Movement Disorders
CLINICAL PRACTICE

CASE SERIES

Diphasic Worsening of Freezing of Gait in Parkinson's Disease

Sahyli Perez Parra, MD,[1] J. Lucas McKay, PhD, MSCR,[2] and Stewart A. Factor, DO[1,*]

ABSTRACT: Background: The relationship between freezing of gait (FOG) and levodopa response is complex. Some patients respond, some have no response and in some patients levodopa causes FOG. We present 2 cases demonstrating a diphasic worsening of FOG after levodopa dosing.
Cases: Two PD patients with FOG were examined during the practically defined *off* state, the transition from *off* to *on* (15 and 22 minutes postdose), and in the full *on* state (45 and 60 minutes postdose). FOG was measured using Movement Disorder Society–Unified Parkinson's Disease Rating Scale part III, item 11: freezing of gait. Both patients experienced worsening of FOG during the transition followed by improvement during the *on* state. Case 1 had serum levodopa levels measured. Videos are provided.
Conclusions: To our knowledge, this diphasic pattern of worsening of FOG has not been previously reported. The cause of this phenomenon is unknown but may relate to an inhibitory action of subthreshold levels of levodopa.

The relationship between freezing of gait (FOG) and levodopa response is complex. Clinical experience points to the existence of several responses: (1) FOG that appears only in the *off* state and disappears in the *on* state (*off*-FOG), (2) FOG that is present in the *off* state and persists in the *on* state (*onoff*-FOG), and (3) FOG present during the *on* state only and absent in the *off* state (drug induced or *on*-FOG).[1–3] One study reported, based on patient self-reports, that 62% of FOG patients have *off*-FOG, 36% have *onoff*-FOG, and 2% have *on*-FOG.[4] In this article, we present 2 cases demonstrating yet another level of complexity. The patients had *onoff*-FOG, where the FOG clearly worsened during the transition period from *off* to *on* and then improved when reaching the full *on* state. This was reported by the patients themselves indicating that they felt the levodopa was worsening their FOG and observed by the examiner and supported by levodopa levels in 1 case.

Case Series

Case 1

Case 1 was a 64-year-old woman with Parkinson's disease (PD) diagnosed 21 years earlier. Her first symptoms were a right-hand tremor and a stooped posture. At 10 years after the diagnosis, she developed balance and gait problems. She noticed start hesitation that would occur unpredictably but was responsive to higher doses of levodopa. In the past 3 years, she noticed worsening of FOG transitioning from *off*-FOG to the *onoff* type. She would notice worsening of FOG within 10 minutes to half an hour after taking carbidopa/levodopa/entacapone, and it would last about 30 minutes. This worsening was so troublesome that she would sometimes choose to skip doses just to avoid the FOG episodes, but she would experience shuffling gait and leg tremor instead. Despite lowering of the levodopa dose, she continued to

[1]Jean & Paul Amos PD & Movement Disorders Program Department of Neurology, Emory University, Atlanta, Georgia, USA; [2]Wallace H. Coulter Department of Biomedical Engineering, Georgia Tech and Emory University, Atlanta, Georgia, USA

***Correspondence to:** Stewart A. Factor, Professor and Director, Movement Disorder Program, Vance Lanier Chair of Neurology, Emory University School of Medicine, 12 Executive Park Drive NE, Atlanta, GA 30329; E-mail: sfactor@emory.edu
Keywords: Parkinson's disease, freezing of gait, levodopa, diphasic.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 21 December 2019; revised 7 February 2020; accepted 15 February 2020.
Published online 9 March 2020 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.12918

have this period of worsening. During the following years she tried numerous medication combinations with no success (including selegiline, rasagiline, ropinirole, pramipexole, amantadine, combined immediate release, and controlled release formulations with entacapone).

The patient was evaluated in the clinic during the *off* state. Her UPDRS motor score was 38 with no FOG seen. A dose of carbidopa/levodopa 25/100 1.5 tabs plus entacapone 200 mg was given. Within 10 minutes she had notable FOG with gait initiation and turning hesitation. Twenty minutes later, during the full *on* state, she had a UPDRS motor score of 20 and no FOG.

Two months later, we performed a levodopa challenge test including serum levodopa levels and examined her using the MDS-UPDRS part III scale in the following 3 settings and videotaped the laboratory exams: the hallway, in our motion capture laboratory with a standard timed-up-and-go (TUG), and with a cognitive TUG (performing calculations). She was examined in the practically defined *off* state (>12 hours after the last dose of levodopa). She was then given her standard morning doses (carbidopa/levodopa 25/100 mg 1.5 tabs, entacapone 200 mg, amantadine 50 mg, and pramipexole 0.5 mg). She was then examined 15 minutes postmedication and then 45 minutes postdose when in full *on* state. Her MDS-UPDRS-III scores (without item 11, FOG) were 44 during the *off* state, 43 during the transition phase, and 27 during the *on* state (Fig. 1). FOG was scored 0 to 4 using item 11, FOG, of the MDS-UPDRS-III (0 = no freezing; 1 = slight, freezes on starting, turning, or walking through doorway with a single halt during any of these events but then continues smoothly without freezing during straight walking; 2 = mild, no. 1 with more than 1 halt during any of these activities; 3 = moderate, freezes once during straight walking; 4 = severe, freezes multiple times during straight walking; Fig. 1). In the *off* state she had no FOG (score 0) during the standard exam in the hallway. In the laboratory, she had freezing when turning left on a standard TUG, scoring a 1 (Video S1, segment 1). During a cognitive TUG she scored 3. During the transition she scored a 2 on the standard exam in the hallway, she scored 2 on the standard TUG (Video S1, segment 2), and she scored 4 on the cognitive TUG. When in the full *on* state, she had mild head and neck dyskinesia. In the full *on* state, FOG scores during the hallway exam and standard TUG were 0 (Video S1, segment 3) and 1 with turning in the lab during cognitive TUG (Fig. 1). The serum levodopa measures were *off* 0.06 ng/mg protein, transition between *off* and *on* 14.78 ng/mg protein, and *on* 18.98 ng/mg protein (Fig. 1). Methodological details for levodopa testing are available in a previous report.[5]

Case 2

This case was a 57-year-old man with a 5-year history of PD. He presented with abnormal posture, loss of dexterity on his left hand, and shuffling gait. He was initially treated with carbidopa/levodopa 25/250. Three years later, he developed dyskinesia of his legs and was referred to our clinic for consideration of deep brain stimulation therapy. At the time of his first evaluation, he was on carbidopa/levodopa 25/250 mg, 1 tablet every 3.5 hours for 5 doses per day, and his physical exam demonstrated FOG upon initiation of gait and with turning during the *off* state. The dose of the levodopa was reduced, and amantadine was added. He later experienced worsening of his FOG and balance resulting in the increased frequency of falls. He was then evaluated in the practically defined *off* state (10 hours after the last dose of levodopa) and then received a levodopa challenge. During the *off* state his motor UPDRS score was 22, and he demonstrated festination and FOG on initiation, turning, walking through doorways, and during straight walking (Video S2, segment 1). He received 1 tablet of carbidopa/levodopa 25/250 mg plus carbidopa/levodopa-controlled release 25/100 and 200 mg of entacapone. Twenty-two minutes later (in the transition from *off* to *on*), he developed severe and more frequent FOG when compared with the *off* state in addition to mild dyskinesias in his legs and left upper extremity (Video S2, segment 2). One hour after he received the medication, in the full *on* state, he had a significant improvement of his FOG only present on starting and turning. His motor UPDRS score was 10, and he had moderate facial and appendicular dyskinesias with mild dystonic posture of his left hand (Video S2, segment 3).

Discussion

We describe 2 patients with PD who presented with FOG that worsens in the transition from the *off* to *on* states before improving in the full *on* state. Both patients complained specifically of worsening during transition from *off* to *on*, but not from *on* to *off*, and the pattern seen with the levodopa challenge matched what they described. We had serum levodopa levels in case 1 to demonstrate she had not yet reached peak levels during the transition state. We did not have serum levodopa levels for case 2, and although the apparent worsening in the transition could be construed as more general FOG variability, the pattern was very similar to that seen in case 1 and to the complaint of transition worsening. Both patients experienced freezing during the *off* and *on* states, with significant worsening during the transition phase and notable improvement approximately 45 to 60 minutes after receiving a therapeutic dose of levodopa. This pattern seems similar to that observed in patients with diphasic dyskinesia.[6]

We note that all authors concurred that comparisons of changes in FOG observed in the videos with changes in the MDS-UPDRS-III item 11 scores gave the impression that the MDS-UPDRS-III scores were underrepresentative. More precise quantitative measures of FOG severity could potentially alleviate this.

FOG was recognized before the levodopa era, although the frequency seems to have increased since that time,[7] suggesting a role of levodopa in the pathophysiology. Different subtypes of FOG have been described based on its phenomenology and responsiveness to levodopa.[5] Its pathophysiology, though,

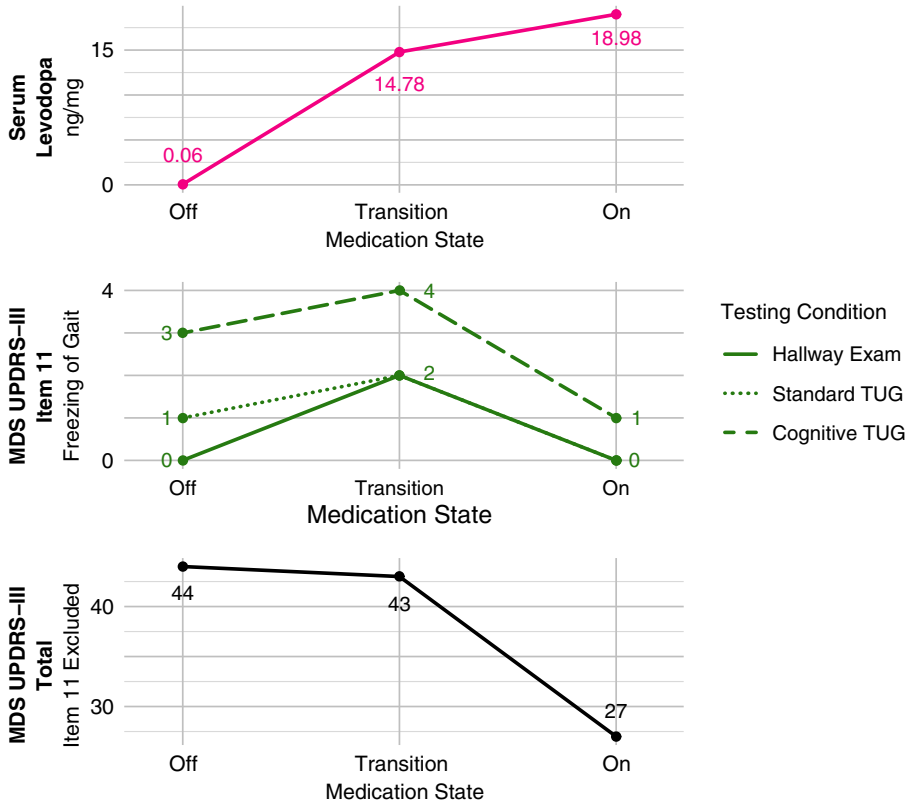

FIG. 1. Case 1. The top (pink line) graph depicts levodopa levels during the *off*, transition, and *on* states. The center (green lines) depicts the MDS-UPDRS item 11 "freezing of gait" in 3 settings: hallway exam (dashed line), laboratory standard TUG test (dotted line), and laboratory cognitive TUG test (solid line) in the *off*, transition, and *on* states. The bottom graph (black line) depicts the MDS-UPDRS part III exam score in the *off*, transition, and *on* states. MDS-UPDRS-III, Movement Disorder Society–Unified Parkinson's Disease Rating Scale part III; TUG, timed-up-and-go.

remains unclear. The existence of different subtypes suggests that they probably have a different pathophysiology.

The reasons for a worsening of FOG in the transition period are unclear. One possibility relates to an inhibitory action of subthreshold levels of levodopa.[8] Nutt and colleagues reported that during 2-hour levodopa infusions, it was found that 5 patients who received subthreshold infusions showed greater motor deterioration than those receiving placebo. The cause is unclear, but hypotheses include the inhibition of dopamine release via presynaptic receptors or perhaps a supersensitivity to specific postsynaptic receptors.[9] Nutt[9] speculated that this was an explanation for *off* period dystonia. Another feature that worsens in transition times is dyskinesia, so called "diphasic dyskinesia." These are rare and complex. They are more frequent in young patients and present at the time of quick changes in levodopa levels, either when they are rising or falling. They usually anatomically also impact the lower body as the legs generally develop choreiform or ballistic movements and in some cases fixed dystonia.[10] The exact pathophysiology of this specific type of dyskinesia is unknown, and the fact that its management is different when compared with other types of dyskinesias raises the concern for a different etiology. For the diphasic FOG, we suspect that approaches that shorten or eliminate transitions through continuous therapies such as infusions of levodopa or the use of rapid-acting rescue therapies such as subcutaneous apomorphine injections will be helpful. These recommendations should be tested.

We propose to denominate the pattern of FOG described here as "diphasic FOG," which will increase awareness regarding the potential different pathophysiology causing the various subtypes of levodopa-responsive FOG and will help to properly identify them. This will hopefully lead to appropriate and timely interventions.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

S.P.P.: 1A, 1B, 2C, 3A, 3B

J.L.M.: 1B, 2A, 2B, 3B
S.A.F.: 1A, 1B, 1C, 2A, 2C, 3A, 3B

Disclosures

Ethical Compliance Statement: The authors confirm that they received approval from the Emory University institutional review board. Informed consent was obtained from the patients for using their clinical video for manuscript submission. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflict of Interest: This work was supported by the Curtis Family Fund, and the Sartain Lanier Family Foundation, the Parkinson's Disease Foundation, and National Institutes of Health K25HD086276.

Financial disclosures for previous 12 months: S.P.P. is a Parkinson Foundation Fellow. J.L.M. has the following disclosures: consulting fees from Biocircuit Technologies and National Institutes of Health Grant K25HD086276. S.A.F. has the following disclosures: honoraria from Lundbeck, Sunovion, Biogen, Acadia, Impel, Acorda, CereSpir; grants from Medtronics, Boston Scientific, Biohaven, Impax, Lilly, US World Meds, Sunovion Therapeutics, Vaccinex, Voyager, Jazz Pharmaceuticals, CHDI Foundation, Michael J. Fox Foundation, and National Institutes of Health (U10 NS077366); royalties from Demos, Blackwell Futura, and Springer for textbooks and Uptodate; and other: Bracket Global LLC and CNS Ratings LLC.

References

1. Bloem BR, Hausdorff JM, Visser JE, Giladi N. Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. *Mov Disord* 2004;19:871–884.
2. Espay AJ, Fasano A, van Nuenen BF, Payne MM, Snijders AH, Bloem BR. "On" state freezing of gait in Parkinson disease: a paradoxical levodopa-induced complication. *Neurology* 2012;78:454–457.
3. Factor SA, Scullin MK, Sollinger AB, et al. Freezing of gait subtypes have different cognitive correlates in Parkinson's disease. *Parkinsonism Relat Disord* 2014;20:1359–1364.
4. Amboni M, Stocchi F, Abbruzzese G, et al. Prevalence and associated features of self-reported freezing of gait in Parkinson disease: the DEEP FOG study. *Parkinsonism Relat Disord* 2015;21:644–649.
5. McKay JL Goldstein FC, Sommerfeld B, Bernhard D, Perez Parra S, Factor SA. Freezing of gait can persist after an acute levodopa challenge in Parkinson's disease [published online ahead of print November 22, 2019]. *NPJ Parkinsons Dis*. https://doi.org/10.1038/s41531-019-0099-z
6. Espay AJ, Morgante F, Merola A, et al. Levodopa-induced dyskinesia in Parkinson disease: current and evolving concepts. *Ann Neurol* 2018;84:797–811.
7. Koehler PJ, Nonnekes J, Bloem BR. Freezing of gait before the introduction of levodopa [published online ahead of print April 10, 2019]. *Lancet Neurol*. https://doi.org/10.1016/S1474-4422(19)30091-2
8. Nutt JG, Gancher ST, Woodward WR. Does an inhibitory action of levodopa contribute to motor fluctuations? *Neurology* 1988;38:1553–1557.
9. Nutt JG. Levodopa-induced dyskinesia: review, observations, and speculations. *Neurology* 1990;40:340–345.
10. Alegre M, Lopez-Azcarate J, Alonso-Frech F, et al. Subthalamic activity during diphasic dyskinesias in Parkinson's disease. *Mov Disord* 2012;27:1178–1181.

Supporting Information

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

Video S1. Case 1 shown in 3 segments: segment 1 = gait in the *off* state, segment 2 = gait in the transition from *off* to *on* states, segment 3 = gait in the *on* state.

Video S2. Case 2 shown in 3 segments: segment 1 = gait in the *off* state, segment 2 = gait in the transition from *off* to *on* states, segment 3 = gait in the *on* state.