INTRODUCTION

Febrile infection-related epilepsy syndrome (FIRES) is a rare, life-threatening complication of febrile illness in previously healthy individuals, who present with a non-specific febrile illness followed by prolonged, refractory status epilepticus, with a mortality of 12% in children and 16%–27% in adults.\(^1,2\) The consensus definition for FIRES includes the onset of refractory status epilepticus within 24 hours to 2 weeks of a febrile illness and is characteristically nonresponsive to traditional antiseizure medications, anesthetics, and immunotherapy.\(^1-3\) Proposed

Abstract

Febrile infection-related epilepsy syndrome (FIRES) is a rare, life-threatening complication of febrile illness in previously healthy individuals followed by super-refractory status epilepticus. Deep brain stimulation (DBS) has been demonstrated to be a promising therapy for the treatment of intractable epilepsy. Here, we present a pediatric patient with FIRES whose seizures were mitigated by acute DBS of the bilateral centromedian thalamic nucleus (CMTN). This is a previously healthy 11-year-old female who presented emergently with altered mental status, fever, and malaise after 1 week of lethargy, anorexia, fever, and abdominal pain. The patient began having seizures shortly after admission. After thorough workup for encephalitis and other potential etiologies, this patient was diagnosed with FIRES due to super-refractory status epilepticus. Status epilepticus persisted despite pharmacologic management, immunotherapy, and vagus nerve stimulation. DBS of the bilateral CMTN (CM-DBS) was pursued after 56 days of hospitalization, and she demonstrated considerable improvement in baseline mental status 30 days after DBS insertion. This report highlights application of CM-DBS for super-refractory status epilepticus in FIRES. This region is a diffusely connected brain region and has been shown to modulate neural networks contributing to seizure propagation and consciousness; therefore, neurostimulation is a potential therapeutic intervention for patients with super-refractory status epilepticus.

KEYWORDS

critical care, drug-resistant epilepsy, neuromodulation, pediatric epilepsy
mechanisms include autoimmune etiologies and widespread activation of inflammatory pathways, although there has yet to be any reliable evidence to conclusively support either of these hypotheses. Despite the profound morbidity and mortality associated with FIRES, the etiology, pathogenesis, and optimal treatment paradigm remain poorly understood (for review).\textsuperscript{1-4}

Centromedian thalamic nucleus deep brain stimulation (CM-DBS) is an emerging therapy for drug-resistant multifocal or generalized epilepsy.\textsuperscript{5-9} The CMTN is a diffusely connected brain region and has been shown to modulate neural networks contributing to seizure propagation and consciousness.\textsuperscript{10-12} Neurostimulation of the CMTN modulates thalamocortical connectivity and is a promising therapy for the treatment of super-refractory status epilepticus (SRSE) in the clinical setting of FIRES.\textsuperscript{8,13,14}

Here, we report a pediatric patient with FIRES who was successfully treated with CM-DBS.

## CASE REPORT

A previously healthy 11-year-old female presented emergently with altered mental status following a 3-day period of fever, lethargy, anorexia, headache, and nonspecific abdominal pain. She was found unresponsive to verbal and physical stimuli by parents who called EMS. Vitals at the time of presentation were T 38.2°C, HR 140, RR 24, BP 122/72, SpO\textsubscript{2} 100%. The patient’s first clinical seizure occurred shortly after arrival to the emergency department, with significant oxygen desaturation and full-body stiffening lasting around 1 minute. She was treated with a loading dose of lorazepam. Evaluation including laboratory tests, head computerized tomography (CT), and lumbar puncture was unremarkable. She was started on levetiracetam, as well as empiric treatment for meningoencephalitis including vancomycin, ceftriaxone, and acyclovir.

Early EEG demonstrated generalized background slowing including frequent epochs of generalized rhythmic delta with superimposed fast activity and right frontotemporal epileptiform discharges, with numerous electrographic seizures arising from the right anterior temporal, right inferior frontal, or poorly lateralized over the bifrontal head regions, 30 seconds to 5 minutes in duration (Figure 1). She was transferred to the pediatric ICU where seizures persisted and increased in frequency despite escalating therapies.

Multiple antiseizure medications were introduced early in clinical course including lorazepam, levetiracetam, fosphenytoin, and lacosamide. See Figure 2 for a summary of antiseizure pharmacotherapy. On Day 2 of admission, midazolam infusion was escalated with continued electrographic seizures. The patient was sedated on Day 3 for seizure control and required a midazolam drip. On Day 4, pentobarbital infusion was initiated, with less frequent but persistent electrographic seizures arising from burst-suppression background. Immunotherapy with IV immunoglobulin (IVIG) and high-dose methylprednisolone was started on Day 6. Ketamine was introduced on Day 6 with resolution of electrographic seizures, and midazolam was successfully weaned. Electroclinical seizures emerged with weaning of midazolam, consisting of clonic right arm jerking, correlating with generalized periodic discharges, and electrographic seizures also re-emerged and increased in frequency. Numerous antiseizure medications were trialed without improvement. The patient underwent five cycles of plasma exchange across 7 days, beginning on Day 21. Anakinra was started as additional immunotherapy on Day 18. Patient was weaned from anesthetics on Day 39 with subsequent increase in electrographic seizure activity characterized by predominantly right frontal multifocal epileptiform discharges. Ketogenic diet was started on Day 19, without noted improvement, and was discontinued on Day 60.

Expanded laboratory workup included negative serum and CSF autoimmune encephalitis panel, elevated CRP (1.94–2.88 mg/dL), low thyroid-stimulating hormone (0.237) with normal T3 and free T4, normal serum and CSF studies (negative for West Nile, Bartonella, and Arbovirus antibodies), negative Lyme titers, and complement levels (C3, C4, CH50). Repeat lumbar punctures demonstrated sustained elevated opening pressure (34 cm H\textsubscript{2}O on Day 3 of admission, and 48 cm H\textsubscript{2}O on Day 13 of admission) but were otherwise unremarkable. Genetic testing was performed including comprehensive epilepsy panel (393 genes and 37 mitochondrial genes) which revealed a variant of unknown significance in GRIN2B [c.2099C>G, p.(Ala700Gly)] and carrier status for a pathogenic mutation in CLN6 [c.775G>A, p.(Gly259Ser)], neither of which were thought to be related to clinical presentation. Deletion/duplication analysis of CLN6 was eventually found to be negative.

Initial brain MRI was negative on Day 2 of admission. Repeat imaging on Day 5 showed increased perfusion in the bilateral frontal lobes and right greater than left temporal lobes but was otherwise normal. Repeat imaging on Days 15, 29, and 51 showed scattered cortical T2 hyperintensities in the bilateral internal capsule and thalami and restricted diffuse in the hippocampal tail bilaterally, as well as diffuse mild volume loss and ex vacuo ventricular enlargement, which were noted to be slightly improved on Day 57. Brain PET imaging on days 21 and 54 demonstrated broad areas of decreased metabolism with scattered focal areas of increased metabolism in the frontal lobes bilaterally. Full-body PET did not reveal evidence of malignancy. Brain biopsy was performed on Day 57 and...
showed only reactive changes with no inflammatory infiltrates or evidence of infection. Immunostaining with 3F4 did not reveal evidence of prion disease.

3 | MANAGEMENT

Neurosurgical therapy was offered for possible mitigation of this patient’s SRSE. Both vagal nerve stimulation and deep brain stimulation were discussed, and the risks and benefits weighed with the patient’s parents. The family opted to pursue VNS placement, although this was ultimately not successful in aborting her seizure activity, even on the highest stimulator settings (rapid cycling [58%], 2.5 output current [Magnet 2.75]). Bilateral CM-DBS was pursued on Day 57 after discussion of risks and benefits.

Electrode trajectories were planned to the bilateral CMTN using a merged stereotactic CTA MP2RAGE MRI, MP2RAGE inversion images (Figure 3), and postcontrast MP-RAGE MRI. Standard indirect coordinates were used and direct targeting methods using the imaging modalities described were also used, as previously reported.8,14–17 Trajectories were planned to avoid sulci and ventricles as well as vascular structures. Stereotactic right frontal brain biopsy was also completed at this time, targeting for which was based on the location of signal abnormality on the T2-weighted FLAIR MRI. Intraoperative CT scan was obtained following placement of each electrode and were registered with preoperative MP2RAGE to confirm location. Boston Scientific DBS electrode leads were used and the device was initially set to amplitude 4 µV, rate 143 Hz, pulse width 90 µsec, cycling off, delivered bilaterally from the deepest contact (contact 1). Lead-DBS software18 (https://www.lead-dbs.org) was used to visualize placement in reference to thalamic nuclei defined by The Thalamus Atlas,19 see Figure 3.

Deep brain stimulation settings were increased on Day 63 to amplitude 5 µV, frequency 143 Hz, Pulse Width 90 µsec, with Cycling off. The patient underwent tracheostomy and percutaneous endoscopic gastrostomy tube placement on Day 69, for which her VNS and DBS were turned off. Upon attempting to turn the DBS back on to the prior settings postoperatively, the patient experienced immediate eye fluttering (left>right) with inconsistent EEG correlate. The amplitude was set to 2 µV with plans to titrate slowly back to 5 µV. The patient experienced a
significant increase in number of electrographic seizures at that time (see Figure 2). DBS amplitude was increased to 2.5 µV on Day 74. Finally, DBS settings were increased adjusted on Day 85 to amplitude 3 µV and Cycling turned on (“ON time” 1 min, “OFF time” 5 min). The following day (Day 86), the patient demonstrated notable improvements in alertness and continued to improve over the next week, including ability to communicate verbally and

non-verbally (limited due to tracheostomy) and movement of extremities. The patient remained largely free from seizures through the end of her hospitalization, while she remained on continuous EEG monitoring.

Serial EEG recordings prior to discharge showed no interhemispheric voltage or frequency asymmetries, epileptiform discharges, electrographic, or electroclinical seizures. Intermittent photic stimulation was performed,
using even flash frequencies between 2 and 30 flashes/sec-
ond, failed to produce a driving response, and failed to ac-
tivate any abnormalities. She was transferred to inpatient
rehab on Day 98, where she made tremendous progress
with mobility, transfers, cognition, feeding, and respira-
tory status. She was discharged home after 4 months of
rehabilitation.

4 | OUTCOMES AND FOLLOW-UP

This patient presented 6 weeks after discharge from in-
patient rehabilitation for increased seizure frequency, in
the setting of a urinary tract infection and was discharged
2 days later. Continuous EEG during admission captured
numerous electrographic seizure interictal multifocal
sharp waves and numerous brief focal seizures, alter-
nating hemispheres. Numerous brief clinical seizures
consisted of alternating hemisphere rhythmic spike and
wave, maximally in the temporal head regions associated
with facial grimacing and drooling.

Patient underwent VNS removal 4 months after dis-
charge from rehab for planned sEEG mapping of seizure
foci at 1 month later. sEEG was pursued to aid in charac-
terization of seizure onset zones with bilateral coverage
(20 electrodes in total). Numerous daily electrographic sei-
zures were captured arising from right frontal and left tem-
poral regions, without clinical correlate. DBS was turned
off at the time of sEEG implantation and was turned on to
prior settings 48 hours later without appreciable change
in seizure frequency or duration. In months following
sEEG removal, the patient has not experienced clustering
of her seizures and is continuing to make functional re-
habilitative progress. Since sEEG mapping, she has been
able to wean from perampanel and is beginning to wean
from phenobarbital. She remains on a complex regimen
of anticonvulsive medications overall, which her clinical
team will continue to attempt to simplify, including bri-
varacatam, clobazam, and clonazepam for seizure cluster-
ing, phenytoin, phenobarbital, lacosamide, and intranasal
midazolam for convulsive seizures.

5 | DISCUSSION

Targeting of the CMTN for DBS is a promising rescue
therapy for SRSE in FIRES, a devastating condition for
which there are currently no reliable treatment options.
Drug-resistant generalized epilepsy has been shown to be
responsive to neuromodulation through CM-DBS5-9 and
CM-RNS.15,17,20-22 DBS has been utilized safely in chil-
dren specifically for drug-resistant epilepsy, including
at least 40 pediatric patients (ages 4–18 years) who have
received DBS treatment for epilepsy (see review23). There
are a total of eight cases published that report the use of
DBS for SRSE, in which seizure frequency decreased fol-
lowing implantation to the CMTN8,13,24,25 or anterior thala-
lamic nucleus (ATN).26-28 This suggests that DBS may be
employed as a rescue therapy to reduce overall morbidity
and neurologic insult related to prolonged epileptic activ-
ity and sedation. Specifically for FIRES, Sa et al (2019)
reports CM-DBS for two pediatric patients, of whom one
responded positively to DBS and adjuvant immunother-
apy (Anakinra).13 Their report demonstrated return of
seizure activity when CMTN stimulation was temporarily
ceased,13 supporting the specificity of CMTN neuromodu-
lation in mitigating status epilepticus (vs progression of
the disease from acute to chronic FIRES).1 Anakinra was
trialed in this patient beginning on Day 18, but the patient
failed to improve. Considerable work is still needed to
measure the timing and stimulation parameters of CM-
DBS for the mitigation of SRSE and to understand how
this therapy interacts with the course and pathogenesis of
FIRES in pediatric patients.

The patient’s response to DBS was promising initially,
although was set back due to decreased tolerability of her
prior DBS settings following DBS and VNS inactivation
for OR placement of tracheostomy and PEG tube. The
patient’s seizures gradually decreased over the following
20 days, while DBS parameters for increased from 2 to 3µV.
On Day 85, her parameters were set to 3 µV and Cycling
turned on (1 min/5 min) without change to her other set-
tings (Frequency 143 Hz, Pulse Width 90 µsec) and the pa-
ient responded with dramatic improvement in seizures
and arousal the day following. The timing of response was not
related to any other change in her care at that time. There
is no consensus on which parameters are best for status ep-
ilepticus, and there is a wide range of reported in the litera-
ture. Most studies report seizure improvement when using
frequencies of 130 Hz and 90–120 µsec pulse width.8,13,24,25
Stavropoulos and colleagues most recently reported patient
responsiveness to low-frequency stimulation to the CMTN
(6Hz/300 µsec pulse width).25 Sa and colleagues report
using high-frequency (130 Hz) stimulation to mitigate gen-
eralized seizures and later low-frequency stimulation (6 Hz)
for bifrontal focal seizures, which resulted in a transient re-
duction. Interestingly, Sa (2019) also describe an increase in
focal seizure activity during a period of DBS inactivation.
Low-frequency stimulation has been discussed for this pa-
tient, though has not been pursued to date. The structural
and functional connectivity of the CMTN supports the suc-
cess of DBS in modulating seizure activity,29 including re-
ciprocal connections to the striatum and cortical premotor,
motor, and sensory areas, as well as direct inputs from brain
stem structures (reticular formation, vestibular nucleus,
solitary nucleus, and nucleus ambiguous).30 Stimulation of
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