Ventral intermediate nucleus deep brain stimulation for treatment-resistant focal aware motor seizures: illustrative case

Osvaldo Vilela-Filho, MD, PhD,1,3,4,6 Paulo C. Ragazzo, MD, PhD,2 Lissa C. Goulart, MD,4 Francisco Arruda, MD, PhD,2 Mariana L. Arruda, MD,6 Caroline B. S. S. Milhomem, MD,6 and Hélio F. Silva-Filho, MD5

1Department of Stereotactic and Functional Neurosurgery, Goiânia Neurological Institute, Goiânia, Goiás, Brazil; 2Department of Neurology, Center of Epilepsy Surgery, Goiânia Neurological Institute, Goiânia, Goiás, Brazil; 3Division of Neurosurgery, Department of Surgery, Medical School, Federal University of Goiânia, Goiânia, Goiás, Brazil; Departments of 4Neurosurgery and 6Neurology, Clinics Hospital, Federal University of Goiânia, Goiânia, Goiás, Brazil; and 5Department of Neurosciences, Medical School, Pontifical Catholic University of Goiânia, Goiânia, Goiás, Brazil

BACKGROUND Resection of the seizure onset zone (SOZ) is considered the gold standard for treating refractory focal aware seizures (FASs). When resective surgery is unadvisable, deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT; ANT-DBS) has been the procedure of choice. However, less than half of patients with FASs respond to ANT-DBS. The need for alternative targets to effectively treat FAS is thus evident.

OBSERVATIONS The authors report the case of a 39-year-old woman presenting with pharmaco-resistant focal aware motor seizures, with the SOZ located in the primary motor cortical area. She had previously undergone unsuccessful resection of the left temporoparietal operculum elsewhere. Considering the risk of new resective surgery, she was offered combined ventral intermediate nucleus (Vim)/ANT-DBS. Vim-DBS proved to be superior to ANT-DBS for seizure control (88% vs 32%), although the association of both provided the best results (97%).

LESSONS This is the first report on the use of the Vim as a target of DBS for the treatment of FAS. The excellent results were presumably obtained by modulation of the SOZ through Vim projections to the motor cortex. This opens a completely new avenue for treating FAS: chronic stimulation of specific thalamic nuclei.

https://thejns.org/doi/abs/10.3171/CASE2320

KEYWORDS anterior nucleus of the thalamus; deep brain stimulation; focal aware seizure; treatment-resistant epilepsy; ventral intermediate nucleus

Approximately 50 million people worldwide have epilepsy, which makes it one of the most common neurological diseases globally.1 It has an estimated prevalence of 0.76%.2 Focal aware seizures (FASs) are responsible for 14% of the cases.3 Despite advances in pharmacotherapy, however, at least 24% of cases with focal seizures are drug resistant.4 In such cases, surgery may be contemplated.

FASs may occur in the presence or absence of structural lesions of the brain. Once one has confirmed the area that corresponds to the seizure onset zone (SOZ), resective surgery is the treatment of choice. Not infrequently, however, the SOZ can be located in eloquent areas, making resection unadvisable. Then, neuromodulatory procedures emerge as alternative possibilities.

Deep brain stimulation (DBS) indications for epilepsy have exponentially grown for the subgroup of cases that remain pharmacoresistant and disabled despite other treatments.5 The following main targets have already been used: anterior nucleus of the thalamus (ANT), hippocampus, and centromedian nucleus (CM), among others.6–8

Specifically regarding focal seizures, the ANT, the target of choice, is usually efficacious for the control of focal impaired awareness seizures (FIASs), but not infrequently ineffective for the

ABBREVIATIONS ANT = anterior nucleus of the thalamus; CM = centromedian nucleus; CT = computed tomography; CSCS = chronic subthreshold cortical stimulation; DBS = deep brain stimulation; EEG = electroencephalography; FAMS = focal aware motor seizure; FAS = focal aware seizure; FIAS = focal impaired awareness seizure; MER = microelectrode recording; MRI = magnetic resonance imaging; RNS = responsive neurostimulation; SOZ = seizure onset zone; TID = 3 times per day; VC = ventrocaudal nucleus; Vim = ventral intermediate nucleus; VNS = vagus nerve stimulation.

INCLUDE WHEN CITING Published April 3, 2023; DOI: 10.3171/CASE2320.
© 2023 The authors, CC BY-NC-ND 4.0 (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Illustrative Case

A 39-year-old left-handed female was referred to our center for presurgical evaluation of refractory epilepsy. She presented with a 28-year history of epilepsy, characterized, on occasion, by brief daily clusters of axial tonic seizures with head version to the right, clonic movements of the right hand, speech arrest, and icatal apnea (focal aware motor seizures [FAMSs]). The seizures were triggered by the wake-sleep transition or intense auditory stimuli. More rarely, however, they evolved to behavioral arrest with automatisms typical of temporal lobe epilepsy or to bilateral tonic-clonic seizures. She was taking phenytoin 100 mg 3 times per day (TID), sodium valproate 1000 mg 2 times per day, lamotrigine 100 mg TID, and clonazepam 0.5 mg TID. A number of other medications had been tried in maximal tolerable doses, without success.

Of significant history, she was delivered by cesarean section after a prolonged labor, showing perinatal distress due to a nuchal cord. She presented with a delay in neuropsychomotor development, and mild right hemiparesis was first noticed when she was 8 months old. At age 11 years, she experienced a severe traumatic brain injury, which was treated conservatively, after which there was a worsening of the previous motor deficit and the onset of seizures. When she turned 26 years, the seizures became pharmaco-resistant. At 31 years, she underwent resection of the left temporoparietal operculum in another service. Postoperatively, language was preserved but there was further impairment through the motor deficit and the appearance of irritability, impulsiveness, and aggressiveness. The seizures, initially reduced in frequency, had a significant change in their pattern. When she was 37 years old, the seizures became, once again, drug resistant.

The neurological evaluation disclosed only right hemiparesis with predominance in the upper limb. Psychiatric and neuropsychological assessments demonstrated organic emotional lability disorder, anxiety, and impulsiveness, as well as memory, executive function, and verbal fluency impairment. Interictal and ictal video-electroencephalography (EEG) monitoring revealed, respectively, focal left fronto-central slow spike-wave complexes and epileptiform discharges with generalized attenuation without clear determination of the SOZ. Magnetic resonance imaging (MRI) showed an extensive cortico-subcortical area of encephalomalacia/gliosis affecting the left frontoparietotemporal region, compensatory dilation of the left lateral ventricle, and hemiatrophy of the left hemisphere, probably secondary to a perinatal ischemic lesion and/or the traumatic brain injury and the previous surgery. Sagittal (C) and axial (D) positron emission tomography (PET) scans demonstrating a large area of hypometabolism coincident with that of encephalomalacia/gliosis.

Informed consent for surgery was obtained from the patient and her parents.

Electrode implantation was performed with the patient awake, under local anesthesia (May 2011). Targeting was based on stereotactic computed tomography (CT); frameless MRI; image fusion; coordinates of the anterior commissure, posterior commissure, and midcommissural point; and the superposition of the digitalized Schaltenbrand and Wahren stereotactic atlas (Fig. 2), as performed by most authors at that time and even later by others. Only later did the use of the mammillothalamic tract as a landmark to localize the ANT became the standard technique.

The initial target was the ANT. Microelectrode recording (MER), starting 10.0 mm above the target, initially showed electric silence, compatible with the lateral ventricle topography. Subsequently, with MER from 1.2 mm above to 1.92 mm below the anatomical target, numerous cells presented high-frequency, high-amplitude discharges, presumably throughout the ANT, as reported by other authors. Macrostimulation (100 Hz/5.0 V/1.0 msec) did not produce any conscious impact or changes on the scalp EEG.

Since CM does not have a classic electric signature, it has been our routine to initially map the ventrocaudal nucleus (VC) and the Vim to establish, respectively, its medial and anterior borders. In the VC, tactile cells and neurons responsive to muscle squeezing of the right hand were identified. In the Vim, located just in front of the VC, numerous kinesthetic and voluntary cells related to movements...
of the upper and lower limb joints were recorded, mainly from 3.9 mm above to 0.6 mm below the anatomical target. Low-frequency macroelectrode stimulation (10 Hz/5.0 V/1.0 msec) of the Vim induced a recruiting response and consistently reduced the bursts of spikes recorded on scalp EEG; high-frequency stimulation (100 Hz/5.0 V/1.0 msec), on the other hand, reproduced the patient’s seizure. At this point, considering these unexpected and promising responses and the fact that the CM was not a particularly helpful target for FAMSs, we consulted the patient and her parents, who agreed to implantation of the second electrode in the Vim.

Contact 1 of both leads (3387 model, Medtronic) was implanted in the ANT (medial) and Vim (lateral) through a transventricular coronal (PC), as well as the ANT (5). Postoperative axial (C) and coronal (D) T2-weighted MR images demonstrating the electrodes implanted in the ANT (medial) and Vim (lateral) through a transventricular approach.

There were no immediate postoperative complications. Postoperative MRI confirmed adequate lead placement (Fig. 2).

There was no insertion effect, and stimulation was started 3 weeks after surgery. Assessment of the improvement was based on the seizure diary. Initially, we tested the ANT alone for 1 month. The best stimulation parameters, reducing seizure frequency by 32%, were as follows: 1–2 case +/90 μsec/145 Hz/5.0 V, intermittent stimulation (1 min on/5 min off). Next, the Vim in isolation was tested for another month, providing a seizure reduction of 88%. Both low- and high-frequency stimulations were very effective, although the latter was even more so (83% vs. 88%). The best settings for the Vim were as follows: 3–2 case +/90 μsec/145 Hz/2.7 V, intermittent stimulation. Finally, simultaneous stimulation of both targets with the best parameters reduced seizure frequency from many clusters of approximately 10 episodes each a day to none or an occasional single cluster of 2–3 very mild seizures (improvement of 97%). Combined Vim and ANT stimulation was maintained afterwards. Considering these results, we did not deem it necessary to perform surgery on the right side.

Four and a half months after surgery the patient presented with meningitis, on which occasion the number of seizures increased. Postcontrast head CT showed no new abnormalities; in particular, there was no evidence of encephalitis. Culture of the cerebrospinal fluid obtained by lumbar tap was negative. She was successfully treated with a 3-week course of intravenous antibiotics. Soon after, the previous degree of improvement was restored. Postoperatively, the medications were kept unchanged, except for lamotrigine, which was progressively discontinued.

A series of three postoperative EEGs (ANT on, Vim on, and both nuclei on) showed no epileptiform activity during prolonged recordings.

The comparison between pre- and postoperative 36-item Short Form Survey (SF-36) scores demonstrated a substantial improvement in all domains. The behavioral comorbidities (irritability, impulse dyscontrol, disruptive behavior, and anxiety) were also significantly ameliorated.

Forty-one months after surgery there was a superficial infection of the head surgical wound, which was successfully treated with oral antibiotic. Three months later, however, the patient returned presenting with a superficial infection of the whole neurostimulation system. The cerebrospinal fluid obtained by lumbar puncture and the postcontrast head CT did not show meningitis or involvement of the brain. Even so, following the recommendation of the infectious diseases team, oral antibiotic was instituted and the neurostimulation system was completely explanted.

To our surprise, the patient became completely seizure-free from then until the last follow-up visit (November 2022), 93 months after removal of the system, despite still using antiseizure medications.

**Discussion**

Resection of the SOZ is considered the gold standard for treating refractory FAS. Not infrequently, however, the SOZ is located in eloquent brain areas, preventing resective surgery due to the high risk of morbidity. In such cases, neuromodulatory procedures may be an option.

The ANT has been the target of choice for DBS in patients with refractory focal seizures. It seems to be more efficacious for temporal and frontal limbic focal seizures. In addition, the results are better in patients without structural abnormalities on MRI. With regard to FASs specifically, it is difficult to ascertain since most authors usually report only the global results, not taking into account the different types of seizures. Fortunately, however, a few authors do. In our review, we were able to identify 19 patients with FASs in isolation or associated with FIASs and/or bilateral tonic-clonic seizures.

Considering a response to surgery to be a decrease of ≥50% in seizure frequency, 9 patients were responders (47.4%), presenting a mean seizure reduction of 63%, with only 1 patient becoming seizure free. Two patients, on the other hand, presented with a significant increase in seizure frequency after ANT-DBS. More recently, other authors have also suggested the use of combined ANT/CM-DBS for treating focal and generalized seizures.
Other techniques may also be used in cases of focal seizures originating from eloquent cortical areas: vagus nerve stimulation (VNS), responsive or closed-loop neurostimulation (RNS), and chronic subthreshold cortical stimulation (CSCS).

Although VNS is usually efficacious for generalized seizures, the responder rate (25%) and median reduction in the frequency of episodes (25%) are both low in cases of focal seizures.26

RNS was approved by the Food and Drug Administration in 2013. The system continuously records electrocorticographic activity at the seizure focus and provides responsive electric stimulation only when predetermined abnormal patterns are detected, increasing significantly the battery life.27 It presents a responder rate of approximately 60% and determines a 67% reduction in median seizure frequency.28 The improvement, like that with ANT-DBS,11 tends to increase over time.27 Unfortunately, RNS for epilepsy is still not widely available and/or approved. Also relevant is the fact that RNS is not MRI compatible.29

The experience with CSCS, a somewhat more recent technique, is very limited thus far. Similarly to RNS, it allows continuous electrocorticographic recording from the electrodes implanted at the SOZ.24,25 Stimulation, on the other hand, is provided in a continuous fashion.28 The responder rate and the median reduction in seizure frequency were 90% and 85%, respectively, in a case series of 13 patients with a mean follow-up of 1.6 years.28

Observations

Considering the aforementioned issues, the need for alternative targets to effectively treat FASs is evident.

We report here the case of a patient with pharmaco-resistant FAMSs who was successfully treated with combined Vim/ANT-DBS. While physiologically exploring the thalamus to determine the boundaries of the CM, it was fortuitously observed that low-frequency stimulation of the Vim consistently reduced the bursts of spikes recorded with scalp EEG, whereas high-frequency stimulation induced the patient’s usual seizure. These findings led us to implant the second lead in the Vim, instead of the CM, as initially planned.

Postoperatively, Vim-DBS proved to be superior to ANT-DBS for seizure control (88% vs 32%), although the association of both provided the best results (97%). It should be noted that the amplitude used for Vim-DBS (2.7 V) was significantly lower than the amplitude (5.0 V) that reproduced the patient’s seizure intraoperatively. Considering that the Vim projects directly to the cortical motor areas and that the ANT projects to the limbic circuit of Papez, one may hypothesize that Vim-DBS was mainly responsible for the decrease in the FAMSs and that ANT-DBS controlled the progression to FIASs and improved the behavioral symptomatology.

Also interesting was the fact that the patient became completely seizure free after removal of the DBS system and has remained so for 93 months, when she was last evaluated. A plausible explanation would be that, after 44 months of stimulation, the SOZ neurons relearned how to normally discharge as a result of the phenomenon of neuroplasticity. However, it is important to emphasize that, to the best of our knowledge, this phenomenon has never been described when Vim-DBS was used for treating movement disorders.

In reviewing the literature, we found only one other study reporting the use of Vim-DBS for epilepsy. This procedure was performed in four patients with progressive myoclonic epilepsy syndrome, and no significant improvement was observed in any of them.31

In the present study we report, for the first time, the use of the Vim as a target of DBS for the treatment of FASs. It was only through pure serendipity that we discovered this completely new indication for the use of this old stereotactic target, which proved to be rather successful in this single case, yielding an 88% reduction in FMAS frequency.

Based on these results, we have received approval and started an open clinical trial on the use of DBS of specific thalamic nuclei for treating FASs: Vim, for motor seizures; VC, for sensory seizures; lateral geniculate nucleus, for visual seizures; and medial geniculate nucleus, for auditory seizures.

If this strategy proves to be successful, it will represent a paradigm shift in the way of treating pharmaco-resistant FASs not amenable to resective surgery—that is, modulation of the cortical SOZ by chronic stimulation of specific thalamic nuclei.

Lessons

The treatment of drug-resistant FASs not amenable to resective surgery may pose a significant challenge. ANT-DBS is not frequently unsuccessful. Alternative possibilities are RNS, which is not widely available and/or approved, and CSCS, which is still at an early stage. Here we describe a new procedure for treating FAMSs, Vim-DBS, which yielded an 88% decrease in seizure frequency, presumably by modulation of the SOZ through Vim projections to the motor cortex. This opens a completely new avenue for treating FASs—that is, chronic stimulation of specific thalamic nuclei.

Acknowledgments

The authors express their gratitude to Walison Morais, MD, for his help with the final preparation of the figures.

References


Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Vilela-Filho, Milhomem. Acquisition of data: Vilela-Filho, Ragazzo, F Arruda, ML Arruda, Milhomem. Analysis and interpretation of data: Vilela-Filho, Ragazzo, ML Arruda, Milhomem. Silva-Filho. Drafting of the article: Vilela-Filho, Ragazzo, Goulart, ML Arruda, Silva-Filho. Critical revising of the article: Vilela-Filho, Ragazzo, Goulart, ML Arruda, Silva-Filho. Reviewed submitted version of the manuscript: Vilela-Filho, Ragazzo, Goulart, F Arruda, Silva-Filho. Approved the final version of the manuscript on behalf of all authors: Vilela-Filho. Study supervision: Vilela-Filho.

Correspondence
Osvaldo Vilela-Filho: Medical School, Federal University of Goiás, Goiânia, Goiás, Brazil. ovilelafilho@clanfer.com.