Tremor and Other Hyperkinetic Movements

Identification and Management of Persistent Stimulation-Induced Dyskinesia Associated with STN DBS: The See-Saw Dilemma

DEEP BRAIN STIMULATION CASE FILE

MATTHEW A. REMZ
JOSHUA K. WONG
JUSTIN D. HILLIARD
TRACY THOLANIKUNNEL
ASHLEY E. RAWLS
MICHAEL S. OKUN

*Author affiliations can be found in the back matter of this article

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ABSTRACT

Clinical vignette: A 73-year-old woman with Parkinson's disease (PD) underwent implantation of bilateral subthalamic nucleus deep brain stimulators (STN-DBS) to address bilateral upper extremity medication-refractory tremor. Post-operatively, she experienced a "see-saw effect" where small increases in stimulation resulted in improvement in one symptom (tremor) with concurrent worsening in another (dyskinesia).

Clinical dilemma: SID is usually considered a positive predictor of DBS outcome. However, there are cases where SID cannot be optimized. Lead location and pre-operative characteristics may contribute to this adverse effect. If the combination of programming and medication adjustments fails to resolve SID, what can be done to "rescue" the outcome?

Clinical solution: Management of SID requires a gradual and steadfast programming approach. Post-operative lead localization can guide advanced programming and decision-making. Rescue surgical interventions may be considered.

Gap in knowledge: In cases where SID is persistent despite deploying persistent optimization strategies, there is limited guidance on next steps.

CORRESPONDING AUTHOR:
Matthew A. Remz, MD
Fixel Institute for Neurological Diseases Campus, University of Florida, Gainesville, FL, USA; Department of Neurology, University of Florida, Gainesville, FL, USA
matthew.remz@neurology.ufl.edu

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small increases in stimulation result in improvement in one symptom (tremor) with concurrent worsening in another (dyskinesia). Alternatively, reduction in medication led to worsening of tremor and improvement in dyskinesia. The clinician may thus apply programming and medication strategies but persistently be unable to balance the clinical see-saw. The question in this case involves the potential impact of underlying disease characteristics, the impact of lead location and the region of stimulation, and weighing the value of continued stimulation that produces SID. This guides shared decision making around consideration of a rescue GPi DBS, lead relocation, or a pallidotomy procedure.

CLINICAL SOLUTION

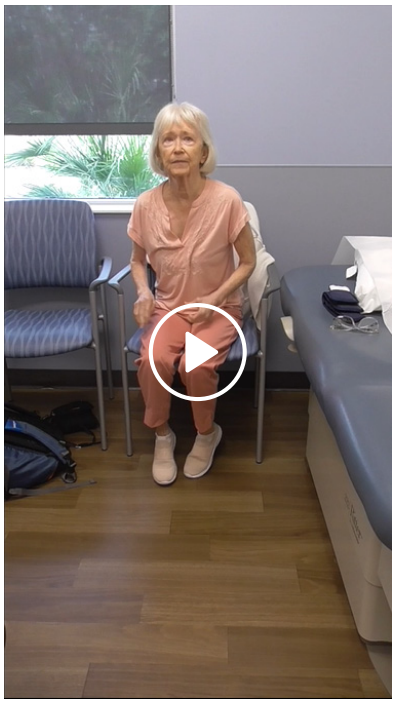
Managing SID is usually approached with the clinician employing slow ramping of stimulation amplitude over several months. Many experts minimize pulse width and frequency, focusing on deploying stimulation to more dorsal regions on the DBS lead. Additionally, directional programming, bipolar stimulation, tripolar stimulation, and interleaving may be trialed. The imaging in this case revealed a relatively ventral and anterior location for both DBS leads. The team used the measured lead localization to "steer current" into a potentially more favorable and more dorsal lateral location for potential optimal neuromodulation. In this case, the programming was complex, comprehensive and time consuming.

Ultimately, a combination of double monopolar and directional stimulation with a reduced pulse width and a reduced frequency was employed (Table 2). Frustratingly, while lower extremity tremor was adequately captured with programming, there was a not a DBS setting which could be identified to consistently capture upper extremity tremor without inducing some degree of lower extremity dyskinesia. Thus, the primary goal became a compromise between tremor suppression and some level of SID (below a bothersome or debilitating threshold).

The post-operative UPDRS part III motor score at the initial programming session, one month following lead placement was 48 off medication and off stimulation. Her 6-month post-bilateral optimized DBS UPDRS part III motor sub-score was 45 off medication/off stimulation and 13 on medication/on stimulation.

A video showing her response to DBS and medications is provided (Video Segment 1) as is a table summarizing the optimized DBS settings (Table 2).

Due to her persistent, bothersome SID, she was offered and is considering a staged approach to adding "rescue" GPi leads, beginning with the left side for the more bothersome right hemibody. This could be done either by leaving the current leads in place or removing and replacing them with leads in the GPi target.



Video Segment 1 Stimulation induced dyskinesia and response to optimized programming. The patient manifested tremor that was severe when both medication and stimulation were "off". There was a manifested reduction in tremor, but increased dyskinesia in the medication "on", stimulation "off" state and in the medication "off", stimulation "on" state. Following optimization of DBS programming, there was no tremor, but there was mild dyskinesia, in the medication and stimulation "on" state.

	CONTACTS	AMPLITUDE (MA)	PULSE WIDTH (μS)	FREQUENCY (HZ)
Left STN: Interleaving, Bipolar	3– C+	1.3	70	150
	3– 2+	0.6	20	60
Right STN Directional, Double Monopolar	11– 9c–	1.4 11– (1.2) 9c– (0.4)	60	150

Table 2 Optimized DBS Settings.

GAPS IN KNOWLEDGE

LOCALIZATION OF DYSKINESIA WITHIN THE STN

Dyskinesia associated with STN-DBS has been widely reported in PD. The dorsolateral and posterolateral regions of applied stimulation have been postulated to underpin the effect, however there are few cases with details for subjects with persistent SID [1, 2]. Notably, there was a single case of persistent SID which resolved when the DBS lead was moved from a more ventral to a more dorsal location [3].

Dyskinesia may occur in other non-PD related hyperkinetic movement disorders. In one recent series of patients with Meige syndrome who were treated with STN-DBS, SID was associated with more ventral (including substantia nigra pars reticulata) rather than the dorsal regions usually observed in SID PD cases. Though the study methods were suboptimal in the application of STN segmentation and relied on stereotactic coordinates, they do raise the important question of influence of the underlying disorder on the SID [4]. Supportive of this notion is an example of STN DBS in obsessive compulsive disorder (OCD) which revealed a more anterior location of neuromodulation within STN, which was observed to trigger hyperkinesia [5, 6]. Finally, STN related SID was the most common "limiting side effect" in a prospective study of isolated dystonia DBS. The cases were likely associated with more dorsolateral neuromodulation than ventral locations [7, 8]. Therefore, we must ask the question whether SID associated with STN-DBS leading to persistent hyperkinesia is a distinct entity from the classical transient post STN-DBS SID, which is usually localized to the dorsolateral sensorimotor STN. Tractography, connectomics, and a closer examination of the neural networks may provide clues to answer this question, however individual baseline disease characteristics may also be a critically important consideration.

HOW TO MANAGE PERSISTENT STIMULATION INDUCED STN RELATED DYSKINESIA

Perhaps the best chance to avoid SID may be the recognition of potential pre-operative risk factors, especially "brittle dyskinesia" (hyperkinesia resulting from the use of ≤ one 25/100 mg tablet of carbidopa/levodopa per dose). Once persistent SID emerges, using empirical trials of dorsal stimulation, bipolar, tripolar or directional stimulation all may provide potential management solutions [9, 10]. Ramping stimulation slowly over many months is considered a mainstay of therapy and in some cases the SID effect may habituate over time, facilitating the use of larger current densities. Dorsal stimulation has been proposed to reduce SID, perhaps through targeting of pallidofugal fibers [11]. However, in many cases the leads have already been placed in the dorsolateral position, and in other cases the trajectory may not include adequate access to the pallidofugal fiber pathways.

Many experts may be swayed to use STN DBS if tremor suppression is the primary goal. However, a recent meta-analysis of STN and GPi DBS has revealed similar tremor suppression outcomes and thus it may be more important to consider "brittleness" and how disabling dyskinesia is pre-operatively [12, 13]. There are a few reports of benefit in cases of SID with dorsal relocation of STN leads and the use of GPi rescue leads [3, 12, 14]. There are no reports of pallidotomy.

EXPERT COMMENTARY

This case underscores the importance of recognizing persistent SID and the "see-saw dilemma" which may emerge during management. There is a paucity of published studies to guide DBS programming and to advise concurrent medication adjustments. The see-saw effect (Figure 2) refers to the frustrating attempts by a clinician to achieve therapeutic equilibrium. The presence of pre-operative "brittle dyskinesia," as in this case, may have been a missed opportunity to pursue a GPi target.

GPi is a well-known dyskinesia suppressor. Well-placed leads in the GPi target afford the managing clinician greater latitude in the administration of higher doses of levodopa, while simultaneously "ramping up" the total amount of stimulation delivered. The clinicians in this case did their best to manage persistent STN SID through slow ramping of stimulation over time, dorsal stimulation, bipolar stimulation, tripolar stimulation and attempts at applying a directional DBS strategy. In our experience, some cases of SID will resolve with the application of slow ramping (e.g. 0.1–0.2 mA per week).

Even when employing these strategies, there are instances where STN lead revision or the addition of a GPi rescue lead will be necessary. In the case of suboptimal lead location, the risks and benefits of repositioning the STN lead into a more dorsolateral position should be weighed. In some circumstances, STN stimulation may be producing partial benefit below the threshold for SID. In this circumstance, maintaining the contribution that STN stimulation provides, while adding a GPi lead to produce concurrent stimulation may aid in a patient's overall therapy and offer more long term programming options. In most of these circumstances, when there is concern for losing positive STN benefit, maintaining the STN lead and adding a GPi lead, rather than revising the STN lead alone, is the safer and higher-yield approach to address persistent SID.

In this case, the anterior and ventral location of the STN DBS leads could argue that repositioning dorsolateral may resolve the issue. Data supporting direct dyskinesia suppression with GPi stimulation may reduce clinical