OFF-Rebound Dyskinesia in Subthalamic Nucleus Stimulation in Parkinson Disease

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Can. J. Neurol. Sci. 2011; 38: 768-771

"OFF-*off* rebound dyskinesia" in subthalamic nucleus (STN) deep brain stimulation (DBS) is a rare form of dyskinesia that occurs immediately after turning off the stimulation in the medication "*off*" state. The underlying mechanism is not known, but Brodsky et al[1] suggested it is a rebound phenomenon of the antidyskinesia induced by the stimulation of the fiber tracts adjacent to the STN since the active contacts were placed on the dorsal fiber tracts in their case.

We report a case of "OFF-rebound dyskinesia" in a patient taking no levodopa when the active contact was placed exactly inside the STN and discuss the possible mechanism of this rare dyskinesia.

Case Report

A 59-year-old woman developed rigidity on the left side of her body and bradykinesia at the age of 47. She was diagnosed with Parkinson's disease (PD) and started levodopa treatment, which produced an excellent response. After seven years of treatment, she developed severe motor fluctuations and two types of dyskinesia, peak-dose and diphasic (Video segment 1 on-line). Her pre-operative medications consisted of 1140 mg and 800 mg daily of levodopa/carbidopa and entacapone, respectively. At the age of 56, she received bilateral STN DBS surgery as previously described.[2]

Postoperatively, she experienced almost no "*off*" time but had stimulation-induced dyskinesias, which was worse on her left side following the initial stimulation. She took 200 mg daily of amantadine as the only antiparkinsonian medication because levodopa and dopamine agonists worsen dyskinesia. Her motor Unified Parkinson's Disease Rating Scale (UPDRS) score improved from 65 in the preoperative "*off*" state to 42 in the DBS-"ON"/medication-"*off*" state at three months after the surgery (Table 1). At around five months after the surgery, an attempt was made to try to adjust the DBS parameters to improve the parkinsonism further (Table 2). The changed parameters resulted in the stimulation-induced dyskinesia becoming worse on both sides; therefore, the stimulator was turned off to reset it during the overnight 12-hour medication-*off* state. However, immediately after turning off the DBS, her dyskinesia was more accentuated, especially on her left side and this aggravation disappeared when the DBS was turned on again.

This pattern of dyskinesia repeatedly appeared at the follow-up evaluations at six months and one year after the surgery in the overnight 12-hour medication-off state (Video segment 2 and 3 on-line). The phenomenology of dyskinesia was similar to the preoperative levodopa-induced dyskinesia, which was also worse on the left side in this patient. By turning the DBS "OFF," the dyskinesia was immediately aggravated and persisted for about 50 minutes when the patient asked for the DBS to be turned back "ON." Turning the DBS "ON" instantly alleviated the dyskinesia. The active contacts were 2-,3-/case+ with stimulation parameters of 2.3 V for 60 μsec at 170 Hz on the right side and 2-,3-/case+ with stimulation parameters of 1.3 V for 60 μsec at 130 Hz on the left side. The evaluation was repeated twice with the phenomenon reappearing exactly as before. From the postoperative computed tomography images and preoperative magnetic resonance images that were fused as previously described,[2] the active electrodes were placed exactly inside the STN (Figure).

At 40 months after surgery, the stimulator was turned off again and the same phenomenon was observed with the stimulation parameters unchanged. All four contacts were tried, and no dyskinesia was induced by both turning on and turning off contacts 0, 1, and 2 separately in a single monopolar configuration. However, with 3-/case+ monopolar configuration, a similar pattern of dyskinesia was observed.

Discussion

The STN belongs to the basal ganglia having the essential role of movement control. A destructive lesion of the STN by ischemia or hemorrhage can cause dyskinesia like hemiballism.[3] Stimulation of the STN may induce choreo-ballistic dyskinesia, but chronic STN stimulation results in the alleviation of levodopa-induced dyskinesia in PD although the mechanism remains unclear.[4,5] An unexpected "OFF-rebound dyskinesia" in the STN DBS of a Parkinson's patient was described, which appeared immediately after the DBS was turned off. It was an interesting case because the patient had not taken levodopa or dopamine agonists for about 40 months postoperatively and the active contacts were placed inside the STN. A previously reported case of "OFF-*off* rebound dyskinesia" was similar to this case in the phenomenology of dyskinesia; however, it differed from this case in that, dopaminergic drugs had been

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Received December 21, 2010. Final Revisions Submitted April 26, 2011.

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https://doi.org/10.1017/S0317167100054172 Published online by Cambridge University Press

Table 1: The Unified Parkinson Disease Rating Scale (UPDRS) part III total scores and part IV dyskinesia scores in the patient at preoperative and at postoperative follow-up periods

Time	Motor scores (total UPDRS part III scores, 0-108)		Dyskinesia scores (UPDRS part IV item 32, 33, 34)		
			Duration (0~4)	Disability (0~4)	Pain (0~4)
Pre-DBS	Med *Off*	Med *On*	2	4	4
	65	49*			
Post-DBS	DBS OFF/Med *Off*	DBS ON/Med *Off*			
6 months	34	22	4	3	2
12 months	33	20	4	1	1
40 months	47	38	4	1	1

DBS=deep brain stimulation; Med=medication; *Note that this UPDRS score did not reflect the best "On" condition of the patient. We had to rate the patient's status according to the DBS protocols of our center although she did not reach the best "On" state at the day of preoperative evaluation with usual effective levodopa dosage for her. However during her hospital stay, we were able to take video of her best "On" condition which are shown in the Video Segment 1. (on-line)

Table 2: The stimulation parameters, features of dyskinesia and the UPDRS motor scores in the patient according to the postoperative follow-up periods

Postop. period	Postop. 3 months		Postop. 5 months		Postop. 6 months	
DBS parameter	right	left	right	left	right	left
configuration	2-3-/ case+	3-/ case+	1-2-3- /case+	1-2-3- /case+	2-3- /case+	2-3- /case+
voltage	2.4V	1.6V	2.6V	1.0V	2.3V	1.3V
pulse width	60μsec	60μsec	60μsec	60μsec	60μsec	60μsec
frequency	130Hz	130Hz	170Hz	130Hz	170Hz	130Hz
Stimulation-induced dyskinesia	on both sides (worse on the left) but tolerable if no levodopa or dopamine agonist was administered		moderately disabling on both sides (worse on the left)		mild nondisabling on the left side	
OFF-rebound dyskinesia	not checked		Noticed initially, prominent on the left side		on the left side	
Anti-parkinsonian medications	amantadine only		amantadine only		amantadine only	
UPDRS part III score at DBS ON	42		not available		22	

UPDRS=Unified Parkinson's Disease Rating Scale; DBS=deep brain stimulation; Postop=postoperative

https://doi.org/10.1017/S0317167100054172 Published online by Cambridge University Press

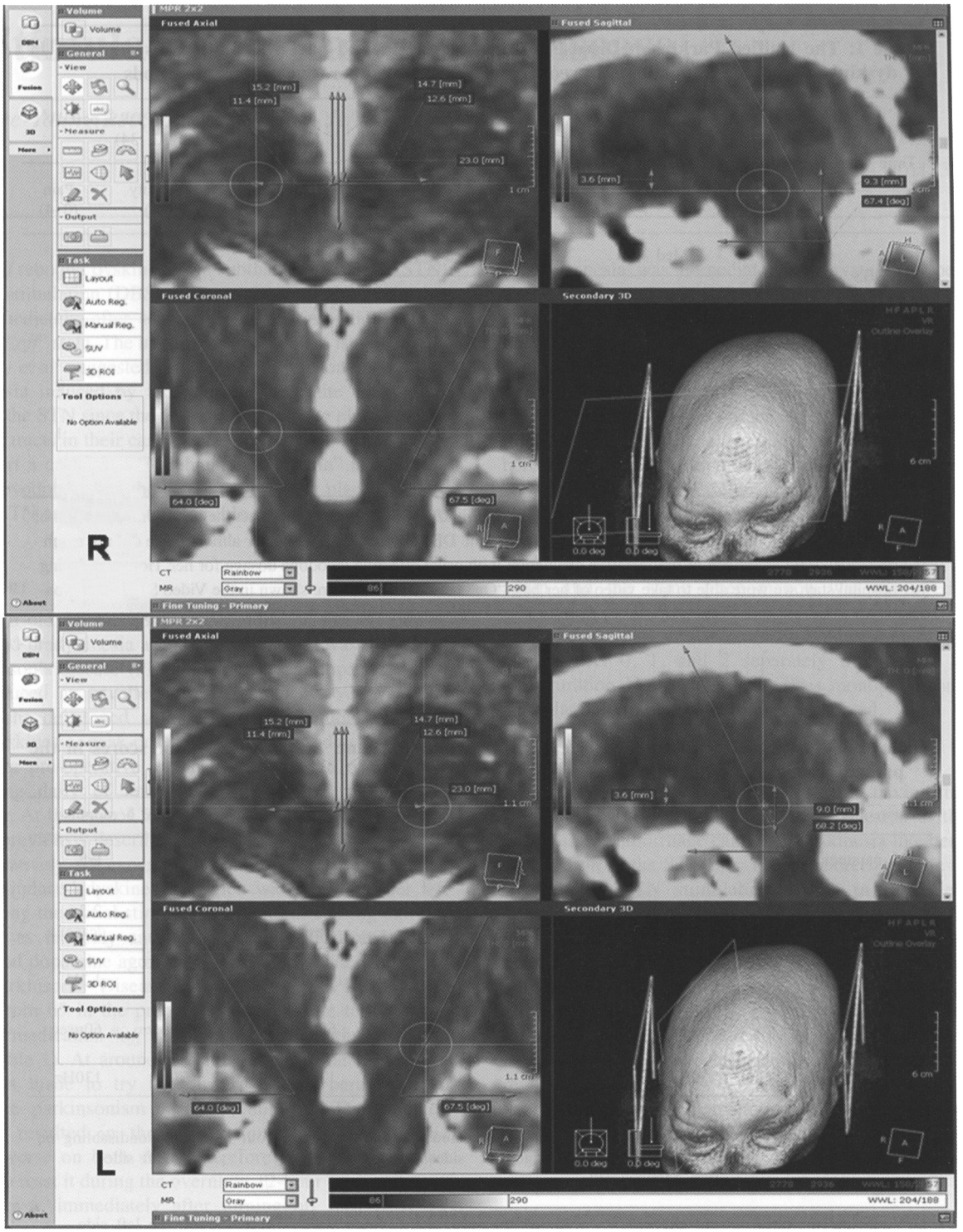

Figure: *Fusion image of the preoperative magnetic resonance image and the 6-month-postoperative computed tomography scans of the patient using a previously described method.*[2] *'R' designates the electrode on the right side and 'L' designates the left side. The locations of the electrodes for each side are shown in three planes: (1) an axial view at a level of 3.5 mm below the anterior-posterior commissural (AC-PC) line (upper left), (2) a coronal view at a level of 3.0 mm posterior to the mid-commissural point (lower left), and (3) a sagittal view at a level of 12 mm lateral to the midline (upper right). In the axial view, the electrodes were located 11.4 mm (for the right electrode) and 12.6 mm (for the left electrode) from the AC-PC line. In the sagittal view, the depths of the lowest contacts were 9.3 mm (for the right electrode) and 9.0 mm (for the left electrode) from the AC-PC line. Contacts 2 and 3 of both sides were placed inside the STN, but contact 2 was near the ventral border and contact 1 was placed over the ventral border of the STN, and contact 0 was placed below the STN in this patient.*

https://doi.org/10.1017/S0317167100054172 Published online by Cambridge University Press

administered postoperatively and the active contacts were dorsally located to the STN.[1]

In this case report, the mechanism of "OFF-rebound dyskinesia" might be explained by the stimulation of the pallidothalamic, pallidosubthalamic, or subthalamopallidal fibers, which serve as an antidyskinetic[1] since current diffusion from DBS to these fiber tracts is possible with multiple monopolar stimulation. Although contacts with a bipolar configuration were not tested, every contact with a single monopolar configuration was checked. Contact 3 produced exactly the same pattern of "OFF-rebound dyskinesia" while stimulation of the remaining lower contacts did not. Thus, another possible explanation is that chronic stimulation of the STN itself might exert antidyskinetic effects.

It should be mentioned that there was a lesioning effect present in the patient since postoperative UPDRS part III scores on the DBS-"OFF"/medication-"*off*" condition was better than the scores on the preoperative medication-"off" condition (Table 1). The presence of dyskinesia on her left side even in the DBS "ON" condition though milder than those in the DBS "OFF" condition, which had appeared postoperatively and lasted during the follow-up periods, could be also explained by a lesioning effect from the STN DBS surgery. However, withdrawing the stimulation of the STN led to the aggravation of the dyskinesia thereby indicating a sudden release of a chronic inhibitory effect on the dyskinesia. Thus, regardless of the presence of a lesioning effect, it is suggested that STN DBS might have an anti-dyskinetic effect and the mechanism for it may be secondary to the stimulation of the fiber tracts passing through the STN or by the stimulation of the STN itself.

With regards to the anti-dyskinetic effect by STN DBS, there have been several studies on levodopa induced dyskinesia.[4,5] The dyskinesia induced by levodopa challenge is immediately alleviated by turning on the STN stimulation.[5] This may be related to changes in the dyskinesia threshold from chronic STN stimulation through the induction of plastic changes in neuronal sensitivity.[4] However, studies regarding the effect of STN DBS on other dyskinesias rather than levodopa-induced dyskinesia are scarce. Our patient did not take levodopa after STN DBS; thus, the effect of the STN DBS on levodopa-induced dyskinesia was not checked in our patient, and the dyskinesia in our patient might be from a lesioning effect on the STN, which had been substantially suppressed by the stimulation of the STN.

However, it is still possible that this rare dyskinesia is not a kind of rebound phenomenon, but rather something like an 'end of dose dyskinesia' which lasts during the decline of the plasma concentration of levodopa.[6] Turning off the stimulator might cause abrupt changes in the concentration of the endogenous dopamine since enhancement of endogenous dopamine release is one of the possible mechanisms of STN DBS.[7] This hypothesis was supported by the observation that the "OFF-rebound dyskinesia" was similar to the preoperative levodopa-induced dyskinesia, which was observed on the same side, and that her parkinsonian symptom on her right side was being simultaneously aggravated while "OFF-rebound dyskinesia" was appearing on her left side, which was also a feature of the levodopa-induced dyskinesia.[8]

In conclusion, this "OFF-rebound dyskinesia" is rare but noticeable in that it may provide useful information regarding the role of chronic STN DBS on dyskinesias in PD and the exact mechanism of it needs to be clarified by further physiological research.

Acknowledgement

The authors deeply thank the Sinyang Cultural Foundation and Mr. Song Foundation for their generous donations and Dr. JM Kim for helpful comments on the present case.

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https://doi.org/10.1017/S0317167100054172 Published online by Cambridge University Press