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Tremor and Other Hyperkinetic Movements

Deep Brain Stimulation Case Files

An Unusual Case of Essential Tremor Deep Brain Stimulation: Where is the Lead?

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Abstract

Clinical Vignette: A 73-year-old female with essential tremor (ET) underwent bilateral thalamic ventralis intermedius (Vim) deep brain stimulation (DBS) surgery. The leads provided tremor benefit, but the location was suboptimal and contributed to stimulation-induced hemichorea.

Clinical Dilemma: Can patients with ET derive benefit when stimulating outside the Vim? What do we know about stimulation-induced hemichorea in the setting of ET?

Clinical Solution: Lead localization combined with advanced programming strategies can be employed to troubleshoot DBS in settings when benefits are observed along with adverse effects.

Gap in Knowledge: Sparse information exists about DBS when applied to neuroanatomic regions outside the Vim for the management of ET. Subthalamic nucleus DBS-induced chorea has been reported in multiple movement disorders, but not in ET.

Keywords: Deep brain stimulation, essential tremor, subthalamic nucleus, chorea

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Clinical vignette

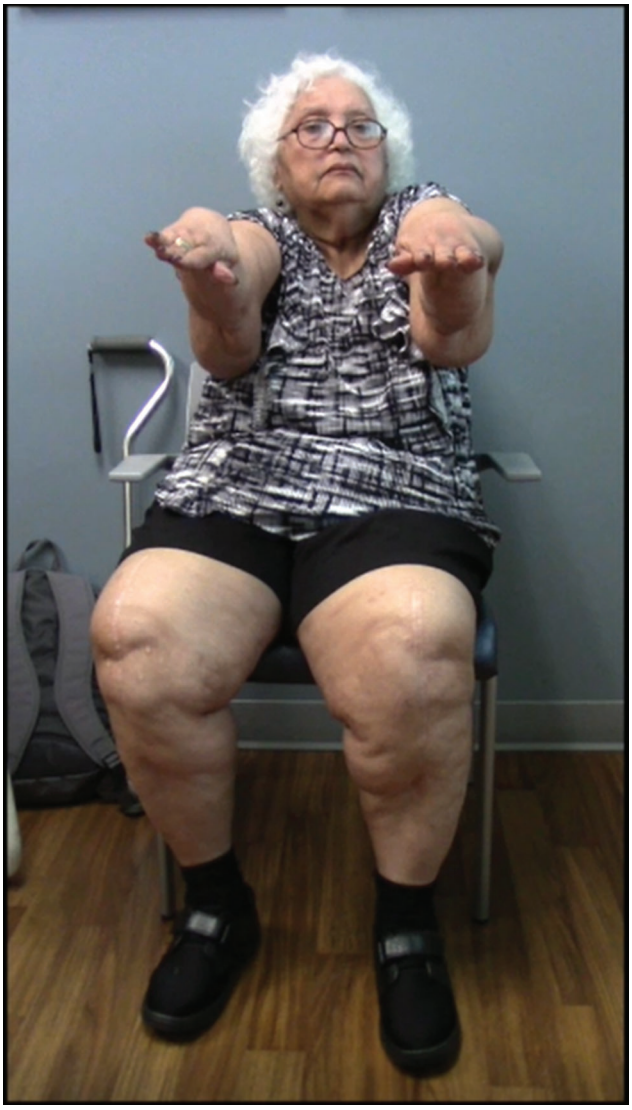
A 73-year-old female with a longstanding history of a disabling essential tremor (ET) underwent planned bilateral thalamic ventralis intermedius (Vim) deep brain stimulation (DBS) at an external facility (Medtronic™, 3387). At the University of Florida (UF), examination was consistent with ET with no evidence of parkinsonism. Tremor benefit immediately following surgery was adequate but mildly waned over the ensuing 2 years with concurrent emergence of a new, bothersome, and near-constant involuntary movement of the right upper extremity. Examination identified the movement as stimulation-induced hemichorea (Video 1).

A monopolar threshold review was performed for both leads (Table 1). The review of the right DBS lead resulted in sensory side effects at modest voltages when activating the most ventral contacts, while the left DBS lead resulted in chorea of the right upper extremity when activating the two deepest (most ventral) contacts.

Post-operative lead localization and three-dimensional mapping identified that the lead locations were both suboptimal. The right DBS lead was placed deep and near the border of the thalamic ventralis oralis posterior (Vop) and ventralis oralis anterior (Voa) while the left DBS lead was placed in the anterolateral portion of the subthalamic nucleus (STN) with the lead trajectory also tangent to the posterior subthalamic area (PSA) (Figures 1 and 2).

Clinical dilemma

While the patient manifested a significant tremor benefit, neither of her DBS leads was within the traditional target for ET – the thalamic Vim. Furthermore, she developed a rare side effect of stimulation, stimulation-induced hemichorea.



Video 1. **Postural and Intention Tremor Examination.** The video starts by tremor examination in the deep brain stimulation (DBS) ON state followed by an examination in the DBS OFF state (1 month apart). It is notable that there is limited DBS control of tremor on the right side of the body with significant tremor control on the left side of the body. The stimulation settings for the left-sided lead are interleaving C+, 2–, 2 V, PW=90 μs, Freq=125 Hz and C+, 3–, 4 V, PW=120 μs, Freq=125 Hz. The stimulation settings for the right-sided lead are C+, 2–, 2.9 V, PW=90 μs, Freq=160 Hz.

This clinical scenario brings to light a few important questions. First, why did the patient have tremor benefit (though suboptimal and limited by hemichorea) with STN–PSA stimulation? Second, why did the patient have significant tremor control with Voa/Vop stimulation?

Clinical solution

Suboptimal lead location, as noted in this case, has been reported as the most common reason for DBS to fail to provide the expected benefit. It is also a common reason for unexpected side effects. Suboptimal lead location accounts for nearly half of the DBS troubleshooting referrals to tertiary care centers.[1,2] It is important to have a quality assessment procedure in place to evaluate the location of the lead (by direct visualization via post-operative imaging) and to determine its effectiveness (by direct stimulation via a monopolar threshold review and programming).

Table 1. **Monopolar Threshold Review**

Contact Tested	Side Effect Threshold (V)	Side Effect Noted
Right lead		
0	0.5	Tingling of the left face, arm, and leg
1	1.0	Tingling of the left face and leg
2	3.0	Tingling of the left hand
3	3.6	Tingling of the left face and leg
Left lead		
0	0.9	Chorea in the right arm
1	1.0	Chorea in the right arm
2	2.6	Subjective "dizziness"
3	3.5	Tingling of the head

There are a growing number of commercial and proprietary platforms capable of performing lead location and visualization. For example, at the UF, we use a UF-built proprietary platform to measure the post-operative lead location and we obtain a monopolar threshold review on all patients implanted with DBS regardless of whether they are implanted in or out of our institution. When combining imaging and programming, the result may clarify the clinical dilemma.

When faced with tight thresholds within the most effective DBS contacts (e.g. you cannot raise the voltage to the desired level), narrowing the stimulation field, which is referred to as the volume of tissue activation, may be a necessary next step. This change is accomplished by using a bipolar programming scheme or by alternating the area being stimulated through the use of interleaving. The latter strategy is sometimes able to provide the desired benefit while avoiding side effects.[3] In this case, prior to presentation at UF, monopolar programming configurations (C+ 1–, C+ 2–, and C+ 3–) were tried for the left-sided lead with no improvement in tremor. Higher settings led to the development of tingling and pulling sensations. Variation in pulse width (PW) using 60, 90, or 120 μs or variation in stimulation frequency (Freq) using 135, 185, 190, 200, and 210 Hz did not result in tremor benefit. An interleaving combination (C+, 2–, 2 V, PW=90 μs, Freq=125 Hz and C+, 3–, 4 V, PW=120 μs, Freq=125 Hz), despite lack of benefit in either setting, was attempted unsuccessfully. A double

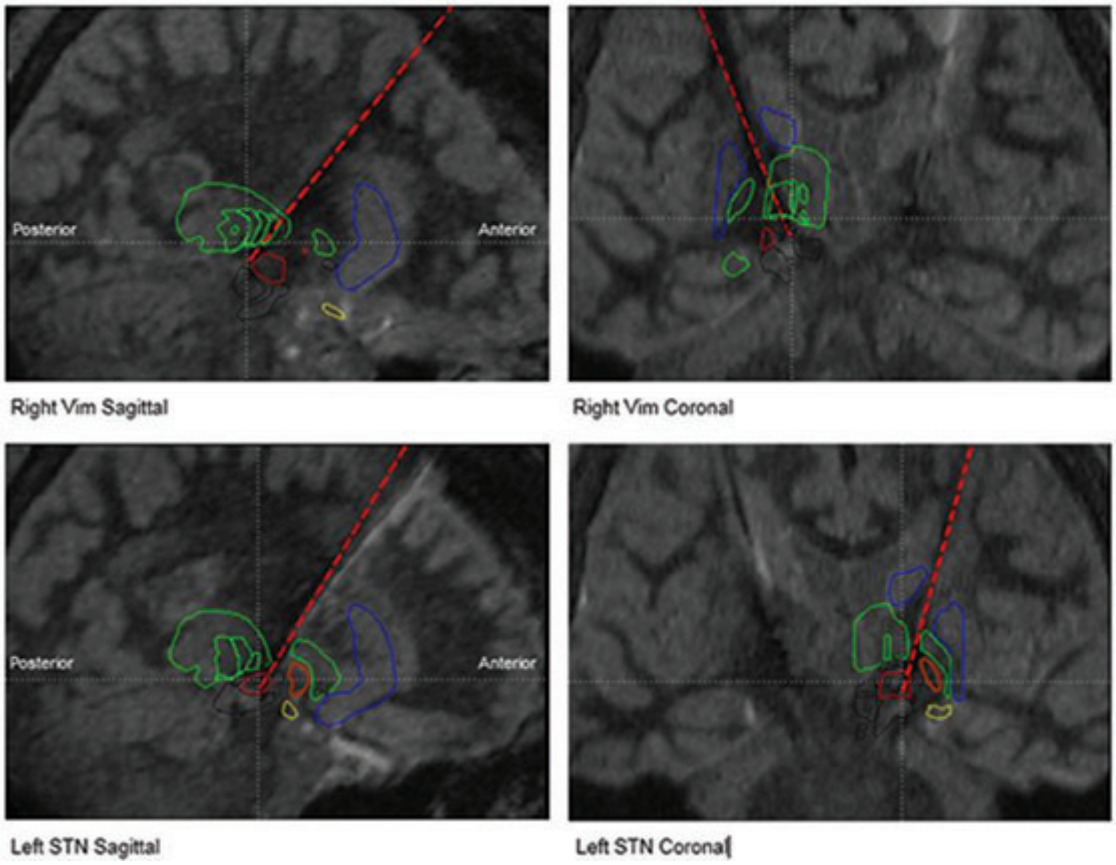


Figure 1. **Postoperative Lead Location Mapping**. The dashed red line is the location of the DBS lead based on magnetic resonance imaging. The thalamus (green), striatum (blue), globus pallidus external segment (green), globus pallidus internal segment (orange) and subthalamic nucleus (red) are outlined as shown. The approximate location of the contacts is shown as white dots.

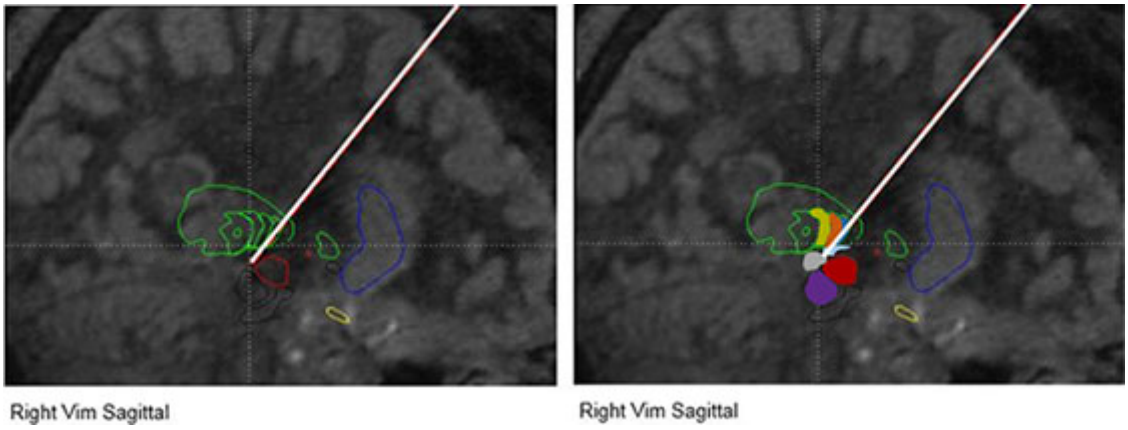


Figure 2. **Important Anatomic Landmarks for Essential Tremor Deep Brain Stimulation.** The left panel shows the unenhanced load location map as noted in Figure 1. The right panel shows the location of important anatomic structures in relation to the deep brain stimulation (DBS) lead. Vim, yellow-filled structure; Vop, orange structure; Voa, dark blue structure; Raprl, gray structure; ZI, light blue structure; red nucleus, purple structure; and STN, red structure. The white solid line represents the right-sided DBS lead of the patient.

bipolar configuration (1+, 2– 3–, 2.5 V, PW=90 μs, Freq=185 Hz) provided mild tremor control with delayed-onset hemichorea. Decreasing the stimulation voltage to 2 V improved but did not resolve the hemichorea and there was not a significant change in tremor. At UF, a simple bipolar configuration of the left-sided lead (2+, 3–, 3.5 V, PW=90 μs, Freq=180 Hz) provided acute, mild tremor benefit

without hemichorea, though the patient was hesitant to try this setting at home and preferred instead to inactivate her left-sided DBS. She was not interested in repeat surgery to revise the lead location. The programming attempts were adequate according to published recommended protocols.[4] For the right-sided lead, a simple monopolar configuration (C+, 2–, 2.9 V, PW=90 μs, Freq=160 Hz) provided significant improvement in tremor (postural and kinetic).

Two interesting observations can be derived from this case. First, suppression of tremor was observed with activation in areas outside of the thalamic Vim. Additionally, anterolateral STN DBS induced hemichorea. We will discuss both observations.

Gap in knowledge

Effective targets for deep brain stimulation in essential tremor

While the thalamic Vim remains the gold standard and most conventional target for DBS in ET, there is ongoing discussion regarding the precise substructure or fiber tract responsible for tremor control. Most experts agree that modulation of the cerebello-thalamo-cortical network is important for providing tremor benefit.[5,6] Within this area, however, recent studies, including those utilizing tractography, have shown that the dentato-rubral-thalamic tract may be important to provide this benefit.[7–9]

A few published cases and studies have examined other targets beyond the Vim for tremor and have observed adequate tremor control.

Stover et al.[5] published a case where posterior STN DBS resulted in control of both ET and Parkinson's disease (PD), though, notably, the patient had a pallidotomy and VIM DBS to address the tremor in the other hand. Another study recruited eight patients with severe proximal ET to undergo placement of DBS in the white matter surrounding the STN, rather than in the STN itself.[10] The stimulated area in this study was thought to involve the PSA, a distinct area that is posterior, superior, and medial to the STN that houses fiber bundles from both the zona incerta (ZI) and prelemniscal radiations (Raprl). This study's result has been reproduced and it suggested that PSA DBS might be more beneficial than Vim DBS for tremor control.[11] Whether this effect was due to stimulation of the ZI[12,13] or due to the Raprl[14] remained unclear.

For now, the Vim remains the target of choice for DBS in ET. Newer technologies have utilized tractography. There has also been advancement in post-operative lead imaging and this has led to a shift toward steering the direction of electrical stimulation. These advances have collectively led to more precision in ablative ET procedures.[15] Tractography, for example, allows the clinician to see the cerebellothalamic tract passing through the PSA, which could be useful for management and placement of DBS.[16]

One important note in this case was that one of the leads was suboptimally placed in the Voa/Vop region and that this lead provided adequate tremor control without the need for revision. Voa/Vop is largely a pallidal receiving area whereas Vim is mostly a cerebellar receiving area. This raises the question of whether the circuitry for ET is circumscribed to cerebellar regions or whether the clinical phenotype includes tremors with contributions from pallidal oscillators. This remains unknown. A recent paper by Oliverio et al.[17] did however show tremor control in multiple sclerosis with an anterior lead located in the Voa/Vop. There are also other papers in the literature showing Voa/Vop may be viable for treatment of ET.[18,19]

Chorea induced by deep brain stimulation

A recent review by Baizabal-Carvallo and Jankovic[20] outlined the movement disorders that can be potentially induced by DBS. Among these was chorea. There was one case that described choreic/ballistic movements occurring during stimulation of the anteromedial STN in a patient with obsessive–compulsive disorder.[21] More often in the literature chorea is included in the single term "dyskinesia" and was observed almost exclusively in the context of STN DBS for PD.[22,23]

The association between STN and chorea is not limited to stimulation. Alvarez et al.[24] published the longitudinal follow-up of PD patients who received unilateral subthalamotomy. Notably, 15% of the patients (14 patients) developed post-operative hemichorea/hemiballism and 57% (eight of the 14 patients) required a rescue pallidotomy to treat this severe complication. In addition, chorea is a known complication of stroke in the subthalamic area.[25]

The overall mechanism by which STN stimulation or ablation resulted in chorea, whether directly or indirectly, has not been well understood and has also not been previously described in the setting of ET. Moreover, the DBS lead causing chorea in this case is located in a relatively more anterior position than is typical for STN DBS in PD, indicating that different subregions of STN can induce this complication.

Since in the future we may be using STN and peri-STN pathways (such as the cerebellothalamic tract in the PSA) more frequently for ET management, a more thorough evaluation of possible stimulation-induced side effects, as observed in this case, will be required.

Expert commentary

This case is of great utility to both the novice and the advanced DBS provider. It highlights the importance of standardized procedures for assessing patients who are receiving suboptimal benefit and/or adverse effects following DBS. Post-operative imaging and review of the monopolar threshold were useful for uncovering the main issues driving the outcome. Programming thresholds should always be combined with imaging to ultimately arrive at a decision about a suboptimal lead. This case draws attention to the continued need to better understand the physiological underpinnings of DBS and it also highlights the need to further characterize different DBS targets for ET. The development of chorea with STN DBS for ET was intriguing but not unexpected. Are there common specific substructures and circuitries within STN that underpin DBS-induced chorea in ET and other movement disorders? In the future, tractography-based surgical targeting may better refine lead placement and possibly reduce adverse effects.[26]

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