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Letter to the Editor

Levodopa-carbidopa intestinal gel therapy may cause "Supra-ON freezing of gate" in patients with Parkinson's disease with diphasic dyskinesia

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Freezing of gait (FOG) is a troublesome motor complication in advanced Parkinson's disease (PD) [1]. FOG generally worsens during the so-called "OFF" period in a levodopa-underdosed state (OFF FOG). Furthermore, FOG can occur during the "ON" period (ON FOG) and infrequently worsens with levodopa overdose (Supra-ON FOG) [2]. Recently, Morales-Briceño and colleagues reported a case of Supra-ON FOG after levodopa-carbidopa intestinal gel (LCIG) infusion therapy [3], and another group reported a similar Japanese case [4]. Supra-ON FOG is currently considered to be an uncommon phenomenon. However, we successively experienced two cases of Supra-ON FOG with LCIG therapy. Here, we report our cases and discuss the mechanisms underlying Supra-ON FOG associated with LCIG.

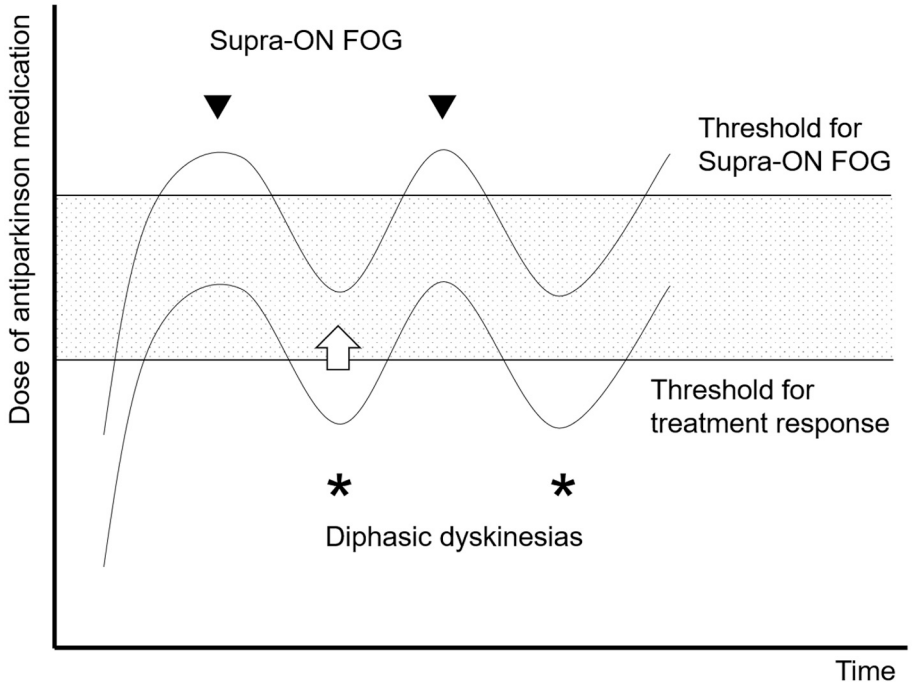

Fig. 1. Increasing the levodopa dose to improve diphasic dyskinesia may lead to levodopa overdose during the ON period and Supra-ON freezing of gait.

Abbreviations: FOG, freezing og gait; LCIG, levodopa-carbidopa intestinal gel; PD, Parkinson's disease; UPDRS, Unified Parkinson's disease rating scale.

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Case 1. A 70-year-old woman was referred to our hospital for LCIG therapy. She developed bradykinesia in her right leg in her late 40s and was diagnosed with PD. Her symptoms were well controlled for a while; however, she developed wearing-off and diphasic dyskinesia at the age of 68, and her motor complications gradually became difficult to control. On examination, she had right-sided rigidity and mild FOG at the beginning of walking (**Video 1**). She scored 26 on the UPDRS Part III. After starting LCIG treatment, 2 mg of ropinirole was continued, and the daily LCIG dose was gradually increased from 1292 mg on Day 1 to 1580 mg one month later. Her wearing-off symptoms were dramatically improved after increasing the LCIG dose; however, she developed severe FOG and mild dyskinesia (**Video 2**). Supra-ON FOG was suspected, and the LCIG dose was tapered down from 1580 mg to 1060 mg. Then, the FOG immediately improved. Her wearing-off symptoms mildly worsened after the reduction of the LCIG dose; however, they improved after increasing ropinirole from 2 mg/day to 8 mg/day without exacerbation of FOG.

Case 2. A 71-year-old man was admitted to our hospital for LCIG treatment. He developed right-sided bradykinesia and was diagnosed with PD in his late 50s. He developed wearing-off and dyskinesia in his 60s, and adjustment of his oral medication did not improve his motor complications. On admission, he showed retropulsion, mild FOG and diphasic dyskinesia with 1100 mg of carbidopa/levodopa and 1.5 mg of pramipexole. After starting LCIG treatment, the daily LCIG dose was increased to 1482 mg/day, and the dose of pramipexole was decreased to 0.375 mg/day. Then, the OFF time was dramatically improved from 7 h/day to 1 h/day, and the UPDRS Part III score improved from 21 to 15 points. However, he showed mild dyskinesia, and his FOG symptoms worsened noticeably. Supra-ON FOG was suspected, and the LCIG dose was gradually tapered down to 1418 mg/day four months later. His FOG symptoms improved, but his wearing-off mildly worsened.

In this report, we described two cases of PD patients who developed supra-ON FOG after LCIG treatment. We performed LCIG treatment for 10 PD patients between 2017 and 2019, and surprisingly, one-fifth of the patients developed supra-ON FOG. The prevalence of Supra-ON FOG with LCIG treatment remains to be elucidated [5]; however, our results raise the possibility that Supra-ON FOG is more common in PD patients who received LCIG therapy than previously thought. It is noteworthy that both of our patients had diphasic dyskinesia before the introduction of LCIG treatment. In general, diphasic dyskinesia is associated with a lower plasma concentration of levodopa, and an increasing levodopa dose is required to treat diphasic dyskinisia [6]. However, in LCIG treatment, increasing the daily LCIG dose only for targeting diphasic dyskinesia may cause excessively higher plasma concentrations of levodopa and easily lead to supra-ON FOG although mechanisms underlying supra-ON FOG still uncovered (Fig. 1). In conclusion, administration of LCIG therapy to PD patients with diphasic dyskinesia may cause supra-ON FOG, and careful adjustment of the daily LCIG dose is needed.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ensci.2021.100387.

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