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LETTER TO THE EDITOR

Successful Treatment of Biphasic and Peak-dose Dyskinesia With Combined Unilateral Subthalamic Nucleus and Contralateral Globus Pallidus Interna Deep Brain Stimulation

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Dear Editor,

Dyskinesia is a disabling motor complication in advanced Parkinson's disease (PD), which can be divided into the common peak-dose dyskinesia and the rare biphasic dyskinesia. The treatment for the coexistence of peak-dose and biphasic dyskinesia is challenging. Here, we report such a case successfully treated with combined unilateral subthalamic nucleus (STN) and contralateral globus pallidus interna (GPi) deep brain stimulation (DBS).

CASE REPORT

A 52-year-old female with a 15-year history of PD complained of disabling dyskinesia almost throughout the daylight hours. The dyskinesia was initially located in the head, neck, and left lower extremity two years prior and then worsened and spread to the whole body.

A suprathreshold levodopa challenge test was scheduled after a 12-hour antiparkinsonian drug withdrawal to better delineate the temporal pattern of her dyskinesia. Thirty minutes after dosing (600 mg), the patient gradually developed choreiform movements, which worsened at 50 minutes. At 1.5 hours, the choreiform movements improved, while mild to moderate dyskinesia was documented at approximately 2 hours. Later, at 3.5 hours, the choreiform movements recurred, favoring a diagnosis of biphasic and peak-dose dyskinesia (Supplementary Figure 1A and Supplementary Video 1. Parts 1 & 2 in the online-only Data Supplement). A second dose of medication was administered, and a similar cycle of dyskinetic movements was observed. The dyskinesia gradually subsided 4–5 hours after the last dose, which disturbed the patient's sleep. The patient scored 81 on the Unified Dyskinesia Rating Scale (UDysRS) at the time of the most severe biphasic dyskinesia. Her dyskinesia remained debilitating despite optimal adjustment of antiparkinsonian medications. The shortened "on" period and severe dyskinesia increasingly interfered with her sleep and caused feeding difficulties (decrease in body mass index [BMI] from 21.7 to 17.4 kg/m^2 in two years), therefore resulting in a poor quality of life (Parkinson's Disease Questionnaire [PDQ-8] score of 22). Thus, the patient was referred to our center for DBS surgery. The levodopa equivalent daily dose (LEDD) was 1,596.75 mg at admission, including levodopa (350 mg, tid), benserazide (50 mg, tid), carbidopa (37.5 mg, tid), entacapone (100 mg, tid), benzhexol (1 mg, bid), and amantadine (100 mg, tid).

A bilateral DBS implant in the STN was initially considered owing to the good responsiveness to levodopa, the need for drug reduction and the excellent efficacy of STN DBS for biphasic dyskinesia in previous reports.[1,2] However, preoperative T2-weighted magnetic resonance imaging (MRI) revealed a localized signal abnormality in the left sensorimotor STN, serving as a contraindication to a STN DBS implant on that side (Supplementary

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Figure 1B in the online-only Data Supplement). Given our previous experience in the application of asymmetrical DBS in the treatment of PD,[3] we offered a combined left GPi and right STN DBS to this patient. The DBS lead (3387, Medtronic, Minneapolis, MN, USA) and pulse generator (37612, Medtronic) were uneventfully implanted under general anesthesia (Supplementary Figure 1C in the online-only Data Supplement). The ventral GPi and the dorsal STN were stimulated, and interleaved stimulation was also used to improve bradykinesia and rigidity. The stimulation parameters for the first six months are shown in Supplementary Figure 1D (in the online-only Data Supplement).

At the 6-month follow-up, the patient's motor symptoms had improved, especially her dyskinesia. Compared to the preoperative baseline, the total Movement Disorder Society-Unified Parkinson Disease Rating Scale part III (MDS-UPDRS III) score was reduced by 36.9% in the med-off state and 23% in the med-on state (Table 1). The UDysRS score was reduced by 76.5% (19 versus 81), with only mild dyskinesia in the head and neck. The mild dyskinesia started 1 hour after the first dose and ended 2 hours after the last dose. The on-off phenomenon disappeared during this period, but the dyskinesia persisted and was slightly more severe during the peak-dose period. However, this mild dyskinesia had little impact on the patient's daily life. Her quality of life improved considerably, with the PDQ-8 score decreasing by 68.2% (7 versus 22). The patient's LEDD decreased to 400 mg, with a 74.1% reduction compared to the preoperative dose. Her BMI was restored to the normal range as well (21.1 kg/m^2). At the ninth month, the parameters were adjusted, mainly by turning down the stimulation frequency of both electrodes because of a mildly reduced step height, as low-frequency stimulation at 60−80 Hz is considered more advantageous for gait impairment (Supplementary Figure 1E in the online-only Data Supplement). The efficacy was even more pronounced at the 1-year follow-up. The dyskinesia completely resolved, and the overall motor symptom improvement was maintained, with the MDS-UPDRS III scores reduced by 49.2% in the med-off condition and 20% in the med-on condition compared to the preoperative scores. The PDQ-8 score decreased by 81.8% (4 versus 22), and the patient's BMI increased to 23 kg/m^2 (Table 1 and Supplementary Video 1. Part 3 in the online-only Data Supplement).

Table 1. Changes from preoperative baseline to postoperative 6-month and 12-month follow-up

Assessment	Preoperative baseline	Follow-up (on-stimulation)	
		6-month	12-month
MDS-UPDRS III			
Off-medication	65	41	33
On-medication	30	23	24
UDysRS	81	19	0
LEDD (mg/d)	1,546.75	400	400
PDQ-8	22	7	4
BMI (kg/m^2)	17	21.1	23

MDS-UPDRS III, Movement Disorder Society-Unified Parkinson Disease Rating Scale part III; UDysRS, Unified Dyskinesia Rating Scale; LEDD, levodopa equivalent daily dose; PDQ-8, Parkinson's Disease Questionnaire; BMI, body mass index.

To elucidate the difference between STN and GPi stimulation, the movement symptoms of unilateral stimulation were compared in the off-medication state. Prior to assessment, medication was withdrawn for 12 hours, and bilateral stimulation was turned off and washed out for one hour. Afterward, STN stimulation was turned on for 1 hour, and motor symptoms (MDS-UPDRS III) were assessed with the STN stimulation on; 1 hour after turning off the STN stimulation and turning on the GPi stimulation, the assessment was performed with the GPi stimulation on. There was no recurrence of dyskinesia in either unilateral stimulation state. The motor symptoms were much better with STN stimulation than with GPi stimulation, with MDS-UPDRS III total scores of 38 and 55, respectively (Supplementary Table 1 in the online-only Data Supplement). The main differences were bradykinesia and tremor in the left upper limb and tremor in the head and neck. Since the preoperative symptoms were nearly symmetrical, a crude conclusion was that for this patient, in the off-medication state, motor improvement was superior with STN stimulation; in addition, STN stimulation improved motor symptoms on both sides of the body, while GPi stimulation mainly improved symptoms on the contralateral (GPi-stim) side. This conclusion was consistent with our previous study.[4] However, the assessments of unilateral stimulation in the on-medication state were not performed because of the patient's complaints about the total assessment duration, which was a limitation of this study.

DISCUSSION

The pharmacological treatment for the coexistence of peak-dose and biphasic dyskinesia could be contradictory. Reducing and fractionating the daily dose of levodopa used in the treatment of peak-dose dyskinesia tends to elicit parkinsonian signs and increase the duration of biphasic dyskinesia, while increasing the medication dose to reduce the severity and duration of biphasic dyskinesia may aggravate peak-dose dyskinesia.[5]

However, DBS may be of value in breaking this deadlock. GPi stimulation seems to induce a more particular and direct effect on dyskinesia, while the anti-dyskinetic effect of STN stimulation may be a combination of a direct effect and a reduction of dopaminergic drug dosages, albeit the latter probably being more dominant. Furthermore, there is a correlation between postoperative levodopa dose reduction and improvements in biphasic

dyskinesia.[2,6] Particularly, the zona incerta (ZI, dorsal STN) and ansa lenticularis (AL, dorsal STN and ventral GPi) are considered critical neural substrates involved in dyskinesia control by DBS.[7] In this case, combined unilateral STN and contralateral GPi DBS provided complete alleviation of both biphasic and peak-dose dyskinesia with a similar drug reduction effect as bilateral STN DBS, suggesting that asymmetrical bilateral DBS may be an alternative option for patients with complex dyskinesia symptoms. We hypothesize that this DBS strategy can combine the more substantial direct anti-dyskinetic effect of GPi and the special drug reduction effect of STN, which needs to be proven by subsequent studies. Certainly, there is insufficient evidence to support the use of asymmetrical bilateral DBS as the first choice for the coexistence of peak and biphasic dyskinesia.

Ethics Statement

The requirement of informed consent was waived by the ethical committee in Ruijin Hospital, Shanghai Jiao Tong University School of Medicine.

Supplementary Video Legends

Video 1. Changes in motor symptoms before and after deep brain stimulation (DBS). Part 1. Biphasic choreiform movements pre DBS. Part 2. Peak-dose dyskinesia pre DBS. Part 3. One year after L-GPi/R-STN DBS, on-medication state.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.22081.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

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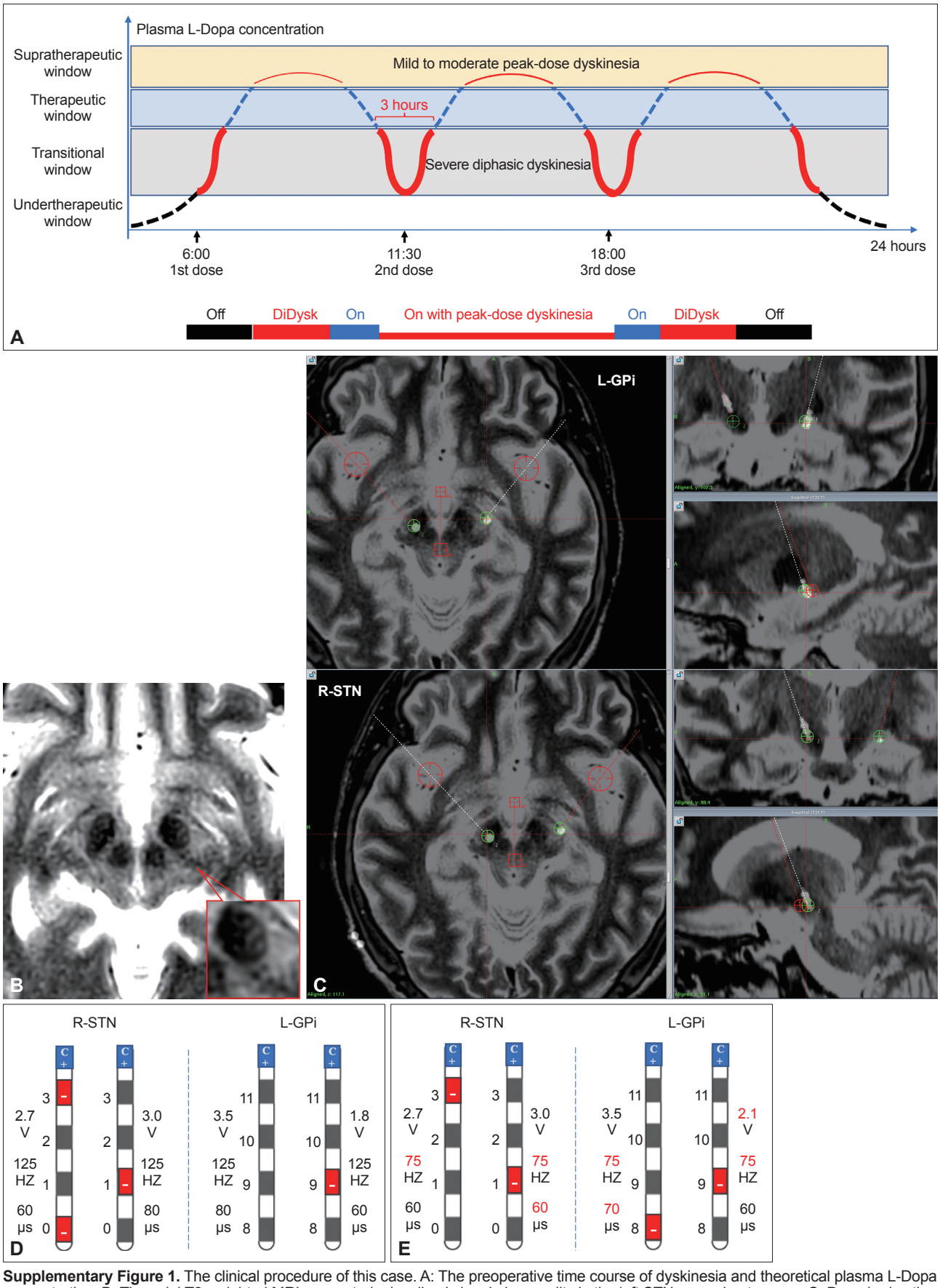
Supplementary Table 1. MDS-UPDRS III scores of unilateral STN/GPi stimulation in the off-medication state

	MDS-UPDRS III total	Bradykinesia	Rigidity	Tremor	Axial sign	Left side (GPi-stim)				Right side (STN-stim)			
						Bradykinesia	Rigidity	Tremor	Total	Bradykinesia	Rigidity	Tremor	Total
STN on/ GPi off	38	23	11	3	1	15	4	2	23	6	3	1	10
GPi on/ STN off	55	28	15	10	2	13	5	1	20	13	6	2	21

MDS-UPDRS III, Movement Disorder Society-Unified Parkinson Disease Rating Scale part III; STN, subthalamic nucleus; GPi, globus pallidus interna.



Supplementary Figure 1. The clinical procedure of this case. A: The preoperative time course of dyskinesia and theoretical plasma L-Dopa concentration. B: The axial T2-weighted MRI suggested a localized signal abnormality in the left STN sensorimotor area. C: Deep brain stimulation electrode's location implanted in the left GPi and the right STN. D: Parameters of chronic interleaved stimulation at the 6-month follow-up. E: Parameters of chronic interleaved stimulation at the 12-month follow-up. STN, subthalamic nucleus; GPi, globus pallidus interna.