THE UTILITY OF TRANSCRANIAL MAGNETIC STIMULATION IN ASSESSING THE CORTICOTHERAPY EFFICIENCY IN MULTIPLE SCLEROSIS PATIENTS DURING RELAPSE

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Summary

Multiple Sclerosis (MS) is the most frequent chronic neurologic pathology diagnosed in young adults. The demyelinating process leads to axonal myelin loss, causing axonal and glial neuronal dysfunctions, clinically manifested by relapse. Transcranial magnetic stimulation (TMS) is a noninvasive method useful in assessing corticospinal tract dysfunctions in Multiple Sclerosis patients, by recording the prolonged central motor conduction time (CMCT), the increase of the motor threshold and also the reduction in amplitude of the motor evoked potential (MEP). Thus, stimulating the cortical motor area will determine a recordable response characteristic for the electrophysiological behavior of the pyramidal tract. We investigated 37 MS patients with relapse, manifesting by motor deficit, performing TMS prior to receiving corticosteroids (1000 mg intravenous Methylprednisolone daily, for 5 days), 5 days afterwards and also after one month from the treatment. 26 patients presented both electrophysiological and clinical improvement after therapy, whereas 11 patients did not show any electrophysiological improvement, in spite of a slight amelioration of the symptoms. TMS proves to be a sensitive tool for investigating the relapse and the corticotherapy efficiency.

Key words: TMS, multiple sclerosis, relapse, corticotherapy

Introduction

Multiple Sclerosis (MS) is characterized by inflammation, demyelination and gliosis. The clinical value is attributed to the lesions that result depending on their dissemination in time and space. The relapse is the clinical and electrophysiologic expression of the demyelinating process. In MS the deficits resulted during the relapse can be present for a certain period of time, with either partial or complete amelioration. One of the characteristics of MS is that a relapse can be associated with a totally different type of deficit compared to the previous ones, thus in time, residual deficits can add to the main clinical picture of the disease.

In establishing a proper diagnosis, even though magnetic resonance imaging (MRI) is superior to evoked potential (EP), especially related to demyelinating lesions located periventricularly, EP are to be preferred in following the progression of the disease, due to their practical use in investigating nervous conduction. Subclinical lesions can be described this way, not to mention the possibility of future predicting of the long term course [1].

Transcranial magnetic stimulation (TMS) is a

modern and useful method, destined to investigate various neurological disorders such as MS, Parkinson's disease, amyotrophic lateral sclerosis and other cerebrovascular diseases, available in its actual form since 1985 [5]. By the use of repetitive stimulation, it can be also used in treating depression as well as other conditions, therapeutic approaches being expected to be established in the closest future [9]. Synaptic long-term potentiation (LTP), the possibility of restoring membrane excitability for neurons that no longer posses a part of their synaptic inputs, explored by TMS, is another promising research direction, as it seems that the LTP reserve tends to contrast the progression of disabilitating deficits in MS [2].

TMS is useful for examining the corticomotor conduction especially in the hand and leg of MS patients with motor deficit, the idea of monitoring the effects of steroids on cortical excitability by investigating the motor evoked potential (MEP) already showing promising results [4,6,7].

The aim of the present study is to determine the MEP modifications of 37 Relapse Remitting MS (RRMS) patients during relapse, by performing TMS prior to, 5 days after and 1 month after the initiation of treatment with methylprednisolone.

Material and methods

We investigated 37 RRMS patients with relapse, with medium age of 37.6 ± 9.46 years. 9 patients presented motor deficit on either right or left side of the body, 14 patients had motor deficit manifesting through paraparesis, 11 patients accused sensory symptoms (paresthesias and formications in both upper and lower limbs) and a minimal hemiparetic deficit, and 3 patients presented monoparetic motor deficit. According to the affect of the pyramidal tract, the Expanded Disability Status Scale (EDSS) had different values: 14 patients with EDSS 2 (37.83%), 8 patients with EDSS 2.5 (21.6%), 6 patients with EDSS 3 (16.1%), 5 patients with EDSS 3.5 (13.55%) and 4 patients with an EDSS of 6 (10.9%). The medium EDSS was 3.4±3.4. In the 37 patients group the EDSS varied from 2 to 6.

The patients with relapse were investigated by TMS prior to and after receiving corticosteroids (Methylprednisolone 1000 mg intravenous, daily, for 5 days). The TMS after corticotherapy consisted in examination after the 5 days, and after one month.

TMS was performed with a Magstim Rapid® device (Magstim Co. Ltd, Whitland, Dyfed, UK). We used the butterfly shaped and the round coil. The butterfly shaped coil has a diameter of 7 cm, and is able of generating a magnetic field of up to 1.2 Tesla. The round coil generates a cone shaped magnetic field, performing a diffuse stimulation. This is the reason why this particular coil is preferred in clinical practice for the stimulation of the cervical and lumbar areas. The MEP was collected from the abductor digiti minimi muscle and tibialis anterior muscle, using surface electrodes.

In order to demonstrate the utility of TMS in following the efficacy of corticotherapy in MS patients with relapse, we measured the motor conduction latency (MCL) and the central motor conduction time (CMCT) from the two cerebral hemispheres, before and after receiving corticosteroid treatment. For the central cerebral stimulation we used the butterfly coil, stimulating in turn the right and the left hemispehere, and collecting information from the abductor digiti minimi muscle. The stimulation for the lower limbs was similar, with difference consisting in collecting the information from the tibialis anterior muscle. For the cervical and lumbar stimulations we used the round coil, stimulating at C7 respectively at L5 level, and collecting information from abductor digiti minimi for the upper limbs, and from tibialis anterior for the lower limbs.

The statistic analysis was performed by applying the Paired-Samples T Test statistic procedure, using SPSS 17 through Analyse – Compare Means – Paired Samples T Test protocol.

Results

The statistic analysis revealed an amelioration of the MEP latency and a discrete amelioration of the CMCT after stimulating the mentioned areas in 26 patients. In 11 patients there were no latency or CMCT improvements, the values obtained possessing no statistic significance.

For the upper limbs, the CMCT for the left hemisphere was 10.14±1.3 before corticotherapy, 10.6 ± 0.67 5 days afterwards and 10.3±0.58 after one month. The MCL for the left hemisphere was 24.85±0.96 miliseconds prior to corticotherapy, 24.62±0.9 5 days after, and 23.58±1.17 after one month, with $p<0.003$.

The CMCT on the right hemisphere before corticotherapy 10.31±1.39, 5 days after corticotherapy 10.46±1.19, and one month afterwards 10.25±1.04. The left cortical latency before the corticotherapy was 24.40±0.89; 5 days after: 23.66±0.70, and one month later 22.58±0.9, $p<0.001$.

At cervical level on the right, the values before corticotherapy were 13.04±0.33, 12.9±0.30 5 days after, and 12.59±0.3 after one month, with $p<0.001$.

At cervical level on the left, the values before the corticosteroid therapy were 12.36±0.41, 5 days after therapy 12.57±0.39 and 12.17±0.40 one month afterwards, with $p<0.001$.

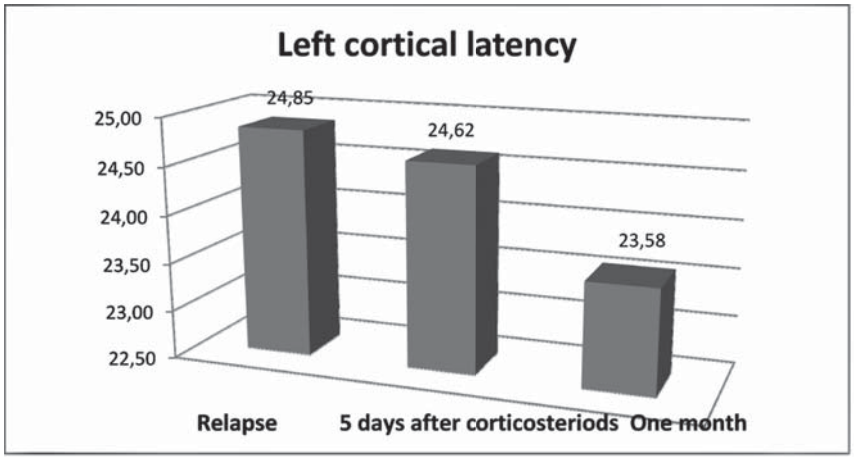

Figure 1. *Modification of the MEP latency measured at cerebral level for the left hemisphere. The vertical column represents the latency's values.*

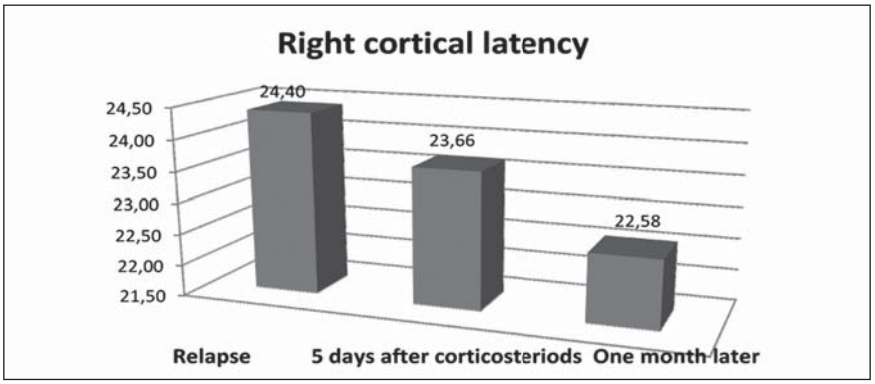

Figure 2. *Modification of MEP latency at left cerebral hemisphere level.*

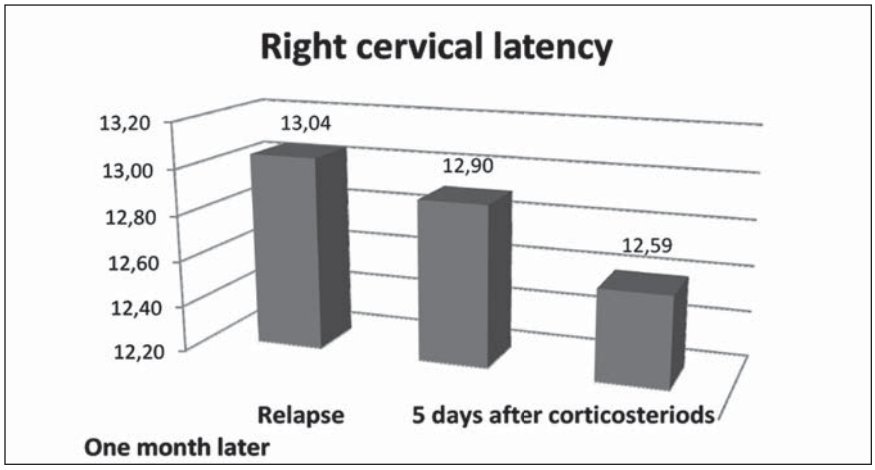

Figure 3. *The modification of the MEP latency at cervical level on the right.*

In the lower limbs, on the right, the cortical latency before corticotherapy was 34.3±2.7, 5 days after was 33.5±2.2 and one month later was 32.3±2, with $p<0.003$. On the left, before steroids the values were 33.96±2.6, 5 days later they were 33.4±2.3 and one month later 33±1.9, with $p<0.003$. The CMCT on the right side was 20.58±3.44 before therapy, 20.3±3.1 5 days later, and 20.15±2.99 one month later. On the left side, the CMCT was 18.95±4.01 before treatment, 18.92±3.7 5 days later and 18.6±3.1 one month later.

At lumbar level on the right side the values were: 12.92±0.6, 12.22±0.41 and 11.11±0.37, according to the three moments of measurement, with $p<0.001$.

At lumbar level on the left side, the values were: 12.79±0.54 initially, 12.34±0.41 after 5 days, and 11.27±0.4 one month later, with $p<0.001$.

Among the 26 MS patients with relapse, a positive influence of the corticotherapy, with statistic significance, is represented by the modifications of the MEP latencies both on the right and left, after 5 days, respectively one month of corticosteroid

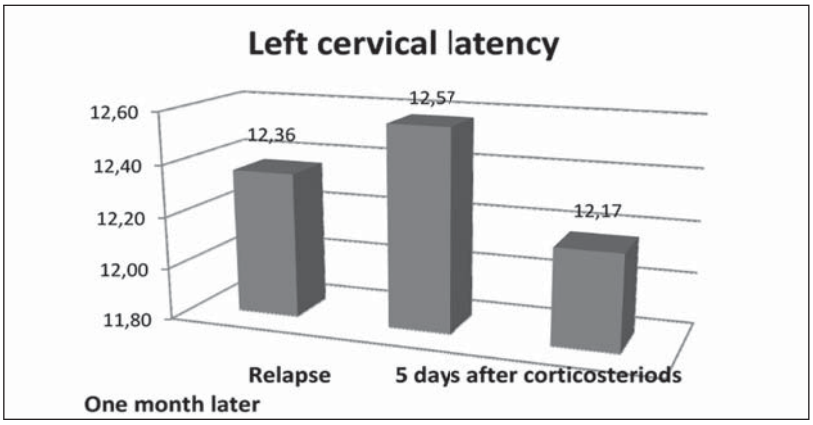

Figure 4. *The modification of the MEP latency at cervical level, one month after the corticotherpy.*

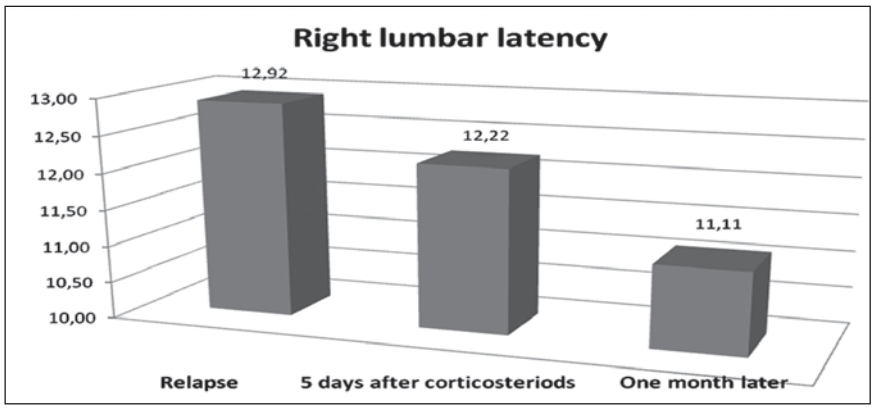

Figure 5. *MEP modifications at right lumbar level.*

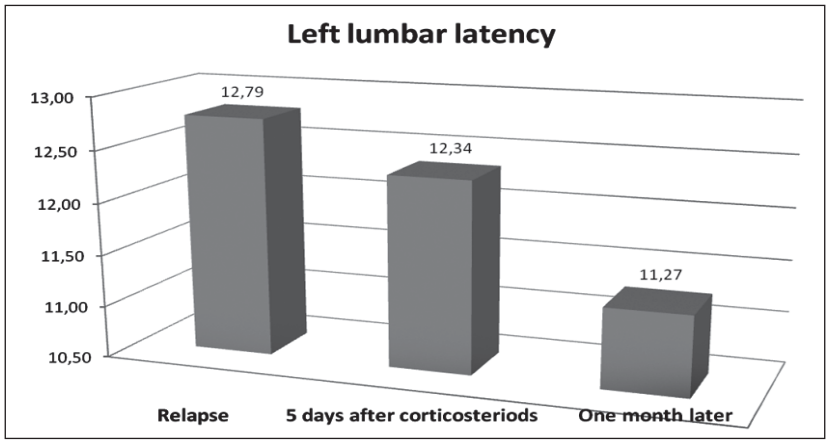

Figure 6. *MEP modifications at left lumbar level.*

treatment, with $p<0.05$. O discrete influence of the corticotherapy can be also observed for the CMCT for both the upper and lower limbs for up to a month from treatment.

On the exploration of the lower limbs, the statistic significant values related to MEP latency were obtained at cerebral level both on right and left, $p<0.003$. CMCT in the lower limbs was discreetly influenced by corticotherapy.

Discussions

From an anatomical perspective, it is well known that the pyramidal tract is the efferent pathway of

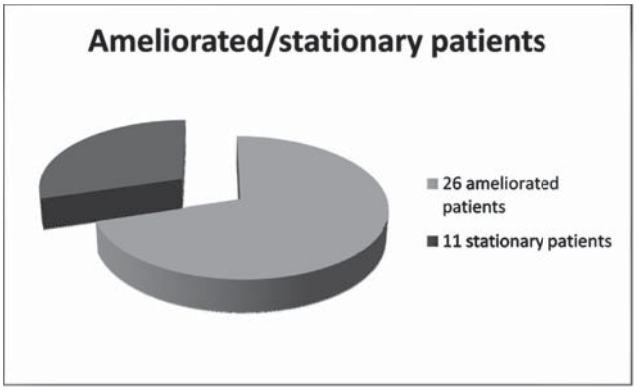

Figure 7. *The ameliorated/stationary patients ratio*

the frontal lobe, the 4th field at this level possessing both motor and motor-analyzer functions. It is responsible for the analysis of sensitive excitations that arrive here, and sending them towards the spinal motoneurons. Thus, a lesion at this level will produce a controlateral hemiparesis.

TMS is a good way to evaluate corticospinal tract dysfunctions in MS patients by interpreting the prolonged CMCT, the increased threshold and also the reduction of MEP amplitudes. The CMCT is the amount of time required by neural impulse from the central nervous system (CNS) towards the muscles. So, it is a time unit depending on the excitation of cortical neurons, the conduction through the corticospinal or corticobulbar tract, and also on the cortical or spinal motoneuron excitation. The muscular response latencies as a result to cortical stimulation actually represent the sum between central and peripheral conduction units of time [14].

CMCT is known to be abnormal in 57-93% of MS patients. Its sensitivity for both improvement and worsening of the motor function make it a useful measurement to be assessed in TMS related studies [15].

TMS also allows the study of transcallosal inhibition, as the interhemispheric transmission is altered in MS patients. The pathological modifications at this level, the correlations with the clinical deficits, as well as estimating the progression of the disease, are all markers to be assessed throughout TMS studies [10].

In our study, a positive influence of the corticotherapy was obtained by recording a modified MEP latency both in the upper and lower limbs, with minimum ameliorations of CMCT, therefore, the 26 patients presenting both clinical and electrophysiological amelioration.

Among the other 11 patients in which minimum electrophysiological improvement was observed, in spite of clinical obvious amelioration, there were no statistic significant values obtained, especially related to the CMCT.

Throughout the recent years TMS has emerged as a method to correlate the clinical manifestations during MS attacks and the disease progression with plasticity and chronic reorganization processes [3]. It has also been showing utility in assessing the relationship between steroid administration and improvement of symptoms, as similar results have been found by other authors [4,11,12,13]. Furthermore it proves its utility as an investigation technique for quantifying electrophysiological pyramidal tract anomalies, as well as representing a good way to monitor the evolution of MS [8].

Conclusions

The benefit of corticotherapy in MS patients with relapse can be assessed by TMS. Significant values suggesting post-therapy amelioration have been obtained at central level, with statistic significance.

Stimulating the motor area will lead to a response, translated by the electrophysiological behavior of the pyramidal tract. We can consider that in MS, this actually represents the semiological basis of the TMS investigations, making this technique useful in the exploration of the pyramidal tract, and a possible way of building up an electrophysiological definition of the relapse.

References

1. Leocani L., Comi G., *Clinical neurophysiology of multiple sclerosis*, Handb Clin Neurol. 2014; 122:671-9.

2. Leon-Sarmiento F.E., Granadillo E., Bayona E.A., *Present and future of the transcranial magnetic stimulation*, Invest Clin. 2013 Mar; 54(1):74-89.

3. Alisauskiene M., Truffert A., Vaiciene N., Magistris M.R., *Transcranial magnetic stimulation in clinical practice*, Medicina (Kaunas). 2005; 41(10):813-24.

4. Weiss S., Mori F., Rossi S., Centonze D., *Disability in multiple sclerosis: when synaptic long-term potentiation fails*, Neurosci Biobehav Rev. 2014 Jun; 43:88-99.

5. Groppa S., Oliviero A., Eisen A. *et al.*, *A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee*, Clin Neurophysiol. 2012 May; 123(5):858-82.

6. Ayache SS, Créange A, Farhat WH *et al*, *Relapses in multiple sclerosis: effects of high-dose steroids on cortical excitability*, Eur J Neurol. 2014 Apr; 21(4):630-6.

7. Firmin L., Müller S., Rösler K.M., *The latency distribution of motor evoked potentials in patients with multiple sclerosis*, Clin Neurophysiol. 2012 Dec; 123(12):2414-21.

8. Udupa K., Chen R., *Central motor conduction time*, Handb Clin Neurol. 2013; 116:375-86.

9. Schlaeger R., Hardmeier M., Fuhr P., *Superficial brain stimulation in multiple sclerosis*, Handb Clin Neurol. 2013; 116:577-84.

10. Schmierer K., Irlbacher K., Grosse P., Röricht S., Meyer B.U., *Correlates of disability in multiple sclerosis detected by transcranial magnetic stimulation*, Neurology. 2002 Oct 22; 59(8):1218-24.

11. Zeller D., Classen J., *Plasticity of the motor system in multiple sclerosis*, Neuroscience. 2014 Dec 26; 283:222-30.

12. Manova M.G., Kostadinova I.I., Chalakova-Atanasova NT, Temenlieva VK, Petrova NS, *Clinico-electrophysiological correlates in patients with relapsing-remitting multiple sclerosis*, Folia Med (Plovdiv). 2001; 43(3):5-9.

13. Fierro B., Salemi G., Brighina F. *et al.*, *A*

transcranial magnetic stimulation study evaluating methylprednisolone treatment in multiple sclerosis, Acta Neurol Scand. 2002 Mar;105(3): 152-7.

14. Cruz-Martínez A., González-Orodea J.I., López Pajares R., Arpa J., *Disability in multiple sclerosis. The role of transcranial magnetic stimulation*, Electromyogr Clin Neurophysiol. 2000 Oct-Nov; 40(7):441-7.

15. Lefaucheur J.P., *La stimulation magnétique transcrânienne : applications en Neurologie*, Rev Neurol (Paris). 2005 Nov.; 161(11):1121-30.