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Effects of continuous theta burst transcranial magnetic stimulation on cortical excitability in patients with idiopathic generalized epilepsy

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ABSTRACT

Introduction: Transcranial magnetic stimulation (TMS) is a noninvasive technique for investigating cortical physiologic functions in the brain. In this study, the effects of continuous theta burst stimulation (cTBS) on motor evoked potential (MEP) parameters in patients with idiopathic generalized epilepsy (IGE) were investigated.
Materials and methods: Fifteen patients with IGE were included. Motor threshold (MT) and cortical silent period (CSP) were determined before cTBS application. Next, cTBS was applied to the dominant (left) hemisphere M1 hand area as the first application. After 1 day, cTBS was applied first to the left M1 hand area and then to the right lateral cerebellar area as the second application. Parameters were again determined after the applications.
Results: There was no difference in resting MT values before and after cTBS application ($p > 0.05$). Although CSP increased after stimulation ($p < 0.05$), it was not significantly different between applications ($p > 0.05$).
Conclusion: For patients with epilepsy, cTBS is a safe technique when applied at a low intensity. The inhibitory effect of cTBS, a noninvasive technique, on cortical excitability in patients with IGE was determined using MEP parameters. The effect lasted at least 1 h. To our knowledge, this is the first study to assess the effect of cTBS on cortical excitability in patients with IGE. Our findings indicate that cTBS decreases cortical excitability in patients with IGE.

1. Introduction

Epilepsy is defined as a clinical condition that is characterized by two or more recurrent and unprovoked epileptic seizures. An epileptic seizure is a temporary clinical condition that emerges because of uncontrolled, excessive, and abnormal discharges of cortical neurons, which is caused by increased, rapid, and local electrical discharges in the gray matter. In neurological practice, epilepsy is the second most frequently observed chronic disease after cerebrovascular diseases, and its etiopathogenesis has not been completely understood. Its prevalence is 0.5%–1% [1].

Epilepsy is divided into subgroups on the basis of whether the seizures originate from a focus or occur in a generalized manner. Most generalized epilepsies are idiopathic generalized epilepsies (IGEs) [2]. In general, two primary characteristics describe the epileptiform activity: hyperexcitability and hypersynchrony of multiple neurons. Diffuse cortical hyperexcitability has been hypothesized to be the primary pathophysiological mechanism in IGE [3].

Transcranial magnetic stimulation (TMS) has been used for investigating cortical excitability hypothesis in patients with epilepsy [4]. Theta burst stimulation (TBS) is a complex stimulation known as continuous TBS (cTBS) or intermittent TBS depending on the interval duration between successive stimulations [5]; cTBS application to the motor cortex of healthy individuals reduced M1 excitability, and because the cerebellum plays a role in sensorimotor adaptation, cerebellar cTBS application decreased M1 excitability in healthy individuals [6,7].

Motor evoked potential (MEP) is an indicator of the integrity of the corticospinal tract and normal excitability of alpha motor neurons by neurons in the motor cortex [4]; MEP is the best-studied parameter for assessing the excitatory effect of TMS [8]. Descending corticomotor neurons are stimulated transsynaptically because of the activation of excitatory cortical interneurons with TMS [9].

The motor MEP amplitude is a measure of cortical excitability. Stimulus intensity is considerably affected by variables such as voluntary muscle contraction before the stimulus and magnetic coil diameter [10]. Motor threshold (MT) is one of the most frequently used TMS parameters in cortical excitability. It represents the excitability of the motor system at the cortical or spinal level. The threshold value varies from person to person, and when parameters such as the cortical silent period (CSP) are studied, stimulus intensity must be standardized

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Table 1
Demographic features of the patients.

Patient number	Gender	Age	Age of the onset	Seizure frequency (n/year)
1	Male	22	19	12
2	Male	21	14	12
3	Male	21	15	2
4	Male	23	18	12
5	Male	23	20	24
6	Male	22	10	18
7	Male	20	15	6
8	Male	24	17	18
9	Male	20	14	2
10	Male	24	19	18
11	Male	23	16	12
12	Female	18	11	48
13	Male	22	17	2
14	Male	24	20	6
15	Male	23	17	18

according to the threshold value. When the motor cortex is stimulated while the target muscle is contracted, a silent period is observed in the trace after the MEP activity, and then electromyography (EMG) activity continues. This period is called CSP. The duration of CSP increases with an increase in the stimulus intensity [11–13].

In this study, the effect of cTBS application to the left (dominant) hemisphere M1 area and then to the right cerebellar area on MT and CSP amplitudes were examined to assess cortical excitability in patients with IGE.

2. Methods and materials

2.1. Participants

Right-handed patients diagnosed with IGE were examined. The exclusion criteria were the presence of intracranial lesions that can cause epilepsy, another accompanying neurological disease, abnormal findings in the neurological examination, pregnancy, use of antiepileptic drugs (AEDs) or any drug that affects the central nervous system in the previous month, presence of a cardiac pacemaker, presence of an intracranial metal implant, nonepileptic case suspicion, and not wanting to participate in the study. The detailed history of the patients was obtained, and neurologic and systemic examinations were performed. Cerebral imaging (brain magnetic resonance imaging) studies were conducted. The study was approved by the local ethics committee, and informed consent for experimentation was obtained from all patients.

2.2. TMS and electromyographic techniques

Stimulation was performed using the Magstim Rapid (Magstim Company Ltd. Whitland, Dyfed, UK) TMS device. Recordings were obtained using the Medelec (VIASYS Healthcare Madison WI, USA) EMG device. Micromed 10-mm waterproof gold-plated disc electrodes were used for recording. The stimulator was connected to the eight-shaped coil (outer wing with 9 cm in diameter). The coil was placed in an optimal position at a 45-degree angle to the left hemisphere to obtain MEP from the contralateral abductor pollicis brevis (APB) muscle. We first defined the hand motor area of M1, where stimulation evoked the largest MEP from the contralateral APB muscle [14]. The best location to stimulate the hand area (M1 hand) was identified.

Initially, the resting MT (rMT) was detected. The lowest stimulus intensity that provides an acquisition of 50-microvolt MEP in 5 of 10 stimulations was accepted to be rMT. The lowest stimulus intensity that provides an acquisition of 200-microvolt MEP in 5 of 10 stimulations, ensuring that patients contracted the APB muscle at 20%–30% of maximum voluntary muscle contraction, was accepted to be active MT (aMT). Next, the patients were asked to contract their ABP muscle at the maximum level, and CSP was obtained by stimulating the M1 hand area at an intensity of 150% of rMT. The stimulus intensity was kept constant to ensure standardization. Cortical silent period was obtained three times, and the average CSP duration was calculated [15,16].

2.3. Experimental design

After the above evaluations, cTBS was applied to the left M1 hand area of the patients. In total, 600 stimulations were performed. As described by Huang, cTBS comprises three-beat bursts at a frequency of 50 Hz that was repeated at 200-ms intervals, representing 80% of aMT [5]. After 1 h, the rMT value and three CSPs were obtained. The interval between each stimulation was 5 s.

Because previous findings indicated that TBS-related behavioral changes might last for up to 10 h, after 1 day (24 h), cTBS was first applied to the left M1 hand area and then to the right lateral cerebellar (1 cm below and 3 cm lateral of the inion) area as the second application [17]. The rMT value and three CSPs were again obtained. Intervals between each stimulation were 5 s. Thus, three values, namely before application, after first application, and after second application, were obtained for comparison.

2.4. Statistical analysis

The variables were investigated using visual (histograms) and analytical methods (Kolmogorov–Smirnov) to determine normal distribution.

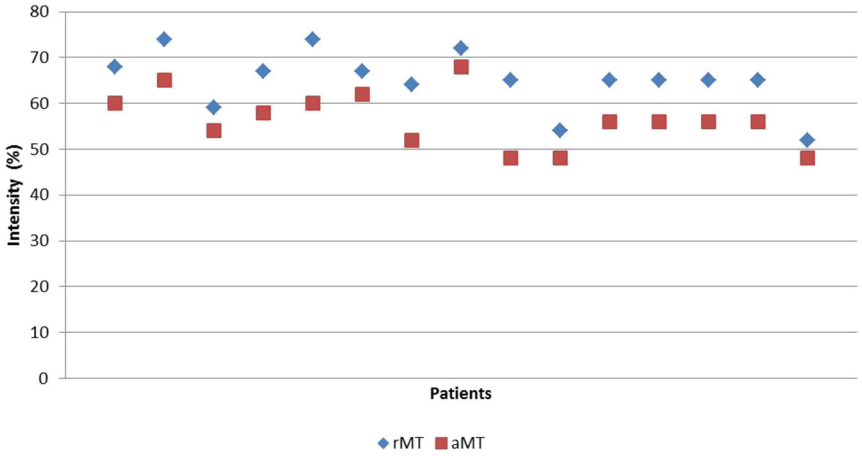

Fig. 1. rMT and aMT values before application.