

Deep Brain Stimulation Case Files

Dorsal GPi/GPe Stimulation Induced Dyskinesia in a Patient with Parkinson's Disease

Ahmad Elkouzi^{1*}, Takashi Tsuboi², Matthew R. Burns³, Robert S. Eisinger³, Amar Patel² & Wissam Deeb³

¹Department of Neurology, Southern Illinois University School of Medicine, Springfield, IL, USA, ²Department of Neurology, Yale school of Medicine, Yale University, New Haven, CT, USA, ³Fixel Institute for Neurological Diseases, Gainesville, FL, USA

Abstract

Clinical vignette: A 68-year-old man with Parkinson's disease (PD) had bilateral GPi DBS placed for management of his motor fluctuations. He developed stimulation-induced dyskinesia (SID) with left dorsal GPi stimulation.

Clinical dilemma: What do we know about SID in PD patients with GPi DBS? What are the potential strategies used to maximize the DBS therapeutic benefit and minimize the side effects of stimulation?

Clinical solution: Avoiding the contact implicated in SID and programming more ventral contacts, using lower voltage, frequency and pulse width and programming in bipolar configuration all appear to help minimize the SID and provide appropriate symptomatic motor control.

Gap in knowledge: Little is known about SID in patients with PD who had GPi DBS therapy. More studies using volume of tissue activated and diffusion tensor imaging MRI are needed to localize specific tracts in or around the GPi that may be implicated in SID.

Keywords: Parkinson's Disease (PD), Deep Brain Stimulation (DBS), Globus Pallidus Interna (GPi), Stimulation Induced Dyskinesia (SID)

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*To whom correspondence should be addressed. E-mail: aelkouzi84@siu.edu

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Clinical vignette

A 68-year-old male with a 16-year history of Parkinson's disease (PD) underwent bilateral globus pallidus internus (GPi) deep brain stimulation (DBS) at the University of Florida. He was treated with DBS for the management of motor fluctuations, levodopa-induced dyskinesia (LID), and dystonia. Surgery was performed with microelectrode recording (MER) guidance. During the initial postoperative monopolar threshold review (Table 1), he developed stimulation-induced dyskinesia (SID) in the right hemibody with monopolar activation of the dorsal contacts (contacts 2 and 3) of the left GPi lead. No SID was noted with the stimulation of the ventral contacts (contacts 0 and 1) of the left GPi lead or with the stimulation of any of the contacts of the right GPi lead. Contact 1 stimulation on the left DBS lead provided benefit for tremor, bradykinesia, and rigidity.

Contact 2 provided a more robust improvement in bradykinesia and rigidity but the benefit was limited by SID.

Postoperative lead localization and three-dimensional (3D) mapping identified that both leads were appropriately placed in the postero-latero-ventral GPi (Figure 1). Contact 2 is located in the dorsal GPi/GPe area and contact 3 is located in the GPe area.

Clinical dilemma

This case represents dorsal GPi and GPe SID in a patient with PD. On the left GPi DBS lead, contacts 1 and 2 provided the best clinical benefit. Contact 1 monopolar stimulation improved the tremor but did not have a robust effect on bradykinesia and rigidity. Contact 2 stimulation on the other hand, improved tremor, rigidity, and bradykinesia, but the benefit

Table 1. Summary of the Monopolar Threshold Review of the Right and Left GPI Leads, Indicating Therapeutic Effect and Side Effect Thresholds

Contact Number	Left GPI DBS		Right GPI DBS	
	Therapeutic Benefit Threshold (in Volts)	Side Effect Threshold (in Volts)	Therapeutic Benefit Threshold (in Volts)	Side Effect Threshold (in Volts)
0	1	1.6 (right leg and neck muscle pulling, capsular side effect)	0.9	1.2 (left facial muscle pulling, capsular side effect)
1	1.1	2.7 (right neck muscle pulling, capsular side effect)	1	2.7 (left face and hand muscle pulling, capsular side effect)
2	0.9	1.3 (SID)	1.1	2.4 (left face and left hand muscle pulling, capsular side effect)
3	1	1.4 (SID)	1.2	3 (left face and left arm muscle pulling, capsular side effect)

Abbreviations: DBS, Deep Brain Stimulation, GPI, Globus Pallidus Interna, SID, Stimulation-Induced Dyskinesia.
 Note: The Medtronic 3387 lead has four contacts numbered 0 to 3 (ventral to dorsal).

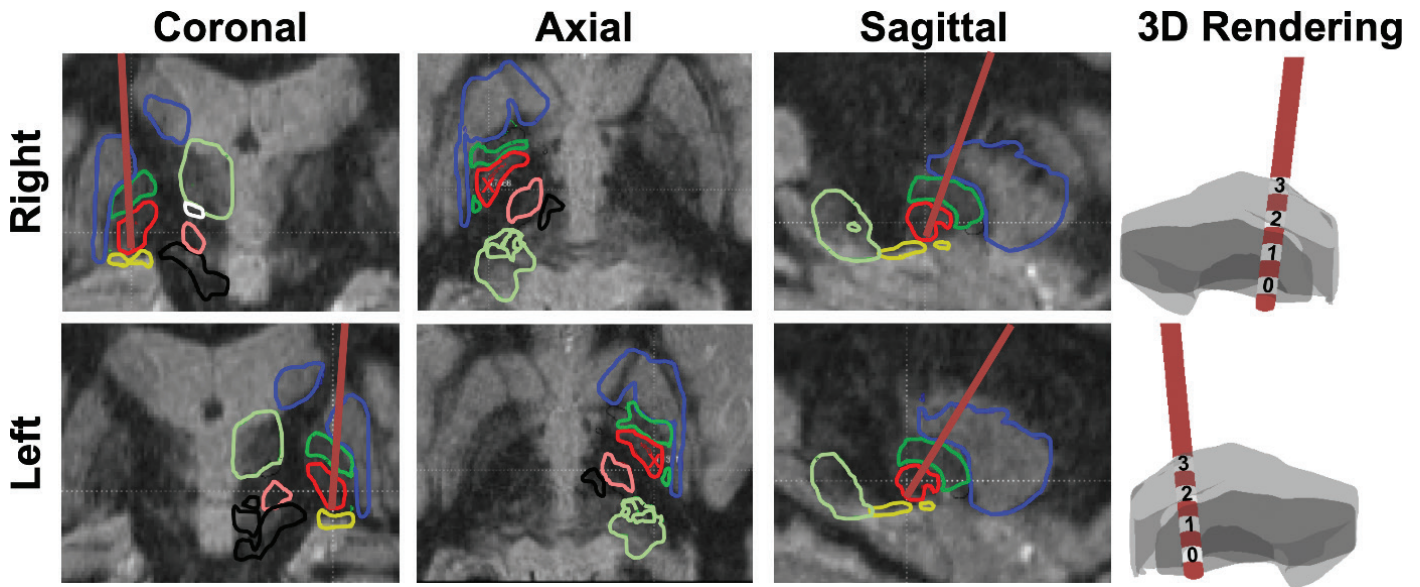


Figure 1. Anatomical positions of the right and left DBS electrodes. Images show coronal, axial, and sagittal MRI with superimposed modified Schaltenbrand- Bailey Atlas, and 3D rendering of the measured electrode. The targeted red structure is the GPI, and the more dorsal green structure is the GPe. The dark red line traversing the image and the red X represent the lead trajectory and position. In the 3D rendering, the dark gray structure is the GPI, and the light gray structure is the GPe. The white regions of the rendered DBS lead represent contacts numbered 0 to 3 and dark red represents insulation.

was limited by SID. The development of SID in this case raises two important questions: First, what is known about the target-specific pathophysiology of SID in DBS for PD? And second, what are the proposed strategies to manage this stimulation-induced complication?

Clinical solution

To overcome the SID noted on contact 2, we considered two strategies: (1) avoiding programs that involve either anodic or cathodic stimulation of contact 2; and (2) stimulation in a bipolar configuration

using contact 2. Table 2 summarizes the programming attempts made. We chose a bipolar configuration with contact 2 as cathode and contact 1 as anode. This configuration helped with the tremor, rigidity, and bradykinesia, without the side effect of SID (Table 2).

Gaps in knowledge

Pathophysiology of SID

Either STN or GPI stimulation shows comparable motor benefit in PD^{1,2} and the choice of target is ideally made after a multidisciplinary

Table 2. Different Programming Trials Used to Optimize Benefit and Minimize Side Effects

Contacts Used for Programming	Stimulation Configuration	Voltage (in Volts)	Frequency (in Hz)	Pulse Width (in μ s)	Effect on Symptoms Compared to Baseline OFF Medication Exam. Presence of SID in Right Hemibody
1	Monopolar (1-;C+)	2.4	130	90	Decreased tremor, minimal effects on rigidity and bradykinesia
2	Monopolar (2-;C+)	2.0	130	90	Decreased tremor and rigidity but minimal effect on bradykinesia. Benefit limited by SID in right hemibody when voltage increased more than 2V
2	Monopolar (2-;C+)	1.8	180	90	Decreased tremor and rigidity. The higher frequency was used in an attempt to better control the tremor. Minimal effect on bradykinesia. SID in right hemibody occurring at lower threshold and are more pronounced
1;2	Bipolar (1-;2+)	2.5	130	90	Decreased tremors, but minimal effect on bradykinesia and rigidity. No SID
1;2	Double monopolar (1-2-;C+)	2.5	130	90	Decreased tremors and rigidity but minimal effect on bradykinesia. SID at 3V
1;2	Bipolar (2-;1+)	2.5	130	90	Decreased tremors, rigidity and bradykinesia. No SID

Abbreviation: SID, Stimulation-Induced Dyskinesia.

team assessment and tailored to the individual needs of the patient.³ Balancing the potential improvement in motor symptoms against the risk of SID is a particular challenge for clinicians and surgeons. GPi targeting is favored by some groups⁴ for the treatment of disabling refractory levodopa-induced dyskinesia (LID) or as a rescue target in cases of severe disabling STN DBS-induced dyskinesia.⁵ “Brittle dyskinesia” is a term used to describe cases of SID in PD patients who were treated with STN DBS, drawing a parallel to brittle diabetes. In a series of 179 patients with STN DBS and 75 patients with GPi DBS, 4 experienced SID (all in the STN DBS group).⁵ It was then postulated that STN DBS carries a higher risk of SID compared to GPi DBS. Classically, dyskinesia induced by subthalamic nucleus (STN) stimulation manifests as hemiballism, choreoathetosis, or dystonia⁶ and can occur immediately postoperatively (potentially due to a subthalamotomy effect⁷) or have a more delayed onset.^{8,9} Female sex, lower BMI, longer disease duration, and longer duration of treatment with levodopa correlated with a higher risk of SID with STN DBS.⁵

Previous studies examined the variable effects of GPi DBS along a ventro-dorsal axis.¹⁰⁻¹² The upper contacts in these studies were located in the dorsal GPi or GPe. Dorsal GPi/GPe stimulation improved parkinsonism but could cause SID that may mimic LID¹⁰; conversely, ventral GPi stimulation suppressed LID but may potentially worsen hypokinesia.^{10,11} This was also observed in dystonia patients, in whom ventral GPi stimulation improved dystonia but induced hypokinesia.¹²⁻¹⁴ This distinct effect of ventral versus dorsal GPi/GPe stimulation has been attributed to the pallidothalamic tracts, which are GPi efferent fibers consisting of the dorsally located fasciculus lenticularis and the ventrally located ansa lenticularis.¹⁰ Moreover, diffusion tensor imaging (DTI) studies suggest that the ventral GPi has stronger connectivity to the primary sensorimotor cortex and supplementary motor area,

whereas the dorsal GPi has stronger connectivity to the pre-supplementary motor area and premotor cortex.^{15,16} The mechanism of SID after GPi DBS remains unclear; however, the distinct connectivity between ventral and dorsal GPi might explain why dyskinesia occurs more frequently with dorsal stimulation in the GPi. Another compelling hypothesis is that the dyskinesia occurs due to spread of the current to the adjacent GPe or due to GPe stimulation. It is possible that the stimulation of the inhibitory efferent GPe axons or excitatory efferent STN axons is implicated in the dyskinesia.

Some insight can be possibly gleaned from the similar phenomenon of LID. The classic model of PD involves loss of dopaminergic input to the striatum resulting in pathologically increased activity of the STN and GPi, and increased inhibition of thalamocortical circuitry. This produces the clinical syndrome of bradykinesia and rigidity.¹⁷⁻²¹ Studies in parkinsonian primates and PD patients consistently show decreased activity of the STN and GPi with LID.²²⁻²⁶ Additional animal studies have linked LID to alterations of striatal projection neuron firing rates and D1 receptor sensitization.²⁷⁻³⁰ At a neurotransmitter level, dopamine does not appear to be solely implicated in LID as more evidence suggests that glutamate may play a role; in a rodent model of PD, high frequency stimulation of the STN increased the expression of the vesicular glutamate transporters 1-3 (VGLUT 1-3) in the basal ganglia.^{31,32} Moreover, glutamate receptor antagonists blocked dyskinesia in the same PD model. The serotonergic system has also been implicated in LID as shown by preclinical and clinical models.³³ Selective serotonergic agonists have been shown to reduce LID in rodent³⁴ and primate models of PD.³⁵ The mechanism by which the serotonergic neurons facilitate LID remains to be elucidated; some studies suggest that dopamine gets released as a “false” neurotransmitter from striatal serotonergic terminals but more work is needed.³⁶

Management of SID

The management of SID can be particularly challenging for clinicians as finding the appropriate balance to improve motor symptoms while avoiding SID may not be easily achieved. The recommendations for the management of SID in GPi-DBS are limited to expert opinion, with scarce evidence-based recommendations for SID in STN-DBS. Initial management approaches for STN DBS patients with SID include decreasing the volume of tissue activated around the optimal contact (e.g., by decreasing the voltage or pulse width of the stimulation), programming alternative contacts (e.g., more dorsal contacts in the posterior STN may have a direct anti-dyskinetic effect^{37,38}), and programming alternative stimulation configurations (e.g., bipolar, double monopolar or interleaved configurations⁶). Additionally, increasing the amplitude of stimulation by smaller increments, and with longer durations of time between changes^{6,39} may also limit SID. Finally, modifying the patient's medication regimen (e.g., decreasing the levodopa equivalent dose or changing levodopa to an extended release formulation) should always be considered in the management of dyskinesia in patients with STN DBS. We would propose applying similar principles to SID due to GPi DBS with the only difference that the more ventral stimulation minimizes the SID. Based on the experience with our patient, we were successful in providing adequate clinical benefit by using a bipolar configuration. Larger cohorts are needed in the future to draw a potential algorithm or guideline for the management of SID in GPi PD patients.

In addition to adjustments in medications and programming strategies, it is important to confirm lead and contact placement as the literature describes a higher risk of SID associated with stimulation of contacts located in or near the globus pallidus externus (GPe).^{40–43} In our case, contact 2 is located at the GPi/GPe border and contact 3 is in the GPe. A contribution of GPe in the pathophysiology of SID in this case and in other published GPi DBS-induced SID cases is possible. In our patient, a Medtronic 3387 DBS lead was used. Implanting a Medtronic 3389 DBS lead could potentially limit the spread of the current and avoid SID. One can also see the benefit of a directional lead in cases of SID with GPi DBS as stimulation away from the GPe can be helpful in cases where the GPe is determined to be the source of the SID. Further evaluation using DTI studies and calculation of volume of tissue activated around the implicated contact may be needed to further understand the pathophysiology of the SID with GPi DBS.

Expert Commentary: This case highlights a common challenge for the DBS programmer: the induction of dyskinesia by stimulation. When programming patients with STN DBS, dyskinesia is typically the sign of a well-placed lead and can be managed with an appropriate reduction in medication. Programming strategies to compensate for dyskinesia in STN DBS (e.g., stimulation of cZi) are also commonly known. Similarly, the functional anatomy of the GPi often guides programming decisions for active contact selection. However, objective data confirming this practical experience are limited. As DBS is utilized in greater numbers, standardizing the approach to the patient with SID will be necessary to maximize outcomes. As novel stimulating technologies and programming platforms emerge, with corresponding increasingly complex programming options, the need for evidence-based standardization will

become ever more important. At the same time, programming platforms that utilize patient-specific anatomic-based models to identify the volume of tissue activated may help clarify the role that target functional anatomy plays in causing SID. Adaptive DBS systems which can reliably detect cortical biomarkers of dyskinesia and adjust stimulation to compensate may eventually help to reduce or eliminate the challenge of troubleshooting SID patients.

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