Direct inhibition of levodopa-induced beginning-of-dose motor deterioration by subthalamic nucleus stimulation in a patient with Parkinson disease

Case report

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Beginning-of-dose motor deterioration (BDMD) is a complication of levodopa medications in Parkinson disease (PD) that is presumably caused by inhibitory effects of levodopa. Only limited experience of BDMD has been described in the literature. The authors report the case of a patient with PD who demonstrated a marked BDMD while being treated with standard levodopa medications. This 55-year-old woman had a 12-year history of PD and a 10-year history of levodopa treatment. Marked exacerbation of symptoms occurred 15 to 20 minutes after every dose of levodopa at 100 mg and lasted approximately 15 minutes. The PD symptoms, particularly tremor and rigidity, were exacerbated more markedly during this period than during the wearing-off deterioration. The BDMD could be controlled very well by subthalamic nucleus (STN) stimulation without any change in the regimen of levodopa medications. These observations suggest that the BDMD was inhibited by STN stimulation through a direct effect.

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Key Words • deep brain stimulation • inhibitory effect • levodopa • motor fluctuation • Parkinson disease • subthalamic nucleus

ON-off fluctuation of motor symptoms, which follows exposure to chronic, repetitive administration of levodopa medications, often complicates levodopa therapy in patients with advanced PD. End-of-dose or “wearing-off” motor deterioration parallels the fall in plasma concentration of levodopa.1,17 In addition, end-of-dose motor deterioration caused by inhibitory effects of levodopa plunges patients into a worsening of disability from their baseline off-medication motor status.2,16 In 1992, Merello and Lees12 first reported that some patients with PD also demonstrate motor deterioration, presumably through similar inhibitory effects of levodopa on the rising phase of the plasma levodopa concentration.6,11–13,16 This phenomenon was designated as “beginning-of-dose motor deterioration,”12 abbreviated in the present paper as BDMD.

Stimulation of the STN can ameliorate on-off motor fluctuations,1,4,8–10,14 by attenuating the wearing-off motor deterioration.18 This effect of STN stimulation is similar to the effects of a maximal dose of levodopa in each patient.1,4,8,9,14,18 In contrast, little is yet known regarding the influence of STN stimulation on the motor deterioration caused by inhibitory effects of levodopa. We report on a patient with PD who demonstrated a marked BDMD under standard levodopa medications, which was found to be inhibited directly by STN stimulation withstanding levodopa medications.

Case Report

History and Presentation. This 55-year-old woman had a 12-year history of PD and a 10-year history of levodopa treatment. Although her PD symptoms had progressively worsened, she was being treated with a restricted dose of levodopa because of levodopa-induced hallucinations: 400/40 mg levodopa/dopa-decarboxylase (100/10 mg four times daily), 750 μg pergolide mesylate (250 μg three times daily), and 10 mg selegiline hydrochloride per day. She eventually developed medically uncontrollable on-off motor fluctuations and came to experience BDMD as well as levo-
dopa-induced dose-onset dyskinesia. For these reasons, she was referred to us for STN stimulation.

When the patient presented to us the total duration of the off-medication period reached 50% of the day. She complained that the BDMD always appeared after every dose of levodopa.

Presurgical Evaluation. During 2 days of observation, we confirmed that the BDMD occurred at 15 to 20 minutes after every dose of levodopa at 100 mg and lasted for approximately 15 minutes, while the intervals from the previous dose of levodopa varied in the range from 2.5 to 8 hours (Fig. 1). The severity of the BDMD was variable, and the BDMD after the first dose of levodopa in the early morning was apparently most severe (Fig. 1B, Table 1). Exacerbation of the PD symptoms, particularly the tremor and rigidity, which predominated in the lower extremities, was noticeably worse during the BDMD than during the wearing-off period. The motor (Part III) score on the UPDRS was increased during the BDMD by 188% from the score during the best on-medication motor condition (on period) and by 44% from the score during the wearing-off motor deterioration (off period). The BDMD was followed by levodopa-induced dose-onset dyskinesia, which consisted of dystonic posture and pain in the left lower extremity (Fig. 1). The temporal relationship between the BDMD and dyskinesia was uniform, the onset and peak of the BDMD always preceded those of the dyskinesia by 15 to 20 minutes. These clinical findings were consistent with the characteristics of BDMD described in the literature. It was impossible to attribute such short-lived motor deterioration to a continuation of wearing-off or end-of-dose motor deteriorations, since it occurred abruptly and invariably after every dose of levodopa, despite varying intervals between doses.

Surgery and Postsurgical Course. The patient underwent implantation of electrodes (Model 3387, Medtronic, Inc.) and pulse generators for deep brain stimulation of the STN bilaterally. The PD symptoms were greatly improved by bipolar STN stimulation, especially during the off periods, at intensities ranging from 2.0 to 2.5 V (pulse width 180 μsec, frequency 135 Hz) during the follow-up period. Subsequent to the initiation of STN stimulation, the doses of medication were reduced to 200/20 mg levodopa/dopa-decarboxylase, 750 μg pergolide mesylate, and 10 mg selegiline hydrochloride per day. The medications were not completely withdrawn, because the patient reported some motor deterioration in the afternoon (lasting approximately 30 minutes). We confirmed that the BDMD was still induced by every dose of levodopa at 100 mg if the STN stimulation was kept turned off, and was immediately attenuated when the STN stimulation was turned on at intensities of > 1.8 V. Complete inhibition of the BDMD was achieved at intensities of > 2.5 V.

Standard follow-up evaluation at 6 months after surgery revealed that the UPDRS motor score was markedly improved by bilateral STN stimulation at an intensity of 2.0 V during the off period, as well as during the on period (78 and 75%, respectively; Table 1). The dose-onset dyskinesia disappeared completely. The BDMD was controlled almost com-

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**Fig. 1.** A: Graph showing the temporal relationship between BDMD and dose-onset dyskinesia (DID) in a patient with PD after administration of levodopa (L-dopa). The asterisks indicate intervals from the previous dose of levodopa in hours. B: Temporal relationship between the appearance of tremor in BDMD and dose-onset dyskinesia after an early-morning levodopa dose (indicated by number sign in A). DRS = dyskinesia rating scale; TRS = tremor rating scale.
It appears possible that BDMD can be inhibited by STN stimulation and further indicates the benefit of STN stimulation for managing the inhibitory effects of levodopa, if they are in fact responsible for the BDMD. In patients with PD, intraoperative microrecording has revealed that intravenous administration of apomorphine induces increased neuronal activities in both the STN and the internal segment of the globus pallidus during BDMD and end-of-dose motor deterioration. Such increased neuronal activities are also observed during wearing-off motor deterioration but are quantitatively more pronounced in that setting. These findings suggest that motor deterioration in patients with PD is closely related to the activities of the basal ganglia, which result in an enhanced inhibitory input to the thalamus. Stimulation of the STN is suggested to suppress such abnormal neuronal activities underlying the PD symptoms and to release the thalamus from excessive inhibition. The present case confirms that STN stimulation can provide benefits in improving off-medication motor status and further indicates the benefit of STN stimulation for managing the inhibitory effects of levodopa.

### Table 1

<table>
<thead>
<tr>
<th>UPDRS Measure</th>
<th>Preop</th>
<th>Off</th>
<th>Postop (% impr)</th>
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<tbody>
<tr>
<td>(max score)</td>
<td></td>
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<tr>
<td>ADL (52)</td>
<td>On WO</td>
<td>BDMD</td>
<td>On Off 6 Mos</td>
</tr>
<tr>
<td>motor (108)</td>
<td>3 17 19 (12)</td>
<td>2 (33) 3 74 (5)</td>
<td>*</td>
</tr>
<tr>
<td>tremor (20)</td>
<td>0 5 10 (100)</td>
<td>0 2 80 (0)</td>
<td>*</td>
</tr>
<tr>
<td>rigidity (32)</td>
<td>5 8 12 (50)</td>
<td>1 (80) 1 92 (1)</td>
<td>*</td>
</tr>
<tr>
<td>akinesia (32)</td>
<td>7 11 13 (18)</td>
<td>0 (100) 2 85 (1)</td>
<td>*</td>
</tr>
<tr>
<td>posture (8)</td>
<td>0 2 2 (0)</td>
<td>0 1 50 (0)</td>
<td>*</td>
</tr>
<tr>
<td>gait (4)</td>
<td>0 1 2 (50)</td>
<td>0 0 (100)</td>
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<tr>
<td>Postop (% impr)</td>
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* ADL = activity of daily living; deter = deterioration; impr = improvement; Off = off period; On = on period; WO = wearing-off period.
† Percentage deterioration compared with wearing-off.
‡ Percentage improvement compared with before surgery.
§ No off-medication assessment was performed at the 12-month follow-up evaluation because a “no off-medication” condition had been achieved.

### Discussion

Merello and Lees reported BDMD occurring at 10 to 20 minutes after intake of levodopa and lasting for 10 to 20 minutes. Before their report, this phenomenon had been regarded as part of wearing-off or end-of-dose motor deterioration that continued until the next dose of levodopa. Although it has been suggested that BDMD might be common, only limited experience of it has been described in the literature. It appears possible that BDMD can be confused with coexisting levodopa-induced dose-onset dyskinesia. In addition, most cases of BDMD have been detected previously under intentional pharmacological examinations, so it remains unknown how common BDMD might be in patients receiving standard levodopa medications. The present case suggests that a marked BDMD similar to the BDMD observed in intentional pharmacological examinations can also occur in patients receiving standard doses of levodopa medications.

Beginning-of-dose motor deterioration has been accounted for on the basis of the inhibitory effects of levodopa, which suppress endogenous dopamine release and synthesis through predominant activation of presynaptic dopamine autoreceptors. This hypothesis implies that BDMD may be induced by a dose of levodopa that is insufficient to activate postsynaptic dopamine receptors. Management of BDMD may therefore be difficult in patients who are already receiving a relatively large dosage of levodopa, and when reducing the levodopa dosage in patients who are distressed by various side effects of the drug.

To the best of our knowledge, the present case demonstrates for the first time that BDMD can be inhibited by STN stimulation and further indicates the benefit of STN stimulation for managing the inhibitory effects of levodopa, if they are in fact responsible for the BDMD. In patients with PD, intraoperative microrecording has revealed that intravenous administration of apomorphine induces increased neuronal activities in both the STN and the internal segment of the globus pallidus during BDMD and end-of-dose motor deterioration. Such increased neuronal activities are also observed during wearing-off motor deterioration but are quantitatively more pronounced in that setting. These findings suggest that motor deterioration in patients with PD is closely related to the activities of the basal ganglia, which result in an enhanced inhibitory input to the thalamus. Stimulation of the STN is suggested to suppress such abnormal neuronal activities underlying the PD symptoms and to release the thalamus from excessive inhibition. The present case confirms that STN stimulation can provide benefits in improving off-medication motor status and further indicates the benefit of STN stimulation for managing the inhibitory effects of levodopa.

### Conclusions

The present case confirms that STN stimulation can provide benefits in improving off-medication motor status through levodopa-like effects, through improving the on-medication motor status in patients who are intolerant to larger doses of levodopa, and through reducing the levodopa dose in patients who are distressed by various side effects of levodopa. In addition, our observations suggest that STN stimulation has direct effects on some of the levodopa-induced motor symptoms, such as BDMD. The combina-
tion of chronic STN stimulation and reduction in dosage of levodopa may contribute further by improving levodopa-induced motor fluctuations through the stabilization of striatal dopamine transmission.

References

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