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Brief Reports

Huntington's Disease-Like 2 in Brazil—Report of 4 Patients

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Video 

Abstract: **Huntington's disease-like 2 (HDL2) is a neurodegenerative disorder found in people of African ancestry with clinical, radiological, and neuropathological manifestations similar to Huntington's disease (HD). HDL2 is caused by a pathological expansion of CAG/CTG triplets in exon 2A of the *JPH3* gene. We describe four cases of HDL2 from four unrelated families, and discuss their clinical findings. HDL2 should be considered in every patient with an HD-like phenotype who tests negative for the HD mutation, even if African ancestry is not immediately apparent.** © 2008 Movement Disorder Society

Key words: Huntington's disease; *junctophilin 3*; Huntington's disease like

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Since the identification of the causative mutation for Huntington's disease (HD) and the availability of genetic testing, a number of patients have been identified who presented with the core manifestations of HD, but who did not have the expected mutation.[1–3] These patients are classified as having a Huntington disease-like (HDL) disorder.

One of these phenotypically similar disorders, HDL2, affects almost exclusively patients of African ethnic background, and is caused by expansion of CAG/CTG triplets in exon 2A of the *junctophilin 3* (*JPH3*) gene. Expansions greater than 40 repeats cause the disease.[4,5] The junctophilins (JPHs) are proteins which are probably involved in regulation of the intracellular influx of calcium.[6] The mechanism involved in neuronal death due to mutant *JPH3* is unknown but may be related to the generation of RNA inclusions, rather than to the distinct polyglutamine-containing inclusions.[7,8]

We report four HDL2 cases from different families of probable African ancestry.

CASE REPORTS

Case 1

A 48-year-old Black woman developed involuntary movements at age 34, which progressively worsened, impairing her gait and daily activities. At the age of 39 she had developed depression and cognitive slowing. At that time, she was noted to have generalized chorea and dysarthric speech. There were no other abnormalities on neurological examination. Cognitive assessment at age 41 revealed temporal disorientation and mild memory impairment. Haloperidol was prescribed and led to an improvement in chorea which remained stable in the following years, however, her cognitive symptoms worsened gradually until she had severe dementia. There was no family history of chorea, although there were several cases of psychiatric disturbance in both maternal and paternal ancestors. Brain MRI disclosed brain atrophy, mainly affecting the caudate nuclei (Fig. 1A). Genetic testing for HD was negative. Trinucleotide repeat analysis of *JPH3* found alleles of 13/47 (Table 1). No acanthocytosis was found in this or the other cases using routine methodology.

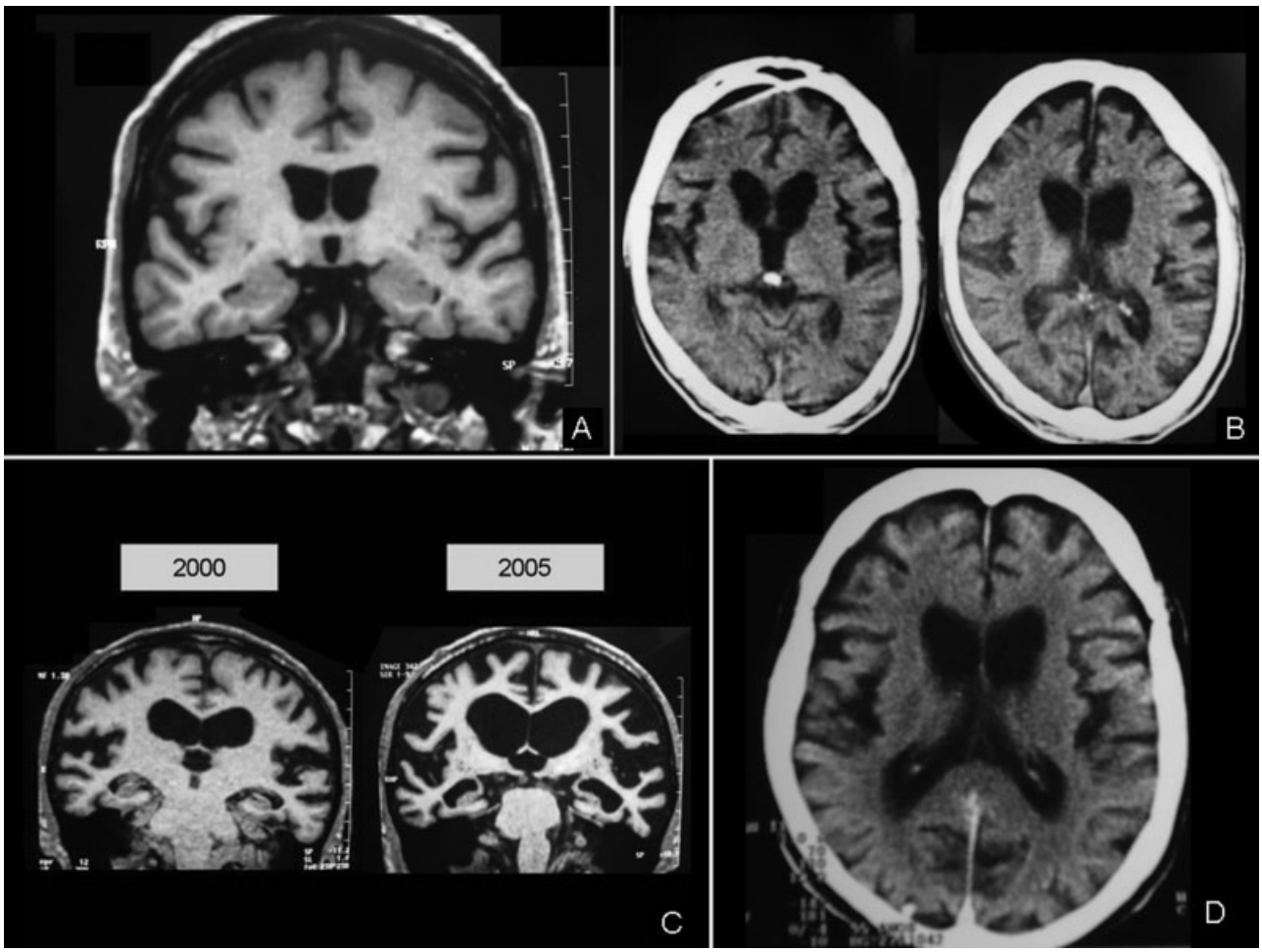

FIG. 1. Neuroimage of HDL2 patients demonstrating brain atrophy particularly affecting the caudate nuclei (A, B, and D). (C) Progression of atrophy over 5 years.

Case 2

A 32-year-old Black man developed involuntary movements at the age of 22. These movements were initially characterized by his family as occasional tics, affecting mainly his arms and face, which progressively became continuous and generalized. At the same time, he was noted to have memory loss and impairment of comprehension. Apart from aggressive behav-

TABLE 1. *Summary of clinical features and CAG repeats of HDL2 patients*

Patient	Age of onset	African ancestry	Movement disorder	Dementia	Psychiatric disturbance	Familiar history	Neuroimaging	CAG repeats
1	34	Present	Chorea	Present	Depression	Psychiatric disturbance	Caudate atrophy	13/47
2	22	Present	Tics? Chorea Dystonia Parkinsonism	Present	Aggressive behavior	Chorea and dementia	Caudate atrophy	17/59
3	60	Present	Chorea	Present	Aggressive behavior	Unknown	Caudate atrophy	16/46
4	48	Probable	Chorea Parkinsonism	Present	Depression Hallucinations	Chorea and dementia	Caudate atrophy	14/48

ior, there were no other psychiatric or behavioral complaints. His mother and maternal grandfather were reported to have similar movements and dementia, ultimately leading to their deaths, although further details are not available. Neurological examination at age 28 revealed moderate cognitive impairment, dysarthric speech, and generalized chorea. There was unstable gait without signs of cerebellar dysfunction. He received haloperidol with partial control of chorea, but this gradually worsened in the following years. At his most recent examination at age 32, there was no chorea, but he had dystonic posturing of the upper limbs, mild rigidity, bradykinesia, severe cognitive impairment, and unintelligible speech. Brain computerized tomography showed generalized atrophy, more visible in the caudate nuclei (Fig. 1B). Genetic testing for HD was negative. Trinucleotide repeat analysis of *JPH3* found alleles of 17/59.

Case 3

A 70-year-old Black man was first seen at age 62 for progressive disturbance of gait and unsteadiness since age 60. At the age of 61, his family noted involuntary movements and 1 year later he developed cognitive complaints and aggressive behavior. His parents were second degree cousins, but further details of family history were not available as he was not in touch with his family from the age of 18. Initial neurological examination revealed generalized chorea and impairment of gait and balance but was otherwise unremarkable. His first brain MRI, at the age of 63, showed moderate generalized atrophy, more pronounced in the caudate nuclei. Five years later follow-up MRI disclosed severe generalized atrophy and almost complete absence of the caudate nuclei (Fig. 1C). From the age of 65 he was bedridden, anarthric, and severely demented. On his last examination there was mild chorea, generalized spasticity, hyperactive deep tendon reflexes, and extensor plantar responses. Genetic testing for HD was negative. Trinucleotide repeat analysis of *JPH3* revealed alleles of 16/46.

Case 4

A 66-year-old White woman developed orolingual chorea at the age of 48, progressing to generalized chorea predominantly affecting the axial musculature. Family history was notable for a similar illness in her father, paternal uncle, and paternal grandmother. Although the family was of remote Spanish/Portuguese origin, her affected paternal grandmother was described as "dark-skinned," suggesting possible African ancestry. By the age of 60, she was wheelchair-bound with less prominent chorea and more bradykinesia. Cognitive symptoms started about the same time as her motor symptoms, characterized by short-term memory deficits, and progressed to severe dementia after about 13 years. Psychiatric manifestations started 3 years after the onset of motor symptoms with depression, social withdrawal, and visual hallucinations. At the last examination, eye movements were severely limited in all directions with markedly slow saccades. Speech was dysarthric and barely understandable with involuntary protrusions of the tongue. She had moderate generalized spasticity with hyperactive deep tendon reflexes and extensor plantar responses. There was severe bradykinesia of rapid alternating movements. No cerebellar signs were noted. She was unable to walk due to akinesia and spasticity. Brain CT demonstrated brain atrophy particularly of the caudate nuclei (Fig. 1D). Genetic testing for HD was negative. Trinucleotide repeat analysis of *JPH3* found alleles of 14/48.

DNA Analysis

JPH3 analysis was performed by sizing fluorescent PCR products encompassing the CTG/CAG expansion site. The PCR products were loaded on 3730 DNA Analyzer and analyzed using GeneMapper software (Applied Biosystems). The number of repeats was calculated by comparison to DNA samples with known number of repeats.

DISCUSSION

These cases presented with a progressive HDL phenotype, and in 3 cases with a family history suggestive of an autosomal dominant disorder (Cases 1, 2, and 4). In the setting of a negative molecular test for HD and probable African ancestry, the diagnosis of HDL2 was considered and molecularly confirmed.[4,9,10]

When Case 4 was initially reported in abstract form,[11] African ancestry was not apparent, but on further questioning her grandmother was reported to be "dark-skinned," presumably indicating African ethnic background. In a recent report, Santos et al.[12] described a Brazilian HDL2 case with apparent European ancestry, but whose molecular analysis showed that the haplotype containing the expanded allele has been found only in Africans. These cases confirm that HDL2 may be diagnosed in apparently Caucasian patients, and emphasize the importance of taking a detailed history of family ethnic origin. Of note, one

case has been reported[13] in a patient of "middle-eastern" background, but further details of ethnic background are not reported.

In HD the parkinsonian phenotype is related to longer trinucleotide repeat expansions, however, this does not appear to be the case with HDL2. Three cases have been reported with the longest expansion found to date—59 repeats. Our Case 2 initially presented with chorea and progressed to a dystonic and bradykinetic/rigid phenotype; another case[14] also presented initially with chorea, and was not reported to develop parkinsonism, although details of follow-up are not available; the son of the Case 2 reported by Greenstein et al. (2007) was parkinsonian from disease onset. Patients with 52 repeats[8] or 57 repeats[10] have been reported who presented with parkinsonism and never developed chorea during their disease course. This suggests that the presence of the choreic or parkinsonian phenotype is independent of the number of CAG/CTG repetitions.

The age of onset of symptoms (22 years) of Case 2 is among the youngest reported to date. As with HD, the age of onset is inversely related to the size of the trinucleotide repeat expansion.[15] Similarly, the age of onset of Case 3 is the oldest reported to date, and he was found to have a trinucleotide repeat expansion at the lower end of the pathological range. However, his rate of disease progression was remarkably rapid, as the disease course usually lasts 10 to 15 years[4] and it is unusual for patients to be bedbound within 5 years of presentation. The reason for this fast progression was not identified.

Cases 1 to 3 were diagnosed from a cohort of 29 HDL patients, defined as a phenotype of progressive chorea, dystonia, myoclonus, or ataxia with cognitive impairment, in whom HD was excluded. The proportion of 10% of HDL cases being diagnosed with HDL2 is higher than in other reports, and is likely to be due to the significant proportion (44.6%) of the Brazilian population being of African descent.[16] A higher percentage of 26% was seen only in black South Africans with an HDL phenotype.[17]

The clinical and neuropathological[8] similarities between HDL2 and HD suggest that they may share pathophysiological pathways. However, in HDL2, in contrast to HD, the phenotypes of parkinsonism or chorea do not correlate with the size of the CAG/CTG repeat expansion, suggesting that another unknown factor may play a role in the clinical expression of disease. In addition to the importance of correct diagnosis for clinical management and genetic counseling, identification of new HDL2 patients may provide insights into the understanding of HD and other trinucleotide repeat disorders.

LEGENDS TO THE VIDEO

Segment 1. Patient 3 presenting dystonic postures in his right hand and face. Lying down, involuntary jerking movements in legs and right shoulder occur.

Segment 2. Patient 4 exhibits involuntary tongue protrusions, excessive eye blinking, head bobbing, hyperactive deep tendon reflexes, and gait apraxia.

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Effects of Dopaminergic Medications on Psychosis and Motor Function in Dementia with Lewy Bodies

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Abstract: **Dopaminergic treatment in dementia with Lewy bodies (DLB) requires balancing risk of worsened psychosis and potential motor benefit. We assessed the effects of increased dopaminergic medication on psychosis and motor function in DLB. We studied 19 subjects fulfilling probable DLB Consensus criteria before and after increased dopaminergic medications. Standard clinical measures included: Thought Disorder score from the Unified Parkinson's disease Rating Scale (UPDRS) Part I, total motor score (UPDRS Part III), and Hoehn–Yahr (H&Y) stage. Motor benefit defined as >10% improvement over baseline UPDRS Part III score, occurred in only one-third of subjects. In this group, worsened hallucinations or psychosis developed in one-third. Considering motor benefit without exacerbation of psychosis as our aim, only 4 DLB subjects (22%) achieved this goal. Our results suggest that dopaminergic medications have limited benefit in DLB because of the low likelihood of motor improvement and the risk of psychosis exacerbation.** © 2008 Movement Disorder Society

Key words: dementia with Lewy bodies; parkinsonism; psychosis; levodopa

Dementia with Lewy bodies (DLB) is characterized clinically by a progressive dementia accompanied by parkinsonism, hallucinations, and fluctuations in cognition and attention.[1,2] Parkinsonism occurs in 65 to 80% of DLB patients at some point during their disease and typically involves greater axial symptoms and less rest tremor as compared with Parkinson's disease.[3–7] Responses to acute challenges and chronic treatment with levodopa (L-dopa) range from no benefit to mild improvement to marked effect.[6,7] Visual hallucinations are present in 50 to 80% of DLB patients and delusions may occur in up to 50%.[8] Use of dopaminergic medications in DLB has been tempered by fears of aggravating psychosis and confusion. Antipsychotic medications have been associated with neuroleptic sensitivity and in severe cases, a neuroleptic malignant-like syndrome.[9] Thus, psychosis poses a particularly troublesome and clinically important problem in DLB. As a result, general clinical practice dictates a "go low and slow" approach to using dopaminergic agents in DLB. To date, the effects of L-dopa on psychosis in DLB have not been systematically assessed. Therefore, we examined the effect of increased dopaminergic medication on psychosis and motor function in a clinical series of DLB patients with parkinsonism.

SUBJECTS AND METHODS

Subjects with DLB were included if they met probable or possible DLB Consensus Criteria[1,2] and underwent increases in dopaminergic medication by their movement disorder's physician, specifically to treat parkinsonism. Subjects with DLB were excluded if adjustments in medications for psychosis or cognition were made simultaneously with dopaminergic medication changes. Subjects with Parkinson's disease dementia were excluded according to the "one-year rule" which classifies subjects as DLB if dementia onset occurs within 12 months of parkinsonism.[1,2] The study was approved by the Rush University Medical Center and Alexian Brothers Neuroscience Institute Institutional Review Boards.

Data were collected prospectively on the DLB subjects and included the following clinical measures: Thought Disorder score from the Unified Parkinson's disease Rating Scale (UPDRS) Part I, the total motor score from the UPDRS Part III, and Hoehn–Yahr (H&Y) stage. Assessments were made before and after increases in dopaminergic medication. Medication changes were made at the discretion of the treating movement disorder physician. On follow-up, decreases from baseline UPDRS motor score >10% were classified as motor benefit. In order to exclude nonhallucinatory events such as sleep fragmentation and vivid dreams, we considered worsened hallucinations and psychosis as Thought Disorder scores that progressed at least one point for subjects with baseline hallucinations or those who developed hallucinations during treatment.

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RESULTS

Subjects

Nineteen subjects were included, all fulfilling probable DLB criteria.[1] At baseline, all subjects had dementia and parkinsonism, and 16 subjects were hallucinators. Sleep disturbances, REM behavior disorder, and fluctuations in cognition were reported in 12 subjects. Baseline characteristics are reported in Table 1. The mean (SD) age at baseline was 74.53 (±4.05) years. The mean disease duration at the time of initial assessment was 4.55 (±2.14) years, range 1 to 9 years. Baseline Mini-Mental State Examination score was 20.5 (±6.04) of 30. The mean interval between initial and follow-up assessments was 3.16 (±1.83) months. The mean daily L-dopa equivalent dose[10,11] at initial assessment was 368.03 ± 234.05 mg. At baseline, L-dopa was used alone in 16 subjects and with additional dopamine agonists in 2 subjects. Antipsychotic medications were used in 6 subjects with a mean daily dose, calculated as chlorpromazine equivalents[12] of 88.89 (±55.44) mg. Of the antipsychotic medications, quetiapine was used in 5 of 6 subjects with a mean daily dose of 72.5 (±43.66) mg and range of 12.5 to 125 mg. Cognitive enhancing medications included cholinesterase inhibitors alone (6 subjects), cholinesterase inhibitors with memantine (1 subject), and memantine alone (1 subject). Doses for antipsychotic or cognitive enhancing medications remained unchanged during the study.

Changes in Psychosis and Motor Function

Dopaminergic medication was increased to treat the subjects' parkinsonism. Only L-dopa was increased (mean follow-up daily L-dopa equivalent dose of 479.47 ± 222.52 mg and mean change of 111.45 ± 74.48 mg); no subject had dopamine agonists increased or introduced. Motor benefit occurred in only 6 of 19 DLB subjects receiving increased L-dopa. In these 6 subjects, mean improvement in UPDRS motor score was −6.42 (±3.98). However, of the 6 DLB subjects who experienced motor benefit, worsened hallucinations and psychosis occurred in 2 subjects. Considering motor benefit without exacerbation of psychosis as our aim, only 22% of DLB subjects achieved this goal.

Because all subjects were at risk for hallucinations or psychosis with increased dopaminergic medication, our primary analysis included all 19 subjects. However, analysis of the 16 subjects with baseline hallucinations achieved similar results. Motor benefit was limited to 6 of 16 subjects, and 2 of these subjects had worsened hallucinations or psychosis. Follow-up data on the 3 subjects lacking baseline hallucinations revealed motor benefit in none. While none developed hallucinations or psychosis at follow-up assessment, 1 subject reported altered dream phenomena.

TABLE 1. *Baseline characteristics of DLB subjects*

Characteristic	Mean ± SD
Age (yr)	74.53 ± 4.05
Gender (M/F)	11/8
Disease duration (yr)	4.55 ± 2.14
Interval follow-up (mo)	3.16 ± 1.83
Mini-Mental State Examination score (of 30)	20.5 ± 6.04
Levodopa equivalents (mg/d)	368.03 ± 234.05
Antipsychotic medications (CPZ equivalents; mg/d)	88.89 ± 55.44
Thought Disorder score from UPDRS (Part I)	1.55 ± 1.28
Total motor score from UPDRS (Part III)	37.64 ± 10.67
H&Y stage	3.29 ± 0.75

DISCUSSION

Our study suggests that clinicians should remain cautious about increasing dopaminergic medications in DLB. Motor benefit was modest, and one-third of the subjects in whom there was motor benefit had worsened hallucinations and psychosis. In a practical clinical setting where our goal was to improve parkinsonism without exacerbating or inducing hallucinations or psychosis, our success rate was only about 20%. Our finding of motor benefit in about one-third of DLB subjects is consistent with previous DLB studies that report an acute L-dopa response in 36%,[6] but is less robust than the 75% with moderate to marked improvement after chronic L-dopa reported in another study.[7] Similar to our study, these motor improvements occurred using relatively small doses of L-dopa, ranging from 103.3 mg (±51.6) in acute challenges[6] to mean total daily doses of 286 mg (±105)[13] to 323 mg (±182)[6] in chronic evaluations. These L-dopa doses are consistent with the general prescribing practice, which also favors L-dopa in cognitively impaired parkinsonian patients. Only L-dopa was increased in our study, and in the 2 subjects receiving L-dopa and dopamine agonists at baseline, agonist doses remained stable during the assessment period.

Our study has several strengths and expands on previous investigations of L-dopa effects in DLB. We include a well-characterized cohort with all subjects fulfilling probable DLB criteria, thereby improving diagnostic accuracy. In addition, our study complements and extends previous studies on chronic L-dopa treatment and tolerability in DLB,[6,13] demonstrating

limited effect of increased L-dopa on motor function and supporting concerns for psychosis exacerbation. Furthermore, our study is the first to focus specifically on changes in hallucinations and psychosis with dopaminergic medications in DLB. A previous study on L-dopa effects on cognitive and behavioral function in DLB reported no change in the total Neuropsychiatric Inventory score after 3 months; however, the total score reflects measures of hallucinations and delusions combined with other mood and behavioral disturbances. We also have utilized rating scales, medication adjustments, and dopaminergic medication doses that reflect a "real world," clinical approach which may be useful to other clinicians who treat DLB patients in daily practice.

We acknowledge several limitations to our study, including the open-label design, small number of subjects, and relatively low doses of dopaminergic medication. To date, we are unaware of any double-blind, placebo-controlled studies of dopaminergic medications in DLB, and open-label studies of L-dopa in DLB vary in sample size, ranging from 7 to 27 subjects.[6,7,13] Dopaminergic doses and changes were similar to those used in other DLB studies and our clinical experience. We cannot exclude, however, greater motor responses, or perhaps even worse Thought Disorder score changes, with higher doses. We recognize that our subject group was mixed with respect to baseline psychosis and treatment with antipsychotics or cognitive enhancers. Despite this, similar results were obtained even when we excluded the 3 nonhallucinating subjects. We cannot determine potential effects of the antipsychotics or cognitive enhancers on clinical measures or interactions with each other or L-dopa. Since our study included only DLB subjects who underwent increases in dopaminergic medication, it also would be of interest to assess DLB subjects in whom dopaminergic medications were decreased, and this is currently underway. Furthermore, since DLB is a progressive and sometimes fluctuating disorder, distinguishing between treatment effects and the natural history of DLB may be difficult.[14] Lastly, while the UPDRS motor score is sensitive to change, the Thought Disorder score may not adequately capture small degrees of clinical change or have ideal psychometric properties to measure clinical response and change overtime.[15] However, scales such as the Thought Disorder scale and H&Y staging are currently used, quick to administer, and readily accessible in clinical practice. Development of a new scale for Parkinson's disease psychosis has been proposed recently,[15] and once developed may prove to be useful in DLB.

Future prospective studies with larger number of DLB subjects, greater increases in dopaminergic medication doses, and more detailed psychosis scales will be needed to further assess the effects of dopaminergic medication changes on DLB psychosis and motor function.

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Effect of Thalamotomy on Focal Hand Dystonia in a Family with DYT1 Mutation

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Video 

Abstract: **We report the clinical and molecular features of a family with focal hand dystonia caused by DYT1 mutation. Four members of a family who underwent thalamotomy showed a marked and sustained therapeutic benefit that lasted for up to 12 years without recurrence of dystonia or any significant surgical complication. The hand dystonia caused by DYT1 mutation may be successfully managed by thalamotomy.** © 2008 Movement Disorder Society

Key words: dystonia; thalamotomy; DYT1

Dystonia is a neurologic syndrome characterized by involuntary, sustained, patterned, and often repetitive muscle contractions of antagonist muscles, causing twisting movements and abnormal postures.[1] A 3 base-pair (GAG) deletion in exon 5 of the TOR1A (DYT1) gene is responsible for most cases of early-onset generalized dystonia and plays a role at least in a proportion of adult-onset focal dystonias.[2,3] The phenotypic spectrum of DYT1 dystonia includes generalized dystonia, patients with DYT1 mutation may present with writer's cramp, cervical dystonia, or life-threatening dystonia.[4–7]

Medical therapies offer variable but usually limited improvement of symptoms, and surgery may be often helpful in refractory cases with dystonia. Currently, deep brain stimulation (DBS) of the globus pallidus is widely used for the surgical treatment of dystonia.[8–10] However, ablative surgery, such as thalamotomy or pallidotomy, may be a viable alternative to DBS in some dystonia patients.

We report herein an excellent therapeutic effect of thalamotomy in a family with a DYT1 mutation, all of whom presented with focal hand dystonia.

PATIENTS AND METHODS

Patients

The index family is a Korean kindred and their pedigree is illustrated in Figure 1. Five clinically affected individuals, III:4, III:1, II:5, II:1, and I:1, were examined by movement disorder experts (M.C.L. and S.J.C.). Video recordings were performed in 3 clinically affected individuals (III:4, III:1, and II:5).

Molecular Studies

Mutation analysis for the DYT1 gene was performed in 3 of the 5 (II:5, III:1, and III:4) clinically affected individuals and in an asymptomatic individual (III:3) after obtaining informed consent from all subjects.

Genomic DNA was extracted from peripheral blood leukocytes by standard methods. The DNA segment spanning the GAG deletion site was amplified using sense primer 5′-CCT GGA ATA CAA ACA CCT A-3′ and antisense primer 5′-GGC TGC CAA TCA TGA CTG TC-3′.[3] Heteroduplex analysis was performed. The 500-ng polymerase chain reaction (PCR) products were denatured at 95°C for 5 minutes and then slowly cooled to room temperature to form heteroduplex. PCR products were run on an 8% nondenaturing polyacrylamide gel at 10 W for 1 hour. Separation of heteroduplex formation was observed by ethidium bromide staining under UV light.

After verifying that single specific PCR product was amplified, DNA sequencing was performed using the same primers used for PCR and BigDye Terminatore V3.1 Cycle Sequencing Ready reaction kit (Applied Biosystems, Foster city, CA) according to the manufacturer's instructions. Reaction was performed 30 cycles for at 94°C for 20 seconds, at 50°C for 20 seconds, and at 72°C for 30 seconds with PTC-200 PCR machine (MJ research, Watertown, MA) using 10 ng

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

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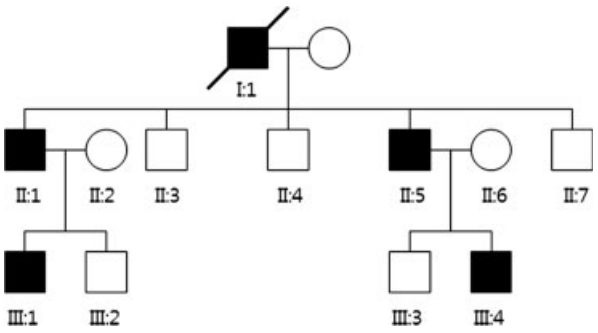

FIG. 1. Pedigree of a family with focal hand dystonia caused by DYT1 mutation.

of PCR product, which treated with exonuclease I and Shirmp Alkaline phosphatase (Amersham Pharmacia Biotech, Piscataway, NJ), as template and 10 pmol of proper primer. To remove incorporated dyes, ethanol precipitation was used. Electrophoresis and analysis of the reaction mixtures were done with ABI 3130xl Genetic analyzer (Applied Biosystems, Foster city, CA).

Stereotactic Surgery

Stereotactic surgery using the Leksell G frame was performed under local anesthesia. Four patients (III:4, III:1, II:1, and I:1) underwent single-staged unilateral thalamotomy. A T2-weighted MRI was used to localize the anterior (AC) and posterior (PC) commissures, and then, the fast spin echo inversion recovery technique (TR/TE, 5100/29) was acquired through the AC-PC line for better anatomic delineation of the medial margin of internal capsule. Axial images were obtained around the AC-PC line, with 2-mm thickness, no gaps. The target was nucleus ventralis oralis complex (Voc), which locates 2 to 4 mm anterior to nucleus ventralis intermedius (Vim). The Vim nucleus was 12 to 14 mm lateral to the AC-PC line, posterior 1/4 of the AC-PC line, and 0 mm below the AC-PC midpoint. Intraoperative electrophysiological recordings (Patients III:4, III:1, II:1, and I:1) and macroelectrode stimulation (Patients III:4) were performed. For thalamotomy, a permanent lesion was produced by radiofrequency thermogenerator (Radionics, Model RFG 3C) applying 1.1 mm $\times$ 3 mm bare tip of a 1.5-mm diameter electrode, heated at a temperature of 70°C for 70 seconds after a temporary lesion (40°C for 40 seconds) to confirm safety. Further thermal lesions were made in 2 mm apart from the previous lesions. Postoperatively, brain CT was performed to assess the lesion confirmation and surgical complications.

RESULTS

Case Descriptions

The clinical characteristics of the affected individuals are summarized in Table 1.

Case III:4

This patient was an 18-year-old male, whose perinatal history and developmental milestones were normal. He developed difficulty in writing at the age of 7 years. The disability of his right hand subsequently progressed over the following years and appeared during all skilled actions. On neurological examination, he showed repetitive dystonic contraction of his right hand (see Video Segment 1A). The dystonic movements were continuous and not suppressible. His writing was severely impaired because of action dystonia of the right hand; however, his left hand did not show dystonia during handwriting. There were no dystonic movements of the face, trunk, or legs. The neurological examination did not reveal any abnormality but dystonia.

This patient did not take any medication for his dystonia, because he and his caregiver refused to take medications. Treatment with botulinum toxin type A was not effective. At the age of 16 years, he underwent left thalamotomy, targeting the Voc, and the dystonia in his right hand resolved after surgery. At 2 years of clinical follow-up, the dystonia of his right hand had not recurred, and the function of his right hand was normal (see Video Segment 1B).

Case III:1

This patient had developed difficulty in writing at the age of 8 years and started writing with his left hand. When writing with his right hand, he showed dystonic flexion of the right wrist (see Video Segment 2A). At the age of 16 years, he also had difficulty using a spoon and chopsticks. He showed no therapeutic response to medications at another hospital and underwent thalamotomy, targeting the left Vim and Voc. The dystonia of his right hand disappeared after surgery (see Video Segment 2B) and did not recur during the clinical follow-up of 12 years. However, he developed mild dystonia of both hands 1 year ago, which initially occurred when he typed keyboard, and had mild difficulty in hand writing (see Video Segment 2C). The patient currently works as an architect.

TABLE 1. *Clinical profile of affected subjects who underwent thalamotomy*

Patient	Phenotype	Age at onset (yr)	Age at surgery (yr)	Follow-up after surgery (yr)	DYT1 mutation
I:1	Hand dystonia, bilateral[a]	20	68	10	NP
II:1	Right hand dystonia	12	42	12	NP
III:1	Hand dystonia, bilateral[a]	8	16	12	Positive
III:4	Right hand dystonia	7	16	2	Positive

NA, not available; NP, not performed.
[a]Hand dystonia was more prominent in the dominant right hand.

Case II:1

This patient had developed difficulty in writing at the age of 12 years and began using his left hand for writing. He also had difficulty in eating because of a dystonic tremor of his right hand at the age of 40 years. He had not taken medications for the hand dystonia. At the age of 43 years, he underwent thalamotomy, targeting the left nucleus Vim and Voc. He showed no dystonia of his right hand after the surgery and had no difficulty in performing daily activities.

Case II:5

This patient was a 50-year-old engineer who developed mild difficulty in writing at the age of 16 years. On neurological examination, he showed dystonic contraction of his right hand, and the severity of the right hand dystonia was still mild. He showed neither dystonic tremor nor dystonia of other body parts. He continued to work as an engineer and did not receive any treatment for his nondisabling dystonia.

Case I:1

This patient died at the age of 79, and only historical information with medical record review was available for this individual. This patient had developed difficulty in writing at the age of 20 years and started using his left hand. By the age of 50 years, he had difficulty in using his right hand for all skilled hand movements. He also developed a dystonic tremor of both hands. At the age of 64 years, he had suffered from right hemiparesis (3 according to the Medical Research Council scale score) caused by cerebral infarction involving the left corona radiata. After the stroke, he began using his left hand for activities of daily living. At the age of 69 years, he underwent thalamotomy, targeting the right nucleus Vim and Voc, which resulted in a marked reduction of dystonia and dystonic tremor of his left hand.

In all patients, there was no task specificity, occurrence of mirroring, motor overflow, and gestes antagonists. Dystonia was not evaluated with electromyography.

Molecular Studies

Heteroduplex shifts caused by heterozygote GAG deletion were shown in 3 of 5 clinically affected members (Patients II:5, III:1, and III:4, Supporting Fig. A). Subsequent sequence analyses showed identical results to heteroduplex assay in 3 of 5 clinically affected members (Patients II:5, III:1, and III:4, Supporting Fig. B).

Surgical Complications

There was no complication during surgery. A brain CT of patient III:4, performed immediately after surgery, showed small high density in the left thalamus, suggesting lesional bleeding (see Fig. 2). The patient had mild tingling sense in the left leg, which resolved 1 month later. There was no surgical complication in remaining patients. Cognitive dysfunction was not observed after surgery, although it was not evaluated by neuropsychological tests.

DISCUSSION

This study illustrated a marked benefit from unilateral thalamotomy in 4 members of a family with focal hand dystonia caused by DYT1 mutation. Moreover, the effects of thalamotomy lasted for up to 12 years without recurrence of dystonia or any significant surgical complication. Two members in the family presented with bilateral hand dystonia, prominent in the dominant right hand, remained localized to the dominant right hand in the other 3 patients for an extended period of follow-up.

DYT1 dystonia is transmitted as an autosomal dominant trait with reduced penetrance (30–40%) and is more frequent in people of Ashkenazi Jewish descendant because of a founder effect.[11] In Korea, 3.1% of

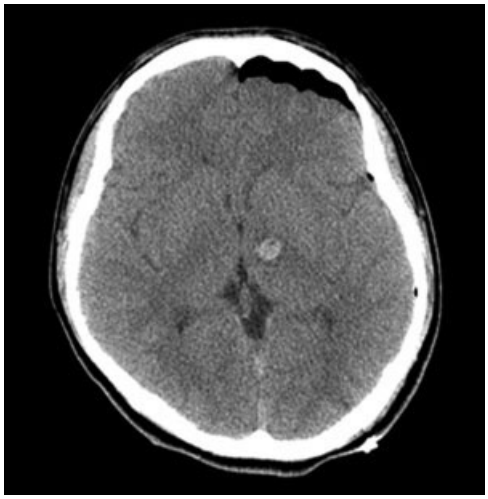

FIG. 2. A brain CT of patient III:4, performed immediately after surgery, shows small high density lesion in the left thalamus.

patients with primary dystonia of various phenotypes were positive for a DYT1 mutation.[12] This percentage is similar to that reported for another non-Jewish population. Although mutation analysis was not performed in all individuals of this family, 3 patients showed an identical GAG deletion in the DYT1 gene, suggesting that it may be beneficial to perform DYT1 mutation analysis in patients with early onset hand dystonia, irrespective of ethnicity.

The clinical features of this family were unique and differ from those of other typical DYT1 dystonia patients in that none of the affected individuals showed dystonia in body parts other than the hands. DYT1 dystonia typically begins in a limb and usually progresses to generalized or multifocal dystonia. In series of Askenazi patients, only 17.8% of DYT1 dystonia patients presented with focal dystonia, and only 11.1% remained segmental at the time of last follow-up.[13] In a recent report, DYT1 mutation was not detected in sporadic and familial writer's cramp, suggesting isolated writer's cramp is a phenotypic manifestation of DYT1 mutation in rare cases, even if a positive family history of writer's cramp is present.[5] Although interfamilial heterogeneity in DYT1 dystonia has been reported,[5,14] all clinically affected individuals in this family exhibited a relatively homogeneous phenotype and consistent therapeutic response to thalamotomy.

In this family, 4 of 5 clinically affected individuals underwent thalamotomy. In dystonia patients, the therapeutic response to surgery has been variable, and there has been no single clinical factor that predicts the magnitude of improvement after surgery.[10,15,16] The presence of DYT1 mutation was associated with a good therapeutic benefit derived from surgery in several previous studies,[16–18] but not in others.[10] Tasker et al. found that thalamotomy yielded the best therapeutic results in patients with involvement of the distal portion of 1 or 2 limbs, lack of dystonia in the trunk or neck, and idiopathic, nonprogressive disease.[19] In this family, 1 patient (Case III:1) received medical therapy and showed no response to medications, whereas all 4 patients who underwent surgery had an excellent therapeutic response to thalamotomy. The effectiveness of surgery was greater in the patients who underwent thalamotomy at an early age than those who received surgery at an older age. Although the recurrence rate of patients with writer's cramp who underwent lesioning surgery has been reported to be 15%, presumably because of inadequate lesioning,[20] 4 patients who underwent thalamotomy in this study showed no recurrence of the hand dystonia contralateral to the site of unilateral thalamotomy.

Regarding the best target for surgical treatment of dystonia, the thalamus was the preferred target of stereotactic lesioning surgery until 1990.[19,21,22] The advent of DBS, however, led to a shift to the globus pallidus internum (GPi) as the preferred target.[10,23–25] Reports on thalamic DBS in patients with dystonia are limited[26,27] compared with GPi DBS. Three patients in this study (Case I:1, II:1, and III:1) underwent thalamotomy because DBS was not available at the time they underwent surgery. Another patient (Case III:4) in this family recently received thalamotomy, because the patient and his caregiver preferred thalamotomy because of the successful surgical outcome achieved in 3 family members. Consistent with previous reports,[28,29] hand dystonia in our patients was dramatically improved by thalamotomy, suggesting that thalamotomy may be a good alternative for GPi DBS in patients with focal dystonia of the hand.

In conclusion, we report a family with focal hand dystonia caused by DYT1 mutation, all of whom showed an excellent and prolonged therapeutic response to thalamotomy. Further studies are needed to elucidate the strengths and weaknesses of individual surgical targets and the best treatment modalities for each subtype of dystonia.

LEGENDS TO THE VIDEO

Segment 1A. Patient III:4. Preoperative state. This patient shows repetitive dystonic contraction of his right hand. His writing was severely impaired because of action dystonia of the right hand.

Segment 1B. Patient III:4. Two years after thalamotomy. The Dystonia was absent while the patient is holding different postures and moving the right hand. He had no difficulty in writing.

Segment 2A. Patient III:1. Preoperative state. Dystonic contraction of the right arm is demonstrated when the patient writes.

Segment 2B. Patient III:1. Postoperative state (3 days after thalamotomy). There was no dystonia of his right hand during handwriting.

Segment 2C. Patient III:1. Postoperative state (13 years after thalamotomy). There was mild dystonia on the right hand.

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