further research assessing the long-term efﬁcacy and side-effect pro- ﬁle of interleaving GPi-DBS stimulation.

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