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Responsive neurostimulation as a therapy for epilepsy following new-onset refractory status epilepticus: Case series and review of the literature

Audrey Oliger [a,*], Caleb Nerison [b], Hao Tan [b], Ahmed Raslan [b], Lia Ernst [a], Proleta Datta [a], Marissa Kellogg [a]

[a] Departments of Neurology, Oregon Health and Science University, Portland, OR, USA
[b] Neurological Surgery, Oregon Health and Science University, Portland, OR, USA

HIGHLIGHTS

- New-onset refractory status epilepticus (NORSE) is strongly associated with the development of drug-resistant epilepsy (DRE).
- Responsive neurostimulation (RNS) for DRE following NORSE can guide treatment in addition to providing therapeutic benefit.
- Neuropsychiatric complications of NORSE are likely common.

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ABSTRACT

Objective: To report clinical outcomes of patients who presented with new-onset refractory status epilepticus (NORSE), developed drug-resistant epilepsy (DRE), and were treated with responsive neurostimulation (RNS).
Methods: We performed a retrospective review of patients implanted with RNS at our institution and identified three who originally presented with NORSE. Through chart review, we retrieved objective and subjective information related to their presentation, workup, and outcomes including patient-reported seizure frequency. We reviewed electrocorticography (ECoG) data to estimate seizure burden at 3, 6, 12, and 24 months following RNS implantation. We performed a review of literature concerning neurostimulation in NORSE.
Results: Use of RNS to treat DRE following NORSE was associated with reduced seizure burden and informed care by differentiating epileptic from non-epileptic events.
Conclusions: Our single-center experience of three cases suggests that RNS is a safe and potentially effective treatment for DRE following NORSE.
Significance: This article reports outcomes of the largest case series of NORSE patients treated with RNS. Since patients with NORSE are at high risk of adverse neuropsychiatric and cognitive sequelae beyond seizures, a unique strength of RNS over other surgical options is the ability to distinguish ictal or peri-ictal from non-epileptic events.

1. Introduction

Status epilepticus is considered refractory when seizures continue despite treatment with benzodiazepines and one or more anti-seizure medications (ASMs) and is considered super-refractory when seizures persist or recur after 24 hours of anesthetic therapy (Rossetti and Lowenstein, 2011; Shorvon and Ferlisi, 2011). Refractory status epilepticus (RSE) is a neurological emergency with a high mortality rate. NORSE is rare subset of RSE cases for which no clear seizure etiology can be determined within the first 48 hours of hospital admission. Febrile infection-related epilepsy syndrome (FIRES) is a subset of NORSE characterized by a febrile illness preceding presentation with RSE by up to 2 weeks. If an etiology of NORSE is determined, most common causes include autoimmune or paraneoplastic encephalitis (with or without an identified antibody), atypical infection, or an

* Corresponding author at: 3181 SW Sam Jackson Park Rd., Portland, OR 97239, USA.
E-mail address: oliger@ohsu.edu (A. Oliger).

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underlying genetic disorder. However, the etiology of NORSE often remains unknown, and these cases are referred to as cryptogenic NORSE. NORSE mortality rate during initial hospitalization has been reported to be as high as 27% (Gaspard et al., 2018).

Many patients who survive NORSE and FIRES develop DRE and neuropsychiatric sequelae (Sculier and Gaspard, 2019; Shrestha et al., 2023; Wickstrom et al., 2022a). In cases where autoimmune encephalitis is suspected, treatment options include immunomodulatory therapies which have variable success (Werbaneth et al., 2022). Surgical resection is sometimes considered, but many patients with NORSE have diffuse seizure networks that are not amenable to surgical resection. Neuromodulatory technologies such as vagus nerve stimulation (VNS), thalamic deep brain stimulation (DBS), and responsive neurostimulation (RNS) have emerged as treatment options for a variety of refractory epilepsy syndromes (Chen et al., 2022a; Ernst et al., 2019; Feyissa et al., 2020; Jobst et al., 2017; Lin and Ko, 2023; Morrell and RNS System in Epilepsy Study Group, 2011; Salanova et al., 2015; Trinka and Brigo, 2019). There are several case reports and series describing the use of these three neurostimulation modalities as alternative treatments for patients with acute NORSE and epilepsy following NORSE (Bonardi et al., 2023; Chen et al., 2022b; Espino et al., 2022; Hect et al., 2022; Kurukumbi et al., 2019; Lehtimäki et al., 2017; Mantoan Ritter and Selway, 2023; Sa et al., 2019; Stavropoulos et al., 2023; Theroux et al., 2020; Wong et al., 2019; Yamazoe et al., 2017; Yang et al., 2021), but the scientific literature is limited by low numbers of patients treated due to the rare incidence of NORSE.

In this article, we report a single-center case series of three patients with cryptogenic NORSE complicated by DRE who were implanted with RNS. RNS is a neurostimulation device that is surgically embedded within the parietal bone and attached to depth or cortical strip leads with electrode contacts planted in or near seizure foci (Jobst et al., 2017; Morrell and RNS System in Epilepsy Study Group, 2011). The advantage of RNS over other forms of neurostimulation is that the device can record and store ECoG during seizures or other clinical events, so the patient's provider can review the ECoG data to help determine if the clinical event was an electrographic seizure. In this case series, RNS was helpful in differentiating epileptic versus non-epileptic neuropsychiatric complications, which dictated different treatment approaches.

2. Methods

We performed a retrospective review of all RNS cases implanted from July 2014 to March 2023 at our institution, Oregon Health and Science University, and identified patients who initially presented with NORSE. All patients underwent extensive testing for possible etiologies of RSE, including infectious, autoimmune, and paraneoplastic based on consensus recommendations established by Wickstrom et al. (2022b, 2022a). We reviewed and compared their subsequent clinical course and treatment including ASMs, trials of immunomodulatory therapies, seizure burden, neuropsychiatric symptoms, and results of neuropsychological testing.

Patient-reported seizure frequency was the primary outcome measure because this was the method used for reporting seizure frequency in the randomized controlled trial for RNS and subsequent long-term trial (Morrell and RNS System in Epilepsy Study Group, 2011; Nair et al., 2020). We additionally reported ECoG-derived "electrographic" seizure frequency estimates as a secondary outcome measure. Frequency measures for both seizure quantification methods were obtained at 3, 6, 12, and 24 months following RNS implantation (if available).

Patient-reported seizure frequency was obtained from chart review. The reported seizure frequency at each follow-up interval refers to an average seizure frequency over the preceding three months, which was chosen because this is the standard interval for RNS programming at our institution. Given moderate to severe memory deficits in all three subjects, as well as inconsistent availability of seizure logs, most "patient-reported seizures" were those observed by family or caregivers; therefore, patient-reported seizure frequency was likely an underestimate of true seizure frequency for the entire cohort. For this reason, we separately reported an ECoG-derived estimate of seizure frequency. ECoG-derived seizure frequency estimates were calculated based on a procedure adapted from a study that investigated "long episode" concordance with electrographic seizures and patient-reported seizures (Quigg et al., 2020). The RNS patient data management system (PDMS) database estimates seizures using a detection algorithm and stores ECoGs thought to represent seizures as "long episodes." Not all stored long episode ECoGs represent electrographic seizures, and conversely many electrographic seizures are overwritten and not stored for review due to device storage limitations. However, the total number and timing of all long episodes are logged by RNS. Thus, we visually inspected all long episode ECoGs within the 3-month epochs to determine what percentage of them were electrographic seizures; we then extrapolated the ECoG-derived seizure frequency estimate from the total numbers of long episodes recorded for each patient over a given time period.

3. Case presentation

3.1. Case 1

Case 1 was a 33-year-old male with a history of polysubstance use disorder and mood disorder who presented with FIRES. He had multiple convulsive seizures followed by non-convulsive super-refractory status epilepticus. During his first admission, he was treated with multiple ASMs and immunotherapies (Table 1). Electroencephalography (EEG) captured seizures with bilateral independent frontotemporal onset, often with evolution to bilateral tonic-clonic activity. His cerebrospinal fluid (CSF) profile was notable for 14 white blood cells with a lymphocytic predominance. Initial magnetic resonance imaging (MRI) showed mild T2 signal hyperintensity in the right hippocampus. Seizure suppression was ultimately achieved after 36 days of hospitalization. He was discharged to an inpatient rehabilitation facility after 57 days on 6 ASMs and no immunotherapy, yet he continued to experience episodic breakthrough seizures.

Seizure frequency increased in the years following initial presentation despite polypharmacy. Repeat MRI after one year showed decreased size of the right hippocampus with resolution of T2 hyperintensity. Due to concern for possible autoimmune etiology, multiple trials of immunotherapy were attempted (Table 1). Epilepsy monitoring unit (EMU) admission one year after presentation revealed bilateral independent onset seizures. VNS was placed 7 months after his initial presentation. The patient continued to have approximately 90 seizures per month despite seven ASMs. Typical seizures include an aura of facial paresthesias followed by manual automatisms and speech arrest, occasionally with loss of awareness.

Approximately 3 years after initial presentation, bilateral hippocampal RNS depth electrodes were placed empirically without preceding intracranial EEG. Postoperatively, seizure frequency decreased dramatically to about six seizures per month at year 1, but then increased to the prior baseline of 90 per month by year 2. Approximately 7 years after RNS implant, seizure frequency

Table 1
Overview of Cases.

	Case 1	Case 2	Case 3
Age at follow-up (years)	40	30	30
Sex	Male	Male	Male
RSE presentation (patient age)	FIRES (33)	FIRES (26)	NORSE (23)
RSE etiology	Unknown, presumed autoimmune	Unknown, presumed autoimmune	Unknown, presumed autoimmune, reported exposure to silica dust
CSF profile	CSF RBC 3, WBC 14 with 85% lymphocytes, protein 37, glucose 74, viral encephalitis panel negative	CSF RBC 18, WBC 14 with 79% lymphocytes, protein 34, glucose 56, viral encephalitis panel negative	CSF RBC 87, WBC < 1, protein 37, glucose 56, viral encephalitis panel negative
Autoimmune and paraneoplastic testing	Mayo autoimmune/paraneoplastic serum and CSF panels negative, anti-TPO antibody 258.9 U/mL, thyroglobulin antibody 99.7 U/mL (of note, had received IVIG; repeat testing was normal), PET/CT negative, CT chest abdomen and pelvis negative, testicular ultrasound negative	Mayo autoimmune/paraneoplastic serum and CSF panels negative, anti-TPO and thyroglobulin antibodies negative, CT chest abdomen and pelvis negative, testicular ultrasound negative	Mayo autoimmune/paraneoplastic serum and CSF panels negative, anti-TPO and thyroglobulin antibodies negative, testicular ultrasound negative
Genetic testing	Invitae Epilepsy Panel negative	Invitae Epilepsy Panel positive for *PIGG* variant, variant of uncertain significance in *ABAT* and *KCNJ10*	None
Anti-seizure medications utilized during acute presentation (alphabetical)	clobazam, fosphenytoin, ketamine, lacosamide, levetiracetam, midazolam, pentobarbital, perampanel, phenobarbital, propofol, and valproic acid	diazepam, ketamine, fosphenytoin, lacosamide, levetiracetam, midazolam, perampanel, phenobarbital, propofol, topiramate, and valproic acid	fosphenytoin, lacosamide, lorazepam, levetiracetam, oxcarbazepine, propofol, and valproic acid
Seizure types	FAS, FIAS, FBTCS	FAS, FIAS, FBTCS	FAS, FIAS, FBTCS
Scalp EEG	Bilateral independent temporal lobe seizures, others with poorly localized onset	Bilateral independent temporal seizures, sometimes evolving to bilateral tonic-clonic activity	Right temporal seizures
Intracranial EEG	None	None	Three right temporal seizures, although onset poorly visualized. Prolonged, 3-week study.
MRI	Right hippocampal T2 hyperintensity on initial presentation. On subsequent imaging, right hippocampal volume loss	Bilateral hippocampal T2 hyperintensity on initial presentation. On subsequent imaging, bilateral hippocampal volume loss	T2 hyperintensity right hippocampus on initial presentation. On subsequent imaging, asymmetric prominence of the right hippocampal tail
Ictal SPECT	Right temporal hyperperfusion	None	None
Immunotherapy	He was treated with methylprednisolone, IVIG, plasmapheresis, and rituximab during initial admission. He later underwent trials of rituximab, steroids, IVIG, plasmapheresis, cyclophosphamide, and mycophenolate mofetil without clear benefit.	Treated with methylprednisolone, IVIG, and rituximab during initial admission. Ongoing rituximab therapy correlated with possible gradual improvement in cognitive impairment and ataxia without a clear effect on seizure frequency or severity.	None during initial admission. Later, he had an initial reduction in seizures in response to corticosteroids and rituximab, but benefit appeared to diminish over time. IVIG was ineffective.
Other treatments	VNS	VNS	Right anterior temporal lobectomy and amygdalohippocampectomy
Time NORSE to RNS stimulation	40 months	31 months	84 months
RNS location	Bilateral hippocampal depth	Bilateral hippocampal depth	Left hippocampal depth, right residual parahippocampal gyrus depth
Initial RNS settings	Left: (+-+-)(0000)(0), 1 mA, 160 μs, 1.0 μC/cm^2, 100 ms, 200 Hz Right: (0000)(+-+-)(0) , 1 mA, 160 μs, 1.0 μC/cm^2, 100 ms, 200 Hz	Left: (+-+-)(0000)(0) 0.6 mA, 160 μs, 0.6 μC/cm^2, 100 ms, 200 Hz Right: (0000)(+-+-)(0) 0.5 mA, 160 μs, 0.5 μC/cm^2, 100 ms, 200 Hz	Left: (+-+-)(0000)(0), 0.5 mA, 160 μs, 0.5 μC/cm^2, 100 ms, 200 Hz Right: (0000)(+-+-)(0) , 0.5 mA, 160 μs, 0.5 μC/cm^2, 100 ms, 200 Hz
Number of programming changes	14	8	1
RNS settings as of 3/1/23	Left: (−−)(0000)(+), 7 mA, 160 μs, 3.5 μC/cm^2, 160 ms, 125 Hz Right: (0000)(−−) (+), 7 mA, 160 μs, 3.5 μC/cm^2, 160 ms, 125 Hz	Left: (+-+-)(0000)(0), 3.0 mA, 160 μs, 3 μC/cm^2, 100 ms, 200 Hz Right: (0000)(+-+-)(0) , 3.5 mA, 160 μs, 3.5uC/cm^2, 100 ms, 200 Hz	Left: (+-+-)(0000)(0), 1 mA, 160 μs, 1 μC/cm^2, 100 ms, 200 Hz Right: (0000)(+-+-)(0) , 1 mA, 160 μs, 1 μC/cm^2, 100 ms, 200 Hz
Patient-reported seizure frequency pre-RNS	90–120 per month (majority FIAS, no FBTCS)	16–27 per month (1–5 FBTCS)	8–12 per month
Patient-reported seizure frequency 6 months post-RNS	75 per month (majority FIAS, no FBTCS)	25 per month (7 FBTCS)	4 per month
Patient-reported seizure frequency 1 year post-RNS	6 per month (majority FIAS, no FBTCS)	20 per month (2 FBTCSa)	2 per month

(*continued on next page*)

Table 1 (*continued*)

	Case 1	Case 2	Case 3
Patient-reported seizure frequency 2 years post-RNS	90 per month (majority FIAS, no FBTCS)	30 per month (4 FBTCS)	N/A
Patient-reported seizure frequency as of 3/1/23	30 per month (majority FIAS, no FBTCS)	30 per month (4 FBTCS)	4 per month (all FIAS or FBTCS)
ECoG seizure frequency 6 months post-RNS	15 per month	68 per month	11 per month
ECoG seizure frequency 1 year post-RNS	21 per month	65 per month	7 per month
ECoG seizure frequency 2 years post-RNS	30 per month	90 per month	N/A
ECoG seizure frequency as of 3/1/23	4 per month	90 per month	4 per month
ASMs at the time of RNS implantation	CBD 710 mg BID, CBZ 400 mg qAM and 600 mg qPM, CLB 20 mg BID, LCM 300 mg BID, LEV 2000 mg BID, PHB 64.8 mg BID and 129.4 mg qPM, VPA 1250 mg BID	CLB 10 mg qAM and 20 mg qPM, LCM 200 mg qAM and 300 mg qPM, LEV 2000 mg BID, OXC 300 mg BID, PGB 150 mg BID, PHB 96.2 mg qAM and 113.4 mg qPM	BRV 100 mg BID, LTG 200 mg BID
ASMs after 6 months of RNS stimulation	CBD 710 mg BID, CBZ 400 mg qAM and 600 mg qPM, CLB 5 mg BID, LCM 300 mg BID, LEV 2000 mg BID, PHB 64.8 mg BID and 129.4 mg qPM, VPA 1250 mg BID	CLB 10 mg qAM and 20 mg qPM, LCM 300 mg BID, LEV 2000 mg BID, PGB 300 mg BID, PHB 97.2 mg qAM and 129.6 mg qPM	BRV 100 mg BID, CNB 100 mg qPM, LTG 200 mg BID
ASMs after 1 year of RNS stimulation	CBD 710 mg BID, CBZ 600 mg BID, CLB 5 mg BID, LCM 300 mg BID, LEV 2000 mg BID, PHB 64.8 mg BID and 129.4 mg qPM, VPA 1500 mg BID	CLB 10 mg qAM and 20 mg qPM, LCM 300 mg BID, LEV 2000 mg BID, PGB 300 mg BID, PHB 97.2 mg qAM and 129.6 mg qPM (unchanged)	BRV 100 mg BID, LTG 200 mg BID
ASMs after 2 years of RNS stimulation	CBD 710 mg BID, CBZ 600 mg BID, CNB 12.5 mg daily, LCM 300 mg BID, LEV 2500 mg BID, PHB 64.8 mg qAM and 97.2 mg qPM, VPA 1500 mg BID	CNB 300 mg daily, LCM 200 mg BID, LEV 2000 mg BID, PGB 300 mg BID	N/A
Change in number of ASMs after 2 years of RNS	None. Decreased by one ASM after 2.5 years	−2	N/A
Length of post-RNS follow-up	45 months	24 months	12 months
Complications	None	None	None

Abbreviations: BID, twice daily; BRV, brivaracetam; CBD, cannabidiol; CBZ, carbamazepine; CLB, clobazam; CNB, cenobamate; FAS, focal aware seizures; FIAS, focal impaired awareness seizures; FBTCS, focal to bilateral tonic-clonic seizures; IVIG, intravenous immunoglobulin; LTG, lamotrigine; LCM, lacosamide; LEV, levetiracetam; OXC, oxcarbazepine; PET/CT, positron emission tomography/computed tomography; PGB, pregabalin; PHB, phenobarbital; qAM, every morning; qPM, every evening; RBC, red blood cell; SPECT, single-photon emission computed tomography; TPO, thyroid peroxidase; VPA, valproic acid; WBC, white blood cell.

stabilized at about 30 per month representing a 67% reduction in reported seizures from baseline. Seizure frequency was heavily impacted by medication adjustments. In particular, phenobarbital had a significant impact on his seizure frequency, but needed to be decreased by 30% between years 1 and 2 due to sedation, transaminitis, and other side effects. This reduction may account in part for the increase in seizures between years 1 and 2. He remains on six ASMs, has ongoing memory problems, and follows closely with neuropsychiatry for panic disorder and depression with psychotic features.

Notably, determining electrographic seizure frequency was particularly difficult in this patient due to infrequent uploads, especially during periods when the patient was doing clinically worse; nonetheless, electrographic seizure frequency was attempted using the same methods as with the other two patients. In general, ECoG showed more seizures arising from the left temporal lobe than the right (Fig. 1).

In addition to treating seizures, RNS helped elucidate the complex relationship between the patient's different neuropsychiatric symptoms and seizures. During a clinic appointment 6 years after presentation, he had two events of tremulousness, rocking back and forth, hitting his head with his hands (a behavior that began around 5 years after initial presentation), and muttering to himself that were concerning for psychotic reaction versus psychogenic non-epileptic event; however, RNS interrogation revealed electrographic seizures preceding each event. During follow-up three months later, he had a similar event and subsequently had a seizure confirmed by RNS interrogation. Notably, not all anxiety/self-harm events correlated with seizures. In addition to the anxiety events, he had episodes of wandering and psychosis that were thought to be post-ictal. Four years after initial presentation, he was admitted to a behavioral health center for psychosis, suicidal ideation, and depression. He has tolerated therapy with clozapine, a drug associated with dose-dependent epileptiform EEG changes, without an increase in seizures or a change in interictal activity as measured by RNS ECoG detections (Varma et al., 2011). Since starting clozapine, self-harm behaviors markedly decreased.

3.2. Case 2

Case 2 was a previously healthy 26-year-old male who presented with FIRES. He developed a febrile illness after a camping

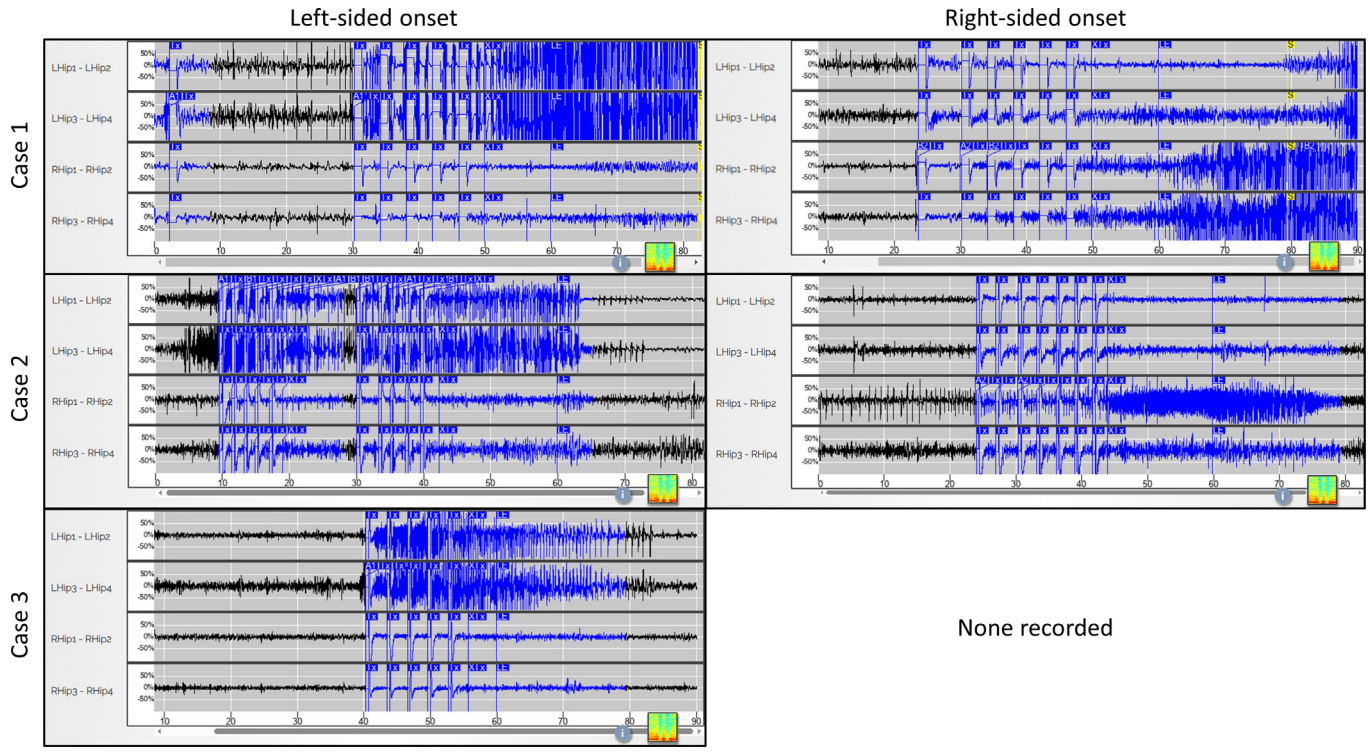

Fig. 1. Representative ECoG seizure onset samples are shown for each patient.

trip associated with headache, encephalopathy, and myalgias. Initial lumbar puncture showed no white blood cells, and glucose and protein were not reported. Six days after symptom onset, he had multiple convulsive seizures necessitating intubation. Lumbar puncture was repeated and showed a non-inflammatory CSF profile (Table 1). He was treated with multiple ASMs and immunotherapies (Table 1). EEG showed frequent bilateral independent temporal lobe seizures, sometimes evolving to bilateral tonic-clonic activity. He underwent prolonged burst suppression to achieve seizure control at hospital day 32. MRI revealed increased fluid attenuated inversion recovery (FLAIR) signal in the bilateral mesial temporal lobes. Upon discharge to an inpatient rehabilitation facility after 57 days, he continued to experience several brief seizures daily despite being on 7 ASMs and rituximab.

The patient's post-discharge course was complicated by near-daily seizures and other complications. He was urgently re-admitted six months after discharge for diagnosis and management of prolonged episodes of agitation and laughter that did not have a scalp EEG correlate. Fifteen months after his initial presentation, he underwent pre-surgical EMU admission that captured bilateral independent frontotemporal onset seizures. A repeat MRI showed bilateral mesial temporal sclerosis. Neuropsychological evaluation 1.5 years after initial presentation showed global cognitive impairment, reduced processing speed, and left greater than right hemisphere dysfunction characterized by impaired verbal language and memory. Despite five ASMs and ongoing rituximab treatment, the patient continued to have at least one seizure per day including frequent bilateral tonic-clonic seizures. Typical seizure semiology was characterized by an aura of extreme déjà vu, behavioral arrest, and variable oral automatisms or upper extremity movements with post-ictal confusion and agitation.

Two and a half years after initial presentation with NORSE, the patient was implanted with RNS with bilateral hippocampus depth leads and stimulation was activated one month postoperatively. After one year, he had approximately one patient-reported disabling seizure per day, and there was a modest improvement in subjective memory and language function. Because the majority of his seizures originated from the right temporal lobe, surgical resection was considered but not pursued based on unfavorable Wada testing. As a component of pre-surgical workup, he underwent neuropsychological evaluation 3.5 years after initial presentation which demonstrated worsened reaction times and persistent deficits in language with mild improvement on tasks correlating with right temporal lobe function.

At most recent follow-up, he was reporting one brief disabling seizure daily and was more alert and awake after tapering phenobarbital and cenobamate. While patient-reported seizure frequency was similar after 2 years of RNS therapy, he experienced fewer disabling seizures. Of note, similar to case 1, this patient had episodic inconsistencies in data uploads from RNS due to neuropsychiatric and social factors, which limited ECoG data interpretation.

RNS has been helpful in differentiating ictal and post-ictal events from non-epileptic events. He has non-epileptic events including non-rhythmic hand movements and breath holding. His typical ictal patterns are shown in Fig. 1. Unfortunately, he continued to have frequent near-daily disabling seizures complicated by falls and limb fracture, so he subsequently underwent VNS placement 27 months after RNS placement. VNS placement was complicated by wound infection necessitating device explantation 2.5 months later, limiting assessment of efficacy. The patient is currently dependent on family for many activities of daily living (ADLs) and expresses significant frustration at his lack of independence. He has persistent ataxia and uses a walker to ambulate. He enjoys his time playing with his two young children while seated on the ground (since he is at high risk for falls).

3.3. Case 3

Case 3 was a 23-year-old male with irritable bowel syndrome and polysubstance use disorder who presented with NORSE. His history was otherwise significant for suspected exposure to silica dust from a nearby pesticide factory; multiple family members and neighbors reported autoimmune conditions. CSF profile was not suggestive of infection or inflammation. Scalp EEG showed numerous seizures with right temporal onset. MRI demonstrated T2 hyperintensity in the right hippocampus. His mental status improved markedly after 4 hospital days, however he continued to have several brief seizures daily. He was discharged home after 5 days on 3 ASMs.

After discharge, he initially improved and was able to taper medications, but seizures later worsened. Semiology was variable but generally included behavioral arrest and loss of awareness with or without subsequent bilateral tonic-clonic seizure. An autoimmune cause was strongly suspected, and he underwent several immunotherapy trials (Table 1). Seizure frequency initially reduced with rituximab, but response diminished over time. He underwent EMU admission with intracranial EEG which implicated a right temporal lobe focus, and he had an anterior temporal lobectomy and amygdalohippocampectomy. He experienced transient improvement, but seizures recurred, and scalp EEG later captured seizures with a left temporal onset during a second EMU admission. Seizure frequency was difficult to quantify because he lived alone and was unaware of most seizures. Estimated seizure frequency prior to RNS was 10 per month.

He was offered the choice between RNS and DBS and selected RNS. He did not undergo repeat intracranial EEG prior to RNS placement; the decision was made to place electrodes empirically in bilateral mesial temporal regions based on prior intracranial EEG data and clinical suspicion. Six and a half years after initial presentation, he underwent RNS with right residual parahippocampal gyrus and left hippocampus depth leads, and stimulation was started five months later. At a clinic visit 7 years after initial presentation, he still reported about 10 seizures per month described as confusional episodes, but no seizures were seen on ECoG. It was unclear initially whether the events were related to inaccurate detection, a source outside of the areas sampled by RNS electrodes, or whether the events might be non-epileptic. Due to this discrepancy, he was referred for a third EMU admission. While awaiting EMU admission, he reported a cluster of seizures (one of which involved finding blood and stool on the ground after regaining consciousness) which finally did correspond to electrographic seizures on ECoG. During the subsequent EMU admission, six seizures were captured with left hippocampal onset confirmed on both scalp EEG and ECoG. Additional events of jaw clenching, body stiffening, and reported episodes of time lapse with memory loss did not demonstrate a correlate on either scalp EEG or ECoG. The EMU admission confirmed that the RNS device was able to correctly detect seizures (Fig. 1), and that some of the events the patient was reporting were not seizures after all.

Determining seizure outcome is difficult in this patient given poor awareness of seizures; with this caveat, clinical seizure frequency had improved by 80% at one year, with no convulsive seizures reported in the prior 3 months at most recent follow-up visit. Electrographically, the estimated seizure frequency improved 36% from the 6 to 12-month mark. However, it is worth noting that the patient's right-sided seizures are brief with subtle evolution, and we have not confirmed whether or not right-sided seizures are associated with clinical symptoms. If we use left-sided seizures only to estimate electrographic seizure frequency, then there has been an average improvement in seizure frequency of 42% between months 6 and 12. The fact that no electrographic seizures were detected between months 0 and 5 can be attributed to both implant effect and early detection settings that were inaccurate for detecting right-sided seizures.

4. Discussion

In summary, this case series demonstrates that RNS is a safe and modestly effective neurostimulation treatment option in patients with DRE due to NORSE. Importantly, none of the three cases had surgical complications from RNS placement including infections, despite all three patients having received immunosuppressive treatment at different times during their treatment course. Of note, only the patient in case 2 was receiving immunotherapy at time of RNS implant (last rituximab dose five months prior to implantation). In terms of efficacy in treating seizures, all three cases have had a modest improvement in seizure frequency and severity. While a modest reduction can improve patients' quality of life, the first two cases have continued to have relatively frequent disabling seizures. RNS and other neurostimulation treatments are palliative, therefore, patients and caregivers must be counseled to have realistic expectations for treatment response and seizure reduction.

In addition to improving seizure control, RNS aided management through its diagnostic utility. Each of the patients in the case series have had both epileptic and non-epileptic events, and RNS proved helpful in categorizing event types as ictal or post-ictal (including patients' emotional reactions to active seizures) versus non-epileptic, thus guiding treatment and minimizing overmedication. One limitation in this use is the limited spatial sampling that RNS provides; it is possible that events without correlating seizures on RNS are seizures arising from alternate seizure foci. Furthermore, RNS enables the accumulation of long-term data quantifying laterality of seizures, which can be used to determine whether the patients could be candidates for palliative surgical resection. Finally, the long-term data monitoring capability has also aided in monitoring response to immunotherapy and ASMs. Therefore, RNS may have an advantage over other neurostimulation devices in patients with NORSE and DRE because of its therapeutic and diagnostic utility, given frequent neuropsychiatric sequelae.

Accurate representation of seizure frequency remains a challenge for clinicians when caring for all patients with epilepsy, but assessing seizure frequency is particularly challenging in this population given high seizure burden and high frequency of cognitive and neuropsychiatric comorbidities. While the patient's clinical report of seizures remains the gold standard for counting seizure frequency, RNS provides supplementary data on seizure frequency via its ECoG recordings and stored "long episode" counts (Morrell and RNS System in Epilepsy Study Group, 2011; Nair et al., 2020). We decided to present seizure frequency using both patient-reported clinical seizures (i.e. "disabling" seizures) as well as ECoG-derived seizure frequency estimates calculated based on RNS data as shown in Table 1. There are pros and cons to both methods of determining seizure frequency. Patients may report seizures inaccurately due to poor memory, poor note-keeping, or the simple fact that patients are often not aware of some seizures. RNS data capture is also flawed; the device may record electrographic seizures that are subclinical and thus not clinically relevant, it may capture long episodes that meet the device's detection criteria to be seizures, but are not in fact seizures when reviewed manually, and it may overwrite relevant data due to infrequent uploads by patients. Nonetheless, the combination of approaches gives a more complete picture of seizure frequency than either approach alone. Estimating seizure frequency in this patient population is especially challenging given frequent neuropsychiatric comorbidity including memory impairment as well

as social factors; notably, both case 1 and 3 lived alone during the majority of the follow-up period and often did not remember their seizures. Case 1 struggled to regularly upload RNS data due to ongoing mental health problems and inconsistent family supervision.

Neurostimulation is an established treatment option in patients with DRE due to NORSE, but the authors can find only three published peer-reviewed case reports of RNS for NORSE to date and no cohort studies or case series. The first was a patient who presented with NORSE with seizures arising from the right occipital lobe who underwent implantation of right anterior and posterior occipital cortical strips 74 days following presentation with a >98% reduction in long (>40-second) events (Yang et al., 2021). The second case was a patient who presented with FIRES in the setting of human herpesvirus 6 (HHV-6) encephalitis with seizures of multifocal but predominantly left orbitofrontal and superior temporal onset who underwent implantation of left orbitofrontal depth and superior temporal cortical strip leads 15 months after initial presentation. The patient had a 30% reduction in long episodes at 6 months, decreased seizure severity, fewer focal to bilateral tonic-clonic seizures, and improved cognition on neuropsychiatric testing (Theroux et al., 2020). The third case was a patient who presented with NORSE in the setting of probable autoimmune encephalitis with seizures arising from bilateral temporal lobes with a greater percentage from left-sided onset who underwent implantation of bilateral sub-temporal strip leads 34 months after presentation with a subsequent mild improvement in seizure severity without improvement in frequency (Chen et al., 2022b). There have been four case reports of pediatric patients who were implanted with bilateral centromedian DBS in the acute stage after presenting in NORSE. The first patient, who had already received a VNS without effect, was implanted with DBS about two months after presentation and experienced reduction in seizure frequency and improved mental status (Hect et al., 2022). The second and third patients received DBS after about one month, and both had resolution of bilateral tonic-clonic seizures and fewer focal seizures (Sa et al., 2019). The fourth patient received DBS after about two months and demonstrated improved EEG background and eventual resolution of acute status epilepticus (Lehtimäki et al., 2017). All four cases targeted the centromedian nucleus of the thalamus. VNS is the most frequently reported neurostimulation treatment reported in the literature with at least 17 published cases both in acute and chronic timeframes as summarized by Ritter and Selway (Mantoan Ritter and Selway, 2023). While long-term outcomes are varied, VNS seemed to confer some benefit in terms of seizure reduction in at least 10 of these patients. In summary, there are limited peer-reviewed publications on neurostimulation for NORSE and FIRES, so this small case series on RNS for NORSE helps fill critical knowledge gaps while larger multicenter studies are conducted.

While this is the largest peer-reviewed published cases series of RNS in patients with NORSE to date, the major limitation of this article is its small sample size. Other limitations include limited follow-up duration and confounding variables including ongoing ASM adjustments and changes in RNS seizure detection parameters. Additionally, all cases were young adult men at the time of disease onset, so the study lacks gender and age diversity. Of note, all three patients were Caucasian, but the patient in case 1 also had Native American heritage. In all three of our patients, an etiology of NORSE was not identified, so all were cases of cryptogenic NORSE. Two of the three cases met the definition for FIRES. Two of the three had CSF profiles notable for lymphocytic pleocytosis, one of whom had possible benefit from long-term treatment with rituximab. All three of our patients experienced significant long-term neuropsychiatric sequelae. There is not yet a robust body of literature describing long-term outcomes, but conference proceedings and abstracts as well as several articles suggest adverse neuropsychiatric sequalae are common in this population (Shrestha et al., 2023; Wickstrom et al., 2022a). More studies on NORSE treatments and outcomes are needed; fortunately, a NORSE/FIRES biorepository has been established, and a multicenter prospective, observational study is in progress (Research Bulletin and Opportunities, 2023).

5. Conclusions

While neuromodulation has been used to treat NORSE in select cases, ours is the first case series of patients with DRE due to NORSE who were treated with RNS. Although all three patients continue to have medically refractory epilepsy, RNS therapy reduced seizure burden and provided clarity regarding non-epileptic events. Our experience indicates that psychiatric and cognitive symptoms are common following NORSE. Further investigations may determine optimal timing of placement, strategies for device programming, and implications on long-term neuropsychiatric outcomes. It is worth noting that all patients in our cohort had a presumed underlying autoimmune epilepsy. NORSE is a heterogenous disorder, and it is not yet known if there are subsets of patients who are more or less likely to benefit from neuromodulation. RNS efficacy and tolerability must be weighed against the cost and invasiveness of the procedure as well as the inconvenience to patients and caregivers of frequent device interrogations and close long-term follow-up. Still, our results suggest that RNS is a safe and well-tolerated therapy that may provide therapeutic benefit following NORSE.

Competing Interests

The authors have no conflicts of interest to disclose.

CRediT authorship contribution statement

Audrey Oliger: Investigation, Writing - Original Draft, Writing - review & editing, Methodology. **Caleb Nerison:** Investigation. **Hao Tan:** Investigation. **Ahmed Raslan:** Writing - review & editing. **Lia Ernst:** Writing - review & editing, Methodology. **Proleta Datta:** Writing - review & editing, Methodology. **Marissa Kellogg:** Conceptualization, Supervision, Methodology, Writing - review & editing.

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