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Case Report

Repetitive transcranial magnetic stimulation; A cost-effective and beneficial treatment option for refractory focal seizures

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We report a 24 year old man with a progressive epilepsy characterized by myoclonic, generalized tonic–clonic and increasing focal seizures, progressing into medication-refractory focal status epilepticus (recurrent seizures without full recovery of consciousness), ultimately controlled with repetitive transcranial magnetic stimulation (rTMS). He was an academically accomplished young man with normal cognitive and physical development. On day 1 of his course, at age 22, he had several myoclonic jerks followed by his first generalized convulsive seizure. At that time, he reported myoclonic jerks for five years prior. His next seizure occurred 8 months later, and was followed by several additional seizures over subsequent days, leading to intensive care unit (ICU) admission and treatment with multiple antiepileptic medications. On continuous EEG monitoring, seizures were seen arising independently from either the left or right occipital pole, before secondarily generalizing. As antiepileptic medications were added, the right occipital focus was controlled, but seizures continued to occur from the left occipital focus. Based on these findings, an atypical progressive myoclonic epilepsy (PME) was suspected. A comprehensive workup was performed (including CSF profile and cultures, paraneoplastic panel, rheumatologic markers, multiple MRIs, muscle biopsy, apocrine gland biopsy, skin exam, retinal exam, small bowel biopsy, celiac antibodies, and 70-gene comprehensive epilepsy panel), without any etiology found.

Over the next few months, his seizures persisted despite several admissions including intermittent treatment to burst suppression with IV anesthetics, trials of multiple conventional anti-epileptic drugs (AEDs), and high dose corticosteroids (Fig. 1a). He continued to have up to 30 nonconvulsive seizures per day (primarily from the left occipital region; Fig. 1b), nearly continuous left occipital interictal discharges, frequent myoclonus, weekly secondary generalized convulsions, and worsening mental status (likely due to the combination of frequent nonconvulsive seizures and high doses of multiple AEDs).

To better localize his seizure focus, he underwent a 256 electrode EEG with source estimation (EGI Inc.), which suggested that the majority of interictal discharges had a source medial to the O1 EEG electrode. Based on this information, the lack of response to pharmacologic treatment, and the reported benefit of rTMS in refractory status epilepticus (Thordstein and Constantinescu, 2012; Liu et al., 2013), approximately 14 months after his initial generalized convulsion and five months after his seizure frequency increased, we initiated rTMS therapy. rTMS was directed at the left occipital focus with the coil center immediately medial to O1 and the handle pointed towards T5 (Magstim Rapid^2, Figure-of-Eight D70 air-cooled coil system). He received 11 sessions of rTMS as a conscious (albeit confused) inpatient on the neurology floor over 10 days (2 sessions the first day, then 1 session every weekday after), with each session consisting of three 10-min trains of 1 Hz pulses at 95–100% resting motor threshold (1 min between trains; 1800 pulses total per session, 19,800 pulses total over the entire course; resting motor threshold defined as the minimum intensity evoking a thumb twitch). The number of electrographic seizures markedly declined in the first few days of treatment, reaching and maintaining zero seizures per day. The left occipital interictal discharges also markedly decreased (Fig. 1c and d). There were no adverse effects from rTMS treatment.

This improvement occurred while few significant antiepileptic medication changes were made (Fig. 1e). While zonisamide and lamotrigine were increased in the week before initiation of rTMS, he had been on zonisamide for four months prior without seizure control, and the dose adjustments before initiation of rTMS were made to maintain therapeutic levels of zonisamide after phenobarbital and phenytoin had been increased in the prior month. Zonisamide level one month prior to rTMS was 17.8 ug/mL, and ten days following rTMS was 20.6 ug/mL. Lamotrigine level was sub-therapeutic at 1.3 ug/mL two days after completion of rTMS.

After seizure control was achieved, his cognitive and motor status began to improve and myoclonic jerks significantly decreased, likely because of decreased seizures and subsequent gradual reduction in AEDs. Approximately one month after discharge, he was started on the low glycemic-index (modified Atkins) diet to help maintain seizure freedom. Although he remained seizure-free, based on prior reports of the time course of effectiveness of rTMS

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(Sun et al., 2012), he underwent empiric maintenance therapy (3 additional daily sessions, identical parameters to inpatient course) approximately one month after his initial session. Subsequently, further sessions of rTMS were deferred, as monthly outpatient EEGs showed relatively few interictal discharges (Fig. 1c). However, seven months after his initial treatment of rTMS and 21 months into his course, he had an increase in interictal activity on his EEG (without breakthrough seizures), in the setting of loss of ketosis; based on this, he underwent 5 additional rTMS sessions (with the prior stimulation parameters), with resulting improvement in his EEG. Nine months following his initial round of rTMS, he has maintained seizure freedom on lower doses of antiepileptic medications, and his overall clinical status has further improved. Follow-up EEGs continue to show fewer left occipital spikes (as well as occasional right occipital and generalized spikes and polyspikes), and there has been no further apparent progression of the underlying epilepsy syndrome.

The relative benefit of rTMS versus pharmacotherapy has never been studied in a formal clinical trial. Two small randomized trials have suggested that rTMS may have beneficial effects in medication-refractory focal epilepsy, with a decrease in seizures of 72–80.6% in selected patients (Fregni et al., 2006; Sun et al., 2012). Case reports have suggested that rTMS may also be beneficial in epilepsia partialis continua (Rotenberg et al., 2009), and more recently, in status epilepticus (Thordstein and Constantinescu, 2012; Liu et al., 2013). This anti-seizure effect is notably larger than in pharmacotherapy trials, which may be due to the fact that the low-frequency rTMS protocol used in this case is believed to induce synaptic plasticity via a long term depression-type mechanism, distinct from the pathways involved in AED mechanisms.

In this patient with a progressive epilepsy syndrome including medically refractory focal seizures, rTMS applied over the active epileptogenic focus was associated with rapid seizure control, stabilization of his progressively worsening epilepsy syndrome, and substantial improvement in cognitive and clinical status (including a return to academic pursuits).

The lack of large controlled clinical trials, poor insurance coverage, lack of technical expertise, and relatively high cost have limited the use of rTMS for treatment of epilepsy in most medical centers. In our particular patient, it was not only clinically effective, but also proved to be cost effective. In the six months leading up to his rTMS treatment, the cost of his medical care totaled $938,790.14 at our hospital alone. The cost of the 11 rTMS sessions totaled $4400, which represents only 0.46% of his total hospital bill and less than a single day in burst-suppression in the intensive care unit. Since discharge, he has remained seizure-free for over nine months, and with no additional hospitalizations.

Our report, in addition to other recent reported cases, suggests that rTMS may be clinically- and cost-effective in the treatment of select patients with refractory focal status epilepticus. Additionally, our case demonstrates effectiveness in patients with presumed multifocal epilepsy but with an active single focus. This

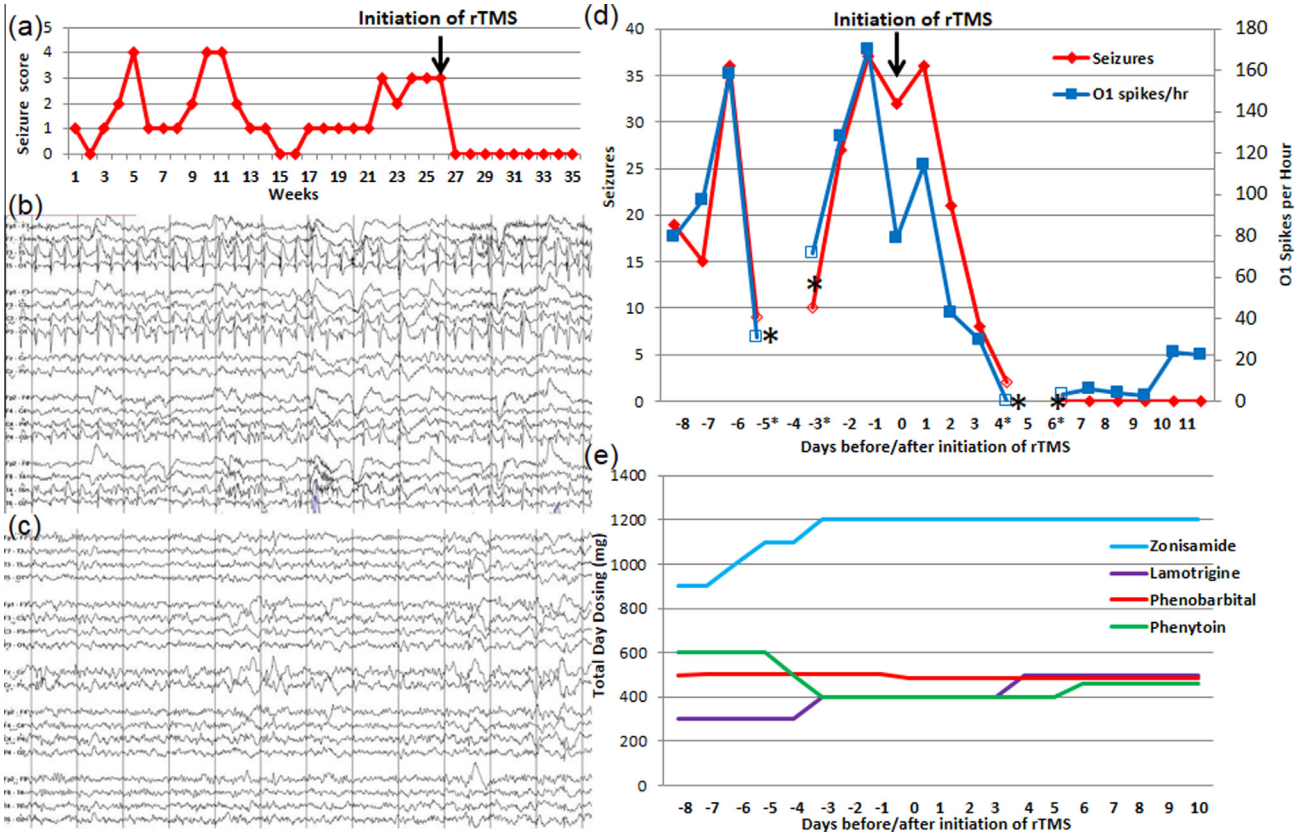

Fig. 1. Seizures, epileptiform activity, and antiepileptic medications at time of rTMS. (a) Weekly estimate of the seizure burden, sorted into the following categories: 0 = no seizures; 1 = at least 1 but <5 seizures; 2 = 5–14 seizures; 3 = 15+ seizures up to nonconvulsive status epilepticus; 4 = convulsive status epilepticus requiring ICU admission and anesthesia. (b) EEG seen on day 1 of rTMS therapy at a sensitivity of 7 μV demonstrating a left occipital seizure focus. (c) Interictal EEG at sensitivity of 7 μV, 29 weeks after initiation of rTMS, shows substantially fewer left occipital epileptiform discharges. (d) The line graph demonstrates the number of seizures per day based on 24 h continuous EEG monitoring at bedside. The graph demonstrates a dramatic decline in seizure burden following initiation of rTMS. On the days where no data point is present, there was either no EEG recording or there was too much electrode artifact to be adequately interpretable. The right hand '*y*' axis demonstrates spikes per hour of sampled EEG recordings (the first 5 min from each hour of recording), with O1 occipital spike detections accomplished by automated Persyst (beta version 12) spike detection algorithms. Asterisks (∗) indicate days with poor quality recordings with limited durations of interpretable data, and likely underestimation of both spikes and seizures. (e) A line plot of the total daily dosing of the different antiepileptic medications during the time of the rTMS sessions.

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non-invasive, novel treatment platform represents a potential new therapeutic option for patients with refractory focal epilepsy, without side effects of traditional AEDs. To confirm and extend these findings, larger randomized clinical trials are necessary.

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Conflict of interest: SV, STH, TP and MMS report no conflicts of interest. APL serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) and magnetic resonance imaging (MRI).

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