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Bilateral thalamic responsive neurostimulation for multifocal, bilateral frontotemporal epilepsy: illustrative case

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BACKGROUND Patients with refractory, bilateral, multifocal epilepsy have few treatment options that typically include a combination of antiseizure medications (ASMs) and vagus nerve stimulation (VNS). A man in his 40s presented with epilepsy refractory to a combination of five ASMs plus VNS; he was still experiencing 7–10 seizures per week. His seizure network involved multiple foci in both frontal and temporal lobes. Bilateral depth electrodes were implanted into the centromedian/parafascicular (CM/PF) complex of the thalamus and connected to the responsive neurostimulation (RNS) system for closed-loop stimulation and neurophysiological monitoring.

OBSERVATIONS The patient reported clear improvement in his seizures since the procedure, with a markedly reduced number of seizures and decreased seizure intensity. He also reported stretches of seizure freedom not typical of his preoperative baseline, and his remaining seizures were milder, more often with preserved awareness. Generalized seizures with loss of consciousness have decreased to about one per month. RNS data confirmed a right-sided predominance of the bilateral seizure onsets.

LESSONS In this patient with multifocal, bilateral frontotemporal epilepsy, RNS of the CM/PF thalamic complex combined with VNS was found to be beneficial. The RNS device was able to detect seizures propagating through the thalamus, and stimulation produced a decrease in seizure burden and intensity.

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KEYWORDS responsive neurostimulation; epilepsy; thalamus

Epilepsy is one of the most common neurological diseases worldwide, affecting approximately 50 million individuals. The incidence of epilepsy is expected to increase, given the rising life expectancy and increased survival after various brain insults, such as traumatic brain injury, stroke, and infection. Accounting for more than 13 million disability-adjusted life-years, epilepsy is a major contributor to the world's burden of disease.[1] Inadequate treatment of epilepsy not only has consequences for the well-being of individuals but also affects economic and social development. In Europe, active epilepsy is estimated to exceed a cost of 20 billion euros per year.[2] Epilepsy remains incompletely controlled in 20%–30% of patients whose epilepsy is resistant to modern drug treatments[3,4] and who do not qualify for advanced surgical methods.[5]

After two antiseizure medications (ASMs) fail to relieve symptoms, a patient is unlikely to respond to pharmacological treatment alone.[6] In patients whose condition is refractory to ASMs, surgical options may be considered, but many patients are not surgical candidates, because their epilepsy is multifocal or generalized in nature.[7] In patients with multifocal epilepsy, palliative stimulation techniques may be considered. Vagus nerve stimulation (VNS) is the most widely used approach because of its potential efficacy and its low risk of complications, such as bleeding and infection.[8] A relatively newer

ABBREVIATIONS AC = anterior commissure; ASM = antiseizure medication; CM/PF = centromedian/parafascicular; CNS = central nervous system; DBS = deep brain stimulation; MRI = magnetic resonance imaging; PC = posterior commissure; RNS = responsive neurostimulation; SD = standard deviation; VNS = vagus nerve stimulation.

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therapy for medically intractable epilepsy is responsive neurostimulation (RNS), which involves a cranially implanted device that detects seizure activity and delivers stimulation directly to the brain's seizure network to modulate or disrupt ictal events[9] and more generally modulates the seizure network.[10] In our patient with multifocal, bilateral frontotemporal epilepsy, ASMs plus VNS failed to adequately improve his epilepsy. RNS was chosen as the next treatment option because we hypothesized his epilepsy could respond to the distributed epileptogenic activity across multiple cortical regions through convergent networks in the thalamus.[11]

Recent evidence suggests that thalamic stimulation is a potentially viable strategy for treatment-resistant multifocal epilepsy. The thalamus is rich in corticothalamocortical circuitry, allowing it to modulate cortical activity widely. Its ability to relay aberrant cortical activity diffusely implicates the thalamus as a potential nexus for the treatment of medically intractable epilepsy using open-loop deep brain stimulation (DBS) and closed-loop RNS. The anterior thalamus and its role in the Papez circuit provides a well-studied example of the ability of the thalamus to modulate seizure-related activity.[12] It has been successfully targeted with DBS to treat partial seizures[7] and has been investigated as a target for RNS in treatment-resistant multifocal epilepsy.[13] Although RNS of the anterior nucleus of the thalamus had positive effects for those with multifocal epilepsy, those benefits were relatively modest.[13]

Within the thalamus, the centromedian/parafascicular (CM/PF) complex has been investigated as a potential target for complex, treatment-resistant epilepsy, given its robust connectivity. The centromedian nucleus of the thalamus receives diverse sensory inputs as well as inputs from the reticular activating system, implicating a role in attention and arousal through reticulothalamocortical modulation. Furthermore, the CM provides direct cortical connections to the frontal and parietal cortex, sends connections diffusely through the basal ganglia, and is involved with a web of neighboring thalamic nuclei that maintain diffuse thalamocortical connections.[14] The CM has more diffuse projections relative to other thalamic nuclei,[15] which include projections to the Papez circuit.[15,16] Given the CM's connectivity, it is now being investigated as a potential target for multifocal and generalized epilepsy.[17]

Treatment-resistant multifocal epilepsy impacts quality of life for millions of people. Recent research provides evidence for the role of the thalamus in seizure initiation/propagation and the potential utility of thalamic RNS in treatment. Multiple thalamic regions have been identified as potential targets; however, the efficacy of neurostimulation of these targets in patients with multifocal epilepsy is currently unknown. Here, we synthesize the current literature to discuss what is known about the treatment of multifocal epilepsy and provide a case in which RNS of the CM/PF nucleus of the thalamus combined with VNS produced a marked decrease in seizure burden, quantity, and intensity.

Illustrative Case

Clinical Presentation

A man in his 40s was diagnosed with intractable epilepsy. He had presented years earlier with status epilepticus in the setting of coxsackie B viral encephalitis. Over the months after this initial hospitalization, he continued to experience focal to bilateral tonic-clonic seizures preceded by auras two to four times per week, with a possible right temporal lobe focus. Subsequent medications (clonazepam, levetiracetam, lacosamide, oxcarbazepine, topiramate, sodium valproate, and medical marijuana) failed to control his seizures, and he continued to have daily focal onset seizures with impaired awareness as well as up to 10 tonic-clonic seizures per month with complete loss of consciousness.

After conservative ASM treatments failed, the patient received a left vagus nerve stimulator. Over the course of nine office visits, VNS output current was increased to 1.75 mA, and the magnet current was increased to 2.00 mA with a magnet-on time of 60 seconds, pulse width of 500 μs, and a signal frequency of 30 Hz. The patient's burden of seizures did not substantially improve. One year after the initiation of VNS, the patient's seizure frequency had increased to 20–30 per month, and VNS settings were increased further to an output current of 2.00 mA and a magnet current of 2.25 mA with a 20-Hz signal frequency.

A repeat scalp electroencephalogram suggested the patient's seizures to be multifocal, bihemispheric, and probably bianterior in origin, with some emphasis involving the right frontotemporal region. However, brain magnetic resonance imaging (MRI) was entirely negative for a correlating focal abnormality. Bilateral depth electrode implantation for long-term epilepsy monitoring over 2 weeks revealed a multifocal, bihemispheric pattern, which likely included the right temporal and left frontal regions. Consequently, resection and ablation were ruled out as potential treatments. The patient was then considered as a candidate for intracranial neurostimulation.

The patient believed that his VNS was partly helpful for his seizure management and reported that he would like to continue VNS therapy. The compatibility of VNS with DBS was not confirmed at that time, whereas simultaneous VNS and RNS was in more routine use. Furthermore, DBS was primarily in use for anterior nucleus of the thalamus stimulation and would not provide objective neurophysiological data regarding epileptic events, whereas RNS was more flexibly employed to treat epilepsy in diverse central nervous system (CNS) locations and would provide neurophysiological recordings. Bilateral centromedian thalamic nuclei stimulation was believed to be potentially advantageous for this patient, given suspected multiple bilateral frontal and temporal neocortical foci in this postencephalitic form of epilepsy. For these reasons, the patient received an RNS implant in the bilateral CM nuclei of the thalamus as well as a replacement battery for the VNS.

Surgical Procedure: Implantation of RNS System and Replacement of VNS Battery

The patient underwent implantation of the RNS system under general anesthesia. Two electrode leads were implanted in the CM/PF nuclei bilaterally through bifrontal burr holes using a three-dimensional printed stereotactic platform (StarFix, FHC Inc.). These leads were tunneled to a separate site where a trap-door incision was made, allowing the RNS processor to be implanted within a small craniectomy. Intraoperative computed tomography fused with preoperative MRI was used to confirm correct placement of the leads within the region of the CM/PF thalamic nuclei bilaterally. Electrode coordinates were 7 mm lateral (left and right), 1 mm anterior commissure (AC) to the posterior commissure (PC), and 0.7 mm inferior to the AC-PC plane, with a 33° sagittal angle and a 22° coronal angle (both from vertical). The baseline function of the RNS system and the ability to record neural activity via these electrodes were confirmed intraoperatively via telemetry. The VNS battery was replaced separately during the same operation.

Discussion

Observations

Patient Report

During the 2.5 years after implantation of his RNS, the patient and his spouse both reported a significant improvement in his seizures. In the months after the activation of RNS-based stimulation, the patient reported periods lasting 3–4 weeks that were seizure free, punctuated by 1–2-week periods with seizures roughly every other day. These seizures were described as generally milder than his pre-RNS seizures. These included focal seizures with impaired awareness and little postictal impairment and, more commonly, focal seizures with preserved awareness involving a feeling or thought intrusion. There was a 1-month period with only sporadic auras. During the last 3 months, mild focal seizures, sometimes with impaired awareness, occurred about four times per month and with more warning before the event. Focal to bilateral tonic-clonic seizures occurred about once per month. Many of the periods with increased seizures seemed to correlate with intercurrent illness. The patient's RNS stimulation amplitude and duration were augmented in steps over this 2.5-year period.

In general, the patient and his spouse reported a significant improvement with a decrease in average seizure frequency from 7–10 seizures per week before RNS to 1 seizure per week after RNS, indicating an 85%–90% improvement in overall seizure frequency. Generalized seizures with loss of consciousness occurred 10 times per month before treatment and now occur about once per month, indicating a 90% improvement. Seizures are described to be milder, on average, than before and often without any impaired awareness or volition. He describes having more warning before seizures and more rapid recovery after seizures. His partner agrees that his seizures have become milder and that his preservation of awareness has improved.

RNS Data

Electrodes of the RNS system detected epileptiform activity: electrode A1 (left CM) and electrode A2 (right CM) were used for treatment and recording purposes. In addition, the patient marked seizure episodes with a magnet swipe to be recorded by the system. We considered representations of clinically significant long episodes as long episodes that were recorded by the patient via magnet. Figure 1 shows an example of electrode detection of seizure activity, initiation of treatment, classification of "long episode," and magnet activation by the patient.

Long Episode Frequency

We were unable to confirm a reduction in total long episode frequency due to variations in detection settings during the control period and the start of treatment.

Dominance

The electrodes constantly detect epileptiform activity. The definition of epileptiform activity varied during the first few months of treatment but was ultimately defined as activity that lasted for more than 35 seconds. Each independent detection from an individual electrode is recorded in the database as one detection. This means that if an event involving both electrodes occurs, it will record two detections—one for each. If both electrodes were involved in every detected event in a day, they would each contribute to exactly 50% of total detections that day.

We examined data over the span of 1.5 years. Out of 382,970 total detections, A2 (right) was involved in 380,264 (99.29%) compared with 284,980 of events including A1 (74.41%). Conclusively, more than 25% (97,990) of detected events involved only A2, and 0.71% (2,719) involved only A1. The remaining events involved both.

We determined daily lateral dominance by determining which electrode was involved in more than 50% of all detections on each individual day. Before treatment, dominance of long episode activity switched from left-sided (A1) to right-sided (A2) as if alternating each day. After the initiation of treatment, there was near-persistent right-sided dominance. Only 31 of 493 days after treatment displayed left-sided dominance. A2 involvement in detections, both in total and daily, during this time supports right-sided dominance of this patient's seizure activity.

The patient was asked to record seizure events with a magnet swipe that created an event marker in the data stream. When we analyzed long episodes associated with magnet events, primary lateralization of seizure onset was considered undetermined if any of the following were true: (1) Patient Data Management System provided an incomplete display of activity initiation, (2) treatment was not initiated and completed, or (3) the activity did not occur at least 30 minutes after a previous episode.

Of the 44 total magnet episodes associated with electrographic seizure activity that met our criteria, 25 (57%) were initiated from the right CM thalamus (as detected by the A2 electrode), 6 (14%) were initiated from the left CM thalamus (as detected by the A1 electrode), and 13 (29%) had undetermined laterality of onset. Of the episodes that began on the right CM thalamus, activity was observed to propagate to the left CM thalamus in 88% of events (22 of 25), with an average latency of 7.72 seconds (standard deviation [SD] 9.72 seconds) and a median latency of 3.25 seconds. Of the episodes that began on the left CM thalamus, activity was confirmed to propagate to the right CM thalamus in 50% of events (three of six), with an average latency of 3.2 seconds (SD 0) and a median latency of 3.2 seconds. The detection frequency data provide evidence that both sides are involved in seizure activity, with the right side being dominant.

Lessons

This is an illustrative case of a patient with postencephalitic refractory multifocal epilepsy with ictal foci involving bilateral frontotemporal head regions. The patient had persistent seizures despite numerous ASMs and VNS. Given stereoelectroencephalographic evidence for bilateral frontal and temporal foci, his surgical treatment options were limited. He underwent neuromodulatory treatment with bilateral centromedian thalamic nucleus stimulation using RNS therapy and has experienced significant improvement with a 2.5-year follow-up to date.

Current evidence suggests that the CM nucleus of the thalamus may be a useful target for the treatment[18] of generalized epilepsy with DBS.[18,19] Although the mechanism is not well understood, it may involve the disruption of synchronized thalamocortical activity and regulation of arousal.[19–22] Another study investigated the use of electrical stimulation of the CM nucleus of the thalamus in treating generalized seizures of Lennox-Gastaut syndrome in 13 patients who presented with generalized tonic-clonic and atypical absence seizures.[23] In this study, stimulation of bilateral CM nuclei of the thalamus led to a greater than 87% seizure reduction. A prospective study of six patients with generalized or frontal lobe epilepsy

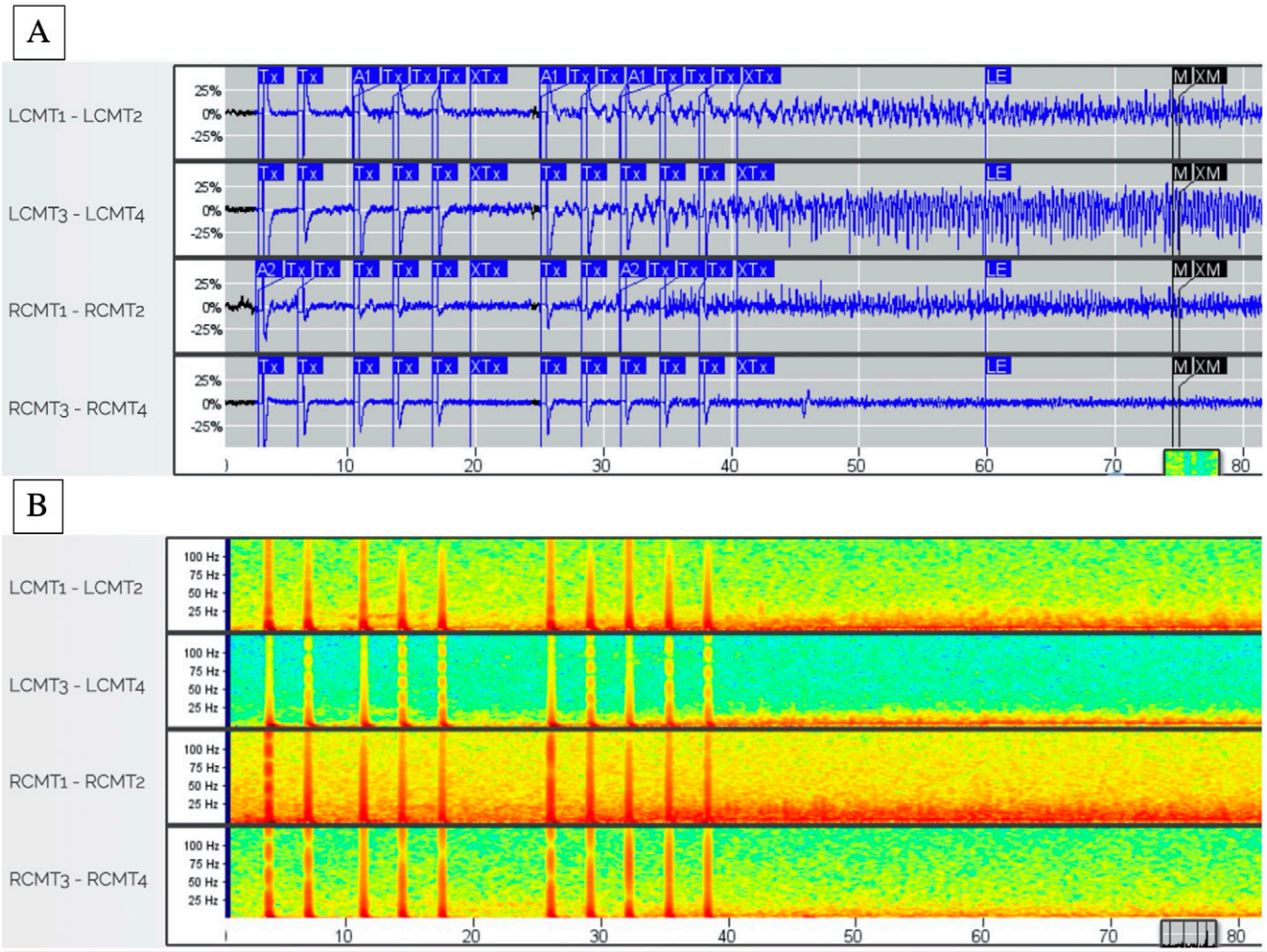

FIG. 1. Magnet long episode example. **A:** Commencement of seizure activity is labeled with the *blue box* A2 in the right CM channel (RCMT1–2). This spike in thalamic activity from baseline (>25% change in this case) triggers treatment. Each administration of treatment is represented by "Tx," and the end of a series of five treatment bursts is represented by "xTx." There is a return to baseline in thalamic activity briefly at the 25-second mark (seen as a *black tracing*). However, seizure activity that has spread to the A1 site is detected by the left CM channel (LCMT1–2), initiating another series of treatment. This treatment does not alleviate the activity, which is again detected in A2. The hyperactivity of the thalamus is sustained from time point of 25 seconds to the time point of 60 seconds, which meets the threshold of 35 seconds to be labeled as a long episode. Shortly thereafter, the *black labels* of M and XM indicate the patient's experience and report of this episode in the form of a magnet recording. **B:** The same sequence of events seen in A represented as a spectrogram of thalamic activity from physiological baseline in the wakeful state. LCMT = left centromedian nucleus of the thalamus; RCMT = right centromedian nucleus of the thalamus.

reported a seizure reduction ranging from 60% to 100% with DBS implantation and stimulation of CM.[18] Furthermore, a study investigating clinical outcomes of 14 patients with DBS of the CM found that all 4 patients with Lennox-Gastaut syndrome (generalized epilepsy) as well as 7 of 10 patients with multifocal epilepsy reported a reduction of seizure frequency by greater than 50%.[24]

The PF nucleus of the thalamus is an important thalamic region that is being studied in drug-resistant multifocal epilepsies. A study in mice reported that the PF nucleus of the thalamus may play an important role in the initiation of epilepsy. More specifically, the researchers obtained thalamic and hippocampal local field potentials and suggested a unidirectional information flow from the PF nucleus to the hippocampus before seizure generation. Furthermore, they were able to suppress seizures by chemically inhibiting the PF nucleus of the thalamus using tetrodotoxin.[25] These studies provide evidence for the role of the thalamus, especially the CM/PF nucleus, in seizure activity and suggest that the thalamus may be a useful therapeutic target.

Investigation of the CM as a target for RNS has yielded promising results in animal epilepsy models as well as recent case reports. In rats, desynchronization of CM dynamics, using a closed-loop feedback control system, has been associated with successful seizure control.[26] In a case report of two pediatric patients with drug-resistant, intractable multifocal epilepsy, RNS of the CM thalamus led to a reported 75%–99% clinical seizure reduction in more than 1 year of follow-up.[17] One of the pediatric patients had multifocal, generalized epileptiform activity of the frontal and temporal lobes, and ASM or VNS had not been effective at controlling her

seizures. After RNS of the bilateral CM nucleus of the thalamus, the patient achieved 70%–90% improvement in drop attacks and 100% improvement in generalized tonic-clonic seizures, with only a few short seizure episodes per month. Furthermore, the seizures were found to have right-sided predominance for seizure onset. These findings are similar to those in our patient, who reported a seizure reduction from 7–10 seizures per week before RNS to 1 seizure per week after RNS was implemented, indicating an 85%–90% improvement in overall seizure frequency and a 90% improvement in loss-of-awareness seizures. Interestingly, our patient's detection frequency data also showed right-sided dominance for seizure onset. Our results add to the body of evidence for the safety and efficacy of CM thalamic RNS use in patients with refractory, multifocal epilepsy. Further investigations are required to examine the use of this approach in larger populations.

Conclusions

This case highlights the potential utility for closed-loop (RNS) stimulation of bilateral centromedian nuclei of the thalamus as another candidate treatment modality for refractory multifocal, bihemispheric frontotemporal epilepsies. These cases, often secondary to profound and diffuse CNS insults (e.g., infectious, hypoxic-ischemic, dysgenetic, inflammatory/autoimmune, or even traumatic), present formidable treatment challenges. The ability to combine two compatible neuromodulatory strategies, VNS therapy plus bilateral CM RNS therapy, may provide a means to treat broad bilateral epileptogenic networks and thereby benefit the care of patients with these most difficult forms of epilepsy.

Limitations

There are several limitations to this study. This is a report of a single patient. Therefore, the findings in this study cannot necessarily be generalized or used to establish a cause-and-effect relationship. Furthermore, the baseline assessments for this patient are relatively short. In addition, we were only able to obtain descriptive reports of seizure quality, loss of awareness, and other qualitative measures. Determining pretreatment versus post-treatment long episodes requires consistent detection settings, which was not feasible in this clinical care format. Finally, the speed of propagation between electrodes is recorded by the device but should be more precise. Future prospective studies are needed to quantify and characterize seizure reduction with bilateral CM/PF thalamic RNS in patients with such complex intractable forms of epilepsy who were previously not considered as surgical candidates.

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Disclosures

Dr. Blum reported other from United Diagnostics outside the submitted work; in addition, Dr. Blum had a patent for copyright with royalties paid from Springer Publishing. Dr. Asaad reported a patent issued (US20210138235A1) Brown/Lifespan and a patent issued (US20190307487A1) Brown/Lifespan. No other disclosures were reported.

Author Contributions

Conception and design: Phillips, Aghagoli, Asaad. Acquisition of data: Phillips, Aghagoli, Blum. Analysis and interpretation of data: Phillips, Aghagoli, Blum. Drafting the article: Phillips, Aghagoli. Critically revising the article: all authors. Reviewed submitted version of manuscript: Phillips, Aghagoli, Blum. Approved the final version of the manuscript on behalf of all authors: Phillips. Statistical analysis: Phillips, Aghagoli. Administrative/technical/material support: Phillips, Aghagoli, Asaad. Study supervision: Blum, Asaad.

Supplemental Information

Previous Presentations

The information in this article was previously presented as an abstract in poster format at the American Association of Neurological Surgeons Annual Scientific Meeting 2021 (Virtual; August 21–25, 2021) and at the 3rd Annual Brown Student Neurology/Neurosurgery Conference (The Warren Alpert Medical School, Providence, RI; January 9, 2021).

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