Effectiveness of Thalamic Ventralis Oralis Anterior and Posterior Nuclei Deep Brain Stimulation for Posttraumatic Dystonia

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Abstract

Herein we report that the ventralis oralis anterior and posterior (Voa/Vop) nuclei of the thalamus may be effective alternative targets for deep brain stimulation (DBS) to improve posttraumatic dystonia when the globus pallidus interna is traumatically damaged. This patient presented at age 35 years with a clinical diagnosis of posttraumatic cervical and bilateral upper limb acquired dystonia resulting from intracerebral and intraventricular hemorrhage after a motorcycle accident at age 19 years. Due to a right globus pallidus interna traumatic lesion, conventional DBS targeting of the inferior basal ganglia was not possible; thus, the alternative Voa/Vop nuclei target was implanted. The patient realized significant benefit and at last follow-up 3 years postoperatively continued to endorse marked benefit and improvement of dystonia symptoms with minimal adverse effects from bilateral DBS implantation in the alternative targets of the Voa/Vop nuclei of the thalamus.© 2022 THE AUTHORS. Published by Elsevier Inc on behalf of Mayo Foundation for Medical Education and Research. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Dystonia is a clinical movement disorder of involuntary, hyperkinetic muscle contractions that can cause sustained or irregular repetitive movements, torsional movements, and unusual postures.1,2 Although dystonia has several different described forms, primary dystonia is the most common classification and has been shown, in some patients, to be partly heritable via certain loci of the DYTn scheme and other genes, such as CIZ1 and GNAL.3-8 The etiology and pathophysiology of primary dystonia remain points of study, but evidence implicates the basal ganglia and cerebellum as the sites of disordered movement generation.9,10 Patients with acquired dystonia (formerly termed secondary dystonia) present with a similar clinical picture as primary dystonia but generally have structural lesions to the basal ganglia caused by insults such as drugs, trauma, and perinatal injury.1,8,11 Acquired dystonia caused by traumatic brain injury is uncommon, accounting for 7% to 9% of patients with hemidystonia in one study and 6.7% of all those with acquired dystonia in another study.12-16

The mechanism associated with therapeutic deep brain stimulation (DBS) targets for primary and acquired dystonias involves modulation of the pallidothalamicortical pathway.17,18 For primary dystonia, the preferred target for DBS is the globus pallidus interna (GPI), a subcortical nucleus of the basal ganglia producing $\gamma$-aminobutyric acid-ergic tonic inhibition of the thalamus.17-20 In some cases of dystonia, the thalamus and the subthalamic nucleus have been studied as additional therapeutic targets for DBS and radiofrequency ablation; however, the GPI remains the preferred target at most centers.17,21,22 In the future, alternative ablation techniques such as magnetic resonance-guided focused ultrasonography ablation may have a role, but at present, the use of that technique is reserved for tremor or Parkinson disease.

The ventralis oralis anterior (Voa) and posterior (Vop) thalamic nuclei serve as neuronal relays that receive inhibitory afferents from the GPIs, which is the primary output of the basal ganglia, and connects them to the supplementary motor cortex (Figure 1).23,24 The GPI comprises neuronal
nuclei that, depending on stimulatory or inhibitory signals received, such as the dopamine receptor D1- and D2-dependent modulating input to the striatum of the basal ganglia from the substantia nigra pars compacta, release a respective decreased or increased \( \gamma \)-aminobutyric acid–ergic inhibitory efferent signal. This signal travels via axons that extend via the ansa lenticularis and lenticular fasciculus through the internal capsule and the field H1 of Forel to form the thalamic fasciculus. The thalamic fasciculus terminates after the thalamic reticular nucleus at the Voa/Vop nuclei of the thalamus.23 Tonic and burst stimulation of the functional neurons of the Voa/Vop nuclei serves as an effective equivalent to stimulating the GPi because these are adjacent and sequential structures in the circuit of the pallidothalamocortical pathway.24 However, DBS of solely the Voa/Vop nuclei for dystonia in the context of trauma is not established in the literature. Very few cases report its use for posttraumatic tremor, dystonia secondary to anoxic brain injury, or dual targeting of the ventral intermediate nucleus of the thalamus for tremor and hemiballismus.20,25,26

In the present case report, we describe a patient with posttraumatic dystonia associated with magnetic resonance imaging evidence of structural damage to the GPi, prompting selection of the alternative targets of the Voa/Vop nuclei of the thalamus.

REPORT OF CASE
The patient presented to our neuromodulation clinic in early 2018 with medication-refractory posttraumatic-acquired dystonia associated with damage to the right GPi secondary to a motorcycle accident 17 years earlier that was complicated by intracerebral and intraventricular hemorrhage. The patient has no family history of dystonia; there was a strong family history of essential tremor not thought to be related to his presentation.

The involuntary movements began gradually 2 years after the accident, starting with abnormal movement of the patient’s left thumb and twitching of the left arm. Subsequently, he developed cervical dystonia.

FIGURE 1. Sagittal schematic map of the ventralis oralis anterior and posterior (Voa/Vop) nuclei of the thalamus with the globus pallidus interna (GPi) in view. STN, subthalamic nucleus; Vim, ventral intermediate nucleus; ZI, zona incerta.
consisting of left laterocollis and retrocollis. Later that year, he developed involuntary pulling of the left arm, curling of the left hand, and elevation of the left shoulder, as well as brief involuntary eyelid closure thought to represent blepharospasm. The following year, the symptoms worsened with progressive left hand jerking. The progression continued, and by the time of his presentation to our team, symptoms had spread to his right side. He also had developed trunk hyperextension and an abnormal gait characterized by a “waddling” appearance with some kicking out of the right leg.

The patient was treated with increasing doses of baclofen and later added clonazepam, but both with little effect and with adverse sedating effects. Gabapentin was later given on a trial basis but without benefit. Botulinum toxin A treatment began at that time and continued for 14 years, increasing to a high dose of 400 U over time. There was some relief of blepharospasm and limb dystonia initially, although, over time, the symptoms became refractory. These therapy outcomes prompted the patient to pursue DBS.

A previous brain MRI from 2007 reported abnormal signals in the right temporal lobe and the periventricular white matter and an abnormal cleft signal in the corpus callosum, reflecting gliotic changes after trauma. In addition, the MRI performed at the time of our evaluation in 2018 showed an abnormal signal consistent with a likely area of previous hemorrhage in the region of the right GPi (Figure 2A), as well as encephalomalacia and hemosiderin in the right medial temporal lobe that extended superiorly into the right inferior lentiform nuclei consistent with evidence of a previous hemorrhage (Figure 2B).

Because the right GPi was damaged and not a suitable DBS target, the Voa/Vop nuclei of the thalamus, which receives afferent input from the GPi, was targeted. The procedure was reviewed by a multidisciplinary (neurology, neurosurgery, psychiatry, and neuroradiology) DBS committee at Mayo Clinic with a consensus that the procedure was medically appropriate and necessary. Because of the bilateral symptoms, the bilateral Voa/Vop nuclei were targeted. A few months later, in 2018, the bilateral operation was performed. The patient was awake for placement of the DBS electrodes.

The Leksell model G stereotactic head frame (Elekta) was used. The Voa/Vop nuclei were targeted with a bilateral approach. The coordinates were 4.5 mm posterior from the anterior commissure—posterior commissure midpoint offset, 0.25 mm superior from the superoinferior offset, and 10 mm lateral from the wall of the third ventricle. During the procedure, the right lead was placed first because his left-sided symptoms were worse, and then the left lead was placed. Due to paresthesia at approximately 1.0 to 1.5 V on macrostimulation on the right, the DBS lead was moved 1.5 mm superiorly from the target. The patient, at that point, did not have any issues with macrostimulation voltages up to 3.5 V. Postoperative computed tomography showed successful bilateral Voa/Vop nuclei thalamic electrode placements, with good lead location and accuracy bilaterally (Figure 3).

The surgery was successful, and the patient recovered very well from surgery. Postoperative symptom alleviation of dystonia was confirmed on examination by the neurology team and by the patient’s local neurologist outside of the clinic. In addition, the patient endorsed some immediate improvement of dystonic symptoms once the DBS system was surgically placed and later endorsed good benefit overall such that he could discontinue botulinum toxin A injections. The patient
discontinued botulinum toxin A injections for 15 months and then restarted at a reduced dose of 170 to 200 U for 6 months while different DBS stimulator reprogramming adjustments were being tried. After 6 months, satisfactory stimulator programming settings were found, and the patient then discontinued the botulinum toxin A injections due to a limited benefit of the injections and a good benefit of DBS. The patient is currently using the following stimulation settings: left C+0-3.25 mA, 60 μs (pulse width), 60 Hz; right 11+10-3.25 mA, 90 μs, 60 Hz. At last follow-up 3 years postoperatively, the patient continued to endorse marked benefit and improvement of dystonia symptoms with minimal adverse effects from bilateral DBS implantation.

DISCUSSION
There are currently not enough patients with medication-refractory dystonia available for large-scale neuro modulation studies, thus placing DBS for medication-refractory dystonia
under the Food and Drug Administration Humanitarian Device Exemption. $^{27}$ Although Voa/Vop (or Voa only) nuclei DBS targeting has been reported to be used for primary and postanoxic dystonia, complicated tremor, postraumatic Holmes tremor, and multiple sclerosis tremor, there has not been sufficient reports in the literature of successful use of Voa/Vop nuclei targeting for postraumatic dystonia. $^{35-38}$ Furthermore, pallidal DBS targeting for postraumatic dystonia has been reported, but the data in the literature remain sparse. $^{35-38}$

The mechanism of DBS is generally thought to involve modulation of aberrant network activity overall rather than modulation of a single structure. Thus, targeting different “nodes” in the same network may yield similar results. The putative motor network begins in the cerebral cortex and, via glutamatergic and $\gamma$-amino- butyric acid–ergic transmission, travels through the basal ganglia and exits via the GPI to the Voa/Vop nuclei of the thalamus and back to the motor cortex. $^{39,40}$ Because the present patient had traumatic damage to the GPI, we targeted the next downstream structure in the circuit: the Voa/Vop nuclei.

The safety profile of DBS targeting of the Voa/Vop nuclei likely mirrors that of implantation of other DBS targets in the region. Stimulation-related adverse effects are likely fewer, with the most likely concern being activation of the corticobulbar or spinal tract due to the spread of current laterally to the internal capsule. In that event, a patient may experience involuntary muscle contractions. This is an adverse effect also possible with more common DBS targets, including the GPI, subthalamic nucleus, or ventral intermediate nucleus of the thalamus. Other adverse effects, such as paresthesia, oculomotor adverse effects, or cognitive/behavioral adverse effects, would be much less likely to occur with Voa/Vop nuclei stimulation given the specific microanatomy of that region.

This case report provides further evidence that the thalamic Voa/Vop nuclei may be an alternative DBS target for patients with dystonia associated with structural damage to the GPI.

ACKNOWLEDGMENT

The views expressed herein are the authors’ own and not an official position of the authors’ institution.

Abbreviations and Acronyms: DBS, deep brain stimulation; GPI, globus pallidus interna; MRI, magnetic resonance imaging; STN, subthalamic nucleus; Vim, ventral intermediate nucleus; Voa, ventralis oralis anterior; Vop, ventralis oralis posterior; ZI, zona incerta

Potential Competing Interests: Dr. Hassan has received grant support from Intrabio Ltd. and serves on the editorial board of Parkinsonism and Related Disorders. The other authors report no competing interests.

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