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Seizure induced by repetitive transcranial magnetic stimulation for central pain: Adapted guidelines for post-stroke patients

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Dear Editor

We report the following TMS-related seizure:

Case description

The patient was a 65-year-old woman who had a right-hemispheric ischemic stroke (middle cerebral artery territory, see Fig. 1) in September 2015. The etiology of the stroke is still undetermined to this day. Except for the brain lesion, the patient had no risk factor for epilepsy. She had no previous seizure history even during the acute post-stroke phase, nor did she have a family history of epilepsy. Her daily treatment was composed of: fluoxetin 20mg, atorvastatin 40mg, acetylsalicylic acid 160mg, gabapentin 800mg.

She was referred for rTMS because she suffered from pharmacoresistent neuropathic pain in her left arm for a year. Indeed, tramadol, pregabaline, gabapentin, lidocaine patches and transcutaneous electric stimulation had been unsuccessful. Past medical history did not contain any rTMS contraindications and no additional risk factors, i.e. sleep deprivation, change in medication, illegal drug use, or doses of caffeine, were noticed the day of rTMS.

Course of treatment

In January 2017, the patient was given one unique session of rTMS following a recommended procedure. Indeed, motor evoked potentials were recorded from the abductor pollicis brevis muscle, using surface electrodes (Neuroline, Ambu®). Signals were sampled at 10kHz, amplified (1000 gain), filtered (20–1000Hz) using LabChart7.3.7 software (ADInstrument). Magnetic biphasic pulses were delivered using a 75mm figure-of-eight coil (Cool-B65 Butterfly Coil, MagVenture®) connected to a MagPro X100unit. The coil was oriented to induce posterior-to-anterior current flow in M1. Resting motor threshold (RMT) evaluation was assessed by using standard protocols [1]. Muscle hot-spot was memorized through neuronavigation with TMS Navigator Software (Localite®) based on the anatomical MRI of the patient. Safety guidelines were followed [2]. A first session of 1200 pulses was applied at 10Hz, with an amplitude 10% lower than the RMT (90% RMT), inter-train interval = 5000 ms, train duration = 5seconds/50pulses.

The seizure occurred 20seconds after the onset of the fourth rTMS train applied on the right hemisphere. The patient was sitting in a comfortable chair in a dedicated room in the Neurology and Electrophysiology department. Few seconds before seizure, the patient reported a headache, then the operators noted a vocalization, a loss of contact with her eye and head turning to the left. This focal seizure was followed by a generalized tonic-clonic epileptic seizure that lasted for 4minutes and which was spontaneously resolved without any medication. rTMS was stopped as soon as the patient reported a headache. The patient was post-ictal for 20minutes, but no tongue-biting or other physical trauma was observed. The neurological examination and mental status exam were performed after the occurrence by a doctor in Physical and Rehabilitation Medicine (MC) and were similar to the usual neurological status of the patient (left hemi paresis with left visual and auditory neglect). Blood samples (i.e. serum electrolytes, blood count, C-reactive protein) were normal. A routine clinical EEG recording (Fig. 1B) performed 18 hours after the epileptic seizure only showed slow delta waves located in the area of the brain lesion without any specific abnormality related to epilepsy. The patient stayed in the hospital for one day for clinical monitoring. Other triggering factors for epileptic seizures were not found. She had no sequel and returned back home without additional drug prescription. Consequently, we decided to avoid further use of rTMS on this patient. We planned to discuss this case internally in order to find other way of care and treatments.

Discussion

We reported a patient who exhibited a focal seizure secondary generalized during a rTMS session for post-stroke central pain after a large ischemia in the right frontoparietal region. Such a case is very rare in the context of rTMS. Indeed, only 2 seizures have been reported among all case reports and more than 30 published studies of rTMS for pain [3,4] since safety recommendations were published [2]. These studies did not respect the recommendation for the maximum duration of pulses for individual trains of 10Hz rTMS (i.e. 5seconds/50pulses [2]). The present letter reports the third case of rTMS-related seizure, and the first one after a stroke in a patient who had no history or risk factor of epilepsy. However, the inter-train interval was short (5seconds) despite compliance

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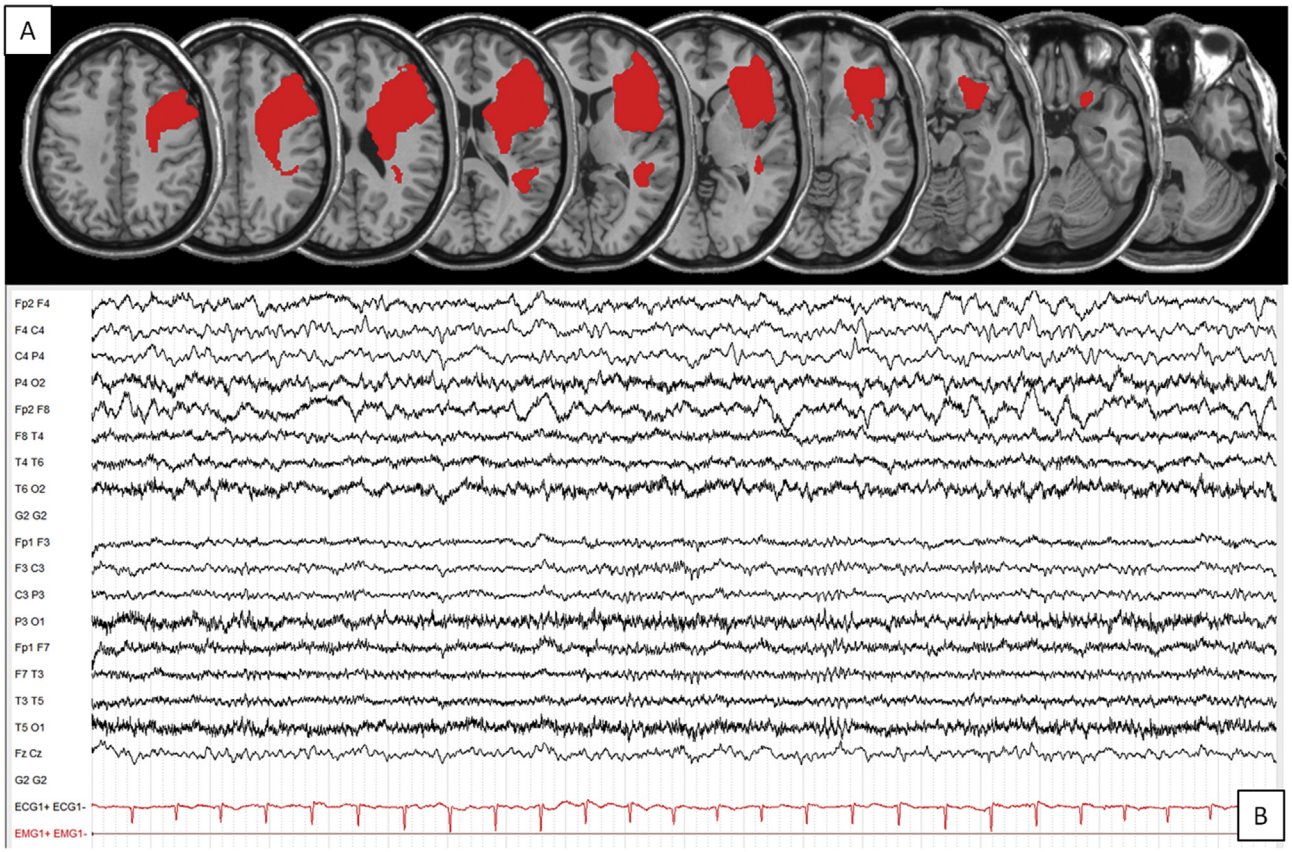

Fig. 1. Lesion and EEG pattern of the patient. A) Reconstruction of the brain lesion in MNI space, on the territory of the right middle cerebral artery. B) EEG pattern longitudinal analysis with slow waves on the right hemisphere, but without epileptic activity.

with the recommendations, especially in the case of a post-stroke patient. While guidelines reported that an inter-train interval of 5seconds is safe for an intensity of 100% of RMT [2], the inter-train interval used in clinical trials was at least 25seconds for post-stroke patients, and 50seconds for almost all studies (see review of Jin et al., 2015 [5]). High-frequency rTMS facilitates cortical excitability but may increase seizure risks [6]. Stroke and other brain lesions are thus described as relative counter indications to high-frequency rTMS, even though this treatment is paradoxically used largely for central pain related to stroke [7] and its efficacy is supported by strong evidence [8]. Faced with this dilemma between rTMS efficacy and seizure risk for stroke patients, future guidelines and trials should take this risk into account and recommend another scheme for high-frequency rTMS sessions after a brain injury in order to prevent this adverse effect. Indeed, altered electrical tissue properties have been shown to perturb the stimulating currents during TMS [9]. The effects of altered neural tissue properties might be taken into account to avoid contradictory outcomes in this pain treatment [10]. Hence, and based on previous studies without adverse effect [5], we recommend the following parameters for rTMS in stroke patients: the intensity of stimulation should not exceed 80% of the RMT at 20Hz, 90% at 10Hz, and 100% at 5Hz, the total number of pulses should not exceed 1000 and 50 pulses by train, and the inter-train interval should be at least 50seconds. Iterative sessions could be a solution to limit highest stimulation parameters.

To conclude, the present case report suggests that guidelines on the use of high-frequency rTMS should be adapted for post-stroke patients, particularly since this tool offers itself as an efficient treatment of central pain.

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