

Seizure freedom after laser amygdalohippocampotomy guided by bilateral responsive neurostimulation in pediatric epilepsy: illustrative case

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BACKGROUND For patients with difficult-to-lateralize temporal lobe epilepsy, the use of chronic recordings as a diagnostic tool to inform subsequent surgical therapy is an emerging paradigm that has been reported in adults but not in children.

OBSERVATIONS The authors reported the case of a 15-year-old girl with pharmacoresistant temporal lobe epilepsy who was found to have bitemporal epilepsy during a stereoelectroencephalography (sEEG) admission. She underwent placement of a responsive neurostimulator system with bilateral hippocampal depth electrodes. However, over many months, her responsive neurostimulation (RNS) recordings revealed that her typical, chronic seizures were right-sided only. This finding led to a subsequent right-sided laser amygdalohippocampotomy, resulting in seizure freedom.

LESSONS In this case, RNS chronic recording provided real-world data that enabled more precise seizure localization than inpatient sEEG data, informing surgical decision-making that led to seizure freedom. The use of RNS chronic recordings as a diagnostic adjunct to seizure localization procedures and laser ablation therapies in children is an area with potential for future study.

<https://thejns.org/doi/abs/10.3171/CASE22235>

KEYWORDS amygdalohippocampotomy; laser ablation; responsive neurostimulation; pediatric epilepsy; lateralization

Pharmacoresistant mesial temporal lobe epilepsy (MTLE) in children is unlikely to resolve with nonsurgical treatment. The effects of persistent seizures as well as antiseizure medications (ASMs) can be debilitating to cognitive development, mood, and activities of daily living. If seizures can be accurately localized, patients may be able to be treated surgically. In unilateral MTLE, 50%–60% of patients can achieve seizure freedom after resection or ablation of the mesial temporal lobe, and even more may achieve significant seizure reduction.^{1,2} However, many patients may not be candidates for resection or ablation, such as those with bitemporal MTLE or those in whom seizure foci may also include eloquent structures. In these patients, including children, responsive neurostimulation (RNS) can be used as a palliative treatment to achieve seizure reduction, although seizure freedom from RNS is not as common.^{3–10}

Accurate seizure localization is tantamount to selecting an effective treatment. Despite the current arsenal of noninvasive and invasive epilepsy monitoring modalities available, some patients' typical seizures may remain difficult to localize or can prove to be different in the real world than in an atypical, inpatient hospital setting with unusual daily rhythms and under the influence of ASM withdrawal. For these patients with bitemporal or difficult-to-lateralize temporal lobe epilepsy, chronic recording with RNS may provide not only palliative seizure reduction but also a means of gathering additional data for precise seizure localization that may allow for subsequent definitive surgical therapy in patients who initially were not eligible based on data gathered from prior monitoring modalities. This is an emerging paradigm that has been reported in adults^{11–17} but not in

ABBREVIATIONS ASM = antiseizure medication; EEG = electroencephalography; MRg-LITT = MRI-guided stereotactic laser interstitial thermal therapy; MRI = magnetic resonance imaging; MTLE = mesial temporal lobe epilepsy; RNS = responsive neurostimulation; sEEG = stereo EEG.

INCLUDE WHEN CITING Published August 29, 2022; DOI: 10.3171/CASE22235.

SUBMITTED May 30, 2022. **ACCEPTED** July 5, 2022.

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children. We report an illustrative case of RNS as a bridge to resection in a pediatric patient.

Illustrative Case

A right-handed 15-year-old girl had a medical history of depression, anxiety, and pharmacoresistant temporal lobe epilepsy due to mesial temporal sclerosis. She had an isolated episode of febrile status epilepticus in infancy and then was diagnosed with epilepsy at 10 years of age, experiencing an average of one to two seizures per month despite maximized treatment with lamotrigine and levetiracetam. Seizure semiology consisted of an olfactory and temperature sensation, at times with shivering and anxiety, with preserved awareness.

To localize her seizures, 3-T epilepsy protocol brain magnetic resonance imaging (MRI) demonstrated right mesial temporal sclerosis, and magnetoencephalography showed interictal activity in the right mesial temporal and insular areas. Positron emission tomography was unrevealing. Phase I long-term video electroencephalography (EEG) monitoring revealed only mild right temporal slowing, with no interictal discharges; two typical seizures were captured, with nonspecific nonlocalizing features. Therefore, she underwent Phase II invasive electrographic monitoring using bilateral symmetric stereotactic EEG (sEEG) implantation of depth electrodes and mapping. A total of 16 leads were implanted, covering areas in the bilateral anterior temporal lobe, amygdala, anterior and midhippocampus, insula, orbitofrontal cortex, cingulate/dorsolateral prefrontal cortex, and midcingulate/premotor cortex (Fig. 1). She required a prolonged admission because no seizures occurred until the third week of recording, despite weaning her off ASMs and inducing sleep deprivation. Ultimately, interictal activity was found independently in the bilateral mesial temporal structures, maximally in the left amygdala, and in the left anterior and midhippocampal

electrodes (Fig. 2). Only one seizure of her typical semiology was captured, arising from the left anterior and midhippocampal electrodes. Cortical stimulation mapping elicited several seizures, following stimulation of both right and left anterior hippocampus and amygdala electrodes, with no evidence of contralateral spread. Importantly, her typical olfactory seizure component was only elicited with left-sided amygdala stimulation.

Based on these independent and bilateral sEEG and cortical stimulation findings, the patient was not considered a candidate for resective or ablative therapies and was offered neurostimulation options. An RNS system was implanted, with bilateral, longitudinal hippocampal leads, to serve as a closed-loop system for both recording and treating detected seizure events. For the first several months postoperatively, she was kept off ASM, and recording-only mode was used. These data revealed that her real-world seizure episodes were associated with unilateral, right-sided electrographic seizures, differently than the bilateral temporal foci elicited during her inpatient course of invasive monitoring. Although interictal activity with scheduled daily electrocorticography was identified independently in bilateral leads, her typical seizures, which she marked by a magnet swipe, were associated most directly with only right-sided electrophysiological correlates. Although they were at times preceded by quasi-rhythmic spiking in the left hippocampal leads, there was no evolution of the left-sided activity. These contralateral interictal discharges were thought to represent an area of secondary epileptogenesis,¹⁸ which resolved after removal of the primary focus, or less likely, given seizure-freedom postoperatively, an independent seizure focus. The RNS was then turned on to stimulate. This decreased the intensity of her seizures overall and was associated with a resolution of her olfactory aura and improvement of her postictal fatigue. However, the frequency of her seizures did not change.

Eleven months after RNS implantation, while the patient was still off both ASMs, a discussion was held with the patient and family to review further treatment options. The patient could continue chronic RNS treatment, given that seizure reduction has been shown to improve over time. Alternatively, she could pursue right-sided laser amygdalohippocampotomy (AHC) in hopes of achieving greater freedom from her typical seizure events because the RNS data demonstrated that her clinical seizures were completely right-sided.

The patient and family opted for right stereotactic MRI-guided laser AHC, with the left-sided RNS hippocampal lead to remain in place to continue treating left-sided activity. A computed tomography scan obtained after skull fiducial placement for this procedure revealed a small pseudoaneurysm in the right temporoparietal branch of the middle cerebral artery, so this was first secured by endovascular coiling before proceeding with the laser ablation. One month later, a right-sided laser AHC was performed using a two-laser technique as has been previously described.¹⁹ Her right-sided RNS electrodes were removed to perform the AHC. The left hippocampal RNS electrodes and the RNS processor and battery remained in place. Intraoperative and postoperative MRI confirmed ablation of the amygdala and medial hippocampus, including uncus and perirhinal structures (Fig. 3). The patient was admitted to the pediatric intensive care unit postoperatively, recovered well, remained neurologically intact, and was discharged the next day.

Postoperatively, the patient has remained off both ASMs and is seizure-free both clinically and based on left RNS data. In fact, the interictal discharges from the left hippocampal RNS leads seen before ablation resolved, further supporting the theory that these had reflected an area of secondary epileptogenesis. Her postoperative

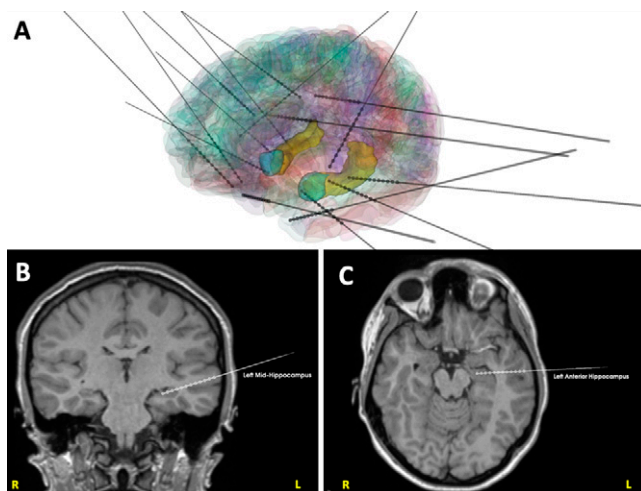


FIG. 1. Invasive monitoring with sEEG. A total of 16 leads were implanted, covering areas in the bilateral anterior temporal lobe, amygdala, anterior and midhippocampus, insula, orbitofrontal cortex, cingulate/dorsolateral prefrontal cortex, and midcingulate/premotor cortex (A). Ultimately, interictal activity was found independently in the bilateral mesial temporal structures, maximally in the left amygdala, and in the left anterior and midhippocampal electrodes. Only one seizure of the patient's typical semiology was captured, arising from the left anterior (C) and midhippocampal (B) electrodes.

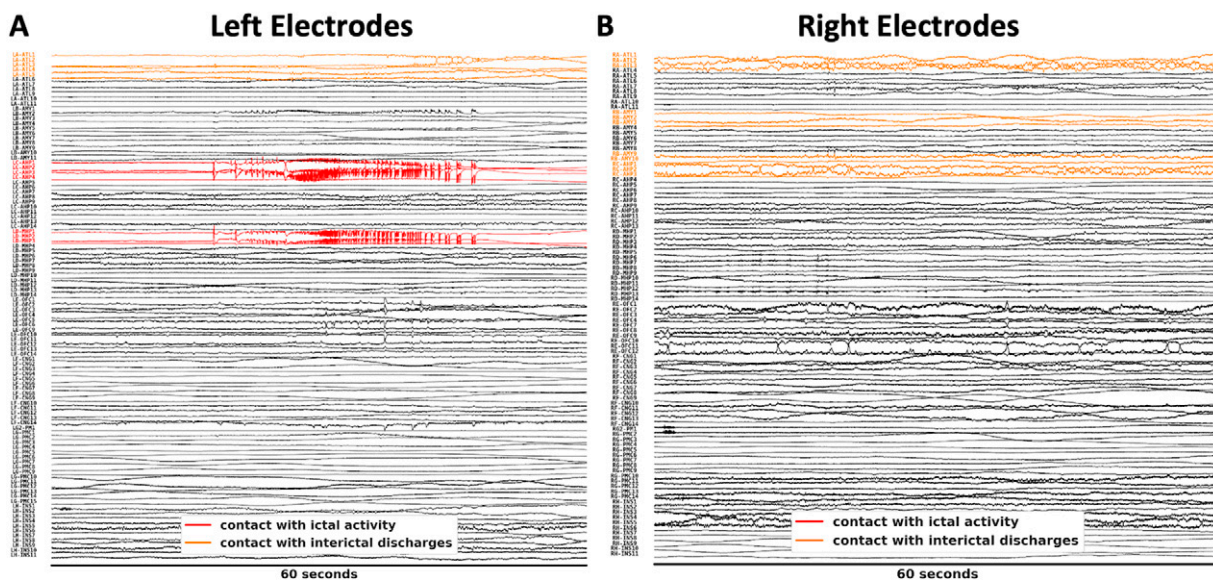


FIG. 2. Invasive monitoring data demonstrated interictal activity (*orange tracings*) found independently in the bilateral mesial temporal structures, maximally in the left amygdala, and in the left anterior and midhippocampal electrodes. Only one seizure of the patient's typical semiology was captured, arising from the left anterior and midhippocampal electrodes (*red tracing*). Cortical stimulation mapping elicited several seizures, following stimulation of both right and left anterior hippocampus and amygdala electrodes, with no evidence of contralateral spread. Importantly, her typical olfactory seizure component was only elicited with left-sided amygdala stimulation.

course was complicated by an acute-on-chronic episode of severe anxiety, triggered by several difficult life events. This episode significantly improved after a 3-month admission to a pediatric partial program for intensive multimodal therapies and adjustment of her antidepressant and anti-anxiety medications. At her 12-month follow-up visit, she remained neurologically intact and seizure-free and was back at school.

Discussion

Observations

We report the case of a 15-year-old girl with pharmacoresistant temporal lobe epilepsy who was found to have bitemporal epilepsy during a prolonged sEEG admission and was therefore considered not a candidate for resective or ablative treatment. RNS implantation helped to reduce her seizure intensity, but she was not seizure-free. However, subsequent RNS recordings revealed that her typical seizures were right-sided only, providing evidence in favor of right-sided laser AHC, which ultimately helped achieve full seizure freedom.

Limitations

This is a single case report and therefore does not intend to provide a high level of evidence for treatment decisions. Rather, it serves to demonstrate the feasibility of this approach and inspire further study.

Lessons

This case demonstrates the use of chronic monitoring as a diagnostic adjunct in seizure localization and subsequent decision-making for definitive treatment of difficult-to-localize pharmacoresistant epilepsy, particularly bitemporal epilepsy.

Resective surgery, specifically anterior temporal lobectomy, is the gold standard of treatment for unilateral MTLE. A less invasive, ablative alternative is MRI-guided stereotactic laser interstitial thermal therapy

(MRg-LITT) to the medial temporal lobe region. MRg-LITT AHC has demonstrated comparable, although somewhat lower, efficacy toward achieving seizure reduction and seizure freedom to resection in adults as well as children. It is at times preferred for its minimally invasive benefit and relative sparing of neuropsychological and mnemonic function.^{20,21} For patients who are not resection or ablation candidates, neurostimulation options can also be used as a palliative treatment toward seizure reduction if not typically seizure freedom. These options include vagal nerve stimulation, deep brain stimulation to the anterior nucleus of the thalamus, and RNS. In children, RNS is used off-label because Food and Drug Administration approval has only been granted for patients age 18 years and older. Increasingly, however, case series are emerging to support the feasibility, safety, and comparable efficacy of RNS in children for achieving seizure reduction.^{3-6,8-10} Complications related to RNS in children have included infection and lead fracture, with no serious adverse events yet reported (e.g., hemorrhages, strokes, or device malfunctions). Theoretically, a child's skull grows to near its adult volume by 7 years of age, with the youngest reported child undergoing RNS implantation to date being 3 years of age.⁶ Nevertheless, many families prefer laser ablation over resection for children given its minimally invasive nature, potentially reduced overall risk, and hope for seizure freedom.

The use of RNS to augment localization data and guide further definitive therapy, however, has not yet been reported in children. Accurate seizure localization, particularly lateralization, is paramount for selecting subsequent therapy for pharmacoresistant MTLE, particularly for determining that a patient is eligible for the gold standard therapy of resection or the alternative of ablation. While most patients undergo extensive seizure localization workup, often including invasive inpatient monitoring as was done in this case, this can sometimes result in false-positive seizure localization, with iatrogenic factors distorting a patient's typical seizure pattern. In patients

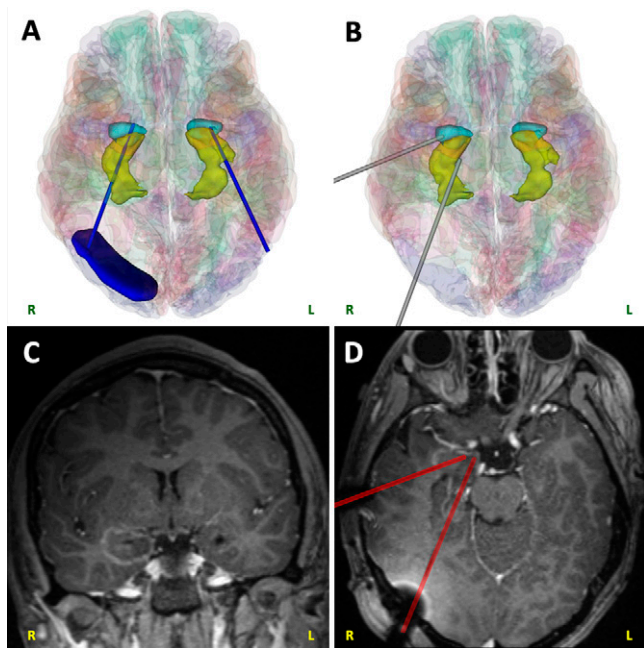


FIG. 3. Postprocedural MRI (**C and D**) overlaid with laser catheter trajectories is shown, as are quantitative three-dimensional renderings (**A and B**) of right-sided AHC with a two-laser ablation technique. Full trajectories are projected onto this single brain slice, although some portions of each trajectory were out of plane. The patient's right-sided RNS electrodes were removed to perform the AHC. The left hippocampal RNS electrodes and the RNS processor and battery remained in place (**A**). Postoperative MRI confirmed ablation of the amygdala and medial hippocampus, including uncus and perirhinal structures (**C and D**).

with multiple seizure foci, some of these foci are nonetheless adequately controlled by ASMs. During inpatient monitoring, ASM weaning may accelerate seizure occurrences by unmasking seizures that are not the typical medication-refractory seizures that all individuals in the real world. Therefore, the presence of such atypical seizures may confound decision-making intended to address the more typical, refractory events. Moreover, chronic recording can provide data that are simply not feasible within the shorter duration of invasive inpatient monitoring. Our patient had a prolonged inpatient monitoring stay and did not have seizures until the third week, despite aggressive efforts. Once RNS was implanted, further chronic monitoring data over 11 months revealed that she suffered from unilateral refractory seizures in her regular environment. Contralateral interictal temporal discharges most likely represented a not fully autonomous seizure focus, or area of secondary epileptogenesis.^{18,22,23}

Reports of such use of RNS to augment lateralization of MTL in adults are increasing. Bilateral RNS may most typically be used when bitemporal epilepsy is suspected but may also be selected in cases favoring unilateral MTL given the risk of misdiagnosed lateralization. In a series of 157 patients with bitemporal epilepsy undergoing RNS, Hirsch et al. reported that long-term chronic recording data revealed at least 5% to have only unilateral seizures in their real-world settings, and 16% ultimately demonstrated lateralization data sufficient to allow subsequent unilateral mesial temporal lobe resection, leading most of these patients to then achieve seizure

freedom.^{14,15} Conversely, King-Stephens et al. investigated chronic recording data in a bitemporal subgroup of 82 patients from the RNS clinical trial. They found that an average of 41.6 days elapsed prior to recording bilateral seizure foci and that approximately one-third of patients required more than 1 month of recordings before capturing bilateral seizures, suggesting that contralateral seizures may be commonly missed during inpatient monitoring admissions of only 1 to 3 weeks.¹⁶ Such temporal sampling limitations are underscored by quantitative analysis of chronic recording data performed by Chiang et al. on 13 patients with bitemporal MTL with bilateral RNS, showing that a reliable seizure laterality ratio could be determined only after observation of many seizures, reached a reliable convergence after a median 8 months of chronic recording, and correlated poorly with lateralization determined by Phase 1 scalp EEG monitoring.¹² Still more authors report patients with nondiagnostic invasive monitoring whose subsequent RNS yielded diagnostic data allowing seizure lateralization and further surgical decision-making.^{11,13,17}

In conclusion, in this case of a 15-year-old girl with apparent bitemporal MTL, RNS recordings provided real-world data that enabled more informative seizure localization than inpatient sEEG data alone. This information allowed her to undergo a right-sided laser AHC that ultimately led to seizure freedom. The use of chronic recordings as a diagnostic adjunct for seizure localization and as a bridge to resective or ablative surgery in children is a promising care pathway for certain children with epilepsy. It is an area with significant potential for future study.

Acknowledgments

We would like to thank Mr. Mike Nozzolillo and Ms. Wendy Wan of Neuropace for their technical support throughout the care of this patient.

Dr. Bartolini's research is supported by a grant from the Institutional Development Award Networks for Clinical and Translational Research (IDeA-CTR, no. U54GM115677) and the Children's Miracle Network.

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Disclosures

Dr. Bartolini reported receiving a salary as editor of *Neurology: Clinical Practice*. No other disclosures were reported.

Author Contributions

Conception and design: Shao, Liu, Svokos, Bartolini, Asaad. Acquisition of data: Shao, Liu, Anderson, Svokos, Bartolini, Asaad. Analysis and interpretation of data: Shao, Liu, Svokos, Bartolini, Asaad. Drafting the article: Shao, Liu, Anderson. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Shao. Administrative/technical/material support: Shao, Zheng. Study supervision: Shao, Svokos, Bartolini, Asaad.

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