

## BRIEF COMMUNICATION

# Rescue Levodopa/Carbidopa Intestinal Gel for Secondary Deep Brain Stimulation Failure

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## ABSTRACT

**Objective** The long-term efficacy of deep brain stimulation (DBS) for motor fluctuations in advanced Parkinson's disease (PD) has been well established; however, motor fluctuations may recur over time despite multiple adjustments of DBS settings and medications.

**Methods** We conducted a retrospective chart review of three patients for whom levodopa-carbidopa intestinal gel (LCIG) was additionally administered as a rescue therapy for secondary DBS failure due to the recurrence of motor fluctuations.

**Results** The three patients had advanced PD with a disease duration of 14–19 years, and had undergone DBS for motor fluctuations refractory to standard medical management. LCIG was administered to the patients because of symptom recurrence years after DBS and provided complementary effects in all patients.

**Conclusion** The cases presented here show that rescue LCIG therapy may be a complementary treatment option for patients with post-DBS advanced PD who have a recurrence of troublesome motor complications.

**Key Words** Deep brain stimulation; Globus pallidus; Infusion pump; Parkinson's disease; Subthalamic nucleus.

Device-aided therapies such as deep brain stimulation (DBS) and levodopa-carbidopa intestinal gel (LCIG) are treatment options for patients with advanced Parkinson's disease (PD) who present with motor fluctuations refractory to standard medical approaches. The major targets of DBS for PD are the subthalamic nucleus (STN) and globus pallidus internus (GPI).<sup>1</sup> The long-term efficacy of DBS has been shown in several studies; however, "secondary DBS failure", which represents a worsening of symptoms or a loss of response after initial improvement, has been reported.<sup>2,3</sup> Motor fluctuations may recur over 5 to 12 years, and dyskinesia might reappear within 1 year despite multiple ad-

justments of DBS settings and medications.<sup>4-7</sup> In these patients, the addition of LCIG, which has a different mechanism of action from DBS, might be beneficial in controlling motor fluctuation recurrence. Here, we describe our experience in 3 of 40 patients who underwent LCIG therapy between 2016 and 2018 at our institute, for whom LCIG was added as a rescue therapy after secondary failure of DBS treatment based on motor complication recurrence.

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## CASE SERIES

### Case 1

A 71-year-old woman with PD had undergone bilateral STN DBS implantation at another institute because of wearing off at age 63. The left DBS lead was revised at our institute at age 65 for insufficient control of PD motor fluctuations because of a suboptimally placed lead. This resulted in good control of motor symptoms until age 70, when she was readmitted for the recurrence of motor complications and evaluation for possible LCIG therapy initiation.

In accordance with the standardized troubleshooting strategy at our institute,<sup>8</sup> the Unified Parkinson's Disease Rating Scale (part III) was used in assessments under four different conditions (off-medication/off-stimulation, off-medication/on-stimulation, on-medication/off-stimulation, and on-medication/on-stimulation). The evaluation revealed an excellent response to intravenous levodopa infusion (52.5% improvement in on-medication/off-stimulation) and a good response to DBS (35.0% in off-medication/on-stimulation), suggesting that the DBS setting was adequate. The patient was already taking levodopa/carbidopa tablets (10/10 mg half tablet five times per day) along with a combination of levodopa/carbidopa/entacapone tablets (50/5/100 mg five times per day) and long-acting pramipexole (1.5 mg once per day). However, owing to the persistence of motor complications, including peak-dose dyskinesia; fluctuations in non-motor symptoms, such as anxiety and hallucinations; and mild impairment on the Frontal Assessment Battery (FAB: 15/18), although the Mini-Mental State Examination (MMSE) score was preserved (30/30), she decided to begin treatment with LCIG. LCIG immediately improved her off state but caused dyskinesia on her left side, which was improved after reducing the DBS setting for the right STN. With this change, motor and nonmotor complications were successfully controlled (Table 1). Her hallucinations improved after the dopamine agonist dose was reduced. She has been receiving DBS with adjunct LCIG therapy for 8 months.

### Case 2

A 64-year-old woman who was diagnosed with PD at age 47 initially presented with left-leg rigidity and gait disturbance. She had a good response to the standard oral medications until wearing-off symptoms occurred at age 53. Owing to the worsening of motor fluctuations and peak-dose dyskinesia with excellent levodopa response (off medication, 40 points and on medication, 24 points; 40% improvement), she underwent bilateral STN DBS at age 58. The inclusion criteria for STN DBS in our institute were previously published elsewhere.<sup>9</sup> The motor fluctuations responded well to DBS, and DBS settings and medications

were easily adjusted according to the symptoms. However, her motor fluctuations and dyskinesia gradually worsened, with freezing of gait, postural instability, and frequent falls, at age 63. On admission, she had been taking levodopa/carbidopa/entacapone tablets (50/5/100 mg) with additional entacapone tablets (100 mg) 11 times per day, as well as cabergoline (3 mg), pramipexole (4.125 mg), and zonisamide (25 mg). The four-condition test revealed an excellent response to intravenous levodopa infusion (37.5%) and a moderate response to DBS (27.0%; Table 1). Further contact screening and trials to optimize the DBS settings offered few additional benefits because of dysarthria. Mild impairment on the FAB (15/18) was also noted, although the MMSE score was preserved (28/30). She then agreed to add LCIG to her treatment, which improved the wearing-off and motor fluctuations but caused right-leg dyskinesia, which was easily managed by reducing left DBS stimulation. Other motor symptoms, mostly axial, such as freezing of gait and postural instability, remained the same after starting LCIG. The patient was on DBS-LCIG for 1 year, with reduced oral dopaminergic medications and stable motor symptoms.

### Case 3

The patient was a 72-year-old woman diagnosed with PD at age 61; she initially presented with left-dominant tremor, rigidity, and mild depressive symptoms 2 years before diagnosis. The administration of levodopa, pramipexole, and an antidepressant improved her symptoms. She experienced wearing off, peak-dose dyskinesia, and off-state dystonia in her lower limbs at age 70. She was taking various oral medications at this time, including half a tablet of levodopa/carbidopa (100/10 mg) with a tablet of entacapone 100 mg 6 times a day, and amantadine 100 mg once a day. Because her dyskinesia and off-state dystonia gradually worsened and she already had a mild decline in her FAB score (15/18), although the MMSE score was preserved (28/30), she underwent bilateral GPi DBS implantation. Her dyskinesia and dystonia dramatically improved; however, motor fluctuations, postural instability, and freezing of gait developed within 1 year after surgery. On admission, the four-condition test revealed a good motor response to intravenous levodopa infusion in addition to DBS (Table 1). Despite the reevaluation with contact screening and trials to optimize DBS settings, no further improvement was attained other than dyskinesia suppression. LCIG therapy was then started, which markedly improved the wearing-off symptoms without inducing dyskinesia. However, freezing of gait did not improve with the addition of duodenal levodopa infusion. Although LCIG therapy provided a better outcome, it was discontinued after 1 month owing to constraints at the nursing home where she was admitted because of her family circumstances.

**Table 1.** Summary of cases

	Case 1 (70 year old, female)	Case 2 (65 year old, female)	Case 3 (73 year old, female)
Age at onset (years)	56	46	59
Age at DBS (years)	63 (L STN was revised at age 65)	58	70
Age at LCIG (years)	71	64	72
DBS target	Bilateral STN	Bilateral STN	Bilateral GPi
Reason for DBS	Wearing off and dyskinesia	Wearing off and dyskinesia	Wearing off, dyskinesia, and off-dystonia
Reason for LCIG	Wearing off, dyskinesia, and hallucination due to DA	Wearing off and dyskinesia	Wearing off
Four-condition test*			
Off-medication/Off-stim	40	48	87
Off-medication/On-stim	26 (-35.0%)	35 (-27.0%)	80 (-8.1%)
On-medication/Off-stim	19 (-52.5%)	30 (-37.5%)	65 (-25.3%)
On-medication/On-stim	15 (-62.5%)	28 (-41.2%)	54 (-37.9%)
UPDRS part III scores <sup>†</sup> (on-medication/on-stim)	19/15	39/33	43/33
UPDRS part IV scores <sup>†</sup>	8/7	8/2	NA
LEDD (mg) <sup>†</sup>	652.5/960	1,327.5/1,246	1,430/1,688.5
LCIG settings			
Morning dose (mL)	8.0	6.8	13.0
Continuous dose (mL/h)	2.5	3.0	4.0
Extra doses (mL)	1.0	1.0	1.0
DBS settings (pre-LCIG)			
	L STN1: 1(-)C(+), 2.6 mA, 60 $\mu$ s, 125 Hz	L STN: 2(-)C(+), 2.6 mA, 60 $\mu$ s, 130 Hz	L GPi: 2(-)C(+), 3.2 mA, 90 $\mu$ s, 130 Hz
	L STN2: 2(-)C(+), 2.4 mA, 60 $\mu$ s, 125 Hz	R STN1: 1(-)C(+), 2.3 mA, 60 $\mu$ s, 125 Hz	R GPi1: 3(-)C(+), 3.1 mA, 60 $\mu$ s, 125 Hz
	R STN1: 1(-)C(+), 2.5 mA, 60 $\mu$ s, 125 Hz	R STN2: 2(-)C(+), 2.5 mA, 60 $\mu$ s, 125 Hz	R GPi2: 2(-)1(+), 3.0 mA, 60 $\mu$ s, 125 Hz
	R STN2: 2(-)C(+), 2.0 mA, 60 $\mu$ s, 125 Hz		
DBS settings (post-LCIG)			
	L STN1: 1(-)C(+), 2.6 mA, 60 $\mu$ s, 125 Hz	L STN: 2(-)C(+), 1.9 mA, 60 $\mu$ s, 200 Hz	L GPi: 2(-)C(+), 2.9 mA, 90 $\mu$ s, 130 Hz
	L STN2: 2(-)C(+), 2.4 mA, 60 $\mu$ s, 125 Hz	R STN1: 1(-)C(+), 2.3 mA, 60 $\mu$ s, 125 Hz	R GPi1: 3(-)C(+), 3.2 mA, 60 $\mu$ s, 125 Hz
	R STN1: 1(-)C(+), 2.3 mA, 60 $\mu$ s, 125 Hz	R STN2: 2(-)C(+), 2.5 mA, 60 $\mu$ s, 125 Hz	R GPi2: 2(-)1(+), 3.3 mA, 60 $\mu$ s, 125 Hz
	R STN2: 2(-)C(+), 2.0 mA, 60 $\mu$ s, 125 Hz		
Oral medications (pre-LCIG)			
	Levodopa/carbidopa 100/10 mg (1/2 tablet $\times$ 5), levodopa/carbidopa/entacapone 50/5/100 ( $\times$ 5), pramipexole 2 mg, and selegiline 5 mg	Levodopa/carbidopa/entacapone 50/10/100 mg ( $\times$ 11), entacapone 100 mg ( $\times$ 11), cabergoline 3 mg, pramipexole 4.125 mg, zonisamide 25 mg, droxidopa 600 mg, donepezil 10 mg, and clonazepam 0.5 mg	Levodopa/carbidopa (100/10 mg) 1,100 mg (6 $\times$ , q3h), entacapone 600 mg (6 $\times$ , q3h), amantadine 100 mg, and donepezil 10 mg
Oral medications (post-LCIG)			
	Donepezil 5 mg, memantine 20 mg, quetiapine 50 mg, clonazepam 0.5 mg, and etizolam 0.5 mg	Pramipexole LA 1.5 mg, donepezil 10 mg, and droxidopa 300 mg	Rotigotine 13.5/24 h (overnight) and donepezil 10 mg

**Table 1.** Summary of cases (continued)

	Case 1 (70 year old, female)	Case 2 (65 year old, female)	Case 3 (73 year old, female)
Outcomes	<ol style="list-style-type: none"> <li>1. Motor fluctuations improved with LCIG</li> <li>2. Hallucination improved with the discontinuation of DA</li> <li>3. Left-sided dyskinesia improved with DBS adjustment on the right side</li> </ol>	<ol style="list-style-type: none"> <li>1. Motor fluctuations improved with LCIG</li> <li>2. Right-sided dyskinesia improved with DBS adjustment on the left side</li> </ol>	<ol style="list-style-type: none"> <li>1. Motor fluctuations improved with LCIG</li> <li>2. Dyskinesia improved by increasing bilateral GPI stim</li> <li>3. LCIG discontinued after a month because of inability to maintain use</li> </ol>

\*UPDRS part III score (% improvement), †Pre-LCIG/post-LCIG. DBS: deep brain stimulation, STN: subthalamic nucleus, LCIG: levodopa-carbidopa intestinal gel, GPI: globus pallidus internus, LA: long-acting, DA: dopamine agonist, UPDRS: Unified Parkinson's Disease Rating Scale, NA: not available, LEDD: levodopa equivalent daily dose, stim: stimulation, R: right, L: left.

## DISCUSSION

We presented three cases of advanced-stage PD in patients who previously underwent DBS and benefited from the addition of LCIG therapy. All patients developed wearing-off symptoms after long-term treatment with DBS and manifested excellent benefits after the addition of LCIG therapy. In the patients who initially underwent bilateral STN DBS, LCIG therapy initiation caused unilateral dyskinesia, which was addressed by reducing contralateral STN stimulation. By contrast, the patient with bilateral GPI DBS tolerated increased LCIG doses without developing dyskinesia. In all three patients, multiple oral levodopa doses were replaced with LCIG. Our experience in these cases may indicate that DBS and LCIG can have complementary actions in reducing motor complications.

Adjunct LCIG therapy has two benefits in patients who previously underwent DBS. First, adding LCIG therapy can address the recurrence of motor fluctuations by continuous infusion of levodopa, thereby maintaining a more constant striatal dopamine concentration. In most cases, disease progression would involve the addition of medications and increased dosages, which may result in the recurrence of motor fluctuations in 7–10 years.<sup>4,5</sup> Klostermann et al.<sup>10</sup> reported two cases involving the addition of LCIG therapy in patients with long-term post-STN DBS that resulted in a 60–80% reduction in off-state time. In addition, they reported that hallucinations were reduced after replacing the dopamine agonist. Kumar et al.<sup>11</sup> reported seven cases of additional therapy with LCIG for post-DBS patients with different targets, including the STN, GPI, and pedunculopontine nucleus, and they reported that LCIG therapy reduced motor fluctuations regardless of the target. Thus, adding LCIG therapy can be considered a rescue treatment for the recurrence of motor fluctuations in cases of secondary failure in patients receiving DBS for a long time.

Second, DBS and LCIG, which have different mechanisms of action, can have complementary effects when used in combination. As shown in the cases presented here, LCIG therapy can

improve wearing-off symptoms by achieving continuous drug delivery and dopaminergic stimulation. By contrast, DBS can separately manage unilateral symptoms by modulating basal ganglia circuits affected by dopaminergic deficits. Regidor et al.<sup>12</sup> conducted an open-label pilot study to compare a group treated with LCIG and bilateral STN DBS with a group treated with only LCIG. They found that among 19 patients who started double therapy, nine decided to continue both treatments.<sup>12</sup> Thus, in selected cases, LCIG with DBS can reduce motor complications. In the same study, five patients were successfully treated with maintenance LCIG monotherapy without replacing the implantable pulse generator after battery depletion. Moreover, five patients discontinued LCIG therapy and returned to DBS monotherapy because of adverse events caused by LCIG. This indicates that the initial selection of device-aided therapy should be carried out carefully. Patients with poor axial symptoms and older age may be more suitable for LCIG than DBS as an initial treatment.<sup>12</sup>

Last, DBS on a second target has also been described as an option for the secondary failure of DBS on an original target.<sup>10</sup> The three cases we described herein included patients who had already developed a mild decline in frontal lobe function or a comorbid psychiatric condition prior to LCIG therapy; therefore, we were hesitant to perform additional DBS surgery. Thus, additional therapy with LCIG instead of rescue DBS or revision surgery may be preferable in cases with cognitive or psychiatric risk in the later stages of disease.

In summary, our cases show that rescue LCIG therapy may be a complementary treatment option for post-DBS patients with the recurrence of troublesome motor complications. While LCIG therapy may control motor fluctuations, it may also cause an asymmetry of symptoms, such as dyskinesia, which can be controlled by adjusting the stimulation settings. However, such findings should be confirmed in a randomized controlled study with quality of life as the main outcome. Last, it is important that the initial selection of device-aided therapy should be carefully evaluated in consideration of various factors, including support and sustainability.

## Ethical Compliance Statement

The authors confirm that institutional review board approval was not required for this work. We confirm that we have read the Journal's position on issues regarding ethical publication and affirm that this work is consistent with the ethical guidelines.

## Conflicts of Interest

The authors have no financial conflicts of interest.

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## Author Contributions

Conceptualization: Genko Oyama and Juan Miguel Pilar Bautista. Data curation: Juan Miguel Pilar Bautista and Maierdanjiang Nuermairaiti. Investigation: Juan Miguel Pilar Bautista and Genko Oyama. Methodology: Genko Oyama. Supervision: Genko Oyama. Writing—original draft: Juan Miguel Pilar Bautista. Writing—review & editing: All authors.

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