Responsive Neurostimulation of the Thalamus Improves Seizure Control in Idiopathic Generalized Epilepsy: A Case Report

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BACKGROUND AND IMPORTANCE: At least 25% of patients with idiopathic generalized epilepsy do not obtain adequate seizure control with medication. This report describes the first use of responsive neurostimulation (RNS), bilaterally targeting the centromedian/ventrolateral (CM/VL) region in a patient with drug-refractory Jeavons syndrome (eyelid myoclonia with absences).

CLINICAL PRESENTATION: A patient, diagnosed with eyelid myoclonia with absences (EMA) and refractory to medication, was offered RNS treatment in the CM/VL region of the thalamus. Stimulation was triggered by thalamic neural activity having morphological, spectral, and synchronous features that corresponded to 3- to 5-Hz spike-wave discharges recorded on prior scalp electroencephalography.

CONCLUSION: RNS decreased daily absence seizures from a mean of 60 to ≤10 and maintained the patient's level of consciousness during the occurring episodes. This therapy should be evaluated further for its potential to treat patients with pharmaco-refractory generalized epilepsy.

KEY WORDS: Generalized epilepsy, Responsive neurostimulation, Centromedian nucleus, Thalamus

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Idiopathic generalized epilepsies (IGEs) constitute almost one-third of the epilepsies, affecting otherwise normal individuals of both genders and all races. IGEs typically appear during childhood or adolescence and remain a life-long diagnosis. Archetypical IGE seizures are absences, accompanied by mild to severe loss of consciousness and a 3- to 4-Hz bihemispheric spike-wave electroencephalographic (EEG) hallmark; myoclonic jerks and generalized tonic-clonic seizures can also occur. Appropriate antiepileptic medication controls seizures in 50% to 75% of IGE patients, but poor initial response to treatment, photosensitivity, and medication-related adverse effects or contraindications result in the remainder of patients being pharmaco-resistant.[1,2]

Deep brain stimulation (DBS) of the centromedian (CM) region of the thalamus improves both the scalp EEG background and the frequency and severity of generalized seizures.[3,4] Current DBS devices, however, do not record brain activity and, therefore, cannot be programmed to deliver personalized therapy in response to patient-specific seizure patterns.[5] The closed-loop responsive neurostimulation (RNS) System has been established as an effective and minimally invasive approach for pharmaco-resistant focal epilepsy, demonstrating significant and durable improvements in seizure control.[6,7] Here, we report the therapeutic approach, features, and outcome of the RNS of the bilateral centromedian/ventrolateral thalamic region (CM/VL-RNS) in an IGE patient.

ABBREVIATIONS: CM, centromedian; **CT,** computed tomography; **DBS,** deep brain stimulation; **ECoG,** electrocorticography; **EEG,** electroencephalography; **EMA,** eyelid myoclonia with absences; **FDA,** Food and Drug Administration; **IGE,** idiopathic generalized epilepsy; **MRI,** magnetic resonance imaging; **RNS,** responsive neurostimulation; **3D,** three-dimensional; **VL,** ventrolateral

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CLINICAL PRESENTATION

The patient is a 19-yr-old female, diagnosed with eyelid myoclonia with absences (EMA)[8] and having an otherwise normal psychosocial

and developmental profile. Absence seizures began at 11, elicited by photic stimulation, often accompanied by persistent eye flutter and occasional facial twitching. Seizures were incapacitating, averaging 1 to 4 per hour (mean 60/d, verified by a 2-d video-EEG recording), each lasting 5 to 10 s without postictal effects. Ictal EEG was characterized by 3- to 5-Hz generalized spike-wave discharges, often incorporating polyspikes. Treatment with valproic acid was not pursued because of the patient's history of polycystic ovary disease[9] and desire to become pregnant. Subsequent medications (clobazam, ethosuximide, lamotrigine, levetiracetam, topiramate, and zonisamide) failed to control her seizures and/or provoked intolerable side effects. The patient was offered CM/VL-RNS, following a review at our multidisciplinary epilepsy surgery conference. The retrospective data analysis was approved by the University Institutional Review Board, and the patient provided a standard written informed consent.

Under general anesthesia, 4-contact depth leads with a contact length of 2.0 mm and intercontact interval of 3.5 mm (DL-330-3.5, NeuroPace, Mountain View, California) were implanted using robotic stereotactic assistance (ROSA, Zimmer Biomet, Warsaw, Indiana). The patient was positioned prone, head restrained by a Leksel stereotactic frame firmly attached to the robot chassis and coregistered by laser surface matching on a preoperative CT-based three-dimensional (3D) head model. Indirect targeting of the CM nucleus of each hemisphere was used, with coordinates 10 mm lateral from the midline, 1 mm anterior to the posterior commissure, and 1 mm above the intercommissural line, consistent with previous studies[10,11] (Figure 1A and 1B). Postoperative visualization of electrode locations was performed with Lead DBS,[12] using a post-implantation volumetric CT, a pre-implantation volumetric magnetic resonance imaging (MRI), and the Morel[13] atlas of the thalamus. Following implantation, the RNS was set to record iEEG without stimulation (baseline) for 8 wk, prior to the initiation of RNS. Electrophysiology data were extracted from the Patient Data Management System (PDMS©) using a custom-built platform (BRAINStim).[5]

Electrode localization using a high-resolution multimodal platform revealed that the most distal contact on each electrode was implanted in the CM nucleus, and the most proximal ones resided in the VL nucleus (Figure 1B). Seizure events marked by the patient by magnet swipes were evident in thalamic recordings and visualized in the PDMS (Figure 1C-1E). Analysis of electrocorticography (ECoG) during the baseline period revealed a multitude of transient (2-5 s duration) bilateral 3- to 5-Hz spike-wave discharges in the CM/VL region, recapitulating the morphology and spectral signature of presurgical scalp EEG ictal discharges (Figure 2A-2F). During the ninth week, bilateral thalamic high-frequency[6,7] prolonged[14,15] stimulation (1-2 mA, 125 Hz, 160 μs for 5000 ms) was enabled, triggered on the detection of ictal-like 3- to 5-Hz spike-wave discharges on Ch2 (left) and Ch4 (right), bilaterally, the 2 channels exhibiting the highest amplitude discharges (Figure 2G-2I); maximal waveform amplitude optimizes the detection yield of RNS and suggests proximity to the electrical source of the discharges for optimal stimulation efficiency. Bipolar stimulation, exclusively performed on the above 2 channels of optimum detection, occurred successfully in response to the identified thalamic spike-wave discharges, with a delivery of 1 to 2 $\mu C/cm^2$ per stimulation pulse, at a mean rate of 100 times (min 30, max 300) per day. We use the term CM/VL region to describe the location of stimulation, because stimulation occurred outside of and lateral to the initial CM nucleus target.

Throughout the first 12 postoperative months, with no changes in her medication regimen, the patient reported a dramatic improvement in seizure control. Currently at the 18th postoperative month, the patient chose to stop taking all antiepileptic medication 6 mo ago. She now experiences periods of >48 h without seizures. When seizures occur, they do not exceed 10/d (84% reduction) and manifest as brief episodes of eyelid myoclonia, without loss of consciousness. CM/VL-RNS has completely prevented the clinical absence component of her seizures. She reports a significant improvement in her quality of life and improved concentration, which allowed her to get and keep a full-time job, as well as pursue independent living. At 1-yr postimplantation, scalp EEG was obtained concurrent with CM/VL-RNS detection and stimulation, demonstrating successful stimulation during the thalamic expression of scalp generalized spike-wave discharges corresponding to absence seizures (**Figure**, **Supplemental Digital Content**).

DISCUSSION

Studies on the mechanism of absence seizures have highlighted the role of the corticothalamic system in the generation and maintenance of the archetypical 3-Hz generalized spike-wave discharges.[16] In the non-ictal state, the flow of information to the cortex is regulated by thalamocortical feedback loops, which assist neuronal organization by means of low-gamma (>30 Hz) oscillations, facilitating focused attention and awareness.[17] The loss of consciousness that characterizes absence seizures is thought to reflect network disruption following thalamocortical loop recruitment by 3-Hz excitatory/inhibitory volleys of postsynaptic potentials.[18] We interpret the prevention of loss of consciousness by 3- to 5-Hz thalamic spike-wave discharge-triggered CM/VL stimulation in this patient as a desynchronization effect, in which ictal thalamocortical low-frequency recruitment is disrupted, allowing the continuation of high-frequency thalamocortical information transfer. It has also been proposed that subcortical structures like the thalamus are responsible for the loss of consciousness experienced in focal epilepsy seizures.[19] Our findings suggest that RNS-guided thalamocortical desynchronization may also affect focal epileptic networks and possibly reduce the burden of focal neocortical seizures on the patient's quality of life. Interestingly, the clinical result observed here reflects a direct effect of stimulation on individual ictal events, in contrast to our recent findings supporting an

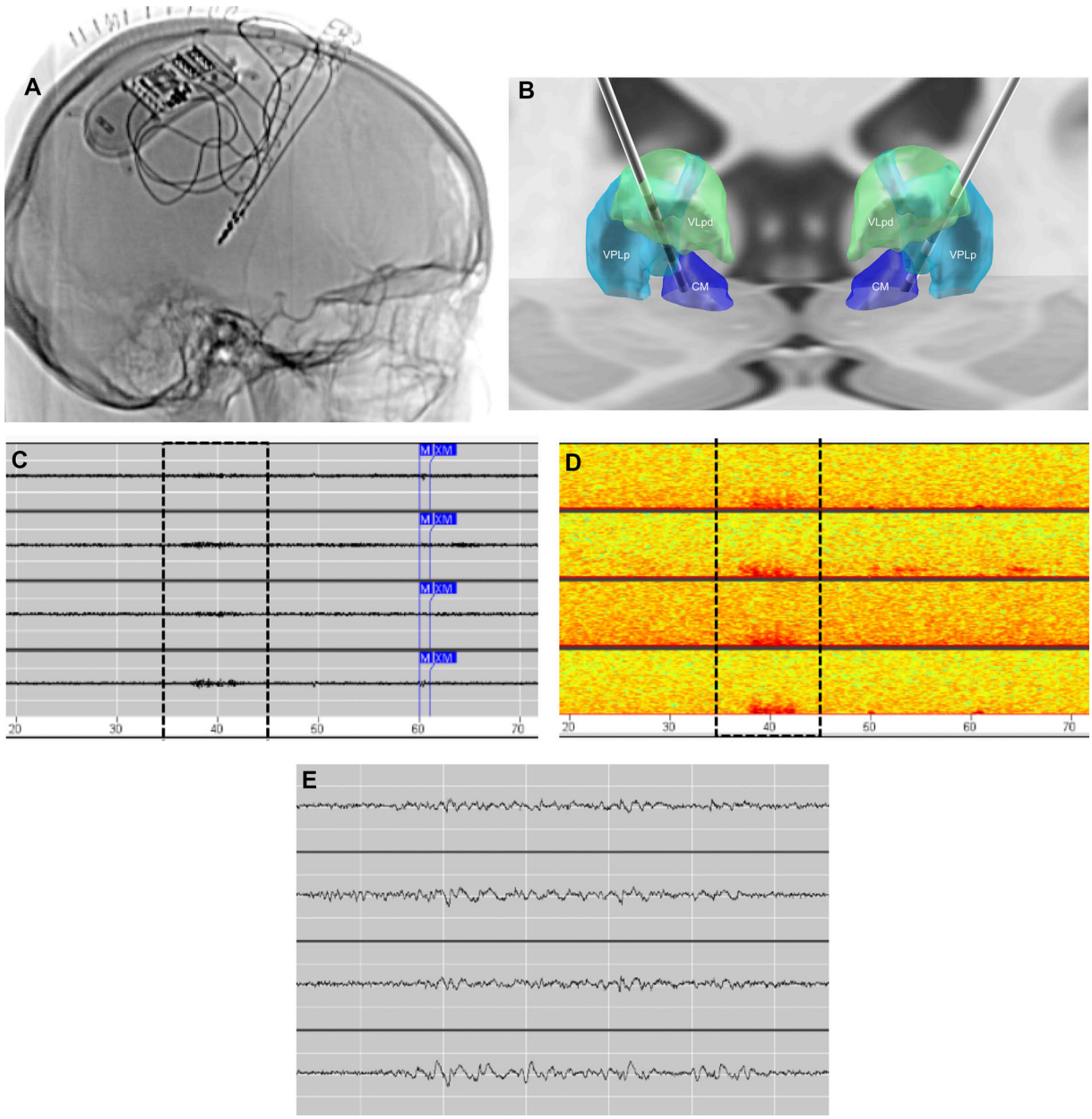

FIGURE 1. *Lead locations.* **A**, *Lateral X-ray of the implanted RNS System.* **B**, *Bilateral leads are represented in MNI space in relation to the CM nucleus, posterior part of the ventral posterolateral nucleus (VPLp), and posterior dorsal part of the ventral lateral nucleus (VLpd).* **C-E**, *Example of a clinical seizure recognized by the patient, as depicted by the NeuroPace Patient Data Management System in the captured ECoG recording* **C** *and spectrogram* **D**, *(blue bars in* **C**, *depict the patient's magnet swipe, which is used by the patient to mark a seizure occurrence), and the ECoG signal within the dashed box in* **C**, *is represented in* **E**.

indirect effect of RNS in focal epilepsy.[20] The highly specialized effect of CM/VL-RNS in this patient supports current network theories underlying absence seizures and strongly suggests a significant advantage in the use of closed-loop stimulation for IGE syndromes.

Although medication-resistant focal epilepsy patients can be offered a variety of targeted surgical options to improve seizure control and their quality of life, drug-resistant IGE patients currently remain without a Food and Drug Administration (FDA)-approved surgical therapy. RNS has the advantage of

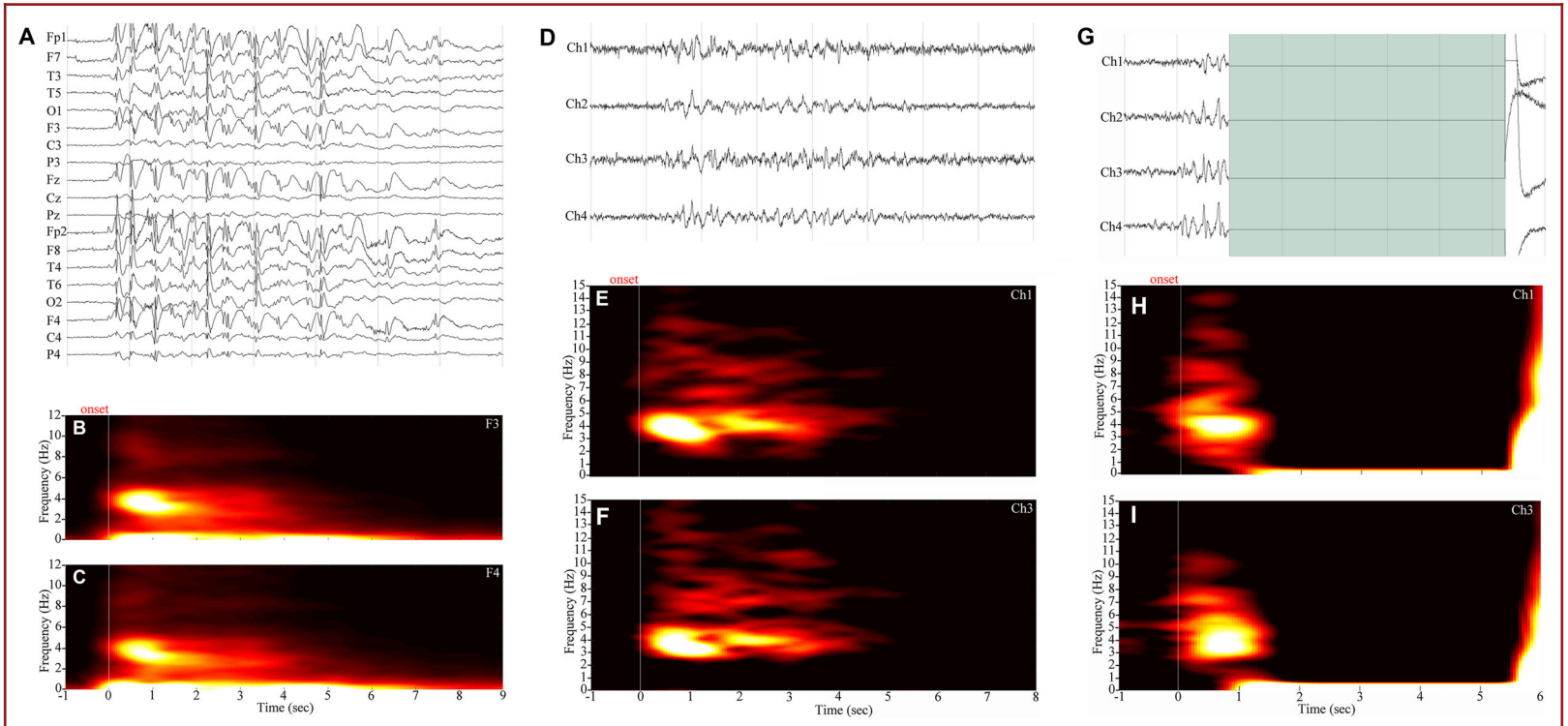

FIGURE 2. *Preimplantation scalp EEG and postimplantation thalamic ECoG.* **A**, *Scalp EEG-recorded absence seizure before RNS implantation showing the 3- to 5-Hz generalized spike-wave discharge of the patient.* **B** *and* **C**, *Average of time-frequency power maps depicting the spectral signature from 70 absence seizures (see Kokkinos et al*[20] *for detailed methodology) for the left (F3) and right (F4) frontal electrodes.* **D**, *iEEG recorded from the thalamus during the immediate baseline postimplantation period, in which therapeutic stimulation is not activated, showing a series of bilateral discharges consisting of spikes and slow waves.* **E** *and* **F**, *Average of time-frequency power maps, depicting the spectral signature from 12 thalamic spike-wave episodes, for the left (Ch1) and right (Ch3) CM/VL regions. Note the common 3- to 5-Hz component dominating the thalamic spike-wave discharges bilaterally, corresponding to the scalp EEG spectral component of generalized spike-wave discharges.* **G**, *iEEG recorded from the thalamus during therapeutic stimulation (green block marks stimulation interval), showing RNS detecting and stimulating bilateral thalamic spike-wave discharges.* **H** *and* **I**, *Average of time-frequency power maps depicting the spectral signature from 22 stimulated thalamic spike-wave episodes, for the left (Ch1) and right (Ch3) CM/VL regions.*

combining a minimally invasive nature and stereotactic precision with neurophysiological monitoring and feedback, which informs clinical decision-making in real time. This personalized medicine approach has low morbidity and proven therapeutic durability in focal epilepsy.[7,8] As we have demonstrated rapid detection of spike-wave discharges in the thalamus, thalamic RNS warrants further study in a larger cohort of IGE patients. We chose the CM target based on its known functional neuroanatomy,[21] having broad connectivity to frontal and parietal areas,[22] and the reported efficacy of bilateral CM DBS in generalized epilepsy from a 2-center, single-blind, controlled trial with open-loop stimulation.[4] The site of stimulation used in this patient, however, indicates that VL thalamic regions, rather than the CM nucleus exclusively, may be a valid target for RNS.

CONCLUSION

We have described the first successful treatment of IGE by closed-loop brain stimulation. In cases in which IGE becomes refractory or first-line medications are contraindicated, CM/VL-RNS may provide an effective means of long-term seizure control.

Disclosures

Dr Richardson has received payment from NeuroPace Inc for speaking engagements. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. This work was funded partially by the Walter L. Copeland Fund of the Pittsburgh Foundation (to Mr Sisterson and Dr Richardson).

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Supplemental Digital Content. Figure. Postimplantation simultaneous scalp EEG and thalamic ECoG during a generalized discharge. Twelve months after RNS implantation, scalp A and thalamic B traces were recorded independently and then retrospectively synchronized by the artifact generated from the stimulator shutdown (red line; green block marks stimulation interval). Note the lead between thalamic intracranial-recording spikes and scalp-recorded spikes at seizure onset (vertical green lines aligned to scalp spikes).

COMMENT

The manuscript reports a single patient with medically refractory generalized epilepsy treated with responsive nerve stimulation, precisely targeting the Centro-Medium (CM) nucleus of the thalamus. The authors reported outstanding results with complete seizure control after surgery. Despite the obvious limitations related to single report and

short outcome, the manuscript clearly highlights, as a proof of concept, the potential benefits of neuromodulation in generalized symptomatic epilepsy. The concept of CM stimulation for generalized epilepsy in not novel, with previous reports in the past, mainly by the Velasco group. Although the authors intended to target in the CM nucleus, it is unclear if the effects are truly caused by CM stimulation of by electrical stimulation of thalamic structures located dorsally, as the intralamic nuclei. Regardless, these findings should promote and incentivize further investigations related to optimal parameters of stimulation, proper target and patient selection. I congratulate the authors for their contribution to the field.

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