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Case Report

Brain-responsive neurostimulation in adult-onset rasmussen's encephalitis

Anteneh M. Feyissa [a,b], Alaa S. Mohamed [a,b], William O. Tatum [a,b], Alana S. Campbell [a,b], A. Sebastian Lopez-Chiriboga [a,b,*]

[a] Mayo Clinic Florida, Jacksonville, FL, United States
[b] Department of Neurology, United States

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ABSTRACT

Epilepsy associated with Rasmussen's encephalitis (RE) is highly resistant to standard therapy and continues to present a therapeutic challenge. While epilepsy surgery remains the most effective management for patients with drug-resistant focal epilepsy and RE, hemispherotomy may debilitating consequences on adult patients. Here we present the outcome of a 32-year-old woman with adult-onset Rasmussen's, who was treated with brain-responsive neurostimulation (RNS) after failure of several immunotherapeutic and anti-seizure medications.

1. Introduction

Rasmussen syndrome (a.k.a Rasmussen encephalitis; RE) is a unihemispheric chronic autoimmune inflammatory process that leads to drug-resistant epilepsy [1]. RE is typically a disease of childhood, but adult-onset occurs in up to 10% of cases. Disease-modifying treatments are limited; however, hemispherotomy is associated with a high rate of seizure freedom [2]. Herein we present the outcome of an adult-onset RE patient treated with brain-responsive neurostimulation (RNS® System, NeuroPace, Inc.) after failure of several immunotherapeutic and anti-seizure medications (ASMs) and when hemispherotomy was not a viable option.

2. Case report

A 32-year-old right-handed female presented with a prodrome of headache, fatigue, and cognitive dysfunction. A few weeks later, she developed focal impaired awareness seizures and focal to bilateral tonic-clonic seizures arising from the left temporal and parietal lobes. She subsequently developed progressive right homonymous hemianopia and further cognitive dysfunction. Brain MRI initially revealed multiple enhancing lesions over the left hemisphere that ultimately evolved to unihemispheric atrophy (Fig. 1). CSF analysis revealed normal findings, and neither oligoclonal bands nor autoimmune antibodies were detected. A brain biopsy showed a prominent lymphocytic infiltrate, CD3 predominant, and activated hypertrophic microglia throughout the brain parenchyma but no evidence of viral inclusions, vasculitis or granulomas (Fig. 2), fulfilling the proposed criteria for Adult-onset RE [1]. Interictal scalp video-EEG revealed multifocal epileptiform discharges over the left temporal, posterior temporal and temporo-occipital regions. In addition, three focal impaired awareness seizures of left posterior temporal onset were recorded. Although her epilepsy was resistant to ASMs and immunotherapy, seizure frequency stabilized on rituximab monotherapy for a duration of four years (Fig. 3). Unfortunately, the seizure frequency and intensity increased in 2016 despite appropriate B cell depletion (Fig. 3). Hence, the patient was discussed at the multidisciplinary epilepsy surgical conference and a consensus was reached to perform invasive intracranial EEG monitoring.

The patient underwent intracranial EEG (iEEG) monitoring using: 1) one 1 X 8 contact depth electrode sampling the left amygdala and hippocampus, 2) one 1 X 6 contact left subdural strip sampling the basal temporal neocortex, and 3) an 8x8 contact grid sampling the left lateral temporal, parietal and occipital neocortex. Interictally, frequent multifocal epileptiform discharges arising from electrode contacts overlying the left parietal grid, subtemporal strips, and the depth contacts, predominantly from the distal contacts of the left temporal depth electrode, were seen. Three focal impaired awareness seizures arising from the left temporal

* Corresponding author at: Mayo Clinic Florida, 4500 San Pablo Rd S, Jacksonville, FL 32224, United States.
E-mail address: lopezchiriboga.alfonso@mayo.edu (A.S. Lopez-Chiriboga).

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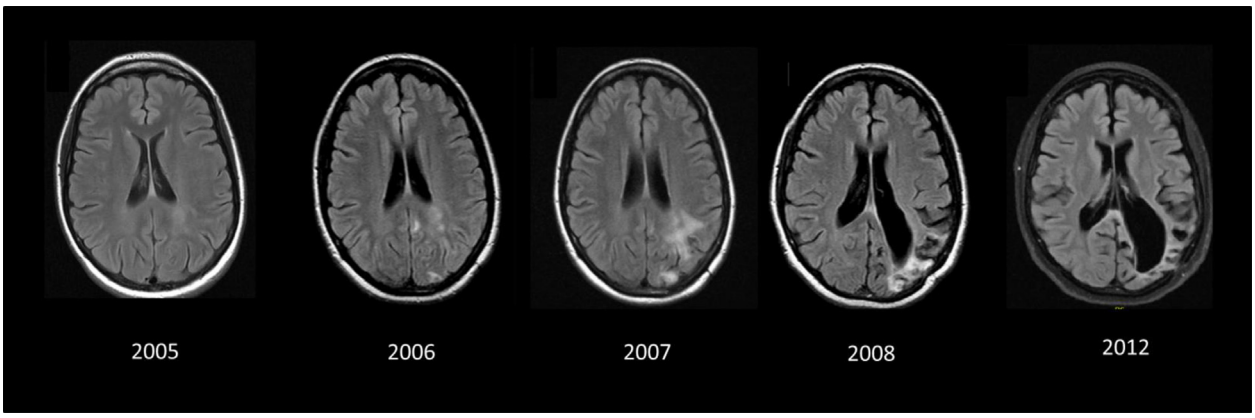


Fig. 1. Serial axial T2/FLAIR weighted MRI brain in adult onset Rasmussen showing the progression of the condition in: 3 months, 17 months, 24 months, 32 months and 7 years after the disease onset. MRIs show multiple enhancing left hemispheric lesions involving primarily the temporal, parietal, and occipital lobes. Progressive left parietal and occipital cystic encephalomalacia and volume loss are very prominent between 2007 and 2008.

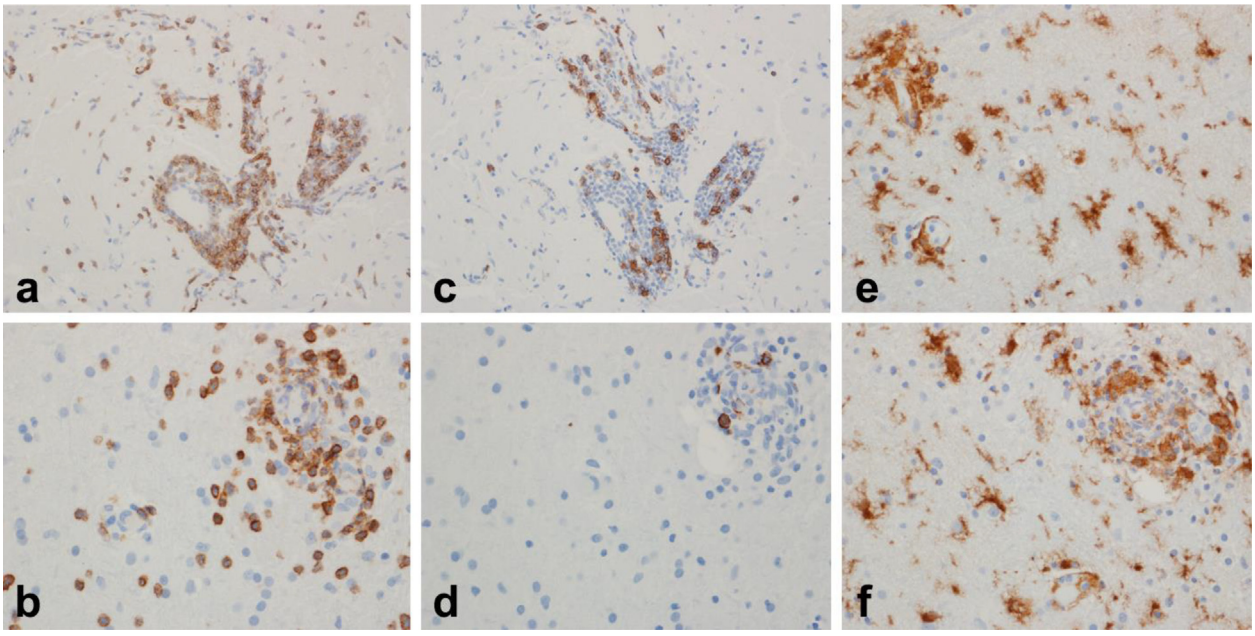
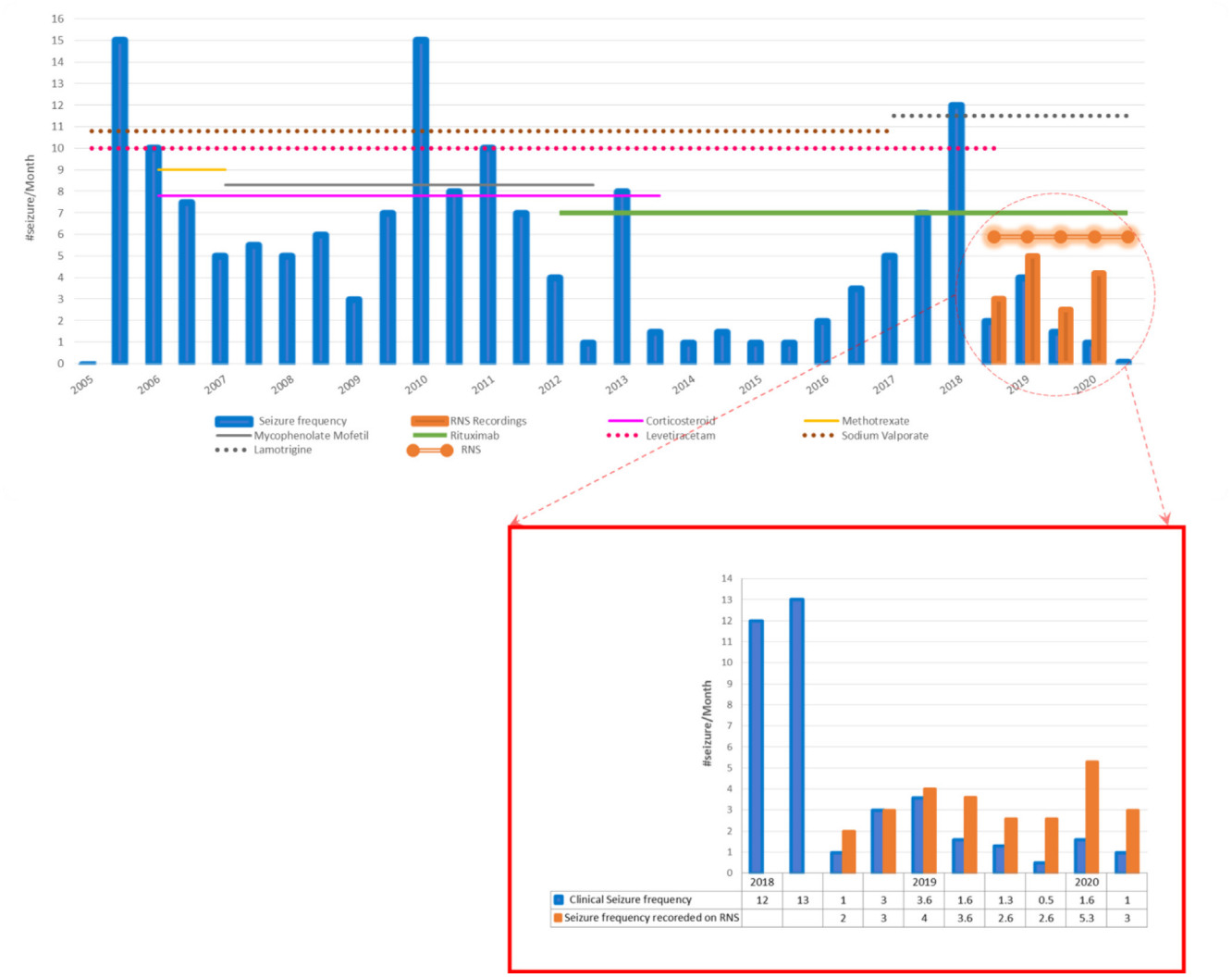


Fig. 2. Histopathology of a brain biopsy in patient with Rasmussen's encephalitis. Panels (a) and (b) show CD3 (T-lymphocytes) around vessels and disperse in the neuropil. Panels (c) and (d) shows the adjacent sections stained for CD20 (B-lymphocytes), which are mostly in the perivascular compartment. Panels (e) and (f) show microglia and macrophages (IBA-1) with perivascular macrophages and activated hypertrophic microglia throughout the brain parenchyma. [(a) and (b) – adjacent sections (200×); (b), (d) and (f) – adjacent sections (400×); e (400×)].

depth contacts were captured. In addition, multiple multifocal subclinical seizures arose from the superior, mid, and inferior banks of the left parietal grid were recorded.

Following the iEEG monitoring, the patient was re-discussed at the epilepsy surgical conference. The patient was deemed not to be a favorable candidate for resective epilepsy surgery, given the multifocal nature of her seizure onset zones. Instead, a consensus was reached to attempt adjunct responsive neurostimulation (RNS) therapy with two leads targeting the left hippocampal and left lateral parieto-occipital neocortex. Following an eight week course of recovery from the iEEG monitoring, the patient was implanted with RNS (model: RNS-300 M) depth and strip electrodes: a four contact depth electrode targeting the left hippocampus and a four contact strip over the left parieto-occippital lateral neocortex, with center-to-center alignment (Fig. 4). Each electrode was spaced 10 mm apart (center-to-center) with an inter-electrode distance of 6.8 mm.

RNS stimulation therapy was initiated three weeks of post-lead implantation (Fig. 3). Initially, a bipolar stimulation pathway with a current of 1 mA, a pulse width of 160μS, duration of 100 milliseconds, frequency of 100 Hz, and charge density of 1μc/cm2, were used. On subsequent follow-ups, various adjustments were made both on detection and therapy, including the stimulation pathways. At the most recent follow-up visit, a cathodal to Can stimulation pathway with a current of 5 mA, pulse width of 160 μS, duration of 100 milliseconds, frequency of 100 Hz, and charge density of 1.3 μc/cm2, was used. After six months of RNS system treatment, the patient reported significant clinical seizure reduction both in frequency and severity (duration). After 24 months of RNS system treatment, clinically, the decline in frequency compared to the pre-RNS baseline was > 50%, which coincided with the RNS System electrocorticography (ECoG) data (Fig. 3). The patient also reported that her seizures become shorter in duration. Follow-up neuropsychological evaluation demonstrated marked



	2018				2019				2020	
Clinical Seizure frequency	12	13	1	3	3.6	1.6	1.3	0.5	1.6	1
Seizure frequency recoreded on RNS			2	3	4	3.6	2.6	2.6	5.3	3

Fig. 3. Epilepsy time course and response to therapy in adult-onset Rasmussen encephalitis treated with RNS. The figure illustrates the seizure frequency and the response to anti-seizure medications (ASM), immunotherapy and the RNS system. The lines symbolize the concomitant immunotherapy, while the dots represent the ASM. The bars represent the seizure frequency by the average number of seizures per one month; the clinical seizures, in terms of focal impaired awareness seizures were reported by the patient or the patient's family, are represented with blue bars, while the orange bars symbolize the seizure frequency that obtained from the RNS recordings.

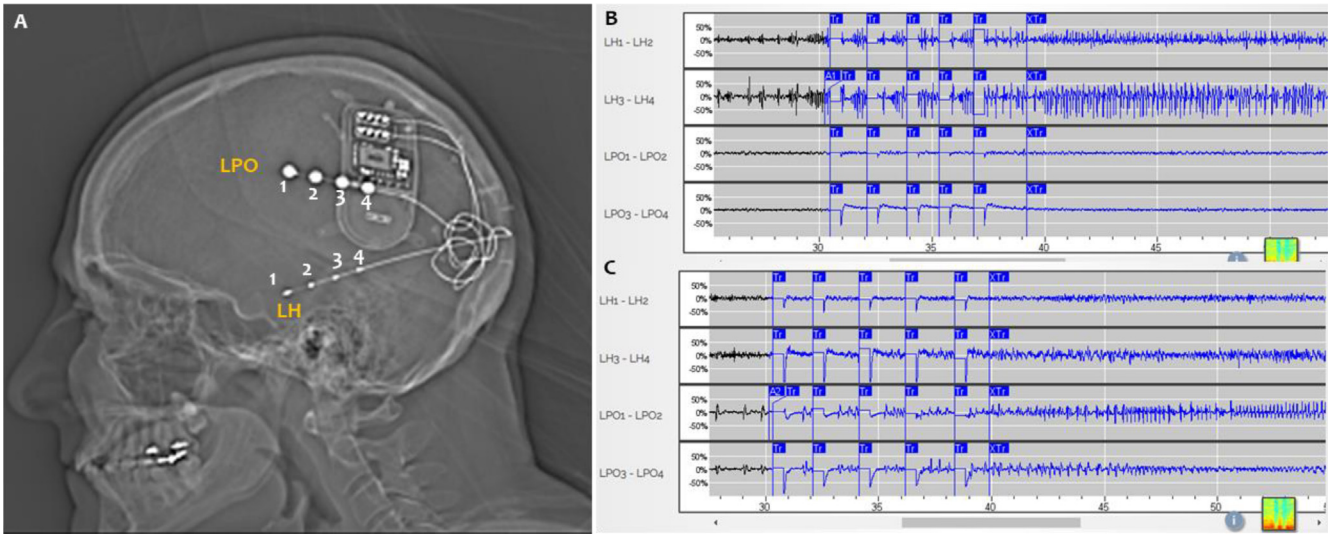


Fig. 4. Sagittal head CT topogram showing the location of a left hippocampal depth and left parieto-occipital strip electrodes. ECoG example showing an electrographic seizure arising from the left hippocampal depth (LH3-LH4) [B] and left parieto-occipital strip electrode contacts (LPO1-2) [C].*Tr = therapy.

improvement in general intellectual function, immediate attention, learning and retention of visual material, and visual constructional skills. Longitudinal data also suggested stability of challenges with verbal fluency, executive function, and cognitive speed over time. No RNS System postoperative complications and no stimulation-related adverse effects were reported.

3. Discussion

There are no FDA approved drugs for the treatment of RE. While immunotherapy may play a role in preventing further inflammatory changes, it is rarely efficacious alone in controlling seizures [3,4]. Surgery remains the most effective management for patients with drug-resistant epilepsy and RE. However, hemispherotomy is rarely performed in adults, given the greater likelihood of postoperative neurological deficit.

The RNS System provides data in a naturalistic setting and may complement inpatient iEEG data and contribute to treatment decisions. Although there have been reports of neuromodulation therapy in autoimmune associated epilepsies [5], very limited data exists on RE. To the best of our knowledge, there is only one reported case of RE with drug-resistant epilepsy treated with RNS system [6]; La Vega-Talbott et al. reported a similar case, however in a childhood-onset RE, where an 18-year-old male with a childhood-onset RE underwent successful RNS therapy after failure of several ASMs, immunotherapy and other neurostimuators.

In our patient, the RNS ECoGs provided useful information about seizure timing and patterns. Although the patient remained stable on rituximab over four years, seizure frequency and intensity increased prior to undergoing presurgical evaluation in 2018 (Fig. 3). Despite appropriate B cell depletion and therapeutic doses of multiple ASM, the patient continued to have breakthrough seizures which became more intense, in terms of seizure duration and frequency. In our patient, RNS was associated with reducing the intensity of her seizures by over 50% at the most recent follow-up. The patient had no device-related infection despite immunosuppressive drug therapy prior to and following RNS System implantation.

The main limitation of this study is single case report and limited follow-up duration. Therefore, the long-term efficacy of this therapy is likely to be submaximal and is expected to continue to improve over time. Moreover, the potential confounding role of the concomitant immunotherapy could also pose a safety risk of infection for an implantable central nervous system device. Moreover, despite the fact that RE is a diffuse hemispheric disease, we have placed only two electrodes in the left hippocampal and parieto-occipital head regions in our patient (given the intracranial findings). Recently, a cortico-thalamic RNS stimulation therapy has been shown to be useful in those patients with diffuse seizure generator [7]. It is unknown whether such approach would have made this patient seizure-free instead of the placement of two leads in the left hippocampus and parieto-occipital neocortex. Lastly, seizure quantification prior to RNS System treatment was based on verbal reports, which could be impacted by recall bias of amnestic seizures.

A responsive neurostimulator could be a therapeutic option for patients with adult-onset RE, especially for patients who are not candidates for epilepsy surgery and have failed other treatment modalities. We suggest that the decision to implant a device as a surgical treatment for epilepsy should be made on a case-by-case basis carefully evaluating the benefits versus potential risks. Further studies are needed to establish the therapeutic and diagnostic utility, and tolerability of the RNS System in patients with RE.

Ethical statement

Written informed consent was obtained from the patient to include results and imaging along with the clinical presentation. Approval by the institution's ethics and research review board was obtained as well.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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