In-session seizures during low-frequency repetitive transcranial magnetic stimulation in patients with epilepsy

Alexander Rotenberg a,b,*, Erica Hyunji Bae a, Paul A. Muller a, James J. Riviello Jr. c, Blaise F. Bourgeois a, Andrew S. Blum d, Alvaro Pascual-Leone b

a Department of Neurology, Children's Hospital, Harvard Medical School, Boston, MA, USA
b Berenson–Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
c Department of Neurology, Texas Children’s Hospital, Houston, TX, USA
d Department of Neurology, Rhode Island Hospital, Alpert–Brown Medical School, Providence, RI, USA

Abstract

Low-frequency repetitive transcranial magnetic stimulation (rTMS) is emerging as a therapeutic tool for patients with intractable epilepsy. Although seizures during treatment have been reported as adverse events in some patients, the nature and severity of seizures that may be provoked by low-frequency rTMS in patients with epilepsy have not been extensively studied. Accordingly, this article documents seizures in patients (n = 5) with intractable epilepsy and average seizure frequency greater than one per day who underwent 1-Hz rTMS for seizure suppression. We report three observations in the present case series: (1) in each instance the in-session seizure was typical in semiology to the patient’s habitual seizures, (2) the duration of each documented seizure was either the same as or shorter than the patients’ baseline seizures, and (3) the overall neurological outcome on follow-up was not affected by the in-session seizures. More data will be required for valid conclusions with respect to safety and tolerability of low-frequency rTMS in patients with epilepsy, but it is noteworthy from our perspective that seizures during rTMS in this series were similar to the patients’ habitual seizures, occurred in patients with epilepsy with baseline seizure frequency exceeding one per day, and did not correlate with a poor neurological outcome or with absence of clinical response to rTMS.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is being explored as a therapeutic tool in some forms of epilepsy [1,2]. TMS is a noninvasive method for cortical stimulation that is based on principles of electromagnetic induction where the brain is stimulated by small intracranial electric currents that are generated by a strong fluctuating extracranial magnetic field [3]. In clinical management of epilepsy, the capacity of low-frequency (<1 Hz) rTMS to induce a lasting reduction in cortical excitability has been applied with some success to suppress seizures. In patients with epilepsy, the adverse events associated with rTMS are generally mild and short-lived [4]. These include headache, neck pain, and transient auditory symptoms. During low-frequency rTMS sessions, seizures were reported as a serious adverse event in one patient with epilepsy [5]. In that case, the seizures appeared similar to those the patient experienced at baseline. However, from these limited data, the nature and severity of seizures that may occur during low-frequency rTMS and their impact on the patient have not been well characterized. Accordingly, to supplement the available literature on the safety and tolerability of rTMS in patients with epilepsy, we describe in the present communication five patients with epilepsy who experienced one or more seizures at the time of low-frequency rTMS treatment.

2. Case series

All patients with intractable epilepsy (n = 5) (Table 1) were aged 12–22 and were treated in the Epilepsy Program at Children’s Hospital, Boston. The patients varied considerably with respect to seizure etiology and seizure frequency, which ranged from approximately 8 seizures per week to greater than 30 seizures per day at the time of treatment. All were referred by their primary epileptologist for rTMS after complete neurological evaluation. The risks and benefits of rTMS were discussed in detail, and verbal as well as written consent was obtained from the patient or his or her legal guardian in each case. Each patient had been scheduled to receive 1-Hz rTMS in 30-min daily sessions by an experienced operator. In
Table 1

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Baseline seizures</th>
<th>Seizure origin</th>
<th>Diagnoses</th>
<th>Medications</th>
<th>rTMS protocol</th>
<th>Total no. of TMS sessions (n)</th>
<th>No of seizures/duration</th>
<th>When in treatment block did seizure occur</th>
<th>Seizures recorded during rTMS sessions in patients with epilepsy ∗</th>
<th>Percent change in baseline seizure frequency</th>
<th>Seizures at first follow-up</th>
<th>Somnolence relative to baseline?</th>
</tr>
</thead>
<tbody>
<tr>
<td>12M</td>
<td>Cortical dysplasia</td>
<td>Simple motor</td>
<td>R frontal</td>
<td>LEV, LTG, GBP, CZP, MTX</td>
<td>1 Hz, 70% MT</td>
<td>100</td>
<td>15–30 min 2/day</td>
<td>30 min Circ</td>
<td>Session 1, &gt;5; between sessions 2 and 3</td>
<td>Reduced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12M</td>
<td>Unknown</td>
<td>Complex partial</td>
<td>R frontal</td>
<td>LEV, ZSM</td>
<td>1 Hz, 70% MT</td>
<td>100</td>
<td>30 min Fig-8</td>
<td>30 min Circ</td>
<td>Session 1, &gt;5; between sessions 2 and 3</td>
<td>Reduced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19F</td>
<td>Unknown</td>
<td>Complex partial</td>
<td>R frontal</td>
<td>LEV, ZSM</td>
<td>1 Hz, 70% MT</td>
<td>100</td>
<td>30 min Fig-8</td>
<td>30 min Circ</td>
<td>Session 1, &gt;5; between sessions 2 and 3</td>
<td>Reduced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21M</td>
<td>Cortical dysplasia</td>
<td>Complex partial</td>
<td>L.R. and 30 min Fig-8</td>
<td>MTX, VNS</td>
<td>No</td>
<td>1 Hz 100% MT</td>
<td>152</td>
<td>Session 5</td>
<td>Reduced</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23F</td>
<td>Unknown</td>
<td>Simple motor</td>
<td>L frontal</td>
<td>LEV, valproate, ZSM, zonisamide</td>
<td>1 Hz, 70% MT</td>
<td>100</td>
<td>30 min Fig-8</td>
<td>30 min Circ</td>
<td>Session 1, &gt;5; between sessions 2 and 3</td>
<td>Reduced</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a LEV, levetiracetam; MTX, methsuximide; OXC, oxcarbazepine; PHT, phenytoin; TPM, topiramate; VPA, valproate; ZSM, zonisamide; VNS, vagus nerve stimulator; Fig-8, figure-of-eight TMS coil; Circ, circular coil.

b The large number of seizures reflects the patient’s recurrent response to 1-Hz rTMS treatment, delivered in blocks of 10–15 daily sessions, and recurrent relapse, over a 3-year period.

c Precise number of sessions is not available as patient had a cluster of seizures during which convulsions were at times separated by seconds and distinction between individual seizures was not obvious.

d For three patients whose baseline seizure frequency was ≤5 per day, rTMS was resumed the following day after the witnessed seizure. For the remaining two patients who reported ≥10 seizures per day at baseline (one with seizures approximately every 5 min in the waiting room before the start of rTMS), the rTMS session was paused for the duration of the seizure, but then resumed after the patient returned to his or her neurological baseline. We based our decision to continue rTMS after each witnessed seizure in the two patients with very frequent seizures on experience with patients with epilepsy partialis continua (EPC) where rTMS delivered during ongoing seizures was well tolerated and did not lead to seizure exacerbation [6].

Each documented seizure was typical in appearance relative to the patient’s habitual seizures (Table 1). In no instance was the seizure longer than typical and indeed, it was considerably shorter than baseline in two patients. Seizures within any one 20- to 30-min rTMS session were distributed approximately evenly (range 6–29 min after start of session). We did not observe a tendency for seizures to cluster toward the end of a session, which would suggest a cumulative effect of individual stimuli. Similarly, within a typical 10- to 15-session block of daily rTMS treatments, seizures occurred throughout the block, without clustering in later sessions. Following the rTMS course, overall seizure frequency was not exacerbated in any of the five patients; seizure frequency was unchanged in two patients and reduced in three. One patient complained of a mild headache and ipsilateral ear pain after minute 23 during the second of 10 scheduled sessions (during which he did not have a seizure). No other adverse events were reported in this group.

3. Discussion

This communication is aimed to supplement the existing literature by documenting several seizures in patients with epilepsy undergoing low-frequency rTMS. Although conclusions with respect to safety and tolerability of the procedure cannot be drawn from these data, it is noteworthy from our perspective that seizures during rTMS in this short series occurred in patients with baseline seizure frequency exceeding one per day, and did not correlate with a poor neurological outcome or with absence of clinical response to rTMS. The observation in this series is similar...
to that in patients with epilepsia partialis continua, where seizure exacerbation or secondary generalization was not identified after rTMS [6]. The present cases are also consistent with published instances of seizures triggered by either single-pulse or low-frequency rTMS which were all similar to the patient’s habitual seizures [4,5,7,8]. In contrast, high-frequency (≥5 Hz) rTMS has resulted in a seizure that is distinct in origin from the patient’s typical seizures [9].

We anticipate that as the volume of patients with epilepsy who are treated with low-frequency rTMS increases [2,5,6,10,11], more data on in-session seizures will become available for analysis. Similarly, more information about rTMS-triggered seizures is likely to come from future trials in which novel rTMS protocols to suppress cortical excitability, such as continuous theta burst stimulation [12], are tested in epilepsy. We hope that these data will be considered in the context of safety guidelines for rTMS in specified patient populations. In the meantime, the warning of a possibility of seizure exacerbation as well as injury from a provoked seizure should remain as an element of the consent process.

Acknowledgments

A.R. is supported by Citizens United for Research in Epilepsy (CURE). A.R. and J.J.R. received support from the Siegel Family Foundation. A.P.L. was funded by NIH K24 RR018875 and the Benson–Allen Family Foundation.

References