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Laser amygdalohippocampotomy reduces contralateral hippocampal sub-clinical activity in bitemporal epilepsy: A case illustration of responsive neurostimulator ambulatory recordings

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ABSTRACT

Responsive neurostimulation (RNS) is a valuable tool in the diagnosis and treatment of medication refractory epilepsy (MRE) and provides clinicians with better insights into patients' seizure patterns. In this case illustration, we present a patient with bilateral hippocampal RNS for presumed bilateral mesial temporal lobe epilepsy. The patient subsequently underwent a right sided LITT amygdalohippocampotomy based upon chronic RNS data revealing predominance of seizures from that side. Analyzing electrocorticography (ECOG) from the RNS system, we identified the frequency of high amplitude discharges recorded from the left hippocampal lead pre- and post- right LITT amygdalohippocampotomy. A reduction in contralateral interictal epileptiform activity was observed through RNS recordings over a two-year period, suggesting the potential dependency of the contralateral activity on the primary epileptogenic zone. These findings suggest that early targeted surgical resection or laser ablation by leveraging RNS data can potentially impede the progression of dependent epileptiform activity and may aid in preserving neurocognitive networks. RNS recordings are essential in shaping further management decisions for our patient with a presumed bitemporal epilepsy.

Introduction

Responsive neurostimulation (RNS) is an increasingly utilized surgical option for the treatment of medication refractory epilepsy (MRE), especially for patients with epileptic foci in eloquent areas of the brain, or those with evidence of multifocal epileptogenesis, such as patients with bilateral mesial temporal lobe epilepsy [1]. The ability of RNS to record chronic electrocorticography (ECOG) and detect epileptic activity and interictal discharges in the ambulatory setting has provided epileptologists and neurosurgeons with more precise, ethologically-relevant data regarding an individual's seizure patterns [2,3]. These data may subsequently guide potentially curative interventional options such as resective or ablative surgery.

In particular, placement of bilateral mesial temporal RNS leads for patients with suspected bilateral temporal lobe epilepsy may reveal predominantly or solely unilateral epileptogenic zone [2]. In these cases, laser interstitial thermal therapy (LITT) for amygdalohippocampotomy, or craniotomy for anterior temporal lobectomy, are viable solutions that may offer patients a greater possibility of seizure freedom. If the contralateral RNS lead is preserved, those ongoing neurophysiological recordings may provide a window to understand the effects of amygdalo-hippocampal ablation on the contralateral mesial temporal lobe circuit.

Here, we follow up on a case of a patient with bilateral temporal RNS for MRE who subsequently underwent a right sided LITT amygdalohippocampotomy based upon chronic RNS data; the RNS system with a lead in the contralateral mesial temporal lobe was left in-place. Here, we aimed to study ECOG signals from that RNS system to identify the frequency of high amplitude discharges and interictal activity recorded from the left hippocampal lead pre- and post- right

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amygdalohippocampotomy to assess the effects of ablating the primary seizure network on contralateral subclinical activity.

Methods

Case Description: A 16-year female with a past medical history of depression and anxiety presented to the comprehensive epilepsy clinic for evaluation of MRE diagnosed at the age of 10. Her seizure frequency was 1–2 focal aware seizures/month, with a semiology consisting of a feeling of anxiety and olfactory sensations with preserved awareness. Magnetic resonance imaging (MRI) demonstrated right mesial temporal sclerosis. Positron emission tomography (PET) was within normal with no regions of hypometabolism. Video electroencephalography (EEG) captured two of her typical clinical seizures without clear EEG localizing or lateralizing features. She underwent phase II monitoring with bilateral depth electrodes of the anterior temporal lobe, amygdala, anterior and mid hippocampus, insula, orbitofrontal cortex, cingulate/dorsolateral prefrontal cortex, and midcingulate/premotor cortex. Anti-seizure medications (ASMs) were weaned, and the patient remained in the epilepsy monitoring unit (EMU) for three weeks. Only one “typical” seizure was captured, with EEG demonstrating ictal onset arising from the left anterior temporal and mid hippocampal electrodes. Interictal epileptiform spikes were captured in the bilateral mesial temporal lobe structures. No subclinical seizures were captured during the admission. Clinical electrical stimulation of either the right or left amygdala and hippocampal contacts with 50 Hz frequency and pulse duration of 0.3 ms and train duration of 2 s elicited several seizures with no evidence of contralateral spread. After the leads were explanted, the patient was discharged off ASMs due to a stable frequency of seizures despite being off these medications. She was kept off ASMs after RNS implantation as well to better understand her seizure burden and tailor therapy accordingly.

After review of these data, the comprehensive epilepsy team deemed her an appropriate candidate for RNS with bilateral hippocampal lead implantation via occipito-temporal trajectories [Fig. 1]. The patient underwent this procedure with no complication and was discharged. During follow up, chronic RNS recording data revealed her seizures arose unilaterally, solely from the right side [Fig. 2]. Review of the data acquired from the contralateral (left) lead showed independent interictal activity, but no clear ictal activity or seizure detections were captured in that lead. The primary team felt that the activity recorded bilaterally using sEEG did not reflect the patient’s habitual seizures, given that the patient was stimulated, sleep deprived, and in a stressful environment while in the hospital. By contrast, the RNS was particularly useful in providing a real life perspective of the patient’s seizure burden and origin. The left-sided interictal discharges were therefore attributed potentially to secondary epileptogenesis, via a kindling-like process, with her primary epileptogenic zone being the right sided mesial temporal lobe. RNS detection parameters were tuned, and the stimulation program was set at post op month 7 to deliver up to 5 100-milli-second burst treatments with frequency of 200 Hz and current of 0.5 mA upon a detection. Stimulation was turned on for 4 months before the next intervention. During this period, the patient was noted to have decreased intensity of her seizures, with elimination of her olfactory auras and post ictal states, though the frequency of seizures had not clearly changed.

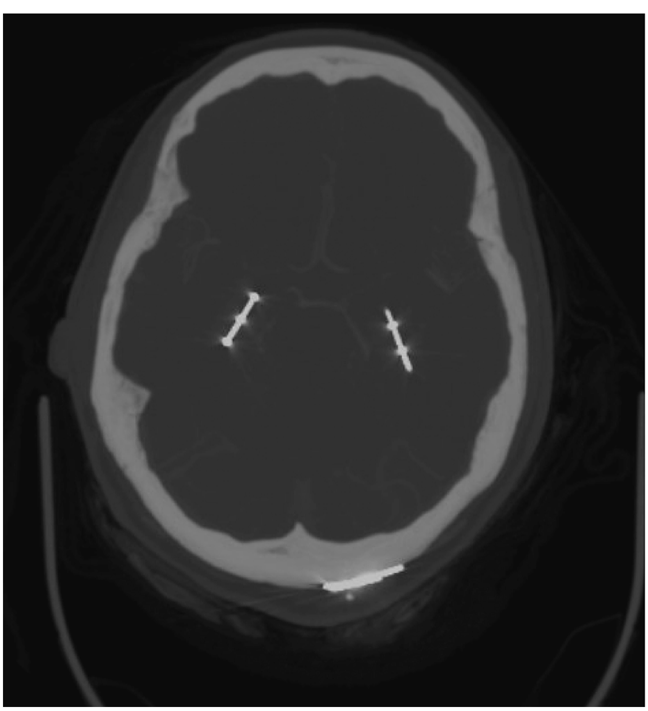

Fig. 1. CT brain status post RNS showing bilateral hippocampal lead implantation via occipito-temporal trajectories.

After review of these data and discussion with the comprehensive epilepsy team and the patient’s family, they were offered LITT of the right amygdalo-hippocampal complex upon removal of the right sided RNS lead as a means hopefully to achieve seizure freedom. The patient elected to proceed with right laser amygdalohippocampotomy, and the left hippocampal RNS lead was kept in place to continue to monitor for any ictal or interictal activity. The patient recovered well after this procedure, and at most recent follow up, 22 months post op, remains seizure free and is off all ASMs.

Results

Typically, the RNS device records data either routinely at scheduled times during the day, or due to specific triggers that are set by the physician. A trigger commonly used for detecting epileptic activity is the “saturation” trigger. This occurs when the ECoG amplitude exceeds the device’s threshold and saturates the amplifiers, which may be due to subclinical discharges or interictal spikes. “Long detection” ECOGs are triggered by activity which lasts beyond a certain duration of time, which may be indicative of clinical or subclinical seizures [4,5]. In our patient, prior to receiving LITT, 17 saturation events were captured over a period of 12 months, occurring on average 2 times per month. Eight of these events had saturation amplitudes recorded exclusively from the right hippocampus, 9 had been recorded exclusively from the left, and 4 events had saturations recorded simultaneously from the bilateral leads. During the patient’s clinical seizure episodes, however, electrographic activity originated exclusively from the right hippocampal lead, though often preceded by rhythmic spiking from the left hippocampal lead which did not evolve.

After the LITT and removal of right sided lead, the left sided lead was kept in place in detection mode to monitor for interictal and possible ictal discharges. Recordings from this lead showed a total of 10 saturation events in the left hippocampus over a period of 24 months [Fig. 3]. Notably, the frequency of these events decreased over time, with the initial two months having 2–3 episodes per month, and the following 2 months having 1 event each, and then only two saturation events over the following year [Fig. 4]. Clinically, the patient did not experience any seizures during these detections. Of note, the system had no “long detection” episodes that were triggered from the left lead after ablation. She remains at Engel class Ia at her most recent follow up 24 months status post LITT.

Discussion

Bitemporal lobe epilepsy is an often challenging entity to diagnose, requiring SEEG implantation in cases where scalp EEG is inconclusive. In some patients, SEEG may reveal epileptic activity unilaterally. In others,

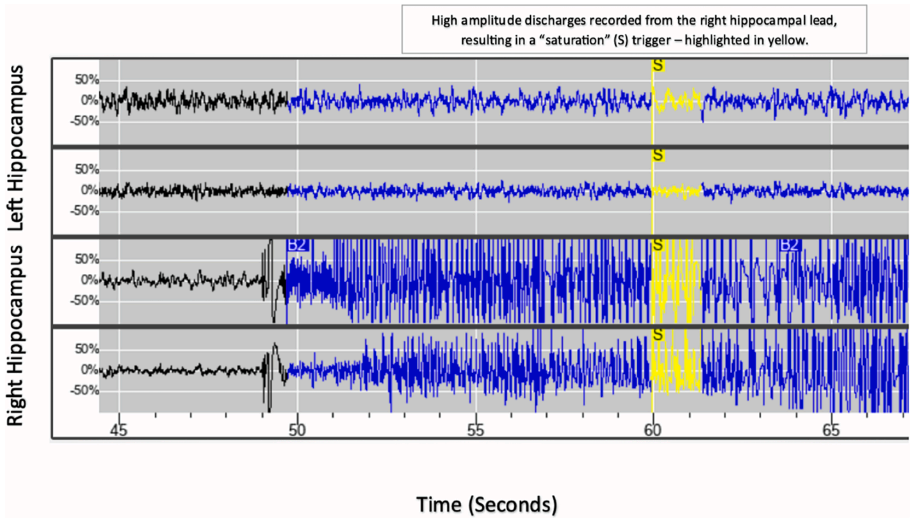

Fig. 2. ECOG recording from the RNS system prior to patient receiving LITT. This event was triggered by saturations detected in the right sided hippocampal leads. Of note, the left sided lead did not reach saturation thresholds.

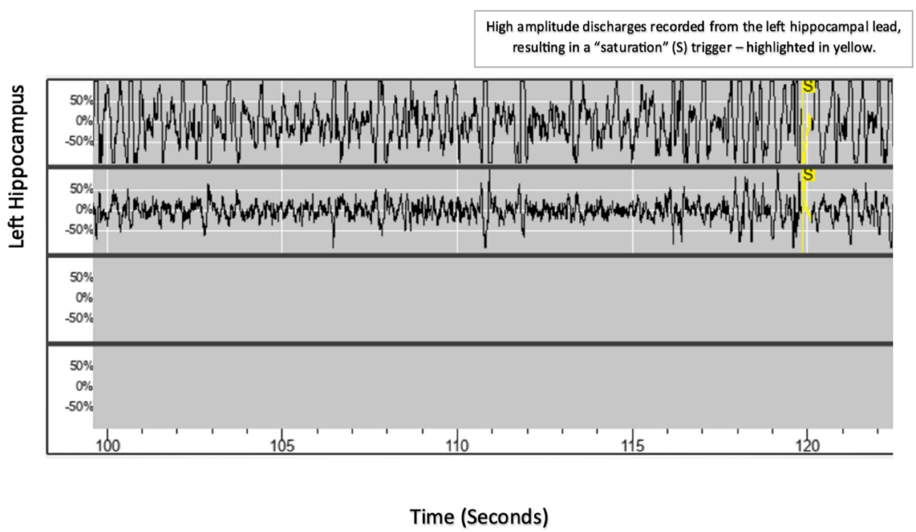

Fig. 3. ECOG recording from the RNS system status post LITT and removal of right hippocampal RNS lead. This event was triggered by saturations detected at above 50% threshold in the left sided hippocampal leads.

bitemporal epilepsy may be evident, particularly after a prolonged hospital admission, such as was the case with this patient, further adding to the difficulty of accurately localizing epilepsy for patients with suspected unilateral vs. bilateral temporal lobe epilepsy [6]. Further complicating the diagnostic process is the presence of interictal spikes in the contralateral hemisphere in patients with unilateral temporal lobe epilepsy, a phenomenon that has been well described [7–9]. Interictal spikes have been detected in the contralateral side in cases of mesial temporal lobe epilepsy, and surgical resection of the primary seizure focus has been shown to cause their cessation [10].

RNS offers the ability to better detect the source of epileptic activity by providing chronic ambulatory recordings in the patient's natural environment, making it a potentially valuable tool for identifying a path toward definitive treatment and possibly cure of mesial temporal lobe epilepsy.

In our patient, SEEG did not provide sufficient information to determine whether she had bilateral independent seizure foci in mesial temporal lobe structures, or a unilateral seizure focus with a contralateral dependent focus of epileptic activity. After RNS implantation, chronic ambulatory intracranial signals implicated the right side only during clinical events, with presence of interictal spikes on the left side. This information, along with the resulting reduction in detected saturations in the left side after the right sided ablation, suggests that left mesial temporal lobe activity was dependent on the primary epileptogenic zone in the right hemisphere.

The existing literature has long debated the pathogenesis of bitemporal lobe epilepsy, and whether secondary epileptogenesis "truly" exists [6,8,10]. The latter is defined as a phenomenon by which repeated seizure spread from an original focus can create a second, independent seizure focus. Some suggest this to be potentially more common in children, as certain forms of epilepsy may evolve from other forms during this critical neurodevelopmental period in which repeated seizure spread through white matter tracts to the contralateral hemisphere may lead to subclinical epileptic activity arising from the previously healthy hemisphere. Here, we sought to leverage a fairly uncommon scenario (bilateral RNS followed by unilateral LITT with preservation of contralateral RNS) to understand the extent to which such contralateral seizure-related discharges may have depended upon the ablated structures.

The initiation of some clinical epileptic activity from the

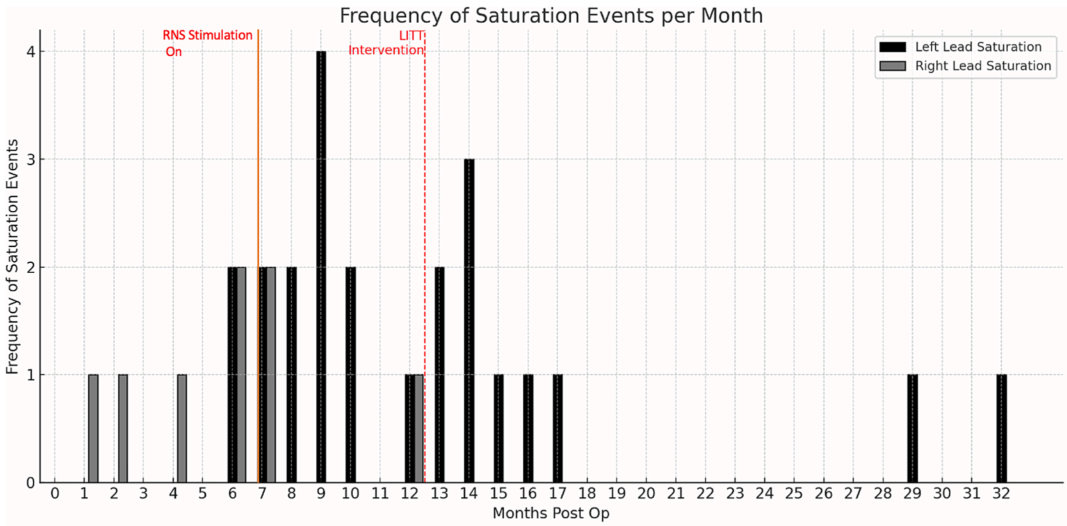

Fig. 4. Frequency of saturation events in the bilateral hippocampal RNS leads per month post op.

contralateral side while the patient was hospitalized suggests that, despite its lack of ictal activity in the chronic, real-world setting, the patient's left side may nonetheless have had the potential to independently serve as a seizure focus while off ASMs.

The loss of contralateral activity over 2 years raises two possibilities for the underlying mechanism of these changes following ablation of the primary epileptogenic zone: 1) The decreased frequency of contralateral (left-side) activity demonstrates possible dependence of that activity on the now-ablated primary right epileptic focus; and 2) the gradual, extended nature of that diminishment implicates a reversible plasticity in this process. In other words, "kindling" of the contralateral circuits may lead to recruited mechanisms for neuronal plasticity, rather than simply being mediated by ictal-induced structural injury. If left untreated beyond a certain window, it is possible that pathologic left-sided activity may have progressed to be permanently independent of the dominant right side, perhaps thereby reducing the efficacy of epilepsy surgery and the potential for cure [11]. Furthermore, definitive surgical treatment of intractable seizures early in the disease course, especially in younger patients, may have benefits not only toward the possibility of cure, but also for preserving neurocognitive networks in the previously healthy side [12,13].

Conclusion

Here we leveraged an uncommon clinical pathway in a patient initially diagnosed with bilateral mesial temporal lobe epilepsy. We sought to understand the influence of a primary seizure focus in one mesial temporal lobe upon seizure-related neural activity on the contralateral side, pre- vs. post-ablation of the dominant side. Using chronic RNS recordings, we observed a gradual "run-down" of interictal epileptiform activity in the 'dependent' side after laser amygdalo-hippocampotomy removal of the primary seizure focus, which has potential implications for the management of these patients.

Ethical Statement

This study is retrospective in nature, and no patient identifiers were included. This project was approved as a retrospective chart review with exemption from informed consent by the local Institutional Review Board (board reference #816619).

CRediT authorship contribution statement

Hael F. Abdulrazeq: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Anna R. Kimata:** Writing – review & editing, Software, Investigation, Data curation. **Belinda Shao:** Writing – review & editing, Software, Methodology, Investigation. **Konstantina Svokos:** Writing – review & editing, Validation, Project administration, Methodology. **Neishay Ayub:** Writing – review & editing, Validation, Formal analysis, Data curation. **Duyu Nie:** Writing – review & editing, Visualization, Validation, Software, Project administration, Methodology, Data curation. **Wael F. Asaad:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

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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