"On-State" Freezing of Gait: Insights and Treatment With Levodopa Intestinal Gel Infusion

Freezing of gait (FOG) is characterized by sudden and brief episodes of inability to produce effective stepping and is a major risk factor for falls in Parkinson's disease (PD).[1,2] FOG in PD can rarely occur paradoxically in the "*on* state" in a dose-dependent manner; however, treatment of this levodopa-induced complication is limited.[3] We report on a patient with *on*-state FOG that responded to L-dopa/carbidopa intestinal gel (LCIG) infusion in a dose-dependent manner, providing new insights into FOG and L-dopa responsiveness.

A 61-year-old female diagnosed with typical PD for 8 years developed recurrent falls secondary to FOG over 12 months. She was taking levodopa-carbidopa CR 200/50 mg five times per day, pramipexole ER 1.5 mg/day, and rasagiline 1 mg/day. During a practically defined *off* (12 hours without medications), she had a narrow-based gait with reduced step height and stride length, but there was no FOG (Video 1). An oral L-dopa

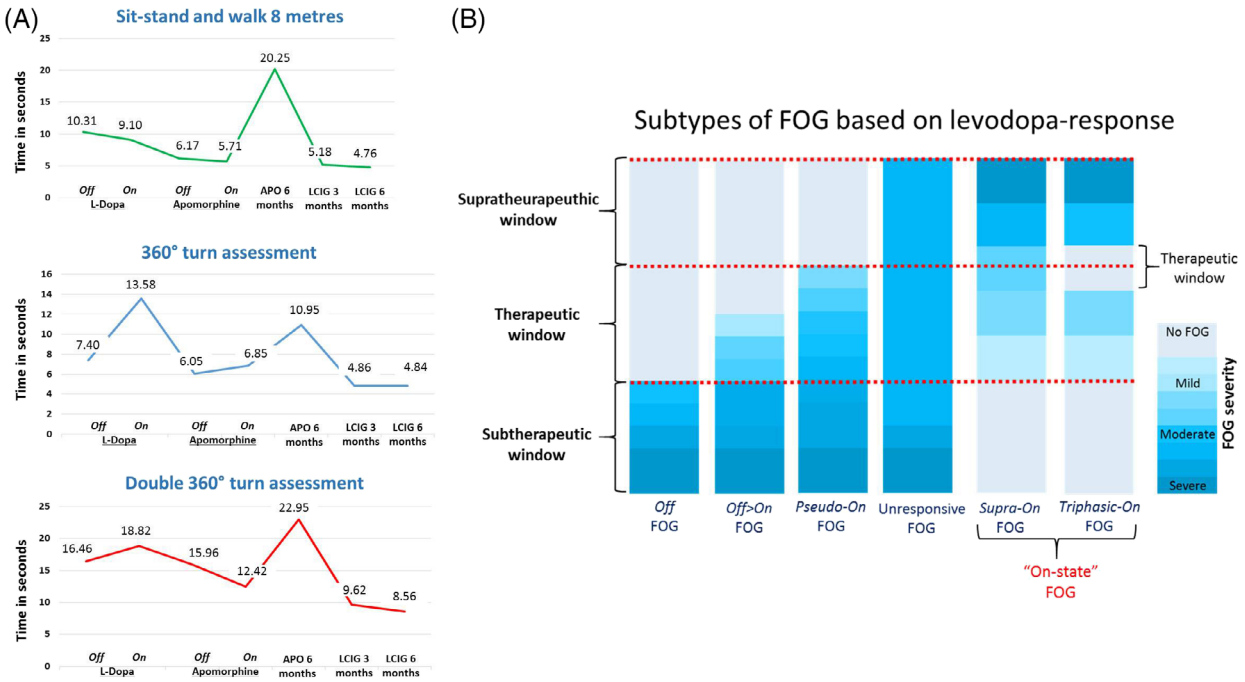

FIG. 1. Gait assessments and subtypes of FOG according to L-dopa responsiveness. (**A**) Three different charts with gait assessments scores according to the *off* and *on* states during the L-dopa challenge and the apomorphine challenge and with chronic apomorphine (6 months) and LCIG therapy (3 and 6 months). The graphic shows that 360-degree and double 360-degree turning times where worse during the on state during the L-dopa challenge and with chronic intermittent apomorphine injection therapy. In contrast, sit-stand and walk and 360-degree and double 360-degree turning times were improved with LCIG infusion. (**B**) Based on the behavioral motor response to L-dopa, FOG in PD can be categorized in five different subtypes.[2] In the figure, the severity of FOG (from severe to absent) is exemplified by different shades of blue in the right colored bar. FOG can occur in the *off* state; however, it improves after L-dopa intake (first left column). Also, FOG can be observed during both *off*-state and *on*-state still improving with the increase of L-dopa dose (second left column). Pseudo-*on* FOG is present in both the *off*-state and *on*-state; however, in the supra-*on* state (twice the patient's usual L-dopa dose) FOG is improved. When FOG is not modified, neither by the *on*-state nor supra-*on* states, this is termed "unresponsive FOG." Rarely, FOG may be absent during the *off*-state and observed only in the supra-*on* state (*on*-state FOG).[3] The relationship between FOG and L-dopa responsiveness observed in our patient is shown in the last right column. In our patient, FOG was not observed during the *off*-state, but was present during both the *on*-state after the acute L-dopa challenge and supra-*on* state using a LCIG infusion. Moreover, a narrow therapeutic window was found where there was an improvement of gait and parkinsonism but without FOG ("triphasic-*on*"). [Color figure can be viewed at wileyonlinelibrary.com]

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250-mg challenge dose produced a 41% improvement in UPDRS-III with dyskinesia (Supporting Information Table S1). However, she developed FOG on gait initiation, straight walking, doorways, and turning. FOG was associated with rising up onto the toes during straight walking and onto the toe of the outer rotating foot when turning, raising the possibility of a dystonic phenomenon (Video 2). She was diagnosed with *on*-state FOG. L-dopa was changed to immediate release and fractionated, amantadine 200 mg daily added, and she commenced gait rehabilitation without improvement. Intermittent subcutaneous apomorphine injections were initiated; however, after 6 months' therapy, FOG severity was increased (Fig. 1), leading to ~20 falls a day. Based on previous observations,[4,5] she commenced a 16-hour LCIG infusion. During week 1 of LCIG titration, FOG persisted despite rates that improved parkinsonism while causing dyskinesia, reaffirming *on*-state FOG. We then performed a rapid infusion titration with hourly increments in the continuous rate of 0.1 to 0.2 mL over 5 hours, starting from 2.1 mL/h, and discovered a higher rate of 3.0 mL/h that led to near-complete resolution of FOG. At 6 months, FOG remained much improved with ≤1 fall per week; however, she still reported FOG when using LCIG extra doses. At 7 months, she converted to 24-hour LCIG with a nocturnal rate of 1.4 mL/h for treatment of nocturnal left foot dystonia. Nocturnal oral L-dopa was no longer required. She reduced her daytime rate from 3.0 to 2.9 mL/h. At 9 months (Video 3), FOG was further reduced, averaging 1 fall every 4 weeks. Pre-LCIG, she had used a wheelchair intermittently for 6 months. She now always walks without aids and no longer avoids escalators or misses lift doors. She experiences two to three occurrences of start hesitation daily and mild, nondisabling dyskinesia of the right leg. Extra doses for mild, nondisabling *off* periods sometimes trigger transient start hesitation. Hand function is excellent and she recently resumed playing piano.

We explored LCIG as treatment for *on*-state FOG[3] because plasma L-dopa levels with an LCIG infusion are more predictable than oral L-dopa dosing. We surprisingly discovered an interaction between L-dopa infusion rates and FOG behavior that suggested the existence of another FOG subtype (Fig. 1). We suggest the term "triphasic-*on*" FOG, to denote its presence in both "*on*" and "supra-*on*" states, but also the presence of a narrow "*on*" therapeutic window in the transition between these two states where FOG improves. It is plausible that "triphasic-*on*" FOG may have been present, but obscured, in at least some of the patients reported on by Espay and colleagues[3] because of the use of a single supra-*on* challenge dose and the unpredictable plasma L-dopa levels following oral L-dopa. In conclusion, our case suggests that some PD patients with *on*-state FOG might be able to be treated successfully and implies the existence of additional FOG subtypes.

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References

1. Nonnekes J, Snijders AH, Nutt JG, Deuschl G, Giladi N, Bloem BR. Freezing of gait: a practical approach to management. Lancet Neurol 2015;14:768–778.
2. Latt MD, Lord SR, Morris JG, Fung VS. Clinical and physiological assessments for elucidating falls risk in Parkinson's disease. Mov Disord 2009;24:1280–1289.
3. 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.
4. Chang FC, Tsui DS, Mahant N, et al. 24 h Levodopa-carbidopa intestinal gel may reduce falls and "unresponsive" freezing of gait in Parkinson's disease. Parkinsonism Relat Disord 2015;21:317–320.
5. Cossu G, Ricchi V, Pilleri M, et al. Levodopa-carbidopa intrajejunal gel in advanced Parkinson disease with "on" freezing of gait. Neurol Sci 2015;36:1683–1686.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

A Homozygous Splicing Mutation in *PDE2A* in a Family With Atypical Rett Syndrome

Rett syndrome (RTT, Online Mendelian Inheritance in Man 312750) is an X-linked dominant neurodevelopmental disease characterized by a normal early postnatal development followed by an arrest of growth that occurs between 6 and 18 months of age. There are 2 main types of RTT: typical and atypical delineated on the bases of clinical and genetic criteria.[1] In the atypical form, patients present with many of the clinical criteria of RTT, but do not essentially have all of the features of the disorder. Dysmorphic features were observed in few RTT cases.[2] *Rett-like syndrome* is a recently introduced term used when a patient presents with an overlap

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