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Cortical excitability in juvenile myoclonic epileptic patients and their asymptomatic siblings: A transcranial magnetic stimulation study

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ABSTRACT

In this study, we aimed to evaluate motor cortical excitability changes in patients with juvenile myoclonic epilepsy (JME) and their asymptomatic siblings (AS) using single-pulse transcranial magnetic stimulation (spTMS). 21 patients with JME and their 21 AS were compared to 20 healthy controls. All of JME patients were receiving antiepileptic therapy and their seizures were well controlled. Firstly, standard EEG examinations and then TMS studies were performed. Resting motor threshold (RMT), motor evoked potential (MEP) amplitudes, the durations of central motor conduction time (CMCT) and cortical silent period (CSP) were measured. After TMS studies, EEG recordings were repeated in an hour to evaluate any effect of TMS study on EEG. There were no significant differences between the first and second EEG recordings. No seizures were recorded during and after the TMS study. RMT was found higher in JME patients than AS and normal controls. There were no significant differences between cortical MEP amplitudes and MEP amplitude/CMAP (compound muscle action potential) amplitude ratio in all three groups. CMCT duration was shorter in JME patients than AS. CSP durations of JME patients were found to be longer than controls. In AS, CSP durations were also found to be longer than controls but this difference was not found statistically significant. Our results suggested that although high MT may be related to antiepileptic therapy, the prolongation of CSP duration may reflect impairment of supraspinal and/or intracortical inhibitory mechanism in JME. To eliminate the drug effect, further studies are needed in newly diagnosed JME patients without medication and large series of their asymptomatic siblings.

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive and painless technique which was introduced by Barker et al. in 1985. It works by creating a very large transient current which passes through the coil, produces a magnetic field and induces electrical current in other conductors (e.g. brain, spinal roots or nerves). TMS can be applied for understanding the physiology and the excitability of the motor cortex.[1–5] It has been used in different epileptic syndromes to investigate the localization of epileptic foci or speech function, changes of the cortical excitability or effects of the antiepileptic therapy (AT).[1–3,5–25] Former studies have shown that epileptogenesis is consisted of both excitatory and inhibitory mechanisms and TMS can be used for evaluating both excitatory and inhibitory effects on motor cortex.[2,5,26–31]

Motor threshold (MT) refers to the lowest stimulus intensity needed to generate the response in the target muscle and anatomically may reflect the density of network targeting the corticomotor neurons and physiologically may indicate the level of corticospinal system excitability.[2,5,6,18,27,30,32,33] Besides exhibiting a motor evoked potential, a period of EMG suppression known as silent period (SP) occurs after single-pulse TMS during voluntary contraction.[2,5,6,27,32] Although the spinal and direct spinal inhibitory mechanisms are involved in the early and intermediate part of SP, the late part of SP is thought to be related to intracortical inhibitory mechanisms in primary motor cortex, leading to a failure of corticospinal drive.[2,3,5,6,27,32,34,35] It has been suggested that using a single stimulus, $(GABA)_B$-ergic intracortical circuits contribute to the generation of transcranially evoked SP, however, short interval intracortical inhibition (SICI) is mediated by $(GABA)_A$-ergic intracortical circuits using paired stimuli. This opinion was supported by pharmacologic studies using GABA agonists such as benzodiazepines, baclofen, tiagabin, vigabatrin, zolpidem.[5,17,19,23,27,32,36,37] Central motor conduction time (CMCT) is an estimation of the conduction time in central motor pathways from motor cortex to the spinal motor neurons.[5,6] CMCT duration

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consists of the period from the excitation of cortical neurons to the motor neurons conducted via the corticospinal/corticobulbar tracts.[5]

Juvenile myoclonic epilepsy (JME) is one of the generalized idiopathic epileptic syndromes with complex inheritance pattern.[38–40] It is characterized by irregular myoclonic jerks of the shoulders and arms upon waking without any disturbance of consciousness, typical absence or generalized tonic clonic seizures.[25,38–42] Typical EEG findings of JME are bilateral synchronous, 4–6 Hz spike/multiple spike and slow waves complexes.[38–41] Different types of idiopathic epileptic syndromes were found in relatives of JME patients.[38–40] In some earlier reports, EEG abnormalities were demonstrated in siblings of JME patients.[38,40,42] In our previous study, we found EEG and somatosensory evoked potential (SEP) abnormalities not only in JME patients but also in their asymptomatic siblings.[40] In the literature, some TMS studies in epileptic patients had controversial results. Moreover, there were no TMS studies which were performed in asymptomatic siblings of epileptic patients. In this study, we mainly aimed to evaluate motor cortical excitability changes in JME patients and their asymptomatic siblings using single-pulse TMS (spTMS). The second aim of this study was to assess the safety of spTMS in this population.

2. Materials and methods

2.1. Subjects

There were three groups in this study. The first group consisted of 21 patients with JME (10F, 11 M; mean age ±SD: 23.9 ± 3.4; range: 17–31) gathered from our epilepsy outpatient clinic. The second group consisted of their 21 asymptomatic siblings (12F, 9 M; mean age ±SD: 22.8 ± 5.0; range: 13–33). They were all compared to 20 healthy controls (10F, 10 M; mean age ±SD: 23.6 ± 5.7; range: 13–33).

JME diagnosis was established according to clinical history and EEG findings. All of JME patients were receiving antiepileptic therapy and their seizures were well controlled. Patients who had generalized tonic clonic seizures in the last one year were excluded. None of the controls or asymptomatic siblings was taking any drugs which effect on central nervous system excitability such as sedatives, hypnotics, anticonvulsants or beta-blockers. All participants had normal neurological examination before and after the study. In all JME patients, CT and/or MR imagings were normal. The duration of the disease was 120 ± 47.6 months (mean ± SD; range: 36–228 months). First seizure type was myoclonic in 13 patients, generalized tonic clonic in 6 patients and absence in 2 patients. All of the patients had myoclonic jerks, except one patient (95.2%). Nine patients (42.9%) had absence, 17 patients (81%) experienced at least one generalized tonic clonic seizure throughout the disease duration. All of the patients were treated chronically with antiepileptic drugs (AED): Nineteen (90.5%) with valproic acid (VPA), one (4.8%) with VPA and lamotrigine (LTG) and one (4.8%) with VPA, LTG and Phenobarbital (PB). VPA dosage varied from 500 mg to 1500 mg, LTG dosage was 50 mg and PB dosage was 100 mg. The dosages of all antiepileptic drugs (AED) were within the therapeutic range at the last clinical admission.

The study was reviewed and approved by a local ethical committee. A written, informed consent form was collected from all subjects who were participated in the study.

2.2. Experimental procedures and recordings

Initially, standard EEG recordings including hyperventilation and photic stimulation were performed with a Medelec1118 device. In order to evaluate any effect of TMS study on EEG, a second EEG recording in each participant was done within the first hour after TMS.

During TMS studies, subjects were sitting on a comfortable armchair in a quiet, semi-darkened room. Hand dominancy was confirmed by the Edinburgh Handedness Test.[43] Motor evoked potential (MEP) responses were recorded from dominant hand abductor digiti minimi (ADM) muscle with Ag/AgCl cup electrodes. The active electrode was placed on the muscle belly and the reference over the fifth metacarpophalangeal joint. Initially, the ulnar nerve was stimulated at the dominant wrist using electrical stimulator and the amplitude of resulting compound muscle action potential (CMAP) was measured. Single-pulse magnetic stimulation was performed using a 135 mm circular coil connected to Magstim200 stimulator over the vertex. If left hemisphere was dominant, the direction of the current in the coil was anticlockwise and if right hemisphere was dominant the direction of the current in the coil was clockwise. MEP responses were recorded by Medelec Sapphire 4ME device.

While the subjects were resting, motor threshold (RMT) was determined. Audio-visual feedback was given to the subjects in order to maintain complete electrical muscle silence. RMT was defined as the stimulus intensity at which a peak-to-peak MEP amplitude of 50 μV was obtained in at least 5 of 10 consecutive trials. During active muscle contraction, using 120% of the RMT as stimulus intensity, the shortest onset latency and the highest amplitude of 7 consecutive MEPs were obtained and latency and amplitude were measured. In order to avoid possible variability of MEP amplitudes, MEP amplitude/CMAP amplitude ratio (MEP/CMAP) was calculated. Cervical roots were stimulated over the spinous process of the 7th cervical vertebra at maximal stimulator output when the subject was in a sitting position with a slight degree of neck flexion. Central motor conduction time (CMCT) was calculated by subtracting the latency of cervical response from the latency of cortical MEP response.

During CSP studies, subjects were held slight contraction of approximately 30% maximum voluntary contraction of contralateral ADM muscle. Audio-visual feedback was given to maintain the correct level activity. Stimulus intensity was maximal output of magnetic stimulator. 5 consecutive stimuli were delivered. The duration of CSP was measured from the end of the MEP until the reappearance of EMG activity and the shortest CSP value was selected for evaluation.

2.3. Statistics

Statistical analysis was performed using SPSS for Windows program. Sex and EEG results were compared to Chi-square test. Kappa test was used for comparing EEG results before and after TMS. The MEP results of three groups were compared to analysis of variance (ANOVA) tests with post hoc Bonferroni and Dunnet tests. A p value of <0.05 was considered to be statistically significant.

3. Results

The demographic data and clinical characteristics of the study are described in Table 1. There were no significant differences between sex and the mean age of study groups ($p = 0.814$; $F = 0.292$, $p = 0.748$ respectively).

Before TMS examinations, six JME patients and one asymptomatic sibling had 4–6 Hz spike/polyspike and wave paroxysms (SPSWP). Three JME patients and 6 asymptomatic siblings had 6–7 Hz theta activity mixed with normal activity. This activity was defined as intermittent generalized slowing (IGS). After TMS examinations, we found 4–6 Hz spike/polyspike and wave paroxysms in 5 JME patients and one asymptomatic sibling; and we found IGS in 3 JME patients and 6 asymptomatic siblings