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Case Report

Deep brain stimulation of the posterior subthalamic area as an alternative strategy for management of Holmes tremor: A case report and review of the literature

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ABSTRACT

Background: Holmes tremor is often refractory to medical treatment and deep brain stimulation of the ventralis intermedius nucleus of the thalamus (VIM-DBS) is the intervention of choice in controlling the tremor. Herein, we present a beneficial alternative strategy for the management of such situations, considering the posterior subthalamic area (PSA) as the target of stimulation.

Case Description: We report a 57-year-old male with the right-sided tremor following a traumatic brain injury 20 years ago. He had been diagnosed with Holmes tremor that was not responsive to nonsurgical therapeutic options. When refractoriness confirmed, he became a candidate for VIM-DBS. During the operation, by performing macrostimulation with a maximum of 2 mA of amplitude, the tremor had no response to the stimulation of different tracts, and severe right hemi-body paresthesia occurred; therefore, we modified our approach and targeted the PSA, which resulted in satisfactory control of the tremor. The permanent lead was implanted into the left side PSA. At 1-year follow-up, the right side tremor was under complete control.

Conclusion: Our case and other similar pieces of evidence are consistently indicating the potential regulatory effects of PSA-DBS in controlling the Holmes tremor as a feasible alternative strategy when VIM-DBS does not provide a satisfactory response. However, further studies with larger sample size are required to evaluate the long-term response and its possible long-term stimulation-related effects.

Keywords: Deep brain stimulation, Holmes tremor, Nucleus ventralis intermedius, Posterior subthalamic area, Thalamus, Tremor

INTRODUCTION

High-frequency stimulation and lesioning of the nucleus ventralis intermedius (VIM) are the conventional surgical procedures used for alleviating tremors of different pathologies. VIM-deep brain stimulation (DBS) was first introduced as the surgical treatment for Parkinson's disease, and its safety and efficacy for the treatment of tremor dominant movement disorders such as essential tremor (ET) and Holmes tremor (HT) have been reported in several studies.[10,22]

HT, caused by a lesion in the basal ganglia and specific tracts, is believed to have a low response to medical treatments.[30] In cases that are unresponsive to pharmacotherapy, DBS is offered with satisfactory control or even resolution of the tremor.[32,36] However, there are cases for whom stimulation of VIM will not alleviate the tremor. Therefore, having alternative target sites seems to be essential.

The posterior subthalamic area (PSA) is among the targets and efficient in controlling the tremor by receiving high-frequency stimulation.[12] PSA, consisting of zona incerta (Zi) and prelemniscal radiation (Raprl), appears to be a desirable target for tremor control, due to its cerebellothalamic connections and concentration of neurons linked with the proximal muscles.[8] PSA was commonly utilized during the lesioning era; however, after lesioning was replaced with brain stimulation, only a few studies have been published on its efficacy.[17] PSA-DBS has been shown to be effective for a variety of movement disorders, including ET, Parkinsonian tremor, and dystonic tremor.[6,7,9]

We present a 57-year-old male with HT who had no response to medical treatment for 20 years and eventually became a candidate for VIM-DBS. Due to the weak response to VIM-DBS during surgery, the PSA-DBS was chosen as the alternative strategy. Herein, we discuss the rationale, technical challenges, and outcome of the PSA-DBS strategy, along with a comprehensive review of the pertinent literature.

CASE REPORT

A 57-year-old otherwise healthy male had fallen off a horse 20 years ago. He had had a traumatic brain injury and had been in coma for a month. Immediately after gaining consciousness, he developed dysarthria, and 6 months after the accident, he gradually developed right-sided hemiparesis and hemi-body tremor. Resting, action, and positional tremor have been significantly debilitating the patient and hindering him to perform his daily activities. He had also been unable to walk even with assistance and had been wheelchair bounded for the past 20 years.

The patient had received various medical treatments over the years, and none of them was effective in the control of the tremor. Eventually, he was referred to our movement disorder clinic in February 2020. As the possible therapeutic surgical intervention to tackle his tremor, unilateral VIM-DBS was suggested to him and his family.

Surgical procedure

Nonstereotactic magnetic resonance imaging (MRI) (1.5 T Integra, Philips, Netherlands) was obtained a few days before surgery under light sedation (to prevent motion artifacts secondary to tremor). On the day of surgery, after installing the Cosman–Roberts–Wells (CRW) stereotactic frame (Integra Life, USA), a stereotactic computed tomography (CT) scan was done.

The planning process was carried out using StealthStation S8 (Medtronic, Minneapolis, USA). Initially, gadolinium-enhanced T1-weighted MRI was selected as a reference, and other MRI sequences and CT scan were superimposed on it and checked if the different sets of landmarks were matched accurately. After defining the anterior and posterior commissures on the axial T1 sequences, indirect targeting of VIM was accomplished through axial and coronal T2-weighted sequences. The stereotactic coordinates of the VIM target were X: −14.6, Y: −5, and Z: −2.

Following the localization of the entrance point and the trajectory, microelectrode recording (MER) was performed using the Leadpoint system (Medtronic, Skovlundae, Denmark, and Shoreview, Minnesota, USA). The action potentials were recorded in the medial, central, and posterior tracts. The recording suggestive of the thalamic tremor was captured in all tracts from 4 mm above to 2 mm below the level of the target. Based on these findings, we decided to perform macrostimulation along the central tract. The high-frequency constant current stimulation was initiated from 4 mm above the target, under the supervision of a movement disorder neurologist. While stimulation was started from 0 mA and was increased stepwise by 1 mA at each level, the patients' tremor was getting assessed continuously along with the ascending stimulation. The gradual increment of stimulation was cautiously continued till any stimulation-related adverse event was observed. Unfortunately, the stimulation was not effective in the central, posterior, medial, and anterior tracts. Resting, action, and intentional tremors did not respond to the stimulation with different amplitudes, and when the amplitude reached 2 mA, severe acute right hemi-body paresthesia was evident as an adverse event of stimulation. Using intraoperative lateral fluoroscopy and trunion reticles, we confirmed that the stimulation electrode was precisely placed in the correct location.

Nonetheless, due to the insufficient response to VIM stimulation, we decided to perform macrostimulation of PSA as a possible alternative strategy [Figure 1]. After informing the patient and his family about the inefficiency of VIM-DBS and explaining the possible effectiveness of the new strategy (PSA-DBS), we proceeded with the revised target coordinates defined as X: −11.5, Y: −5.59, and Z: −5. To avoid unnecessary drilling, the entry point of the new trajectory was chosen in a way that would be placed at the previous burr hole site. It is worth noting that we preferred not to perform thalamotomy due to the possible irreversible complications of lesioning. We did not use MER in PSA, because our setup had been modified for macrostimulation and we did not anticipate finding a significant MER finding.

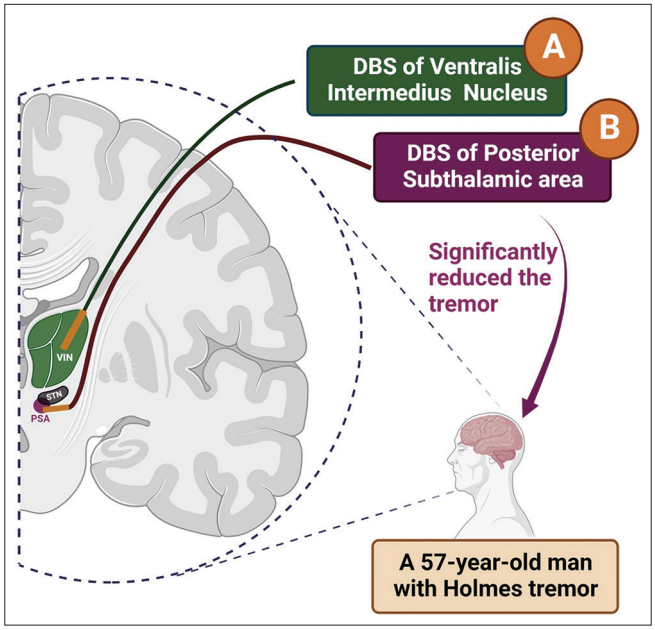

Figure 1: Conventional VIM-DBS versus the alternative approach, PSA-DBS.

A: Deep brain stimulation of VIM as the conventional intervention of choice was not helpful in reducing tremor. **B:** Deep brain stimulation of PSA as the alternative strategy resulted in satisfactory control of the tremor. #Trajectories of the leads demonstrated in this figure are putative and do not represent the actual tracts in the surgery. (The figure is created with BioRender.com).

Interestingly, PSA stimulation (2 mA) resulted in a considerable alleviation of all types of tremors. The patient and his family were reinformed about the favorable response of PSA-DBS, and after obtaining the consent, the permanent lead (DB-2201, Boston Scientific, USA) was implanted in the left PSA in a way that contact 1 was placed 2 mm below the defined target.

An immediate postoperative CT scan was done and the images were superimposed on the preoperative imaging to check the final location of the lead and any possible surgical inaccuracy or complications. The CT scan showed no misplacement or deviation of the lead from the defined target. As the last step, the neurostimulator (Vercise PC, Boston Scientific, USA) was implanted in the right upper part of the chest under general anesthesia. We avoided the left side insertion because implanted pulse generator (IPG) would interfere with the function of implanted cardiac devices (ICD) if the patient ever needed an ICD. After recovery, the patient was transferred to the intensive care unit and then transferred to the ward after 1 day.

Follow-up

The initial programming was performed 2 weeks after the surgery. Contact No. 2 of the implanted lead was selected as the active contact, and the unipolar stimulation parameters were adjusted as follows: Amplitude: 1.5 mA, pulse width: 60 μs, and frequency: 130 Hz.

Afterward, the tremor was significantly controlled and the patient gradually gained the ability to have a walker-assisted gait within 10 months and could accomplish his daily activities. At the time of the 1-year follow-up, he had an infrequent mild tremor and needed modest assistance with gait. Furthermore, no stimulation-related adverse event was observed, and the patient and his family were completely satisfied with the outcome of the surgery. Due to the unprogressive and completely alleviated tremor at the 1-year follow-up, the stimulation parameters were not readjusted at that point.

DISCUSSION

Among the movement disorders, HT usually does not show a satisfactory response to medical treatment. There are pieces of evidence indicating the efficacy of the surgical intervention, including DBS or lesioning, for the management of this disorder.[19,36]

VIM has been the conventional target used for the surgical treatment of tremor; however, new targets have been applied for cases in whom stimulation of the VIM seemed to be ineffective.[37] While various targets such as globus pallidus internus, ventralis oralis anterior, and lenticular fasciculus have been investigated for the treatment of HT,[4,36] PSA has not been fully evaluated.

Before the routine application of DBS, lesioning of PSA was a common procedure for the surgical management of tremor and Parkinson's disease.[10,18,33] PSA stimulation was first introduced by Mundinger in 1977, where the stimulation of extrapyramidal motor thalamic nuclei and Zi led to successful control of torticollis.[25] Thereafter, several studies demonstrated the efficacy of the PSA-DBS in the management of different types of movement disorders. In a study by Blomstedt *et al*.,[10] 19 cases with Parkinson's disease were included; 10 patients received the best medical treatment (oral anti-Parkinsonian medications) and nine underwent DBS of cauda zona incerta (cZi-DBS). The authors observed that cZi-DBS could be more effective than VIM-DBS in controlling the PD tremor, and it affects the Parkinsonian tremor more than the bradykinesia component.

In another study by Blomstedt *et al*.,[9] the authors reported their experience with PSA-DBS for the management of ET in a group of 21 patients. Based on the ET rating scale, the severity of the tremor was reduced by 60%, and some reversible side effects, including transient mild dysphagia and dizziness, were observed.

There are a few reports in the literature representing the application of PSA-DBS on HT. Table 1 summarizes those

Table 1: List of case reports/series on PSA-DBS for HT.

Author, Year	Type of tremor	Number of cases	HT etiology	Stimulation target	Outcomes	Side effects	Follow-up
Plaha *et al*., 2007	HT	1	No anatomical abnormality in the MRI	Bilateral cZi	70.2% improvement (Fahn-Tolosa-Marin Tremor Rating Scale)	Dysphagia for three months	N/A
Kobayashi *et al*., 2014	HT	4	Brainstem hemorrhage due to leukemia, brain tumor in cerebellum; cerebral infarction; intracerebral hemorrhage; post trauma	VO/ VIM+PSA	From the mean score of 16.5 preoperatively to 0.5 at the last visit (Fahn-Tolosa-Marin Tremor Rating Scale)	None	Mean of 25.8 months
Martinez *et al*., 2018	HT	1	HIV-related vasculopathy associated with central nervous system (CNS) toxoplasmosis	Unilateral Raprl	Decreased tremor and rigidity at follow-up	None	Over 2 years
Yuk *et al*., 2018	HT	1	Brainstem hemorrhage	VIM+PSA	Symptom severity from 16 to 8, specific motor task function from 31 to 25, functional disabilities from 30 to 21, tremor severity sustained but specific motor task function and functional disabilities were worse in the follow-ups (clinical rating scale for tremor)	None	3 years
Dec-Ćwiek *et al*., 2019	HT	3	Multiple sclerosis; vascular; vascular	Unilateral PSA	From the mean score of 57.3 preoperatively to 27.3 at the last visit (Fahn-Tolosa-Marin Tremor Rating Scale), from the mean of score 6.6 preoperatively to 2.6 at the last visit (Clinical Global Impression scale)	Stable dysarthria; none; none	Mean of 28 months
O'Shea *et al*., 2020	HT	1	Artery of Percheron infarct	Unilateral VIM Zi	Score improvement from 26 to 16 postoperatively (Unified Parkinson's Disease Rating Scale)	None	N/A

cZi: Caudal zona incerta, DBS: Deep brain stimulation, HIV: Human immunodeficiency virus, HT: Holmes tremor, MRI: Magnetic resonance imaging, N/A: Not available, PSA: Posterior subthalamic area, Raprl: Prelemniscal radiation, VIM: Nucleus ventralis intermedius, VO: Nucleus ventralis oralis, VOA: Ventralis oralis anterior, Zi: Zona incerta

case reports.[12,21,23,26,29,38] All cases, regardless of their HT etiology, revealed significant improvements with no or mild stimulation-induced adverse events.

Furthermore, some studies suggest dual-target stimulation [Table 2] when the single-target strategy does not seem to be effective. Of note, PSA was stimulated as one of the targets in some of these dual-target stimulations.[2,3,15,16,21,27,28,31,34,35]

Some studies have done head to head comparison between the effectiveness of PSA-DBS and VIM-DBS. In a randomized and clinical trial by Barbe *et al*.,[5] the efficacy of PSA-DBS and VIM-DBS was compared in 13 cases with ET. Their findings revealed that there is no significant difference in frequency and severity of complications between the two groups. Regarding the observed effectiveness, they concluded that stimulation of PSA was at least as effective as VIM-DBS while requiring lower amplitudes of stimulation.

As the cerebello-thalamo-cortical circuit is related to ET, interfering with this circuit may alleviate the tremor.[14] Some imaging studies showed the connection between dentato-rubro-thalamic tract (DRT) stimulation and the tremor control.[1,11] Thus, PSA stimulation may lead to a superior outcome due to the fact that PSA is closer to the DRT.[14] In another study, the relation between the distance of the stimulation site (active electrode) and DRT and the clinical outcome was assessed in 13 patients with ET who underwent either PSA-DBS or VIM-DBS. Their investigation revealed

Table 2: List of case reports/series on dual-site stimulation for resolution of tremor with different etiologies.

Author, Year	Type of tremor	Number of cases	Etiology	Stimulation targets	Outcomes	Adverse events	Follow-up
Romanelli *et al*., 2003	HT	1	-	VIM+STN	66% improvement in tremor UPDRS	None	24 months
Foote *et al*., 2005	HT	1	Posttraumatic	VIM+VOA/VOP	9 at baseline to 3 at 12-month with both stimulators, 5 with VIM stimulation, and 4 with VOA-VOP stimulation (Tremor Rating Scale)	-	12 months
Foote *et al*., 2006	Posttraumatic tremor, MS	4	Posttraumatic in three cases	VIM+VOA/VOP	From 5.06 when both stimulators off to 4.02 with VIM stimulation, 3.75 with VOA/VOP stimulation, and 2.94 with both on (Tremor Rating Scale)	-	11.8 months
Papuć *et al*., 2013	Thalamic tremor	1	Ischemic stroke	PAG/PVG+PVL	Alleviation of the thalamic tremor	-	-
Aydin *et al*., 2013	HT	1	Midbrain cavernoma	VIM+GPi	From 11 for the proximal and for the distal arm to 3 for the proximal and 4 for the distal arm (Fahn-Tolosa-Marin Tremor Rating Scale)	None	6 months
Thompson *et al*., 2014	MS	1	-	VIM/VOP+VOP/VOA	-	Intraoperative euphoria	-
Kobayashi *et al*., 2014	HT	4	Brainstem hemorrhage due to leukemia, brain tumor in cerebellum; cerebral infarction; intracerebral hemorrhage; post trauma	VO/VIM+PSA	From the mean score of 16.5 preoperatively to 0.5 at the last visit (Fahn-Tolosa-Marin Tremor Rating Scale)	None	25.8 months
Aydin *et al*., 2017	HT	1	Thalamic hemorrhage by accident	VIM+GPi	From 20 for the proximal and 36 for the distal arm to 3 for the proximal and 4 for the distal arm (Fahn-Tolosa-Marin Tremor Rating Scale), from VAS of 9 for shoulder pain to VAS of 1	None	6 months
Oliveria *et al*., 2017	MS	11	MS	VIM+VO	29.6% improvement (Fahn-Tolosa-Marin Tremor Rating Scale)	Superficial wound infection, transient altered mental status, late multiple sclerosis, intraoperative seizure, death, extension fracture, deep infection	6 months

(*Contd*...)

Table 2: (*Continued*).

Author, Year	Type of tremor	Number of cases	Etiology	Stimulation targets	Outcomes	Adverse events	Follow-up
Toda *et al*., 2017	HT	1	Midbrain injury	VO+STN	Effective	-	6 years
Yuk *et al*., 2018	HT	1	Brainstem hemorrhage	VIM+PSA	Symptom severity from 16 to 8, specific motor task function from 31 to 25, functional disabilities from 30 to 21, tremor severity sustained but specific motor task function and functional disabilities were worse in the follow-ups (clinical rating scale for tremor)	None	3 years

HT: Holmes tremor, PSA: Posterior subthalamic area, VIM: Nucleus ventralis intermedius, VO: Nucleus ventralis oralis, VOA: Ventralis oralis anterior, GPi: Globus pallidus internus, MS: Multiple Sclerosis, PAG: Periaqueductal gray matter, PVG: Periventricular gray matter, STN: Subthalamic nucleus, UPDRS: Unified Parkinson's Disease Rating Scale, VPL: Ventral posterior lateral

that the proximity of implanted active electrodes in the PSA to the DRT can explain the significant favorable outcomes, compared to the VIM cases, using lower amplitudes.[13] However, the authors mentioned that the superiority of PSA-DBS is inconclusive, and further investigations are required.[13]

The exact underlying mechanism of tremor in HT is not known, which explains why the effectiveness of PSA-DBS has not been sharply demonstrated as well.[12] Nonetheless, current hypotheses explain that the etiology of HT may be due to abnormality in the neuronal firing of both basal ganglia-thalamo-cortical and cerebellar-thalamo-cortical loops.[12,37] Accordingly, the GABAergic connection of the Zi with these two loops may be the underlying reason for the effectiveness of the stimulation of the Zi and Raprl in reducing the tremor.

Despite the advantages, PSA-DBS can be accompanied by stimulation-related adverse events. A study by Kim *et al*.[20] compared the side effects of PSA-DBS with VIM-DBS in a series of 93 subjects with ET. Of the patients underwent PSA-DBS, 14.0% presented gait disturbance, 14.0% paresthesia, and 4.3% dysarthria. However, they have reported that changing the stimulation configuration to the bipolar mode or decreasing the amplitude resolves the paresthesia without losing tremor control. Furthermore, dysarthria and gait disturbance could get resolved by changing to dual-site stimulation (VIM and PSA) or changing stimulation to bipolar mode. Besides, gait disturbance and dysarthria were presented more in bilateral DBS than unilateral ones.

Furthermore, a mini-review assessing the efficacy of PSA-DBS in patients with various types of tremors, including multiple sclerosis and posttraumatic-induced tremor, cerebellar tremor, HT, and spinocerebellar ataxia, reported that complications including dysphasia, dysarthria, or disequilibrium were mostly mild, transient, and not accompanied by tolerance, while the latter can be observed among the subjects who undergo VIM-DBS.[24,37]

CONCLUSION

In HT cases that are unresponsive to conventional VIM-DBS, PSA-DBS can be a potential substitution approach to control the tremor effectively. However, almost all supporting evidence are limited to a few case reports. Therefore, further studies, especially the ones with larger sample size and possibly quasi-controlled designs, are needed to justify its potential efficacy along with the limitations and challenges compared to other targets, especially VIM.

Acknowledgment

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Statement of ethics

The Ethics Committee of the Research Center for Neuromodulation and Pain (Shiraz, Iran) approved this study, and written informed consent from the presented case was obtained.

Data availability statement

All relevant data have been reported in the manuscript.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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