



Letter to the Editor

Can low-frequency repetitive transcranial magnetic stimulation precipitate a late-onset seizure in a stroke patient?

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) therapy is being increasingly used in various neuropsychiatric conditions. The literature suggests accidental induction of seizure as the most serious adverse effect of rTMS. Several incidents of seizure induction were reported before the establishment of safety guidelines for TMS parameters (Wassermann, 1998; Rossi et al., 2009). However, after the publication of updated safety guidelines (Rossi et al., 2009), only two cases have been reported, where rTMS was found to be within the safety framework. One case was reported in a patient with no predisposing condition (Edwards et al., 2011), whereas the other had multiple risk factors (Gómez et al., 2011). Both the patients were receiving high-frequency rTMS. Low-frequency rTMS has been postulated to be beneficial in reducing the frequency of seizures in patients having epilepsy (Bae et al., 2007). To the best of our knowledge, no case of seizure has been reported to be associated with low-frequency rTMS, since the updated guidelines were published.

In this article, we report a case of late seizure precipitation in a post-stroke patient receiving low-frequency rTMS.

2. Case report

Mr. IA, a 48-year-old male suffered an ischemic infarct of the middle cerebral artery, involving the left frontal lobe and left operculum, 4 months ago. He reported slurred speech and right-sided hemiplegia, which gradually improved to some extent over the next few months. He had been compliant with the medication as advised and undergoing physiotherapy.

The patient was diagnosed with type II diabetes mellitus 6 years ago, and he was initiated on glimepiride 3 mg and metformin 1 g, one tablet each daily. He was operated for deep-vein thrombosis about 1.5 years ago. He developed foot drop 6 months ago, after wound debridement of the right lower limb infected with gangrene. A 2D echocardiogram of the patient showed a severe left ventricular dysfunction, ejection fraction (25–30%), moderate mitral regurgitation, and akinetic left anterior descending and right coronary artery territory. He was taking atorvastatin 20 mg and warfarin 2 mg one tablet each daily, together with antidiabetic medication.

The patient never reported any loss of consciousness, altered sensorium, or seizure in the past. There was no family history of seizure or other neuropsychiatric disorders.

The patient was recruited to an ongoing randomized control study to assess improvement in motor and cognitive functioning

and disability. The study was also conducted to observe changes in BDNF levels of a patient with acute ischemic stroke receiving real or sham rTMS and undergoing physiotherapy at the same time. Mr. IA was recruited in the real rTMS arm.

We used a Magstim Rapid² TMS device with a 70-mm figure-of-eight air-film coil delivering single pulses. The resting motor evoked potential (MEP) was determined using an electromyogram, recording from the left-sided abductor pollicis brevis in accordance with the International Federation of Clinical Neurophysiology (IFCN) recommendations (Rossi et al., 2009). The resting motor threshold (RMT) was defined as the minimum stimulus intensity that produced an MEP (about 50 µV in five out of 10 trials) at rest. The RMT was 82% of the maximum stimulator output. The simulation parameters used were 1-Hz frequency, stimulation intensity at 110% motor threshold, 10-s train duration, 75 trains per session, and 45-s inter-train interval (total 750 pulses). The coil was placed over F4 of the 10–20 electrode system, which is thought to correspond to the right dorsolateral prefrontal cortex. Mr. IA underwent four sessions of real rTMS (including a mapping session) daily in the afternoon with the same parameters.

About 18 h after the fourth session and about 1 h after waking from sleep in the morning, Mr. IA developed an episode of generalized tonic-clonic movement of the body with deviation of head, clenching of teeth, and bleeding from mouth lasting for about 40 s, followed by loss of consciousness. After regaining consciousness, he remained disoriented for few minutes before completely regaining his faculties. There was a large laceration on the left side of the tongue. He did not experience any bowel or bladder incontinence, and no metabolic derangements were observed on biochemical investigations (including blood glucose levels).

Electroencephalography (EEG) revealed a background activity consisting of 8–9-Hz, 30–50-µV posterior dominant alpha activity and the presence of rhythmic slowing delta waves of 2–3 Hz and 15–20 µV in the fronto-central region of the left hemisphere, suggesting abnormal findings with left fronto-central slowing. Computerized tomography (CT) scan of the brain did not reveal any newer changes.

The patient was initiated on phenytoin 300 mg once daily after neurology consultation, and further rTMS was withheld. Subsequently, he reported having another seizure after 2 months, when he missed the phenytoin dose.

3. Discussion

Almost all the TMS-induced seizures reported till date are associated with high-frequency rTMS, during or immediately after stimulation. However, few cases have been reported on seizures associated with low-frequency TMS (Tergau et al., 1999; Theodore et al., 2002; Schrader et al., 2005; Nowak et al., 2006) or presented late after stimulation (Homberg and Netz, 1989;

Kandler, 1990). All these cases were reported before the updated safety guidelines were published (Rossi et al., 2009).

Researchers suggest the use of low-frequency rTMS in the management of epilepsy with varying results (Bae et al., 2007; Sun et al., 2012), and it has also been safely used in stroke patients (Carey et al., 2008). In patients with epilepsy treated with low-frequency rTMS, it has been observed that the in-session seizures are similar in semiology to the patient's habitual seizures, equal to or shorter in duration than baseline seizures, and they do not affect the overall neurological outcome or clinical response to rTMS (Rotenberg et al., 2009).

Several mechanisms have been proposed explaining induction of seizures with TMS, such as excessive activation of pyramidal cells, cortical spread of excitation to neighboring neurons, and/or overwhelming of inhibitory mechanisms (Daskalakis et al., 2005). It has been speculated that an enduring change in neural activity may be established by TMS, particularly in repetitive type rather than single-pulse TMS (Anand and Hotson, 2002).

The effect of low-frequency rTMS has been shown to modify depending on the preexisting state of cortical excitation. It was observed that the application of transcranial direct current stimulation (tDCS) to change the baseline motor cortex excitability before administering 1-Hz rTMS displayed a homeostatic effect: rTMS reduced corticospinal excitability when prior anodal tDCS increased it ("facilitatory preconditioning"), whereas the rTMS increased corticospinal excitability when prior cathodal tDCS decreased cortical excitability ("inhibitory preconditioning") (Siebner et al., 2004). Studies also suggest that the aftereffects of tDCS are different between patients with stroke and healthy individuals. Although both anodal and cathodal tDCS increased the affected motor cortex excitability in patients with stroke, they increased and decreased the excitability in healthy individuals, respectively (Suzuki et al., 2012). A similar phenomenon has been observed in patients with juvenile myoclonic epilepsy (JME) depending upon the plasma concentration of valproate. A reduction of the corticospinal excitability was observed after applying 1-Hz rTMS in JME patients with low plasma concentration of valproate, whereas high plasma concentration of valproate resulted in an opposite effect, that is, an increase in the corticospinal excitability (Fregni et al., 2006).

Low-frequency rTMS was delivered to the hemisphere contralateral to the ischemic lesion in the patients. Another hypothesis could be that low-frequency rTMS could have suppressed an inhibitory influence from the intact, right hemisphere to the hyperexcitable, damaged left hemisphere.

Another reason for the increased risk of induction of seizure may be ascribed to a falsely large MEP generation during mapping, leading to a stronger-than-needed protocol intensity threshold value (Edwardson et al., 2011).

The presence of generalized tonic-clonic movement of body, clenching of teeth, tongue laceration, head deviation, loss of consciousness, and a postictal state in the patient indicates this episode was a generalized tonic-clonic seizure. The EEG findings further support the observation. No new changes in the CT brain scan were observed, refuting any structural cause. Family-tree assessment did not reveal any significant association of seizure with the family. The metabolic parameters were within normal limits, including blood glucose levels, excluding the possibility of hypoglycemia-induced seizure, as he was known to have diabetes. However, considering the delay of seizure onset relative to rTMS and the occurrence of the subsequent second seizure, the possibility that this was a perfect coincidence cannot be excluded, given also the relatively high rate of late seizures (3–67%) in post-stroke patients (Camilo and Goldstein, 2004). This demonstrates that, in

future, one should be careful toward late emergence of seizure in stroke patients treated with low-frequency rTMS.

Acknowledgment

None.

Conflict of interest: None of the authors have potential conflicts of interest to be disclosed.

References

Anand S, Hotson J. Transcranial magnetic stimulation: neurophysiological applications and safety. *Brain Cogn* 2002;50:366–86.

Bae EH, Schrader LM, Machii K, Alonso-Alonso M, Riviello Jr JJ, Pascual-Leone A, Rotenberg A. Safety and tolerability of repetitive transcranial magnetic stimulation in patients with epilepsy: a review of the literature. *Epilepsy Behav* 2007;10:521–8.

Camilo O, Goldstein LB. Seizures and epilepsy after ischemic stroke. *Stroke* 2004;35:1769–75.

Carey JR, Evans CD, Anderson DC, Bhatt E, Nagpal A, Kimberley TJ, Pascual-Leone A. Safety of 6-Hz primed low-frequency rTMS in stroke. *Neurorehabil Neural Repair* 2008;22:185–92.

Daskalakis ZJ, Christensen BK, Fitzgerald PB, Fountain SJ, Chen R. Reduced cerebellar inhibition in schizophrenia: a preliminary study. *Am J Psychiatry* 2005;162:1203–5.

Edwardson M, Fetz EE, Avery DH. Seizure produced by 20 Hz transcranial magnetic stimulation during isometric muscle contraction in a healthy subject. *Clin Neurophysiol* 2011;122:2326–7.

Fregni F, Boggio PS, Valle AC, Otachi P, Thut G, Rigonatti SP, Marcolin MA, Fecteau S, Pascual-Leone A, Fiore L, Valente K. Homeostatic effects of plasma valproate levels on corticospinal excitability changes induced by 1 Hz rTMS in patients with juvenile myoclonic epilepsy. *Clin Neurophysiol* 2006;117:1217–27.

Gómez L, Morales L, Trápaga O, Zaldívar M, Sánchez A, Padilla E, Grass D, Díaz A, Morales H. Seizure induced by sub-threshold 10-Hz rTMS in a patient with multiple risk factors. *Clin Neurophysiol* 2011;122:1057–8.

Homberg V, Netz J. Generalised seizures induced by transcranial magnetic stimulation of motor cortex. *Lancet* 1989;2:1223.

Kandler R. Safety of transcranial magnetic stimulation. *Lancet* 1990;335:469–70.

Nowak DA, Hoffmann U, Connemann BJ, Schonfeldt-Lecuona C. Epileptic seizure following 1 Hz repetitive transcranial magnetic stimulation. *Clin Neurophysiol* 2006;117:1631–3.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009;120:2008–39.

Rotenberg A, Bae EH, Muller PA, Riviello Jr JJ, Bourgeois BF, Blum AS, Pascual-Leone A. In-session seizures during low-frequency repetitive transcranial magnetic stimulation in patients with epilepsy. *Epilepsy Behav* 2009;16:353–5.

Schrader LM, Koski L, Nuwer MR, Engel J, Stern JM. Therapeutic efficacy of low frequency repetitive transcranial magnetic stimulation (LF-rTMS) stereotactically directed at a well-defined epileptogenic region (ER). Presented at: American Epilepsy Society and American Clinical Neurophysiology Society Joint Annual Meeting; 2005.

Siebner HR, Lang N, Rizzo V, Nitsche MA, Paulus W, Lemon RN, Rothwell JC. Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex. *J Neurosci* 2004;24:3379–85.

Sun W, Mao W, Meng X, Wang D, Qiao L, Tao W, Li L, Jia X, Han C, Fu M, Tong X, Wu X, Wang Y. Low-frequency repetitive transcranial magnetic stimulation for the treatment of refractory partial epilepsy: a controlled clinical study. *Epilepsia*. 2012;53:1782–9.

Suzuki K, Fujiwara T, Tanaka N, Tsuji T, Masakado Y, Hase K, Kimura A, Liu M. Comparison of the after-effects of transcranial direct current stimulation over the motor cortex in patients with stroke and healthy volunteers. *Int J Neurosci* 2012;122:675–81.

Tergau F, Naumann U, Paulus W, Steinhoff BJ. Low-frequency repetitive transcranial magnetic stimulation improves intractable epilepsy. *Lancet* 1999;353:2209.

Theodore WH, Hunter K, Chen R, Vega-Bermudez F, Boroojerdi B, Reeves-Tyer P, Werhahn K, Kelley KR, Cohen L. Transcranial magnetic stimulation for the treatment of seizures: a controlled study. *Neurology* 2002;59:560–2.

Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the international workshop on the safety of repetitive transcranial magnetic stimulation, June 5–7 1996. *Electroencephalogr Clin Neurophysiol* 1998;1:1–16.

Nand Kumar

Department of Psychiatry, All India Institute of Medical Sciences, New Delhi, India

M.V. Padma Srivastava

*Department of Neurology, All India Institute of Medical Sciences,
New Delhi, India*

Rohit Verma

*Department of Psychiatry, All India Institute of Medical Sciences,
New Delhi, India*

Email address: rohit.aiims@gmail.com

Hina Sharma

*Department of Neurology, All India Institute of Medical Sciences,
New Delhi, India*

Tamonud Modak

*Department of Psychiatry, All India Institute of Medical Sciences,
New Delhi, India*