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Levodopa-Induced Ocular Dyskinesia in an Early-Onset Parkinson Disease Patient With *GBA* Mutation

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Objectives: The aim of this study was to report a case of levodopa-induced ocular dyskinesia in an early-onset Parkinson disease patient and to investigate the pathogenic gene.

Methods: We report the case of a 49-year-old male patient with a 13-year history of Parkinson disease. Involuntary eye movements were noticed after treatment with amantadine for limb dyskinesias. Levodopa-induced ocular dyskinesias involving repetitive, transient, and stereotyped rightward deviations of gaze appeared after intake of an antiparkinsonian drug. Limb dyskinesias also occurred simultaneously. We used a next-generation sequencing targeted gene panel and found a heterozygous missense mutation (p.R535H) in *GBA*. Direct Sanger sequencing verified the missense mutation.

Conclusions: We report the case of an uncommon early-onset PD patient carrying a *GBA* mutation presenting ocular dyskinesia. Genetic screening may provide a better mechanistic insight into dyskinesias.

Key Words: amantadine, glucocerebrosidase, ocular dyskinesia, Parkinson disease

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Levodopa is the most effective drug for treating Parkinson disease (PD), but its long-term use is complicated by motor fluctuations and dyskinesia. Dyskinesia, often mild at the beginning, may progress to become disabling and interfere with the quality of life.[1] Different types of movement disorders are seen in levodopa-induced dyskinesia (LID) including chorea, ballism, dystonia, myoclonus, or any combination of these movements. Levodopa-induced dyskinesia is usually seen in the neck, facial muscles, jaw, tongue, hip, shoulder, trunk, and limb or may appear as involuntary flexion of toes.[2,3]

In addition, disorders in eyelid motor control, such as blepharospasm or eyelid apraxia, are also seen in PD patients following levodopa treatment.[4,5] However, levodopa-induced ocular dyskinesias (LIODs) is very uncommon. This condition is characterized by an intermittent lateral and upward gaze lasting for a few seconds that may occur simultaneously with levodopa-induced limb dyskinesias.[6]

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The development of LID (most common in females) depends on several clinical risk factors including early onset and severity of PD, as well as with a higher dose and longer duration of levodopa therapy.[7,8] However, these clinical variables may only partially account for the risk of developing dyskinesia, and a considerable proportion of PD patients will never develop dyskinesia. Genetic risk factors could lead to individual variations in the development of dyskinesias. Previous studies have revealed several genetic mutations that can increase the risk for dyskinesias. These include *PARK2* (parkin), *PARK6* (pink-1), and *PARK7* (DJ-1).[9,10] Other studies have shown that polymorphisms in the dopamine receptor D_2 gene may reduce the risk of dyskinesia.[11,12] Recognition of the relationship between genetic factors and dyskinesia may help to clarify the underlying mechanisms. However, few studies have described a genetic variation in PD patients with rare types of dyskinesia including LIOD. Here we investigated an early-onset PD patient with specific LIOD. Genetic factors relating to development of dyskinesia were also analyzed.

CASE PRESENT

A 49-year-old man with a 13-year history of slowness of movement came to our neurology clinic for movement disorders. The initial symptoms started in 2007 when the patient complained of rigidity. This was mainly in the right upper arm, but gradually involved the lower right arm as well as the left arm. Besides motor symptoms, the patient also presented anosmia and constipation. He had no history of neurologic disorders, head injury, tics, stroke, toxic exposures, or any other significant neurologic or related health problems. Based on his clinical manifestations, the patient was diagnosed with PD. Following treatment of levodopa/benserazide dose (125 mg 3 times), the patient's rigidity and other motor deficits improved significantly.

Three years after the initial treatment, the benefits from levodopa gradually declined. Other antiparkinsonian drugs (pramipexole 0.5 mg 3 times per day, entacapone 0.1 mg 3 times per day, and selegiline 5 mg per day) were added. This drug adjustment greatly improved his condition. After 1 year, he started to experience peak-effect dyskinesia, which was presented with choreic movement of the right limbs. The dyskinesia developed half an hour after each levodopa/benserazide dose (125 mg) and lasted for 1 hour. At his neurologic examination in our clinic, the patient presented mask face, hypomimia, bradykinesia, and limb rigidity that were more prominent on the right side. He had no gaze palsy, cerebellar signs, or autonomic dysfunction. Interestingly, the patient was observed to have abnormal involuntary eye movements that appeared half an hour after taking levodopa/benserazide. The involuntary eye movements presented with a repetitive, transient, and stereotyped rightward deviations of gaze (Figs. 1A, B), which worsened when the patient was speaking or felt nervous (Supplementary Video, http://links.lww.com/CNP/A20, informed consent obtained from the patient). He could not look forward or actively control eye movements during the episode. There were no related changes in nystagmus, pupils, or blepharospasm. He was usually unaware of the eye movements and did not have any related thoughts or mood changes when it occurs.

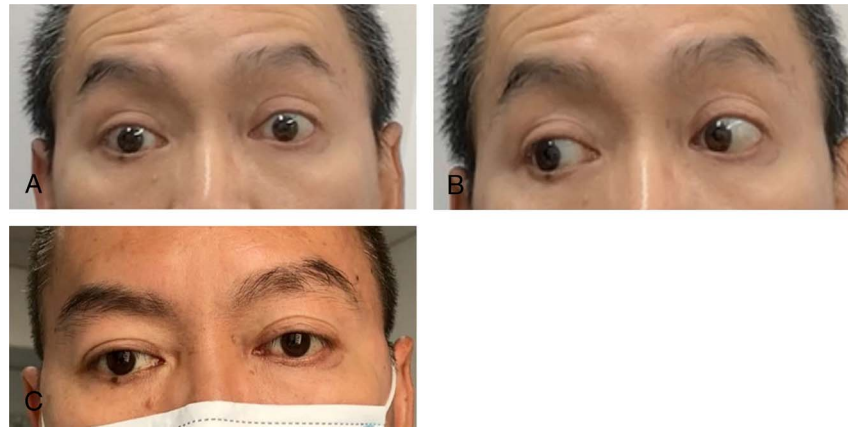

FIGURE 1. A and B, Photographs extracted from video segments show typical LIOD in the patient. C, Follow-up after taking amantadine for 1 year shows no LIOD in the patient.

Whenever his overall motion returned to normal, these eye motions also disappeared.

The patient's abdominal ultrasonography, chest computed tomography, and brain magnetic resonance imaging were normal. Ultrasound of the substantia nigra revealed that the echo of bilateral substantia nigra was patchy enhancement, and hyperechoic areas of 0.34 cm^2 (left) and 0.23 cm^2 (right) could be detected.

The following laboratory test results were normal: full blood cell count, renal function, liver enzyme, thyroid function, plasma ceruloplasmin levels, and screen for autoantibodies and antineuronal antibodies. The patient tested negative for Epstein-Barr virus, HIV, and Toxoplasmosis, Others, Rubella, Cytomegalovirus, and Herpes infections. Assays for paraneoplastic syndrome–associated antibodies, including Hu, Yo, Ri, CV2, PNMA2 (Ma-2/Ta), and amphiphysin, did not reveal any abnormalities.

In consideration of patient's prominent peak-effect dyskinesia, amantadine (200 mg/d) was added. The adjustment was effective in ameliorating the dyskinesia, and the duration of chronic movement of the right limbs reduced significantly. Surprisingly, amantadine also improved the patient's involuntary eye movements. In a 1-year follow-up, the duration of abnormal eye movement was further reduced (Fig. 1C).

After the written informed consent was provided, a comprehensive genetic analysis of the patient was then performed using a capture-based next-generation sequencing targeted gene panel (Precisionmdx Co, Beijing, China; http://www.precisionmdx.com/). This gene panel covers more than 22 highly prevalent PD-associated genes including *UCHL1*, *SNCA*, *GCH1*, *LRRK2*, *PANK2*, *PARK2*, *DJ-1*, *ATP13A2*, *DCTN1*, *DNAJC13*, *DNAJC6*, *SPG11*, *EIF4G1*, *FBXO7*, *GBA*, *PINK1*, *PLA2G6*, *POLG*, *VPS35*, *TH*, *VPS13C*, and *SYNJ1*. In our patient, the missense variant c.1604G > A(p.R535H) in the *GBA* gene was identified. Direct Sanger sequencing further verified the heterozygous c.1604G > A missense mutation in the patient (Figs. 2A, B). This heterozygous mutation, resulting in the amino acid change p.R535H (arginine>histidine), has been reported as a pathogenic mutation in Gaucher disease.[13]

DISCUSSION

We report an early-onset PD patient with involuntary eye movement that followed treatment with a high-dose levodopa. The patient demonstrated intermittent lateral deviations of gaze lasting for several seconds, as well as levodopa-induced choreoathetosis limb movements. Notably, the manifestation of these abnormal eye movements is similar to LIOD as shown in the video provided by LeWitt.[6] Levodopa-induced ocular dyskinesia was described in detail by Shimizu et al[14] in 1977 as an adverse effect of prolonged exposure to levodopa. This dyskinetic eye movement involved smooth, large-amplitude, "to-and-fro" ocular deviations of gaze lasting for several seconds. Levodopa-induced ocular dyskinesia appears to be different from the oculogyric crises commonly described for striatal dopamine deficit conditions in which eye deviation is tonic for several hours and is frequently accompanied by psychiatric and autonomic symptoms.[15] Thus, in our patient, the oculogyric crises can easily be excluded.

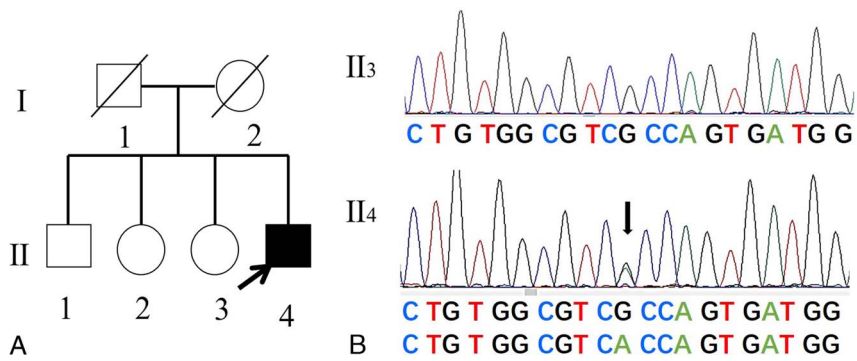

FIGURE 2. A, The patient's pedigree chart. Circles and square represent female and male family members; arrow indicates proband; filled square represents PD patient. B, Sanger sequencing result from healthy family member II3 and case II4 showing the heterozygote variant p.R535H in GBA. Arrow indicates the variant.

TABLE 1. Demographics and Relevant Clinical Data of the Previous Reports and of Our Case of Levodopa-Induced Ocular Dyskinesias Patient

Study	No.	Gender	PD Onset Age	Disease Duration, y	Daily Treatment	Dyskinesia Involved Other Body Parts	Involuntary Eye Movement Direction
Shimizu et al,[14] 1977*	1	F	61	8	1500 mg of levodopa, 150 mg of carbidopa, 120 mg of piribedil, 100 mg of diphenhydramine, and 30 mg of flurazepam	No	Horizontal and vertical
	2	M	41	20	1600 mg of levodopa, 150 mg of carbidopa, and 180 mg of BL-14	Oral facial and limb	Horizontal
LeWitt,[6] 1998	3	F	40	13	Levodopa 350 mg	Left side–predominant limb	Upward and rightward deviations, toward the side less affected
	4	M	54	11	Levodopa 800 mg, pergolide 3 mg	Left limbs, repeated eyelid closure	Upward and rightward deviations, toward the side more affected
Linazasoro et al,[17] 2002	5	M	55	5	Levodopa 800 mg, pramipexole 4.5 mg, budipine 30 mg, amantadine 300 mg	Peak-dose choreiform dyskinesia	Upward and leftward deviations, toward the side more affected
Grötzsch et al,[16] 2007	6	M	61	16	Levodopa 800 mg	Mild limb and trunk dyskinesia	4 of 5 patients exhibited gaze deviation toward the side more affected
	7	M	53	7	Levodopa 800 mg		
	8	F	63	8	Levodopa 600 mg, amantadine 150 mg, ropinirole 1.5 mg		
	9	F	57	10	Levodopa 1000 mg, pramipexole 1.5 mg		
	10	M	53	11	Levodopa 600 mg		
Our case	11	M	36	13	Levodopa/benserazide 375 mg, pramipexole 1.5 mg, entacapone 0.3 mg, selegiline 5 mg	Limb dyskinesia and repeated eyelid closure	Rightward deviations, toward the side more affected

*The detailed clinical characteristics of the other 6 cases were not described.

F, female; M, male; PD, Parkinson disease.

According to the reports by Grötzsch et al[16] and Shimizu et al,[14] the prevalence of ocular dyskinesias is as high as 16% and 29.6%, respectively. Despite this, only a few publications have reported these manifestations. Possibly, most patients neglect to complain of ocular dyskinesias at the clinic. We searched MEDLINE and evaluated all correlative articles reporting on 11 patients (Table 1).[6,14,16,17] Seven of them were males presenting this type of PD between 36 and 63 years of age. Affected subjects presented clinically with similar features including a long duration of high-dosage L-dopa, levodopa-induced dyskinesias in the other parts of the body, and a gaze deviated toward the side more affected by PD. As compared with other reports, the present case exhibited an earlier age at onset. This could imply that genetic risk factors may lead to the development of the disease.

It is widely accepted that heterozygous mutations in *GBA* (which encodes for the enzyme glucocerebrosidase, which is deficient in Gaucher disease) are the most important genetic risk factors for PD.[18,19] In this study, we performed a screening of 22 PD-related genes in our early-onset PD patient. This screening revealed the heterozygous missense mutation c.1604G > A(p.R535H) in *GBA*. This variant has been reported to be involved with Gaucher disease in varied ethnicities and is categorized as a pathogenic mutation in the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/variation/4311/). An earlier age at onset and increased risk of motor complications have been reported in *GBA*-related PD compared with idiopathic PD.[20,21] However, there is very little published research on PD patients carrying a *GBA* mutation presenting with ocular dyskinesia.

The discovery of the link between *GBA* mutations and PD has opened up a new field for precision medicine research. A widened understanding of the molecular pathogenesis of *GBA* mutations may lead to the development of novel drugs to restore glucocerebrosidase activity. Some related studies are currently in clinical trial.[22] Ambroxol, a drug that breaks up phlegm, has been shown to improve lysosomal function and increase glucocerebrosidase enzyme activity in in vitro and vivo studies.[23,24] The effects of ambroxol are being studied in a phase II, single-center, double-blind, randomized, placebo-controlled trial involving 75 individuals with mild to moderate PD and dementia.[25] In another example, LTI-291 (a small-molecule activator of glucocerebrosidase) was studied in a 1-month phase 1b trial involving 40 *GBA*-PD patients. There were no safety events, and the data showed good dose-dependent brain penetration.[26]

Despite significant advances, the pathophysiology of dyskinesia remains poorly understood. It is well accepted that nigrostriatal denervation is a requirement of dyskinesia and that dopamine decrease in the caudate nucleus is lower than that in the putamen.[27–29] Recent data from optogenetic manipulation in animals have revealed that the caudate tail–substantia nigra pars reticulata–superior colliculus network initiates saccadic eye movements. Specifically, selective optical activation of caudate tail inhibits the substantia nigra pars reticulata neurons. Substantia nigra pars reticulata projects to the intermediate layer of the superior colliculus, a key region for the generation of saccadic eye movements. The optical stimulation causes prolonged excitation of visual-saccadic neurons in the superior colliculus and induces contralateral saccades.[30] However, it is still unknown if anti-LID compounds affect the circuit mechanisms of ocular dyskinesia. The ocular dyskinesia symptoms of our case were relieved with amantadine, suggesting that the *N*-methyl-D-aspartic acid–type glutamate receptors may

regulate related pathways.[31] Further positron emission tomography scanning with the use of *N*-methyl-D-aspartic acid receptors could be helpful in supporting this hypothesis.

In conclusion, we report a case of an uncommon early-onset PD patient carrying a *GBA* mutation presenting ocular dyskinesia. We plan further studies in the pathogenesis and pathophysiology of ocular dyskinesia.

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