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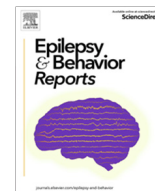
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Case Report

Repetitive transcranial magnetic stimulation (rTMS) as therapy in an infant with epilepsy partialis continua



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ABSTRACT

Introduction: We present a case of a 10-month-old girl undergoing repetitive TMS (rTMS) for the treatment of drug-resistant epilepsy. **Case report:** A 10-month-old girl, later diagnosed with pathogenic POLG1 mutations, presented to our institution with chronic progressive EPC (epilepsia partialis continua) manifesting as a frequent, left-sided, synchronous continuous jerking of the arms and legs. The seizures were drug-resistant to multiple antiseizure medications and epilepsy surgery, responding only to continuous anesthesia. rTMS therapy was attempted to interrupt seizures. **Results:** rTMS therapy, using an activating protocol to introduce a temporary lesion effect, was used to interrupt persistent, ongoing seizures. **Conclusion:** rTMS can be safely used to abort seizures in patients as young as 10 months old.

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Introduction

rTMS has been used as a noninvasive interictal intervention for neocortical epilepsies by inducing long-term depression of seizure activity through direct electromagnetic low-frequency cortical stimulation by a rapidly pulsing extracranial magnetic field [1–3]. rTMS may also be used to interrupt ongoing seizures related to EPC by disrupting neuronal activity and altering focal cortical excitability [4]. However, consensus is that patients with a single, well-circumscribed epileptogenic focus such as focal cortical dysplasia are most likely to respond to rTMS [5].

rTMS is increasingly used in the pediatric population as noninvasive therapy for refractory seizures of neocortical origin because of its ability to target superficial cortical structures, its localized effect, and its favorable risk/benefit profile. Across reports, adverse events of rTMS are relatively mild and stop immediately after stimulation. In a review of 13 pediatric patients with EPC undergoing rTMS, 2 patients (15%) reported headache, scalp, arm, and leg pain with no correlation to rTMS intensity (Hz), frequency, number or duration of rTMS trains. Notably, both instances of adverse events occurred in stroke patients and for one patient, side effects resolved with a second train of stimulation. No evidence exists of

rTMS leading to an increase in seizure severity or generalized seizures even during high frequency stimulation [6].

Of published cases in which rTMS was used to treat EPC, the youngest patient is 7 years old. In the pediatric population, rTMS shows relatively inconsistent efficacy in treating EPC with some achieving transient seizure suppression while others show more durable response and still others with only subjectively minimal improvement or no response [7–8]. The etiology of EPC in these case reports includes focal cortical atrophy, post-operative trauma, neuronal ceroid lipofuscinosis, and unknown. Currently, no consistent patient characteristics or etiology have been identified that predict response of EPC to rTMS therapy.

Here, we report the case of a 10-month-old girl with refractory EPC to antiseizure medication and surgical intervention who was successfully treated with adjunctive rTMS.

Case Report

This female infant was born at term with no significant perinatal course and had been in her usual state of good health until 8.5 months of age when she developed frequent, left-sided, synchronous, continuous jerking movements of her arms and legs. On neurological exam, the patient had continuous left upper extremity twitching as well as palpable left thigh rhythmical contractions though no definite movement was observed. Otherwise, the patient moved all extremities spontaneously and was responsive and tracking faces. She was admitted and treated for presumed EPC with focal aware-motor seizures with levetiracetam

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and lorazepam. IVig and steroids were used to treat possible Rasmussen's encephalopathy but this approach had little effect. After a 14-day inpatient stay which included phenobarbital coma induction, the patient was discharged on levetiracetam with continued intermittent jerking movements reflecting EPC. During this initial hospital course, electroencephalography (EEG) did not show epileptiform abnormalities correlating with her jerking movements, which is often the case with EPC [9]. An MRI and head CT were unremarkable as was an autoimmune CSF panel (CSF IgG, IgG synthesis rate, IgG:albumin ratio, oligoclonal bands, alpha-1 CSF, alpha-2 CSF, beta-CSF, gamma-CSF, and NMDA receptor IgG CSF), a CSF monoamine neurotransmitter metabolite assay, an inborn errors of metabolism workup including an acyl carnitine profile, plasma amino acids, and urine organic acids, and a single nucleotide polymorphism chromosomal microarray.

In the next few months, the patient was admitted several times due to increased seizure frequency and an evolving seizure semiology. Focal aware-motor seizures were now continuous, of higher amplitude, and had spread to the right side. Loading doses of oxcarbazepine, fosphenytoin, and multiple courses of phenobarbital and escalating doses of midazolam were tried with minimal effect. For recurrent refractory focal motor status epilepticus, the patient was admitted to the PICU for a second therapeutic pentobarbital coma.

After coma induction, no seizures were observed though video-EEG showed focal epileptiform discharges over the right central head region. Repeat MRI showed decreased white matter throughout with possible gray-white blurring of the right superior frontal gyrus suggestive of focal cortical dysplasia. A lumbar puncture was unremarkable. Given the risk for neurological deterioration with prolonged intubation and sedation, sedating medications were weaned, and the patient was extubated but shortly thereafter developed clinical focal left-sided jerking movements. Levetiracetam and clonazepam were tried to little avail and the patient was discharged following a 10-day hospitalization.

At 9 months of age, she was readmitted for increasing frequency and duration of jerking movements with long episodes lasting 20 minutes occurring every hour. Given the possibility of an immune-mediated disease, the patient was restarted on high-dose steroids which had no clear benefit. She ultimately underwent electrocorticography-guided resection of the right frontal gray-white blurring as seen on MRI. In the operating room, pre-resection electrocorticography demonstrated epileptiform activity of the right Rolandic and paramedian regions which were resected. Post-resection electrocorticography showed no additional epileptiform activity. Pathology showed cortical dysplasia Type 2a. Unfortunately, immediately post-op, she had worsening left arm jerking. Over time, her jerking movements improved from the pre-op baseline though persisted, and with a left hemiparesis. She was treated with clonazepam, fosphenytoin, and lacosamide. By post-operative day 7, following reduction of antiseizure medications, the jerking movements of the left upper extremity had much improved, as had her mental status and motor exam. The patient was discharged by post-operative day 9 on clonazepam and phenytoin.

Three days after discharge, now 10 months old, she was readmitted for acute worsening of seizures involving the right arm and leg. Video-EEG monitoring showed left hemisphere spiking independent of right hemispheric spikes indicating possible bilateral dysplasia associated with EPC [10]. The patient was placed on topiramate, clonazepam, phenytoin, vigabatrin, diazepam PRN, and was started on a ketogenic diet for seizure control. While anti-seizure medications helped reduce the intensity of movements, the patient now had periods of whole-body clonic jerking including the face that occurred approximately 20 times a day with corresponding generalized epileptiform discharges on EEG. Despite higher antiseizure medication, the patient had continued clonic jerks of

the left arm with no right hemispheric electrographic correlate on scalp EEG, consistent with persistent EPC. Video-EEG was also notable for nearly continuous (1/second) epileptiform discharges over the left centro-parietal region and a lack of organization (anterior-posterior gradient, reactive 6-Hz posterior-dominant rhythm (PDR) during wakefulness, or normal sleep architecture) over the left hemisphere but appropriate organization over the right hemisphere. Repeat MRI was significant only for post-surgical changes while MRI spectroscopy was unremarkable. Given elevated liver function tests and rare incidence of topiramate-induced hepatotoxicity, an underlying metabolic disorder was suspected and whole exome sequencing was performed. Having exhausted numerous trials of antiseizure medications, ketogenic diet initiation, and electrocorticography-guided surgical resection with minimal impact on her continuous large amplitude left arm jerks, experimental repetitive transcranial magnetic stimulation (rTMS) was scheduled.

Given the seizures involved the patient's left hand, rTMS of the contralateral (right) motor cortex was undertaken. To map the hand motor cortex, single pulse TMS (Nexstim 4.3 Navigated Brain Stimulation System, Helsinki, Finland) a 8x15 cm Figure-of-8 coil with biphasic pulses was placed over the motor cortex. Taking care to maintain the magnetic field polarity in orthogonal relationship to the orientation of the central sulcus, the right peri-Rolandic region was mapped using a 5 mm raster. Motor evoked potentials were recorded using real-time EMG from the left abductor pollicis brevis (APB) and adductor digiti minimi (ADM) muscles. Once the hotspot had been identified, the resting motor threshold was determined, using standard technique [11]. See Fig. 1.

Once the hand motor cortical hotspot had been identified, attention was turned toward targeting that region for therapy. The TMS coil was oriented orthogonal to the patient's right primary motor cortex hand-knob to apply an anterior-posterior (AP) current. The protocol was set at 10 Hz pulses at 50% maximal output with 10 pulses per burst and 1 burst per one-second train. The rTMS session lasted 20 minutes and totaled 1,200 pulses. The patient tolerated the procedure well with no provoked seizures visible on examination or detected by EMG. An image of select stimulation loci for her rTMS session are shown in Fig. 2.

After completion of rTMS, the patient experienced no clinical seizures for 2 days. During this time, the patient was kept on 0.5 mg clonazepam TID and topiramate 6 mg/kg twice daily that was started prior to rTMS. Thereafter, the seizures resurfaced as frequent, low amplitude jerks of the shoulder and elbow compared to the continuous high amplitude jerks seen pre-rTMS. Her physical examination also showed diffuse hypotonia and now right arm weakness. EEGs were taken 11 days before and 3 days after rTMS. Pre- and post-rTMS EEGs, both over normal backgrounds, showed the same rare electrographic correlate of the patient's semi-rhythmic clonic jerking of her left arm, likely as post-rTMS EEG was obtained only after resurfacing of her clinical seizures. See Fig. 3. Notably, post-rTMS EEG showed normal sleep architecture, anterior-posterior organization, and a reactive posterior-dominant rhythm over both hemispheres. FDG PET was performed to assess the extent of dysplasia and identified a focus of increased FDG uptake anterior to the prior resection cavity in the right temporal lobe, and slightly increased uptake in right temporal and parietal lobes compared to the left. Despite identification of a new unilateral structural lesion, in the 1-month period following rTMS the family expressed ongoing concern of worsening quality of life and preferred no further interventions, including TMS treatments. The patient was discharged 20 days after rTMS on clonazepam 0.75 mg three times daily.

Three months after discharge, at 12 months of age, the patient was readmitted for altered mental status in the setting of focal status epilepticus. Given the lack of response to high-dose

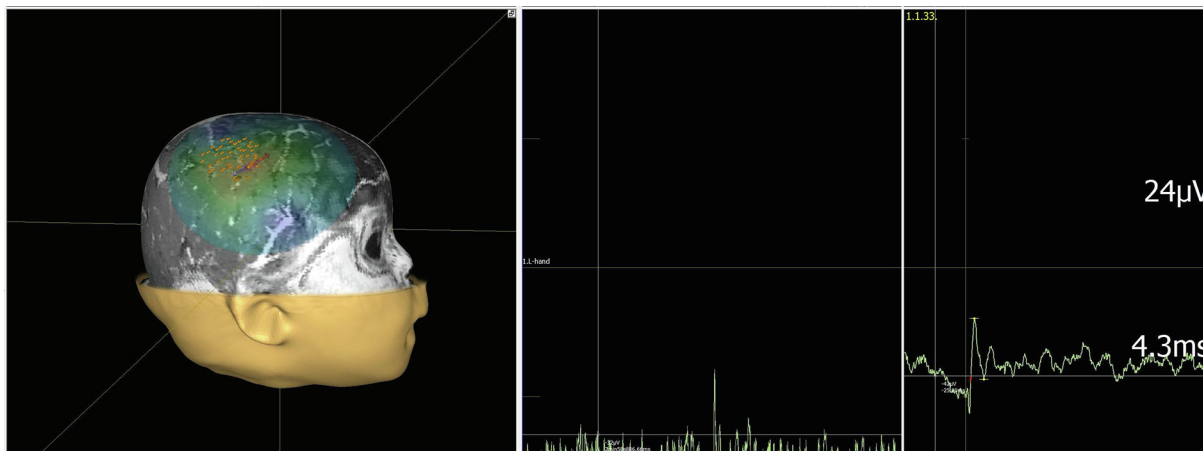


Fig. 1. Localizing transcranial magnetic stimulation. Transcranial magnetic stimulation was used to map cortical representation of the patient's right 'hand-knob' responsible for the left arm jerking. Resulting EMG (24 μ V, 4.3 ms delay) recorded from the patient's left hand is shown on the right.

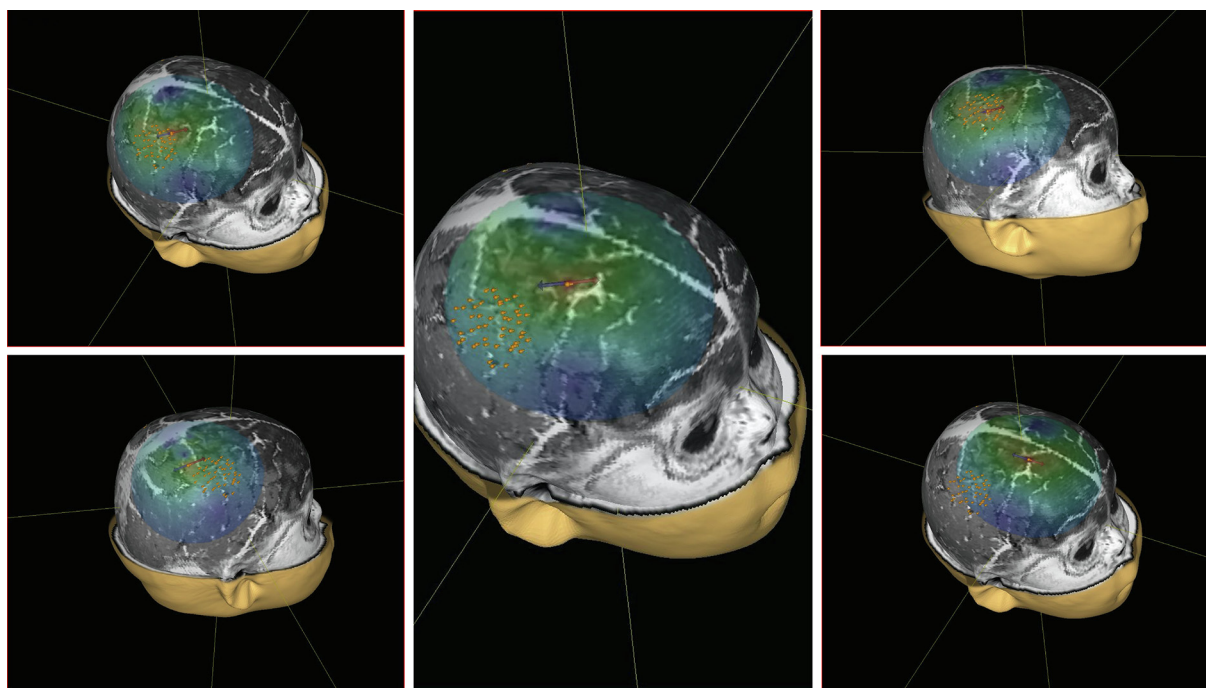


Fig. 2. rTMS targeting primary motor cortex 'hand-knob'. Sample of representative stimulation sites demonstrating orthogonal orientation of the figure of eight coil to approximate the cortical surface with a resultant anterior-posterior current and dipole field.

levetiracetam, fosphenytoin, and midazolam, the patient was intubated for a third time and was begun on pentobarbital. During this intubation, the patient coded and pentobarbital was discontinued. EEG showed near-continuous high amplitude right temporal/parietal spike-wave discharges. MRI showed restricted diffusion of cortex over right parietal, temporal, and occipital lobes. Clonic movements were bilateral and asynchronous and was no longer a surgical candidate.

At this time, in addition to the findings of FCD2A on brain pathology, exome sequencing revealed a POLG1 (genotype p.W748S/p.G848S) compound heterozygous mutation. Given the patient's steady decline despite maximal therapy, the family ultimately elected to pursue palliative care. She expired at home at 17 months of age.

Discussion

This is the first report on the efficacy of rTMS in interrupting ongoing EPC in an infant. At 10 months, to our knowledge, she is also the youngest patient reported thus far undergoing rTMS. Though single-pulse TMS has been used before as a diagnostic tool in infants as young as 3 months, to our knowledge, rTMS had not been utilized [8,12].

This case demonstrates that temporary relief from EPC can be achieved safely through rTMS even in infants as young as 10 months. Early rTMS for seizures largely employed low-frequency (1 Hz) rTMS protocols to depress cortical activity and decrease the risk of cognitive side effects [13]. Subsequently, researchers have successfully interrupted EPC with frequencies

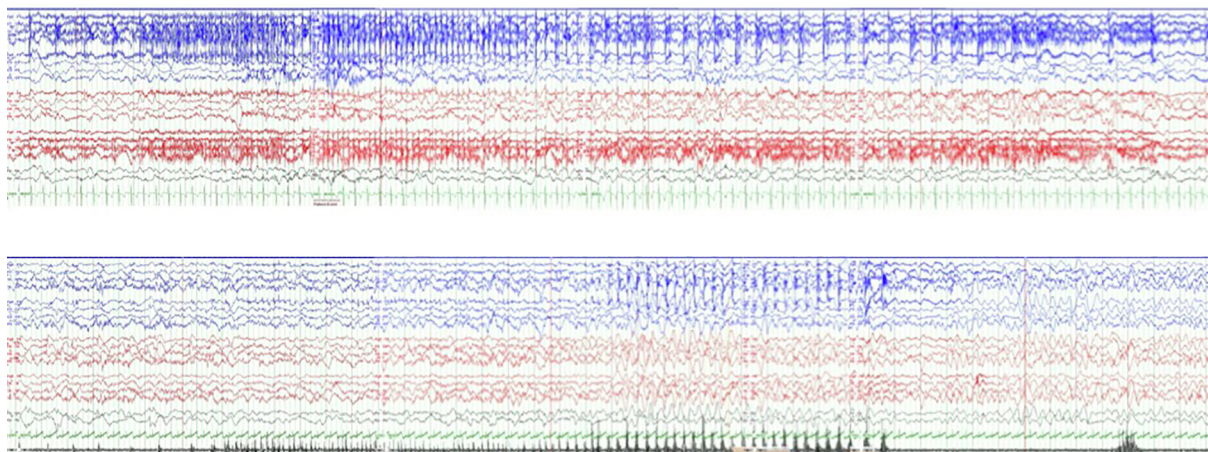


Fig. 3. EEG pre- and post-rTMS session. EEG recorded 10 days prior (above) and 6 days after rTMS session (below) demonstrating no significant difference though post-rTMS EEG was recorded following resurfacing of clinically observed seizures.

Table 1
rTMS protocols for treatment of epilepsy pars continua.

Reference (FA, year)	Age (yrs)	Etiology/Imaging	Coil Position	rTMS intensity	rTMS frequency	Train duration	No of trains	Outcome	Adverse events
<i>Prsent Case, 2022</i>	10 mo.	POLG1 mitochondrial mutation	Sz focus	50% MO	10 Hz	1 s	120	Clinical seizures stopped and resumed in 2 days, no further sessions	None
<i>Graff-Guerrero 2004¹⁰</i>	7	focal cortical atrophy on MRI	Sz focus	50% MO	20 Hz	2 s	15	Clinical seizures became intermittent and stopped in 24 h	None
<i>Graff-Guerrero 2004¹⁰</i>	11	focal cortical atrophy on MRI	Sz focus	128% MT	20 Hz	2 s	15	No clinical change, improved EEG	None
<i>Schrader 2005¹⁷</i>	48	normal MRI	Sz focus	100% MT	0.5 Hz	900 s	16	Clinical seizures decreased during rTMS, decreased further post-rTMS	None
<i>Misawa 2005¹¹</i>	31	cortical dysplasia	Sz focus	90% MT	0.5 Hz	200 s	1	Clinical seizures stopped, resumed in 2 months, stopped with repeat session	None
<i>Morales 2005¹¹</i>	8	neuronal ceroid lipofuscinosis	Sz focus	100% MO	6 Hz, then 1 Hz	6 Hz: 5 s 1 Hz: 600 s	3	No change	None
<i>Morales 2005¹¹</i>	16	perinatal stroke	Sz focus	76% MO	6 Hz, then 1 Hz	6 Hz: 5 s 1 Hz: 900 s	2	No change	Mild headache
<i>Agac 2021¹⁹</i>	33	autoimmune	NA	NA	NA	NA	NA	Complete seizure resolution of unclear duration	NA

ranging from 0.5 to 20 Hz [7–8,14–16]. See Table 1. In this case, trains of 10 Hz were chosen not to induce cortical depression, but to introduce a temporary lesion effect in the focal hand knob. Likewise, Kimiskidis et al. has shown that for rTMS to have an abortive effect (i.e. ictal rTMS), higher frequencies than those used for interictal seizure prevention (i.e. interictal rTMS) were required [17]. Furthermore, the practical difficulty of administering targeted stimulation in an infant prone to continuous movement prompted a higher frequency of stimulation to maximize dose. Of note, the 10 Hz per 2 second train is still well within the safety criteria for rTMS that are commonly accepted in clinical practice [18–19].

The choice of stimulation intensity based on resting motor threshold (RMT), or the minimum intensity required to induce a motor response in 50% of trials, is standard practice for determining TMS dose. RMT is typically different for children and adults, with children requiring higher motor thresholds than adults. This difference is theorized to be due to lower degrees of myelination and the technical difficulty of using a large coil on a small brain [20]. This inverse relationship makes designing safer TMS protocols for children more difficult, reinforcing the need and value of reported pediatric cases. Unfortunately, as additional rTMS therapy was declined in this case, the effect of repeated sessions is unclear

though one may suspect that any relief would have been temporary given the widespread cortical degeneration seen in POLG1 mutations [21].

We demonstrate rTMS can successfully interrupt ongoing seizures in refractory EPC in children as young as 10 months old. Notably, in this case, the diagnosis of a mitochondrial POLG mutation was unknown when rTMS was applied. Recently, in a different variant of POLG-mutation (A467T), ongoing EPC was successfully treated with transcranial direct current stimulation (tDCS) in an adolescent [22]. Most case series thus far have grouped results of pediatric and adult EPC, though the etiology of EPC is likely different in these two populations and theoretically, children may be better candidates than adults because of their capacity for cortical plasticity. More studies with a longer length of follow-up are needed on the safety and efficacy of rTMS treatment for refractory EPC in children.

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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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