Immediate and sustained relief of levodopa-induced dyskinesias after dorsal relocation of a deep brain stimulation lead

Case report

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The authors demonstrate that high-frequency electrical stimulation dorsal to the subthalamic nucleus (STN) can directly suppress levodopa-induced dyskinesias. This 63-year-old woman with idiopathic Parkinson disease underwent surgery for placement of bilateral subthalamic deep brain stimulation (DBS) electrodes to control progressive rigidity, motor fluctuations, and levodopa-induced dyskinesias. The model 3389 DBS leads were implanted with microelectrode guidance. Magnetic resonance imaging confirmed proper placement of the leads. Postoperatively the patient exhibited improvement in all of her parkinsonian symptoms; however, her right leg dyskinesias had not improved. Based on their previous experiences treating levodopa-induced dyskinesias with subthalamic stimulation through the more dorsally located contacts of the model 3387 lead, the authors withdrew the implanted 3389 lead 3 mm. Following relocation of the lead they were able to suppress the right leg dyskinesias by using the most dorsal contacts. The patient's dopaminergic medication intake increased slightly. These findings indicate that electrical stimulation dorsal to the STN can directly suppress levodopa-induced dyskinesias independent of dopaminergic medication changes. The 3389 lead may provide inadequate coverage of the subthalamic region for some patients.

KEY WORDS • Parkinson disease • stereotactic neurosurgery • deep brain stimulation • subthalamic nucleus • dyskinesia

High-frequency electrical stimulation (that is, DBS) in the region of the STN enhances the motor performance of patients with idiopathic PD and reduces their dopaminergic medication requirements.^{3,7,11–14,19,21} Each of the cardinal features of PD (tremor, rigidity, bradykinesia) is improved by DBS, as are levodopa-induced dyskinesias, which are a complication of chronic dopaminergic therapy. Because the clinical effects of subthalamic DBS are so similar to the effects observed after ablation of the STN in primates with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonian symptoms^{1,5} and because hyperactivity of the STN is a physiological hallmark of the parkinsonian brain,²⁶ Benabid, et al.,^{2,3} hypothesized that DBS achieves its effects by reversibly inhibiting STN activity. Furthermore, because both ablation and stimulation of the STN are known to induce hyperkinesia sug-

gests that the amelioration of levodopa-induced dyskinesias after subthalamic DBS surgery is not a direct effect of high-frequency stimulation, but arises secondarily due to postoperative reductions in levodopa intake.^{4,7}

Based on this thesis, Medtronic, Inc. (Minneapolis, MN) developed the model 3389 lead to increase the number of electrodes that can be placed within the STN. Like the original model 3387 lead, the 3389 lead is equipped with four 1.5-mm-long cylindrical platinum contacts (Fig. 1); however, on the 3389 lead the contacts are spaced just 0.5 mm apart, compared with the 1.5-mm spacing found on the 3387 lead. Using the 3387 lead, one can position only two of the four stimulating contacts within the STN. The narrower interelectrode spacing of the 3389 lead permits one additional contact to be implanted within the nucleus, but at the cost of a 3-mm reduction in the lead's "effective stimulating length" (10.5–7.5 mm).

Satisfied with the results we had achieved with the 3387 lead, we did not adopt the 3389 lead when it became available. Moreover, we have found that different PD symp-

Abbreviations used in this paper: DBS = deep brain stimulation; MR = magnetic resonance; PD = Parkinson disease; STN = subthalamic nucleus.

Fig. 1. Photograph showing the Medtronic, Inc., models 3387 and 3389 DBS leads. Each is equipped with four 1.5-mm-long cylindrical contacts; however, on the 3389 lead, which is depicted on the right side in the photograph, the interelectrode spacing is reduced from 1.5 to 0.5 mm. This results in a 3-mm reduction in the effective stimulating length of the lead.

toms are best treated through activation of contacts at different anatomical locations in the subthalamic region.²⁴ In our experience, stimulation dorsal to the STN properly actively suppresses levodopa-induced dyskinesias, regardless of whether dopaminergic medications are reduced.^{24,25} We present an interesting case in which the 3-mm dorsal relocation of an otherwise properly implanted 3389 lead dramatically reduced levodopa-induced dyskinesias that were unaffected by stimulation within the STN itself.

CASE REPORT

History and Initial Treatment. This 63-year-old woman has suffered from idiopathic PD since 1993. Her PD was diagnosed after she had experienced unilateral resting tremor for some months. A regimen of Sinemet was begun in July 1994 and yielded a good clinical response. Progressive gait difficulties and rigidity, worsening on/off phenomena, and the onset of dyskinesias necessitated bilateral subthalamic DBS surgery in December 2000; this procedure was performed at another institution by a reputable and experienced team. Model 3389 DBS leads were implanted with microelectrode guidance without complication. Postoperative MR imaging (Fig. 2 *upper*) demonstrated proper placement of the electrodes. Stimulation commenced in January 2001 and led to improvement in the patient's balance, gait, and tremor. Stiffness and left-sided dyskinesias were lessened; however, right-sided dyskinesias and rigidity persisted despite repeated stimulator adjustments.

Presentation and DBS Adjustment. We began treating the patient in February 2002. At that time she reported gait difficulties, poor speech, and worsening right leg dyskinesias. Multiple stimulator adjustments improved her rigidity and gait; however, her right-sided dyskinesias proved resistant, responding only to cathodal stimulation through the most dorsal contact (Contact 3) on the left and then

Fig. 2. Coronal T₁-weighted MR images before (*upper*) and after (*lower*) dorsal repositioning of the left DBS lead; this lead was withdrawn 3 mm as measured directly during the procedure.

only minimally. Based on our previous observations, we postulated that by withdrawing the left DBS lead 3 mm (the difference in the effective stimulating lengths of the 3387 and 3389 leads) we could better control the patient's right-sided dyskinesias. The surgery was performed after delivery of a local anesthetic agent and mild propofol sedation. The 3389 lead was withdrawn 3 mm as measured directly; dorsal repositioning of the lead was confirmed with MR imaging (Fig. 2 *lower*). There were no complications.

Postoperative Course. Postoperatively, we were able to gain better control of the patient's right leg dyskinesias. In the attached videos we demonstrate the effects of unipolar cathodal stimulation through each of the implanted left subthalamic contacts on the patient's right leg dyskinesias before and after repositioning. After repositioning, stimulation through the dorsal-most contacts (Electrodes 2 and 3) yielded better control of the involuntary leg movements than was achieved preoperatively. The patient's medica-

tion regimen and stimulator settings immediately before and 6 months after repositioning are given in Table 1. Better control of the patient's levodopa-induced dyskinesias permitted a modest increase in her intake of dopaminergic agents.

DISCUSSION

This case is instructive for three reasons. 1) It demonstrates that electrical stimulation in the subthalamic region can directly suppress levodopa-induced dyskinesias independent of changes in dopaminergic therapy. 2) Dyskinesias were not suppressed by stimulation within the STN itself, but by stimulation dorsal to the STN, a region that includes the zona incerta, the H₂ field of Forel, and the anterior thalamus.^{6,23} 3) Rather than improving the results of subthalamic DBS surgery, the model 3389 lead may provide inadequate coverage of the subthalamic region for some patients, yielding suboptimal results even with leads that are accurately implanted within the dorsolateral STN.

The precise therapeutic target of subthalamic DBS is not known. If all of the clinical effects of this DBS treatment were generated through inhibition of the STN, only contacts that are positioned within the STN proper would be useful for therapy. Multiple investigators using a variety of localization techniques, however, have found quite the opposite: that the best clinical response may be generated by stimulation at a number of locations in the subthalamic region and that the majority of therapeutic contacts are located at the dorsal margin of the STN or dorsal to the nucleus entirely.^{10,15,16,22,27,28} Moreover, the anatomical position of the clinically most effective contact may be determined by the specific symptoms being treated.²⁴

Similarly, the volume of neural tissue that is affected by an electrical stimulus and the physiological impact of that stimulus on both the intended target and on neural structures at a distance from it are largely unknown. Theories about the true mechanism of action of DBS remain somewhat speculative and include hyperpolarization blockade, modulation of dendritic inputs and/or local interneurons, and facilitation of axonal transmission.^{8,18} Mathematical models of stimulation within neural tissue are beginning to shed light on this important topic.

TABLE 1
Medication and stimulation regimen
before and after repositioning of the left STN DBS lead
in a patient with PD*

Regimen	Preop	3 Mos Postop
lt generator settings	3.6 V/60 μsec/185 Hz; Contacts 1–, 2+, 3–	3.6 V/120 μsec/185 Hz; Contacts 2–, 3–, C+
rt generator settings	3.6 V/60 μsec/185 Hz; Contacts 1–, 2+, 3–	3.6 V/120 μsec/185 Hz; Contacts 1–, 2+, 3–
daily medication intake	levodopa 550 mg, ropinirole 11 mg	levodopa 600 mg, ropinirole 11 mg, entacapone 1000 mg
daily levodopa meq	770	880

* Better control of the patient's dyskinesias after repositioning allowed a modest increase in the patient's dopaminergic therapy, expressed as levodopa milliequivalents (see study by Razmy, et al.). Abbreviation: C = pulse generator case.

McIntyre, et al.,¹⁷ found that cathodal stimulation at the dorsal margin of the STN delivers sufficient energy to propagate action potentials in axons up to 3 mm away. Moreover, the distribution and physiological effects of a delivered stimulus may be influenced by a number of factors, which will vary for every deep brain target. Grill and coworkers^{8,9} have demonstrated that a given stimulus can have opposing effects on different components of the same neuron. Specifically, stimulation at the parameters typically used for DBS can inhibit activity at the cell body while facilitating transmission along its axon. Furthermore, stimulation above a critical frequency induces regular axonal outputs that are informationally neutral. These reports expose our poor understanding of the effects and distribution of therapeutic electrical stimulation within the human brain and highlight the need for additional study.

Given the uncertainty surrounding the true therapeutic site(s) and mechanism(s) of action of subthalamic DBS and the suggestion that the effects of stimulation may be observed at least a few millimeters beyond an activated contact, and given that there is no published evidence to indicate that subthalamic stimulation through the 3389 lead yields superior results to stimulation with the 3387, we believe that it is more prudent to use the 3387 lead to broaden coverage of the subthalamic region until a more precise target is identified.

CONCLUSIONS

High-frequency electrical stimulation dorsal to the STN can directly suppress levodopa-induced dyskinesias independent of alterations in dopaminergic medications. The Medtronic model 3389 DBS lead may provide insufficient coverage of the subthalamic region in some patients.

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