Management of levodopa-induced jig-like gait disorder with pallidal stimulation

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Levodopa, a metabolic precursor of the neurotransmitter dopamine, is the most effective symptomatic therapy for Parkinson disease (PD); however, long-term treatment with levodopa is complicated by fluctuations in motor response (“wearing off”) and medication-induced dyskinesias in the majority of patients.

Levodopa-induced dyskinesias are thought to arise from neuroplastic changes brought on by pulsatile stimulation of striatal dopamine receptors. While phenomenologically diverse, levodopa-induced dyskinesias have traditionally been divided into 3 categories: (1) peak dose dyskinesias, which are often choreic trunk and limb movements that arise when levodopa’s effects are at their peak (i.e., in the ON state); (2) diphasic dyskinesias, which are often mobile dystonic or ballistic leg movements that arise at the onset or the end of the ON state; and (3) OFF state dyskinesias, which are often less mobile, dystonic foot spasms that arise when levodopa’s effects have worn off. In some cases, however, levodopa-induced dyskinesias are unusual in their anatomic distribution (e.g., ocular or respiratory dyskinesias),¹ phenomenologic appearance (e.g., bizarre stereotypic gaits),² or timing in relation to the intake of dopaminergic medication.³

Case Report

A 53-year-old woman was in good health until age 45, when she experienced gradual onset of right-sided parkinsonism. She was diagnosed at age 47 and started treatment with carbidopa-levodopa, but levodopa-induced dyskinesias developed after about 1 year of treatment. She presented to our clinic at age 50 because of severe, involuntary leg movements upon standing that prevented independent ambulation (videos 1 and 2 at Neurology.org/cp). Brain MRI was normal. PCR amplification of the *GBA* (glucosylceramidase) gene detected a heterozygous *L444P* mutation.

Medical management was ineffective in lessening her gait disorder, including amantadine (100 mg twice daily), attempts to introduce a dopamine agonist, and dosing adjustments of

Practical Implications

An unusual, dyskinetic pattern of gait in patients with PD is an exception to the principle that DBS is ineffective for levodopa-refractory gait disorders.

Video

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

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levodopa. The high-amplitude, repetitive, leg-stomping, and jig-like gait worsened after stopping levodopa for over 36 hours, and a longer washout could not be tolerated by the patient because of intolerable OFF symptoms. Best motor function was achieved at dose of carbidopa/levodopa 25/100 mg, dosed 1/2 tablet 4 times daily (video 2); higher levodopa doses resulted in generalized, choreatic, peak-dose dyskinesias without further improvement in gait.

At age 52 years, the patient underwent bilateral deep brain stimulation (DBS) surgeries. Leads (model 3387; Medtronic, Inc., Minneapolis, MN) were implanted stereotactically using a frame-based, microelectrode-guided approach in the posteroventral portion of the globus pallidus internus (GPi). DBS provided a marked benefit in gait superior to her best medication effect at the following monopolar settings (left/right GPi): amplitude 2.5/2 V, pulse frequency 160/160 Hz, pulse width 90/90 μ s (video 3).

DISCUSSION

This patient's stereotypic gait disorder closely resembles that of 4 recently reported patients with PD with "silly walks."² As the authors point out, the pattern is reminiscent of the gaits portrayed in Monty Python's satire "The Ministry of Silly Walks," and its bizarre appearance may falsely give the impression of a psychogenic movement disorder.

Our patient's gait disorder remained disabling, albeit less severe, in the ON state, suggesting a diphasic pattern, yet it persisted after a prolonged levodopa washout, making it difficult to definitively classify within the 3 accepted categories of dyskinesias described above. It should be noted that stereotypic, rhythmic movements of the lower extremities in the OFF state were relatively common in younger patients with PD following stem cell transplantation, but the underlying pathophysiologic mechanisms for dyskinesias in that setting are not understood.³ Of the 4 previously described cases, 2 patients had a diphasic pattern of dyskinesia with gait improving in the full ON state.² The other 2 patients showed resolution of their dyskinetic gait in the practically defined OFF state with re-emergence of typical parkinsonian features, and both benefited from bilateral subthalamic nucleus (STN) DBS.

Apart from pathophysiologic considerations, there are therapeutic implications of the lack of improvement in our patient's gait disorder following levodopa withdrawal. Pallidal stimulation has direct antidyskinetic effects, while STN stimulation lessens dyskinesias mainly due to reduction in dopaminergic drug dosage. As dyskinesias in our patient did not remit in the practically defined OFF state, we targeted the GPi, which provided a robust improvement in gait, superior to her best medication effect. Accordingly, this case serves to illustrate an uncommon exception to the tenet that DBS is ineffective for levodopa-refractory gait and balance disorders.

Established risk factors for levodopa-induced dyskinesias include female sex, earlier age at PD onset, longer duration of treatment, and higher doses of levodopa.⁴ Our patient was a *GBA* mutation carrier, which is a known risk factor for PD. Patients with PD with *GBA* mutations also have a higher risk of developing dyskinesias compared with PD controls with a similar age at onset, and this increased risk is the case independent of sex, levodopa dosage, and treatment duration.⁵ Whether *GBA* mutations also influence the phenotypic expression of dyskinesias has not yet been explored.

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STUDY FUNDING

No targeted funding reported.

DISCLOSURES

J.M. Ferrara reports no disclosures. D.J. Houghton has received travel and speaker honoraria from the National Parkinson Foundation; serves as Editor of *Parkinson's Disease Monitor and Commentary*; serves on the speakers' bureau of Teva Pharmaceuticals; and receives research support from the National Parkinson Foundation. C. Knoop reports no disclosures. M.C. Park reports no disclosures. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

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