

**LETTER TO THE EDITOR**

# Benefits of Levodopa-Carbidopa Intestinal Gel Infusion in Patients with Parkinson's Disease Experiencing Gait Dysfunction Following Subthalamic Deep Brain Stimulation

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Dear Editor,

Three patients with relatively young-onset levodopa-responsive Parkinson's disease (PD) underwent subthalamic (STN) deep brain stimulation (DBS) surgery for the management of severe motor response complications following oral dopaminergic therapy. All patients experienced a substantial motor function benefit postoperatively but developed a delayed (> 5 years following DBS) deterioration in gait, characterized by freezing of gait (FOG), slowing of gait and lower limb dystonia. The patients reported that gait dysfunction did not fluctuate according to levodopa intake and was refractory to the optimization of the DBS settings and oral medication regimen, including levodopa at doses  $\geq 600$  mg/day.

This study was deemed exempt from formal ethical review by our institution's Research Ethics Committee (R20180718). All patients gave written informed consent for their data to be published. Patients were started on daytime levodopa-carbidopa intestinal gel (LCIG) infusion via jejunostomy following a nasoduodenal trial of this therapy. Walking and 180-degree turn times in the "on-stimulation/on-medication" state were recorded on video before initiation of LCIG infusion and again after at least 6 months. Baseline (i.e., pre-LCIG) videos were recorded 1–2 hours after the standard morning dose of levodopa. Follow-up (i.e., post-LCIG) videos were recorded during daytime LCIG

infusion at each patient's prescribed continuous rate. The DBS settings were identical at the pre-LCIG and post-LCIG assessments. Clinical details of the patients are summarized in Table 1.

Walking and 180-degree turn times and distances one day before LCIG initiation and at variable times (6–23 months) after LCIG initiation are shown in Table 1. Changes in walking and 180-degree turn times were analyzed by a two-tailed paired t-test. Supplementary Video 1 in the online-only Data Supplement shows the 10 meter walk times (10 meter walk to target, 180-degree turn, then return to origin) of patient 2 recorded one day prior to and six months after commencement of LCIG infusion.

There was a mean 28% improvement (range 14–41) in follow-up walking time relative to the baseline walking time ( $p = 0.118$ ). There was a mean 36% improvement in the 180-degree turn time ( $p = 0.057$ ). All patients reported a significant reduction in episodes of FOG while they were on LCIG. Patients reported that the improvement in gait occurred within days or weeks of commencing LCIG and were sustained with long-term use. All patients remain on LCIG at the time of writing and continue to live independently or semi-independently.

STN DBS is an effective treatment for a range of motor problems in PD, including cardinal manifestations (tremor, rigidity, and bradykinesia) and medication response complications (motor fluctuations and dyskinesias).<sup>1</sup> Improvement in these aspects

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**Table 1.** Patient characteristics before LCIG infusion and change in gait parameters following LCIG infusion

	Patient 1	Patient 2	Patient 3
Age at PD diagnosis (years)	51	46	46
Age at STN DBS (years)	58	53	58
Nature of gait dysfunction post-DBS	FOG, slowing of gait, foot dystonia, falls	FOG, slowing of gait, left ankle dystonia	FOG, slowing of gait, left foot dystonia
Maximum medical therapy for gait dysfunction pre-LCIG	Levodopa 800 mg/day; botulinum toxin lower leg	Levodopa 600 mg/day; rotigotine 4 mg/day	Levodopa 800 mg/day; pramipexole 0.75 mg/day
Time post-DBS of LCIG initiation (years)	9	8	8
Maintenance LCIG infusion rate (mg levodopa per hour)	40	52	70
Walking time and distance pre-LCIG	12.5 sec <sup>†</sup> (12, 13); 10 m	16 sec* (22, 10); 8 m	11 sec <sup>†</sup> (11, 11); 10 m
Walking time and distance post-LCIG	9 sec <sup>†</sup> (8, 10); 10 m	9.5 sec* (11, 8); 8 m	9.5 sec <sup>†</sup> (9, 10); 10 m
180-degree turn time pre-LCIG (seconds)	3	4	4
180-degree turn time post-LCIG (seconds)	2	2	3
Time on LCIG at time of gait assessment (months)	6	8	23
Time on LCIG at time of writing (months)	36	37	31

\*in the case of patient 2, walking times are the mean of (a) a sit-to-stand then 8 m walk and (b) the 8 m return walk. The absolute times of the two segments measured are shown in brackets after the mean; <sup>†</sup>walking times for patients 1 and 3 are the mean of two 10 m walk trials, recorded one after the other. The absolute times of the two trials are shown in brackets after the mean. LCIG: levodopa-carbidopa intestinal gel, PD: Parkinson's disease; STN: subthalamic, DBS: deep brain stimulation, FOG: freezing of gait.

of motor dysfunction following STN DBS typically persists at long-term follow-up.<sup>2</sup>

Improvements in gait are evident at short- to medium-term follow-up after STN DBS (i.e., 1–4 years postoperatively).<sup>3</sup> However, in the longer term, a gradual worsening of gait to levels approaching or worse than baseline often occurs.<sup>2</sup> This late deterioration in gait appears to be particularly marked in the “on-stimulation/on-medication” state,<sup>2</sup> indicating that, in the longer term, oral levodopa commonly fails to provide an additive benefit to that of STN DBS on gait dysfunction.

The implications of this diminution of the benefit of STN DBS on axial motor function are substantial, as axial symptoms such as FOG and falls have a significant impact on quality of life and are a major determinant of the need for long-term residential care.<sup>4</sup>

Our patients experienced a lasting improvement in gait dysfunction on LCIG that had not been achievable with prior adjustment of DBS settings and oral levodopa. Improvements in walking and 180-degree turn times following LCIG did not reach statistical significance in this small cohort. However, all patients reported the improvement in their gait to have been of practical benefit in their daily life. Furthermore, these improvements were evident over a time course of up to 23 months post-LCIG initiation, during which one would have expected gait to have deteriorated further had the patients remained on DBS and oral medication alone.<sup>2</sup>

Our findings support those of a previous report showing that LCIG can improve axial motor function (as measured in that

report by the Unified Parkinson's disease rating scale axial subscale) in PD patients previously treated with STN DBS.<sup>5</sup> There are several potential explanations for these observations. The improvement may have occurred as a result of the greater bioavailability of levodopa when given via jejunostomy compared with oral administration. This may have enabled patients to achieve an “on-stimulation/on-medication” response with LCIG that was not possible with the administration of levodopa via the oral route. Alternatively, the benefits of LCIG on gait may be secondary, not to an increase in peak levodopa concentrations but to the beneficial adaptive effects of continuous dopaminergic stimulation (CDS) on locomotor circuits. Chang et al.<sup>6</sup> have reported that 24-hour LCIG infusion can lead to a reduction in FOG and falls in patients experiencing FOG on daytime LCIG alone. This observation might also potentially be explained by the beneficial effects of CDS on locomotor circuits. However, we note that the improvement in gait dysfunction in our patients was evident within days or weeks of LCIG initiation. This suggests that improved levodopa bioavailability rather than adaptive effects on locomotor circuits is the more likely explanation for the improvement.

It is possible that the relatively young age of our patients increased the likelihood of a beneficial response to LCIG infusion. It remains to be seen whether older patients, with more advanced degeneration in apparently non-levodopa-responsive circuits governing axial function and gait, would experience the same benefit.

In summary, LCIG infusion may be a useful therapy in patients who experience disabling late-onset, progressive gait dysfunction

tion following STN DBS for PD. A trial of this therapy via the nasoduodenal route should be considered even in patients who do not manifest a benefit from oral levodopa. Further studies are warranted to confirm our findings in a blinded fashion and in patients of differing ages.

### Supplementary Video Legend

Video 1. The 10 m walk time of patient 2 before and 6 months after commencement of levodopa-carbidopa intestinal gel (LCIG). In addition to the improvement in walk time following LCIG, improvements are also evident in time taken to stand from a seated position, stride length and turning. The patient provided written informed consent to publication of the video showing his face.

### Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.14802/jmd.19022>.

### Conflicts of Interest

The authors have no financial conflicts of interest.

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