MOTOR EVOKED POTENTIALS MODIFICATION IN DIFFERENT FORMS AND STAGES OF MULTIPLE SCLEROSIS

Orest Bolbocean, Valentin Bohotin, Cristian Dinu Popescu
Department of Neurology, Rehabilitation Hospital
"Gr. T. Popa", University of Medicine and Pharmacy, Iasi, Romania

ABSTRACT

Background: In patients with Multiple Sclerosis (MS), transcranial magnetic stimulation (TMS) has shown significant prolongation of central motor conduction time (CMCT). Abnormal CMCT may reflect sub-clinical involvement of motor pathways and correlate with clinical motor disability.The present study was undertaken to determine the diagnostic yield of TMS in MS, to assess the strength of the correlation between clinical disability and motor evoked potentials (MEP) abnormalities in different stages of progression of MS and to evaluate the possibility that TMS may be used to monitor clinical evolution in MS over time.
Materials and methods: Fifty nine patients with clinically definite multiple sclerosis and eighteen healthy volunteers were included in the study. Patients were divided in three subgroups according to the moment and the character of disease. Transcranial magnetic stimulation (TMS) parameters were evaluated using single pulse TMS and a figure of eight coil. Parameters determined included: motor threshold, central motor conduction time (CMCT), latencies and amplitude of MEP at 120% of motor threshold.
Results: Modifications of at least one parameter were observed at 91% cases. We noticed an increase of motor threshold, CMCT, cortical latencies and decrease of motor evoked potential (MEP) amplitude at 120% of motor threshold.
Conclusion: There are significant correlations observed between the abnormalities in CMCT and the degree of motor disability. The changes of MEP parameters were more pronounced in secondary-progressive MS. TMS is a highly sensitive technique to evaluate cortico-spinal conduction abnormalities in MS, in monitoring motor disability and the course of the disease.

Key words: multiple sclerosis, magnetic stimulation, motor evoked potentials

INTRODUCTION

Multiple Sclerosis (MS) is a chronic demyelinating and degenerative disease of the central nervous system and it is one of the most important by virtue of its frequency, chronicity, and tendency to attack young adults. It is a chronic condition characterized clinically by episodes of focal disorders of the optic nerves, spinal cord, and brain, which remit to a varying extent and recur over a period of many years. Motor symptoms represent one of the most frequent and disabling syndrome of MS (1). Transcranial magnetic stimulation (TMS) is a technique able to measure the modifications of the cortico-spinal tract at any level of motor pathway (2). In patients with multiple sclerosis (MS), transcranial magnetic stimulation (TMS) has shown significant prolongation of central motor conduction time (CMCT). Abnormal CMCT may reflect subclinical involvement of motor pathways and correlate with clinical motor disability (3).

The present study was undertaken to determine the diagnostic yield of TMS in MS, and to assess the strength of the correlation between clinical disability and motor evoked potentials (MEP) abnormalities in different stages of progression of MS and to evaluate the possibility that TMS may be used to monitor clinical evolution in MS over time.

Author for correspondence:
Cristian Dinu Popescu, "Gr.T.Popa" University of Medicine and Pharmacy, 16 Universitatii Street, Zip Code 700115, Iasi, Romania
email: cdpopescu@ssnn.ro

MATERIALS AND METHODS

The study was carrying on 78 subjects: 59 patients with clinically definite MS (according with McDonald's criteria) and 18 healthy volunteers which form a control group. According with the moment and the character of disease the patients were divided in the following groups:

- group I active phase (relapse/onset) 6 patients
- group II passive phase (in remission) 41 patients
- group III secondary progressive form of MS 12 patients

TMS was applying over the motor cortex as single pulse with a figure of eight coil of 90 mm diameter of Magstim Rapid® (Magstim Co Ltd, Whitland, Dyfed, UK). The stimulator pulse was very brief (less than 200 microseconds) and the maximum generating magnetic field 1.2 Tesla. The center of the coil was positioned over the motor projection of the hand around 5 cm lateral and 1 cm anterior in relation with vertex. For people in which we did not obtain a motor response in the position the coil was move 1-2 cm around that point in order to identify the motor hot spot. The muscle contraction was recorded with a Nihon-Kohden EMG device, bilaterally, from the abductor pollicis brevis (APB) on the upper limbs using surface silver/silver chloride electrodes.

The subjects were seated comfortable in an armchair and motor threshold (MT) was recorded in a relaxed target muscle. MT was taken as the minimum stimulus intensity (measured as a percentage of maximum stimulator output) needed to evoke a motor response >50 mV in three out of five consecutive trials. If no response was recorded even at maximum coil output (100%), the subjects were asked to contract target muscle and if still no response was recorded, then TM was considered as 101%. For motor evoked recorded the subjects keep the same relaxed position and the stimulus was applied over the motor hot spot at 120 % of MT. The magnetic stimulation of the spinal roots was done by placing the rim of the same coil over the seventh cervical vertebrae. The parameters evaluated were: MT; cortical latencies (CL) and spinal cord latencies (SL); amplitude (AM) of MEP at 120% of motor threshold; central motor conduction time (CMCT). CMCT was measured by subtracting the latency resulting from spinal stimulation from that on cortical stimulation.

Statistical analysis: Means and standard deviation were calculated for each parameter and each group. Statistical calculations were carried out with STATISTICA 6.0 (Statsoft Inc., USA). Student t-test was used to assess the relationships. All results were considered significant at the 5% level ($p < 0.05$).

RESULTS

Modifications of at least one parameter were observed at 91% cases. We notice an increase of motor threshold, CMCT, cortical latencies and decrease of MEP amplitude at 120% of motor threshold (TABLE 1). There was a significant correlation between abnormalities of MEP parameters and clinical disability.

In patients with MS we notice an increase of CMCT which generated an increase of cortical latency. The cervical latency was not modified in comparison with healthy control group (TABLE 2, FIGURE 1).

All MEP parameters at patients in active phase of MS in comparison with healthy volunteers were significantly modified except for cervical latencies. We found an increase of motor threshold, cortical latencies, CMCT and decrease of amplitude of MEP at 120% of MT (TABLE 3).

The mean MT, cortical latencies and CMCT were significantly higher in group II in comparison with healthy volunteers. The motor evoked potentials amplitude on cortical stimulation was statistical significantly reduced in the upper limbs in patients in passive phase of MS in comparison with healthy volunteers (TABLE 4).

TABLE 1. *MEP parameters at patients with MS and healthy volunteers*

MEP parameters	MS Patients	Healthy volunteers	p
Spinal cord latencies (ms)	13.53 ± 2.13	12.3 ± 1.6	0.760
Motor threshold %	66.94 ± 14.29	57.85 ± 7.60	< 0.001
Cortical latencies (ms)	24.57 ± 5.17	20.6 ± 1.7	< 0.01
CMCT (ms)	12.38 ± 4.86	8.4 ± 0.7	< 0.001
Amplitude of MEP at 120% of TI (mV)	1.08 ± 1.15	2.5 ± 1.5	< 0.001

TABLE 2. *MEP parameters at patients with MS according with the moment and the form of disease and healthy volunteers*

MEP parameters	Healthy volunteers	Active phase	Passive phase	SPMS
Motor threshold %	57.85 ± 7.60	60.25 ± 11.29	69.75± 15.14	74.59 ± 18.02
Cortical latencies (ms)	20.6 ± 1.7	21.56 ± 1.21	24.85 ± 5.78	28.67 ± 5.48
Spinal cord latencies (ms)	12.3 ± 1.6	13.61 ± 2.80	13.49 ± 2.26	14.01 ± 1.95
CMCT (ms)	8.4 ± 0.7	8.7 ± 2.58	11.43 ± 6.12	14.65 ± 5.08
Amplitude of MEP at 120% of MT (mV)	2.5 ± 1.5	1.12 ± 0.68	1.15 ± 1.49	0.53 ± 0.40

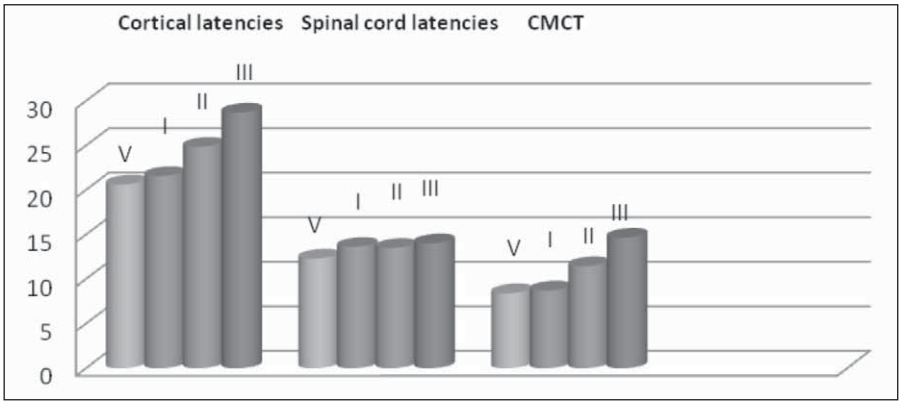

FIGURE 1. *MEP latencies at all studied subjects (ms): V – healthy volunteers, I – active phase, II – passive phase, III – SPMS*

TABLE 3. *MEP parameters at patients with MS in active phase and healthy volunteers*

MEP parameters	Healthy volunteers	Active phase	p
Spinal cord latencies (ms)	12.3 ± 1.6	13.61 ± 2.80	0.28
Motor threshold %	57.85 ± 7.60	60.25 ± 11.29	< 0.01
Cortical latencies (ms)	20.6 ± 1.7	21.56 ± 1.21	< 0.01
CMCT (ms)	8.4 ± 0.7	8.7 ± 2.58	0.05
Amplitude of MEP at 120% of TI (mV)	2.5 ± 1.5	1.12 ± 0.68	< 0.01

TABLE 4. *MEP parameters at patients with MS in passive phase and healthy volunteers*

MEP parameters	Healthy volunteers	Passive phase	p
Spinal cord latencies (ms)	12.3 ± 1.6	13.49 ± 2.26	0.59
Motor threshold %	57.85 ± 7.60	69.75± 15.14	< 0.05
Cortical latencies (ms)	20.6 ± 1.7	24.85 ± 5.78	< 0.001
CMCT (ms)	8.4 ± 0.7	11.43 ± 6.12	< 0.001
Amplitude of MEP at 120% of TI (mV)	2.5 ± 1.5	1.15 ± 1.49	< 0.05

At patients with secondary progressive multiple sclerosis were observed statistically significant modifications of all cortical MEP parameters in comparison with healthy volunteers (TABLE 5).

An analysis of MEP between groups of patients with MS in different phases and clinical form were made and we noticed a statistically significant modification at patients with SPMS in comparison

TABLE 5. *MEP parameters at patients with SPMS and healthy volunteers*

MEP parameters	Healthy volunteers	SPMS	p
Spinal cord latencies (ms)	12.3 ± 1.6	14.01 ± 1.95	< 0.19
Motor threshold %	57.85 ± 7.60	74.59 ± 18.02	< 0.001
Cortical latencies (ms)	20.6 ± 1.7	28.67 ± 5.48	< 0.001
CMCT (ms)	8.4 ± 0.7	14.65 ± 5.08	< 0.001
Amplitude of MEP at 120% of TI (mV)	2.5 ± 1.5	0.53 ± 0.40	< 0.001

TABLE 6. *Significancy coefficient in different phases and clinical forms of MS*

MEP parameters	Active phase – SPMS	Active phase – Passive phase	Passive phase – SPMS
Spinal cord latencies (ms)	< 0.05	-	-
Motor threshold %	< 0.01	-	< 0.01
Cortical latencies (ms)	< 0.001	-	< 0.001
CMCT (ms)	< 0.001	-	< 0.001
Amplitude of MEP at 120% of TI (mV)	< 0.01	-	< 0.001

with subjects with MS in active and passive phase. Also, significantly prolonged cervical latencies were observed at patients with SPMS in comparison with subjects with active phase of MS (TABLE 6).

DISCUSSION

Almost all parameters of MEP of m. Abductor digiti minimi obtained with TMS were modified at patients with MS in comparison with healthy controls. Modifications of MEP latencies were determined by increase of CMCT and not by cervical latencies, that demonstrate the significance of cortical demyelinating process in MS which is in according with other literature data (4-6).

Modified parameters of MEP are determined by two pathological mechanisms – demyelinization and secondary degeneration of cortico-spinal tract fibers, processes that are more evident in advances stages of illness.

Non-uniformly defeat of pyramidal axons conduct to different degrees of delay and desynchronized nervous impulses. This process is responsible for modifications of all essential MEP parameters (MT, increased latencies, decreased amplitude and appears of polyphase motor evoked potentials) (7-9).

Significant modifications of MEP parameters at patients with SPMS in comparison with subjects with MS in active and passive phases could be correlated with advanced stage of MS and appearing of new demyelinated and degenerative lesions in both cerebral and in cervical segment.

Even if we found an increase of CMCT in relapsing group in comparison with group II (remitting patients) the difference did not reach the statistical significance. The fact could be explained by the small number of patients in the first group.

MT is a measure of the cortico-cortical excitability of pyramidal neurons and it is one of the most important modified parameters in MS. The increased MT and reduced MEP amplitude may occur due to temporal dispersion of descending volleys or conduction blocks in the descending motor pathways. The CMCT prolongation in MS occur secondary to delayed supra-threshold stimulation of smaller and slower conducting motor neurons and a compromise in the stimulus conduction in large diameter demyelinated or incompletely remyelinated cortico-spinal fibers, resulting in lack of temporal summation. The absence of MEP elicitation results from conduction failure secondary to demyelination across the zone of pathology (10-11).

Statistically significant between group difference or trend toward changing of TMS parameters were found that indicates a slow-down of the impulse conducting along the cortico-spinal tract, which is characteristic for the demyelinization process. The changes were more pronounced in secondary-progressive MS that are correlated with exacerbation of the disease.

CONCLUSIONS

1. There are significant correlations between the abnormalities in CMCT and the degree of motor disability.
2. The changes of MEP parameters were more pronounced in secondary-progressive MS (the most valuable was CMCT).
3. TMS is a highly sensitive technique to evaluate cortico-spinal conduction abnormalities in MS and in monitoring the course of the disease.
4. TMS should be taken into account as a tool in monitoring motor disability in patients with MS.

REFERENCES

1. **Ropper AH, Brown RH** – Adams and Victors principles of neurology. 8th edition. McGraw-Hill Medical Publishing Division. 2005; 771-797
2. **Paulus W, Tergau F, Nitsche MA, Rothwell JC, Ziemann U, Hallett M** – Transcranian magnetic stimulation and transcranial direct current stimulation. *Elsevier Science* 2003; 24-33
3. **Wassermann E, Epstein C, Ziemann U, Paus T, Lisanby S** – Oxford Handbook of Transcranial Stimulation. 2008; 259-261
4. **Sokolov PL** – Analiza clinico-electromiografica a parezelor centrale in scleroza multipla, Lucrare doctorat. 1994; p. 25
5. **Mayr N, Baumgartner C, Zeitlhofer J, Deecke L** – The sensitivity of transcranial cortical magnetic stimulation in detecting pyramidal tract lesions in clinically definite multiple sclerosis. *Neurology* 1991; Vol. 41; p. 566-569
6. **Hess CW, Mills KR, Murray NMF, Schriefer TN** – Magnetic brain stimulation: central motor conduction studies in multiple sclerosis. *Ann Neurol* 1987; Vol. 22; p. 744-752
7. **Panteleeva EA** – Pareza spastica la pacientii cu scleroza multipla: un studiu clinic, neurofiziologic si biochimic. Lucrare doctorat. 2008; p.11
8. **Cruz-Martinez A, Gonzalez-Orodea JI, Lopez Pajares R, Arpa J** – Disability in multiple sclerosis. The role of transcranial magnetic stimulation. *Electromyography and Clinical Neurophysiology* 2000; vol. 40(7), p. 441-447
9. **Rosler KM, Petrow E, Mathis J, Aranyi Z, Hess CW, Magistris MR** – Effect of discharge desyncronisation on the size of motor evoked potentials: an analysis. *Clin Neurophysyol* 2002; 113:1680-1687
10. **Nikitin SS, Kurenkov AL** – Stimularea magnetica in diagnosticul si tratamentul bolilor sistemului nervos central. Moscova, Editura SASKO 2003; p. 142-160
11. **Sahota P, Prabhakar S, Lal V, Khurana D, Das CP, Singh P** – Transcranial magnetic stimulation: Role in the evaluation of disability in multiple sclerosis. *Neurol India* 2005; 53:197-201