Holmes Tremor due to Artery of Percheron Infarct: Clinical Case and Treatment Using Deep Brain Stimulation of the Vim and ZI Targets

Sarah A. O’Shea1,2*, Mitchell Elkind1,2, Seth L. Pullman2 & Blair Ford2

1Department of Neurology, Boston University School of Medicine, Boston University, Boston, MA, USA, 2Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA

Introduction

Holmes tremor (HT) is characterized as a 3–4-Hz flexor-extension oscillation and was initially described by Gordon Holmes in 1904 as a tremor that is present at rest, then exacerbated with posture, and further intensified with movement.1 The etiologies of HT vary, and are associated with lesions involving the cerebellothalamic pathways. HT is frequently associated with vascular lesions, but may also result from demyelinating lesions, infectious diseases, malignancy, vascular malformations, and traumatic brain injury (TBI).2,3 The localization also varies significantly, and lesions associated with HT are known to occur in the midbrain, pons, thalamus, and cerebellum.4 Cases of HT and parkinsonism involving vascular lesions secondary to the occlusion of the artery of Percheron (AOP) have also been reported5; however, successful treatment of such a tremor secondary to this particular lesion with both the ventral intermediate nucleus of the thalamus (Vim) and the zona incerta (ZI) have not yet been reported.

Cases of HT have been reported to respond to levodopa7 and to deep brain stimulation (DBS) of several nuclei and structures, including the bilateral thalami,5 ventral Vim,8 subthalamic nucleus (STN), globus pallidus interna (GPi),2 and prelemniscal radiations (Raprl).9 The use of the ZI target has been reported to be advantageous for treating more complex and proximal tremors,10 and has been previously reported as a target to independently treat HT.11 The pathophysiology of HT is complex, and it the combined dysfunction of the pallidothalamic pathways that
necessitates implantation of more than one target. Vim is known to be effective in treating distal limb tremors, and has been successfully used in treating HT in the setting of TBI. ZI has been targeted in treatment of more proximal tremors by overriding oscillations of the interpositus nucleus (IO) and medial reticular formation (MRF). Given both the distal and proximal characteristics of HT, combined Vim and ZI targets were pursued.

**Case report**

A 62-year-old right-handed woman presented to the Columbia University Movement Disorders Center for evaluation of a rest tremor of her left hand and leg that began 5 months after developing a right medial cerebral peduncle and bilateral thalamic strokes. In addition to abnormal movements, her stroke symptoms included anterograde amnesia, fluctuating consciousness, somnolence, and vertical gaze palsy.

Approximately 2.5 months after the onset of tremor, a repeat MRI of the brain was obtained, which revealed stable bilateral thalamic and right medial cerebral peduncle strokes (Figure 1). A DaT scan (I 123-FP CIT) was obtained, which revealed absent radiotracer activity in the right caudate and putamen, corresponding to the location of her prior strokes. There was also reduced radiotracer uptake within the left putamen, with relatively preserved uptake in the left caudate (Figure 2), suggesting that in addition to the vascular insult...
contributing to her left-hand tremor, she may also have underlying presynaptic nigrostriatal dopaminergic dysfunction.

Our examination, which was performed approximately 2 years after her ischemic stroke, revealed slightly reduced blink rate, mildly increased tone of the left arm, and moderate rest tremor of the left arm and leg. She had a mild kinetic tremor on the left, which intensified with posture, and was further exacerbated by movement. She also had a mild jaw tremor. Finger tapping, heel tapping, and rapid alternating movements were significant for slight decrementing of amplitude on the left (total Unified Parkinson’s Disease Rating Scale, UPDRS, Part III score of 26).

The patient was prescribed carbidopa-levodopa, with titration to a total of 1,500 mg/day. She reported significant improvement of her tremor symptoms, notably in her follow-up examination during her clinical on-state. She had slight rest, postural, and kinetic tremor of the left arm and no rest tremor of the legs, and she was noted to have improved bradykinesia (total UPDRS Part III score of 11). The patient developed worsening somnolence while taking levodopa, however, and therefore underwent right Vim/ZI DBS placement.

Mapping and trajectory planning were performed with a volumetric CT scan preoperatively and fused to the MRI volumetric images using BrainLAB™ software. Permanent stimulating electrodes of the Abbott St. Jude Medical Infinity™ DBS system were inserted with a guide sleeve through the Alpha Omega guidance system to just above the stereotactic target. The thalamic target was 11 mm lateral to the lateral wall of the third ventricle and the ZI contact was below the anterior-to-posterior commissure plane.

The patient did well postoperatively and was noted to have significant improvement of her left arm tremors at rest, posture, and with movement, as well as subtle improvements in her bradykinesia on low output settings. She received symptomatic benefit after one programming session, which was approximately 2 weeks after her surgery, with optimal contacts at monopolar contact of Case+ 2- (3.5 V; 140 Hz; 70 PW). Her UPDRS part III score postoperatively on these settings was 16 and 24 postoperatively when DBS was turned off (see Video 1).

Computerized spiral analysis was performed pre- and postoperatively to quantify the effects of DBS. This is a technique for measuring kinematic and other attributes of spiral drawing that uses a digitizing tablet and computer and calculates a series of mathematical indices to assess upper limb motor function. Spiral analysis has been used to evaluate neurological disorders, to show motor learning in Essential Tremor (ET) and to help predict the responses to DBS in ET subjects. For this study, we used spiral analysis outcome measures with specific clinical relevance to tremor, parkinsonism, and cerebellar dysfunction.

Quantitative spiral analysis findings revealed overall improvement in measures of upper limb motor execution post-DBS, though the left side still remained abnormal. There was clear improvement in tremors bilaterally, with lower tremor power, lower Degree of Severity (DoS), improved secondary smoothness, and fewer tremor axes. Other measures remained the same or worsened slightly. Spiral loop width variability (SWVI), a measure of ataxia, did not improve and remained high, indicative of a cerebellar component to the tremors as well as associated with DBS resistance. It has also been suggested that tremors with high SWVI may not be optimally treated with Vim alone, and the addition of ZI for such tremors should be considered. Tightness, a correlate of micrographia, and drawing speed worsened slightly post-DBS, showing that some of the parkinsonian features of this case were not affected (Figures 3 and 4; Table 1). Overall severity and number of axes showed improvement, but tremor amplitude did not. This tremor profile is consistent with the previous finding that the DoS and tremor amplitude are separable motor physiologic components in tremor that may be independently mediated.

The tremors in this subject were complex, with multiple axes, varying frequencies, drawing irregularity, and several other abnormal motor physiological features. Postoperatively in this subject, we found overall improvement in most, but not all, objective measures.

![Image](http://www.tremorjournal.org)

**Video 1.** The Patient is Evaluated Preoperatively without Levodopa in this Video. She is then evaluated postoperatively with the DBS turned on, then turned off. Note the improvement in the amplitude of the tremor at rest, action, and posture when the DBS is turned on.

![Figure 3](http://www.tremorjournal.org)

**Figure 3.** Axes Analysis: (A) Preoperatively and (B) Postoperatively. Note the reduction in number and range of tremor axes.
Discussion

We present a case of a woman with onset of levodopa-responsive HT secondary to a lesion of the bilateral thalami and cerebral peduncle within the territory of the AOP, who was successfully treated with Vim/ZI DBS. We believe this is also the first case report where quantitative spiral analysis was used to document objective details of the motoric changes, revealing improvement in several kinematic features of spiral drawing, as well as lack of improvement in other features. There were asymmetric DaT scan findings, which suggest possible underlying presynaptic nigrostriatal dopaminergic dysfunction in addition to the vascular lesion of the thalamus.

Prior reports of HT with underlying parkinsonism have been reported; however, the treatment of HT that is associated with vascular injury in the distribution of the AOP with Vim and ZI DBS targets has not yet been reported. Although prior reports have suggested treatment of HT with Vim and ZI targets independently, the addition of ZI to treat this particularly treatment-resistant tremor has not yet been used and should be considered in patients with complex and difficult-to-treat tremors such as HT.
Table 1. Key Tremor Axes Analysis (Top) and Spiral Analysis (Bottom) Findings of the Left, Nondominant Hand, Pre- and Postoperatively

<table>
<thead>
<tr>
<th>Axes</th>
<th>Pre-DBS</th>
<th>Post-DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency range (in Hz)</td>
<td>3.74–7.17</td>
<td>3.27–3.77</td>
</tr>
<tr>
<td>Primary axes range (in degrees)</td>
<td>40–115</td>
<td>50–90</td>
</tr>
<tr>
<td>Tremor Degree of Severity</td>
<td>2.87 ± 0.288</td>
<td>2.67 ± 0.327</td>
</tr>
<tr>
<td>Tremor frequency</td>
<td>5.09 ± 0.152</td>
<td>3.506 ± 0.074</td>
</tr>
<tr>
<td>Max power</td>
<td>4.830 ± 1.862</td>
<td>3.909 ± 0.055</td>
</tr>
<tr>
<td>Amplitude (cm)</td>
<td>3.065 ± 0.861</td>
<td>4.370 ± 1.367</td>
</tr>
<tr>
<td>Tightness</td>
<td>0.979 ± 0.057</td>
<td>1.295 ± 0.109</td>
</tr>
<tr>
<td>Width variation</td>
<td>0.493 ± 0.104</td>
<td>0.497 ± 0.073</td>
</tr>
<tr>
<td>Second-order smoothness</td>
<td>1.873 ± 1.206</td>
<td>−0.133 ± 1.631</td>
</tr>
</tbody>
</table>

Abbreviation: DBS, Deep Brain Stimulation.

Note the reduction in frequency range in the axes analysis. Also note the reduction in tremor power and Degree of Severity (DoS) postoperatively, as well as the improvement in second-order smoothness (negative values indicate improved execution of spiral drawing, with the normal value being ~4.19). Spiral loop width variability is indicated by “width variation” is indicative of cerebellar dysfunction and did not significantly change postoperatively.

References


