Neurostimulation in Drug-Resistant Epilepsy

This case illustrates the clinical assessment and process for choosing neurostimulation devices for epilepsy.

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CASE. Drug-Resistant Epilepsy

Clinical Presentation

BA, age 20 years, is a right-handed musician and vocalist. He has a history of premature birth complicated by intraventricular hemorrhage and hydrocephalus status after intraventricular shunt placement, and depression. BA presented to our level IV epilepsy center for evaluation for treatment of drug-resistant epilepsy (DRE).

BA's seizures began 7 years before this evaluation and were described as being preceded by lightheadedness, followed by tonic posturing and head deviation to 1 side, and then generalized clonic activity. BA had multiple injuries and was unable to drive. His seizures occurred 8 times per year but had been increasing in frequency more recently. BA's seizures were severe, causing self-injury, including a fall with subsequent subdural hematoma. Prior antiseizure medication (ASM) trials included levetiracetam, which caused suicidality, and valproate, which caused liver dysfunction. At the time of this evaluation, BA was taking lamotrigine 500 mg total daily dose and brivaracetam 300 mg total daily dose; he was tolerating both and had adhered to this treatment for months without improvement in seizure frequency.

Diagnostic Studies

BA had a brain MRI with and without contrast and a functional MRI (fMRI) of the brain to evaluate hemispheric language dominance. His brain MRI demonstrated periventricular leukomalacia with dilatation of the occipital horn and atrium of the left lateral ventricle, with diffusely abnormal cortical sulcation (Figure 1A-1C). fMRI showed left hemisphere dominance for language (Figure 1D & 1E).

BA was admitted to our epilepsy monitoring unit (EMU) for scalp videoEEG monitoring to characterize his seizures. His interictal EEG showed occasional left centrotemporal slowing, as well as paroxysmal bursts of 2 to 3 Hz spike and slow-wave complexes, some demonstrating phase reversal at P3. Lead-in from the left centroparietal electrodes was seen, suggesting left hemisphere onset with bilateral synchrony. BA had 4 electrographic seizures (3 clinical, 1 subclinical), all with left hemisphere onset and possible onset in the left centroparietal region. The 3 clinical seizures had a clinical correlate of behavioral arrest followed by right versive head turn and right arm clonic jerking, which then secondarily generalized with tonic-clonic activity. During admission, BA also underwent an ictal single-photon emission computed tomography (SPECT), which localized seizure onset to the left anteromedial frontal lobe.

Differential Diagnosis & Diagnosis

This case was discussed at a multidisciplinary surgical epilepsy conference. BA's seizures were stereotyped clinically and electrographically and suggested focal epilepsy with tendencies for focal to bilateral tonic-clonic seizures arising from the left hemisphere. As such, we decided to pursue intracranial videoEEG monitoring for better localization of the epileptogenic zone to determine options for further treatment.

BA underwent stereotactic surgery with depth electrodes placed at 8 different sites within the left hemisphere for intracranial videoEEG monitoring (Figures 2 and 3). His first clinical event had a semiology of left head deviation and left

CASE. Drug-Resistant Epilepsy (Continued)

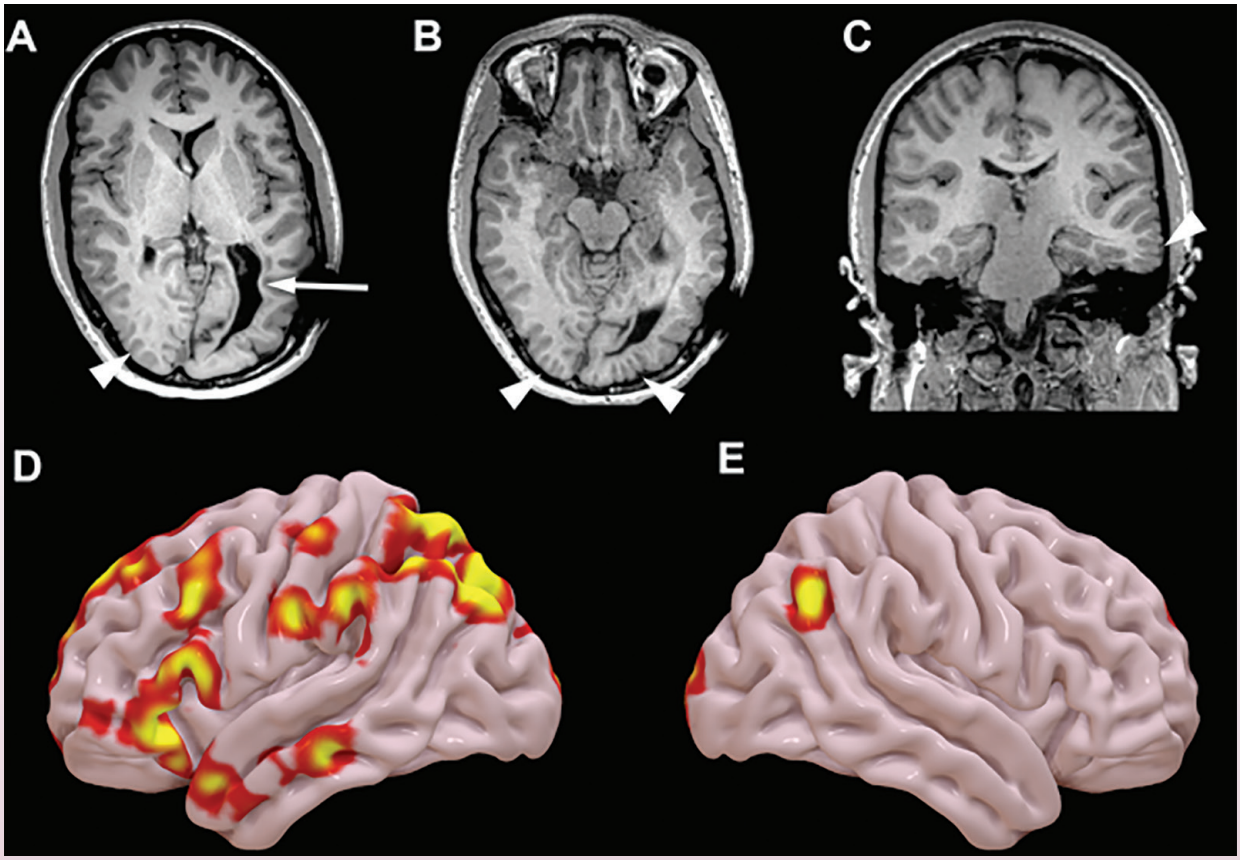

Figure 1. Axial (A,B) and coronal (C) T1-weighted images showing periventricular leukomalacia and associated enlargement of the left occipital horn and atrium of the lateral ventricle (arrow) with diffuse areas of abnormal sulcation and gyrification (arrowheads) throughout both hemispheres. Left (D) and right (E) hemisphere images of a functional MRI study using a sentence completion task shows strong left hemispheric dominance for language.

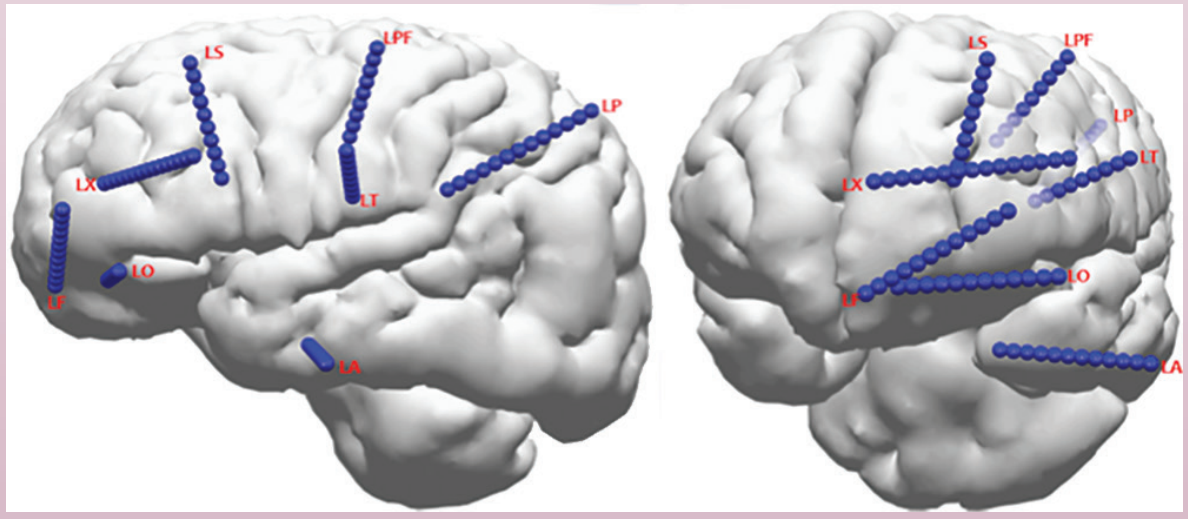

Figure 2. 3D electrode localization using CT/MRI coregistration after depth electrode placement. Abbreviations: LA, amygdala; LF, frontal polar; LO, orbital frontal; LP, parietal cortex; LPF, posterior frontal gyrus; LS, superior frontal gyrus; LT, inferior frontal gyrus; LX, anterior pericingulate gyrus.

CASE. Drug-Resistant Epilepsy (Continued)

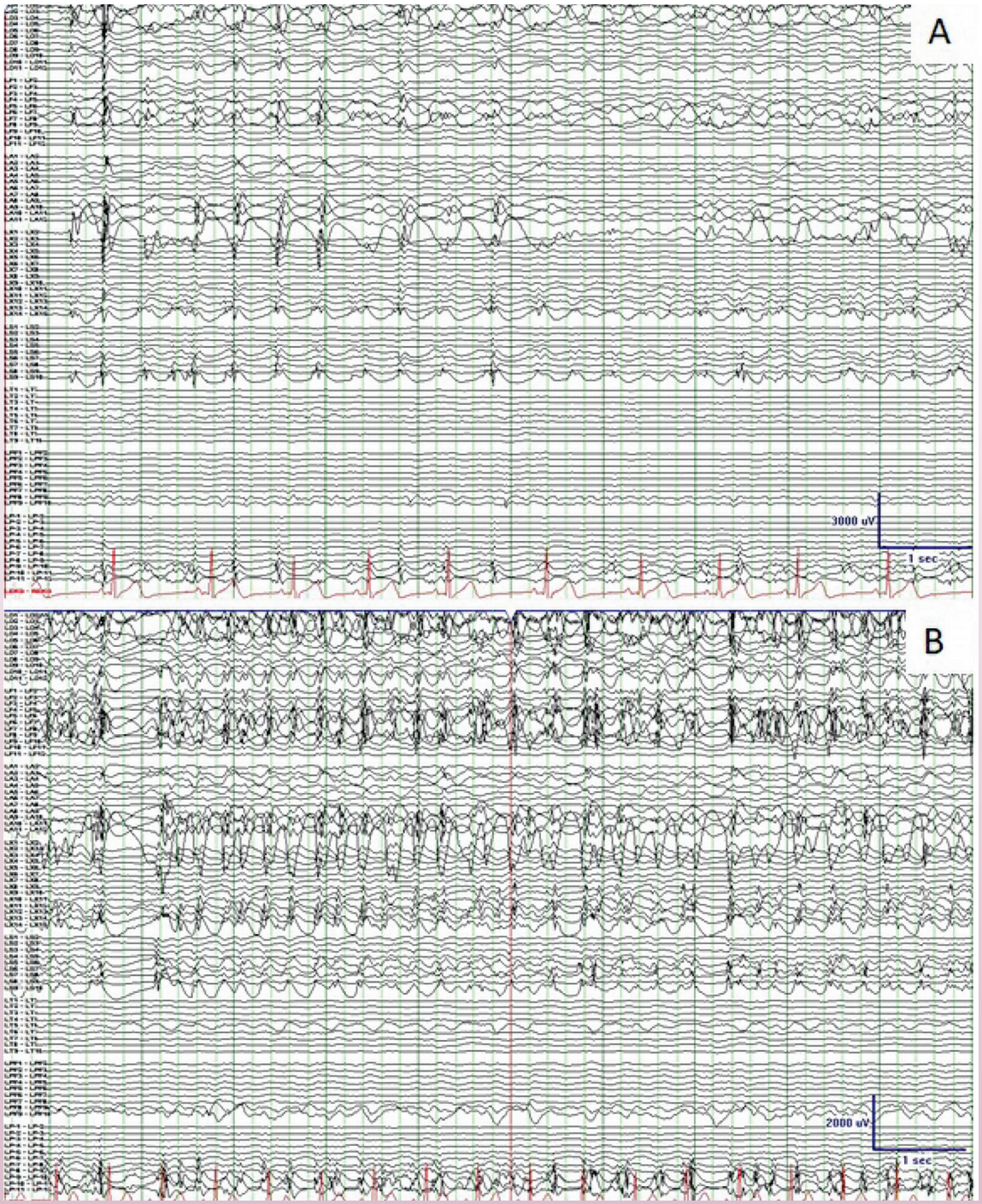

Figure 3. Stereoelectroencephalography at onset of each seizure shows that a clinical seizure (A) began with unresponsiveness; this correlates on EEG with rhythmic delta activity that continues as the seizure evolves clinically, which is suggestive of a more distant focus in the right hemisphere. Seizure has not yet clearly begun clinically at the onset of this EEG (B); this correlates on EEG with sentinel spike and high frequency gamma activity then attenuation in contacts in the amygdala, frontal polar and orbital frontal regions, and the anterior pericingulate gyrus before evolving and spreading throughout all of the contacts as seizure progresses clinically and electrographically (not shown).

CASE REPORT: Drug Resistant Epilepsy (Continued)

hemibody jerking prior to generalized tonic-clonic movements. Electrographic onset occurred after clinical onset and showed evidence of a more distant seizure focus before generalization, suggesting a likely right hemisphere onset (Figure 3A). Within 1 hour, a second event demonstrated likely left hemisphere onset clinically with right head deviation before the generalized tonic-clonic activity. When right head deviation began, EEG showed a broad left hemisphere onset (Figure 3B). Given these videoEEG findings, it was concluded that BA had broad epileptogenic zones that were not amenable to resection, and his depth electrodes were surgically explanted.

Management

At our second surgical conference, considering the presence of at least 2 broad epileptogenic foci, we decided to offer treatment with bilateral anterior thalamic deep brain stimulation (ANT-DBS).

Summary

This case report highlights the presurgical evaluation and decision-making process for treatment in DRE. In our case, we first performed scalp videoEEG monitoring and neuroimaging. There was left hemisphere lateralization but discordant localization for seizure onset based on videoEEG and neuroimaging. Seizures demonstrated a clinical and electrographic stereotype, so focal epilepsy with tendencies for focal to bilateral tonic-clonic seizures was still suspected. Intracranial videoEEG monitoring was pursued to better localize a possible seizure focus for targeted surgical therapy. Surprisingly, despite multiple seizures captured on scalp videoEEG lateralizing seizure onset to the left hemisphere, there was a focal seizure with secondary generalization originating from the right hemisphere during intracranial videoEEG monitoring. It was concluded that this was a case of multifocal epilepsy, meaning the patient was not a resective surgical candidate and would be better treated with a neurostimulation device.

Background

Drug-resistant epilepsy (DRE) is defined as the failure of an adequate trial of 2 antiseizure medications (ASMs), tolerated as well as chosen and dosed appropriately, to achieve seizure freedom (defined as being seizure-free for a period 3 times the patient's greatest interseizure interval if at least 1 seizure has occurred within the previous 12 months, or at least 12 months, whichever is longer).[1] Approximately 30% of epilepsy will be considered drug-resistant at some point during the course of treatment. Despite the development of new medications with novel mechanisms of action, there has not been a significant improvement in drug responsiveness or incidence of DRE.[2,3]

CLINICAL GEMS

People with DRE should be referred to level IV epilepsy centers for evaluation of surgical candidacy as soon as possible.

Commonly prescribed nonpharmacologic options to treat DRE include specialized diets (ie, ketogenic diet or modified Atkins diet), resective epilepsy surgery, or neuromodulation device implantation. Treatment should be individualized, but epilepsy surgery should be considered early in DRE. The goal is to find a single epileptic focus that is amenable to resection or ablation, which can lead to seizure freedom.[2,4]

In many cases, however, people with DRE are not candidates for resection because they have either a) an epileptic focus that is localized in an eloquent or surgically inaccessible cortical area; b) multifocal seizures; or c) a generalized seizure disorder.[5,6] The development and improvement of neurostimulation devices has expanded our surgical armamentarium, allowing palliative treatment of DRE in those who are not candidates for resective surgery.[7]

Currently, 3 approved neurostimulation devices are used to treat DRE: vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS). When choosing the device, consider the specific mechanism of action, risk of adverse effects, and seizure type and localization.[6]

In this report, we highlight the diagnostic workup and clinical decision-making process in evaluating a patient with DRE who is not a candidate for resective surgery and briefly review neuromodulatory therapies in DRE.

Diagnosis

Determining the proper treatment in DRE requires diagnosis and characterization of any and all seizures in each individual. This is first done using scalp videoEEG and neuroimaging, typically an epilepsy protocol MRI (3T or 7T). Other noninvasive tests can also be performed when clinically indicated and available. These include magnetoencephalography (MEG), positron emission tomography (PET)/CT, PET/MRI, or ictal SPECT.[2,4,8] Although these studies can help localize the epileptogenic zone, each has limitations in sensitivity and specificity regarding localizing seizure foci. If the results of noninvasive studies are concordant, intracranial videoEEG is typically not needed, and a treatment plan can be initiated.[6-8]

CLINICAL GEMS

DRE evaluation requires noninvasive videoEEG monitoring and structural and functional neuroimaging.

In some cases, noninvasive testing is not concordant or does not localize seizure foci well enough to develop a proper treatment plan; however, there is enough clinical data to support focal epilepsy (or possibly more than one focus) that is surgically amenable to resection, ablation, or neurostimulation. In these situations, intracranial videoEEG is performed using depth electrodes and or subdural grids or strips that are implanted to localize the epileptogenic zone(s) more accurately.[2,8] See Figure 4 for a stepwise presurgical approach with a particular focus on candidates for neurostimulation.

In this case, intracranial videoEEG monitoring was pursued to better pinpoint presumed focal epilepsy in the left hemisphere. Ultimately, at least 2 broad epileptogenicity areas were found, making BA a candidate for neurostimulation therapy.

CLINICAL GEMS

If discordant information is obtained or better localization is required, more specialized neuroimaging and possibly intracranial video-EEG are needed.

Treatment

As noted above, resection of a focal epileptogenic zone is the ideal treatment, but is not always an option. Neurostimulation is available for palliative treatment of DRE in those who are not resective surgical candidates.[9] However, each neurostimulation device has different mechanisms of action, indications, and risks for adverse effects. Currently, there is no randomized study comparing their efficacy in treating DRE.

CLINICAL GEMS

Neurostimulation therapy provides palliative treatment with significant benefit for DRE not indicated for resective surgery.

VNS. Approved by the Food and Drug Administration (FDA) in1997 as adjunctive therapy for medically refractory focal epilepsy in adults and children over age 12 years,[6,10] VNS is also used off-label in generalized genetic epilepsy.[6] It is speculated that VNS stimulates the vagus nerve to generate feedback to the nucleus tractus solitarius, exerting antiseizure effects on brain stem and cortical regions to which the nucleus tractus solitarius connects.[10] VNS is an "open-loop" system with stimulation occurring at regular intervals set as ON and OFF periods. Some models can also stimulate in response to an increase in heart rate, often seen with seizures. A magnet is available for the patient to place over the generator, increasing stimulation to potentially abort a seizure, if they experience aura.[11] The 50% responder rate in short-term clinical trials was 30% to 40% but has been reported as high as 58.8% at 3 years.[10,12-14]

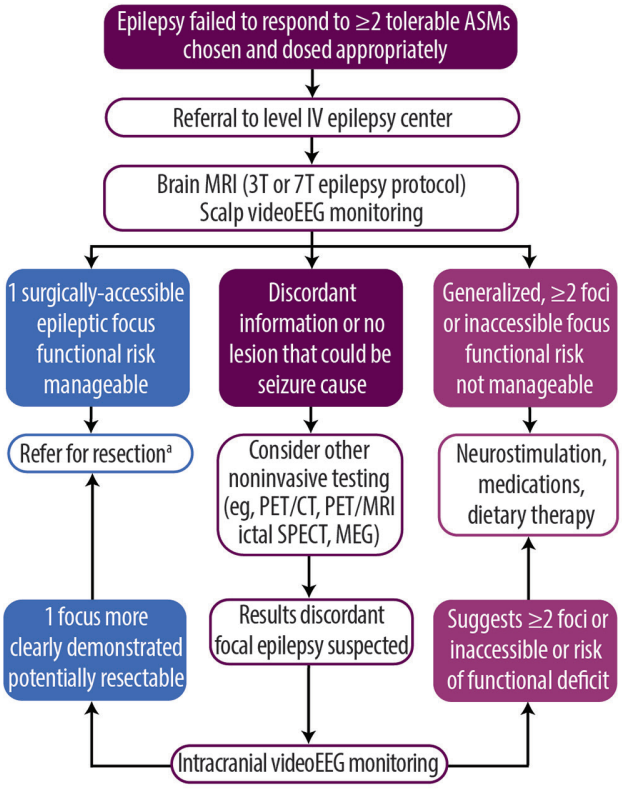

Figure 4. Approach to drug-resistant epilepsy. This approach assumes there is no lesion that warrants resection because of its underlying cause (eg, malignancy, vascular malformation, or space-occupying lesion). [a]When referring for resection, consider further testing for language/memory dominance. Abbreviations: ASM, antiseizure medication; MEG, magnetoencephalography; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

VNS has a broader range of indications that includes more people and seizure types.[11] VNS is also a less invasive option than other neurostimulation devices. Adverse effects include rare incisional or device infections; stimulation effects including cough, voice changes, dyspnea, paresthesia, headache, and localized discomfort, which usually decrease with time; and negative effects on sleep-disordered breathing.[10,11]

RNS. The FDA approved RNS in 2018 for DRE in adults. RNS involves applying electrical currents directly to the brain with depth electrodes implanted into deep, surgically inaccessible cortex or subdural strips on the cortical surface. RNS can detect seizure activity and respond by stimulating the cortex to abort the seizure, using a "closed-loop" paradigm. Up to 2 separate electrodes are inserted into the stimulator and remain active at any given time. The stimulator itself is implanted under the scalp.[15] The pivotal study in RNS was performed in 191 people with DRE, showing a 37.9% seizure reduction compared with 17.3% in the sham stimulation

group at 84 weeks.[16] In longer-term follow-up, there appeared to be an improvement in seizure frequency and sudden unexplained death in epilepsy (SUDEP) incidence over time.[17,18]

RNS not only provides a unique mechanism of action of neurostimulation, unlike DBS and VNS, it can record electrocorticographic data, allowing for monitoring response to therapy or guiding future surgical treatment (ie, bilateral mesial temporal lobe epilepsy).[19] RNS, however, is not indicated for generalized or multifocal epilepsy with more than 2 foci.[2,5] Adverse effects are typically periprocedural and occur within a median onset of 36 days postoperatively; these include intracranial hemorrhage in 2.7% and infection in 12.1%, although all but 1 infection involved only the soft tissue.[18] Depression and suicidality were also reported, but most of the cases were unrelated to the device placement and were confounded by the majority having a preceding psychiatric history.[18]

DBS. DBS is well known in the management of movement disorders but is also currently approved in the US and Europe for treating adults with focal epilepsy with or without secondary generalization who have failed at least 3 ASMs, with an average of at least 6 seizures per month in the 3 previous months, and no more than 30 days between seizures. In DRE, depth electrodes are typically implanted in the bilateral anterior nucleus of the thalamus (ANT-DBS)[20] (Figure 5). The SANTE trial studied ANT-DBS in patients with focal and multifocal DRE with or without concomitant secondarily generalized seizures.[21] There was a significant benefit in treatment compared with sham stimulation in the short-term,[20] and seizure reduction and decreased incidence of SUDEP showed sustained and gradual improvement over time.[22]

DBS provides another neurostimulation option besides VNS in multifocal epilepsy, with some suggesting possible efficacy in generalized epilepsy, which may depend on the location of implantation within the thalamus.[19] There may also be cases in which DBS would be preferable to VNS, including in those with younger age of onset of epilepsy and longer duration of epilepsy,[23] although randomized trials have not compared these devices. Adverse effects in the periprocedural period occur in about 6.5% of cases.[24] The concern with ANT-DBS, in particular, relates to possible short and long-term neuropsychiatric effects[24] likely relating to its connections within the limbic system. Despite early subjective reports of worsened mood and memory, however, longer-term studies have shown these issues can improve or resolve. Further, these cases where psychiatric effects were noted were usually confounded by a prior history of neuropsychiatric illness before surgery.[21,25] Stimulation parameters may be the key to avoiding neuropsychiatric effects.[25]

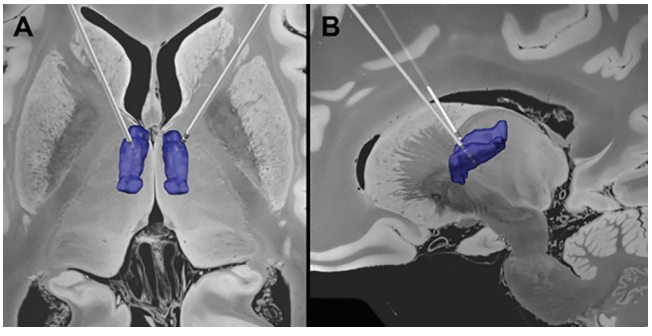

Figure 5. (A) Axial and (B) sagittal reconstructed images of bilateral deep brain stimulator electrodes placed in the anterior nucleus of the thalamus (blue regions).

In the case reported, considering the broad left hemisphere epileptogenic zone noted on intracranial EEG and the presence of a separate, more distant focus, RNS was not an option. VNS was considered, but there was concern about the patient's musical career and possible effects on his voice, the relatively early age at onset of seizures, and his longer duration of epilepsy. Seizures were frequent but may have been less than 6 per month; however, they caused severe injuries. Therefore, we decided to offer palliative treatment with ANT-DBS. We did consider the underlying mood disorder and will counsel the patient appropriately and consider adjusting the settings of his DBS if needed.

CLINICAL GEMS

When considering neurostimulation, the number and location of seizure foci, possible adverse effects, and patient preference should be considered.

Summary

DRE is a commonly encountered problem that requires further evaluation at a surgical epilepsy center to consider therapeutic options considering the implications of ongoing uncontrolled seizures. Despite this, referrals are often delayed or not pursued in most cases. Even in patients who are not resective surgical candidates, neurostimulation techniques are an option for palliative therapy to reduce seizure burden, which will also decrease the risk of self-injury and mortality. Many factors play into the decision on which device to use. Further study is needed to determine if each device, when indicated, may be more beneficial than other treatment options and if there are additive benefits to using multiple devices simultaneously. Understanding the possible adverse effects and the specific seizure characteristics are vital in counseling patients on the best therapeutic option. This case highlights the multimodal and highly individualized approach to neurostimulation in DRE. ■

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