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

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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.

Keywords

Repetitive transcranial magnetic; stimulation; Epilepsy; Safety; Seizure; Adverse event

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

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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 four cases, rTMS was delivered by a figure-8 coil, and in one patient with a broad seizure focus, rTMS was delivered by a circular coil. The coils were held tangentially to the scalp and with the handle pointing posteriorly. Coil placement in all patients was over the dominant seizure focus. The stimulating coil was positioned by visual inspection using the 10–20 international system of EEG electrode placement as a guide, and where the patient's initial seizure symptoms were simple motor, the coil position was adjusted until a limb movement similar to a habitual seizure was elicited. Stimulation intensities were either 100% resting motor threshold or 70% machine output (Table 1) using either a Mindcare MagPro X100 (Tonica, Farum, Denmark) or a Magstim Rapid (Magstim Company, Whitland, UK) magnetic stimulator, each set to deliver biphasic stimuli. rTMS sessions were scheduled generally in blocks of 10–15 on consecutive weekdays; however, in some instances the patient's clinical picture or scheduling conflicts required missing one or more sessions of the scheduled block. The patients' anticonvulsants were not changed during treatment. A board-certified neurologist was present and available for emergent patient management in each case. Follow-up information was obtained by the TMS operator as well as the primary epileptologist by office visit or by personal communication with the patient or guardian.

In every instance, rTMS was paused as the patient experienced a seizure. For three patients whose baseline seizure frequency was $\leqslant 5$ per day, rTMS was resumed the following day after the witnessed seizure. For the remaining two patients who reported $\geqslant 10$ 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 epilepsia 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 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.

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Table 1

Seizures recorded during rTMS sessions in patients with epilepsy[a].

Age/sex	Diagnosis	Baseline seizures	Seizure origin	Medications[b]	Prior epilepsy surgery?	rTMS protocol	Total no. of TMS sessions (*n*)	No. of seizures/duration	When in treatment block did seizure occur	Seizure typical relative to baseline?	Seizures at first follow-up
12/M	Cortical dysplasia	Simple motor 15–30 min 2/day	R frontal	OXC LEV PHT TPM	Yes	1 Hz 70% MO 30 min Fig-8	11	Simple motor (L thumb clonic adduction; *n* = 1) 5 min	Session 4	Yes	Reduced
12/M	Unknown	Simple motor 15–20 s 2–4/day	R frontal	OXC LEV ZSM Sertraline	Yes	1 Hz 100% MT 30 min Fig-8	10	Simple motor (tonic L arm abduction; *n* = 2) 3–4 s	Sessions 4, 7	Yes	Unchanged
19/F	Unknown	Complex partial 10 s to 20 min 8/week	L, R, and bifrontal	ZSM LEV LTG GBP CZP MTX VNS	No	1 Hz 100% MT 30 min Circ	152[c]	Complex partial or primary generalized (unresponsive forward stare, *n* = 1) 10 s	Session 5	Yes	Reduced
21/M	Cortical dysplasia	Complex partial 20–60 s 10 to >30/day	R frontal	PHT OXC VNS	Yes	1 Hz 70% MO 30 min Fig-8	35	Complex partial (R leg or R arm shaking, then secondary generalization; *n* > 15[d]) 10–30 s	Session 1, >5; between sessions 2 and 33 (1–4/session)	Yes	Reduced
23/F	Unknown	Simple motor 10–15/day	L fronto-parietal	VPA LEV PGB TPM	No	1 Hz 70% MO 30 min Fig-8	10	Simple motor (R hand clenching; *n* = 3) 2–4 s	Sessions 2, 8, 10	Yes	Unchanged

[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] Whether patient had a VNS implanted is indicated in the column.

[c] The large number of sessions 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.

[d] Precise number of seizures 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.