UDC 616.8:616-004:616-009:616.092 DOI: 10.32471/umj.1680-3051.161.250459

The role of transcranial magnetic stimulation in multiple sclerosis prognosis

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Abstract. ***The aim.*** This study describes the difference of transcranial magnetic stimulation (TMS) indicators among patients with different courses of multiple sclerosis (MS) and Expanded Disability Status Scale (EDSS), usage of motor evoke potentials (MEP) and motor threshold (MT) indicated by paired TMS stimulation. ***Materials and methods.*** 130 patients with MS were examined neurologically by usage of EDSS. TMS was performed on 96 patients with MS. TMS inventory included magnetic coil 90 mm that was connected to TMS stimulator machine. Pulses from the abductor major muscle of the dominant upper limb were recorded by electromyography device. TMS parameters included MT, cortical MEP and MEPs recorded on 2, 3, 12 and 15 seconds after delivered stimulus. ***Results.*** Comparison between groups of different EDSS showed significant difference of MT: higher EDSS had higher MT. When data was divided into MS types, significant negative correlation was found in group of PMS between EDSS and MEP amplitude 1 (r=–0.43; p=0.018), MEP2 (r=–0.45; p=0.072), MEP3 (r=–0.41; p=0.05), MEP4 (r=–0.51; p=0.018). ***Conclusion.*** The relationship between EDSS, disease course and TMS electrophysiological parameters might be useful in usage of paired TMS as a tool to show the cortical degeneration. It is a perspective direction in future research of finding additional tool for MS prediction.

Key words: multiple sclerosis, transcranial magnetic stimulation, neurophysiology, diagnostic, demielinative disease of central nervous system, multiple sclerosis biomarker

Introduction

Multiple sclerosis (MS) is the most well-known widespread non-traumatic disease affecting people of young working age [1, 2]. The incidence and prevalence of MS is increasing in both developed and developing countries [1], although the underlying cause of which remains unclear. As a result of the autoimmune process, the central nervous system (CNS) is affected [3, 4]. Traditionally, MS has been viewed as two-stage disease, with early inflammation responsible for relapsing-remitting disease and delayed neurodegeneration causing non-relapsing progression, i.e. secondary and primary progressive MS [1, 5].

The basic pathophysiology of the disease involves demyelination of gray and white matter, loss of axons, atrophy of the cerebral cortex [3, 4]. It is believed that this process is initiated by environmental factors in genetically susceptible individuals, but specific factors are not known for sure, because there are many of them [3, 4].

As a result of damage to the white and gray matter of the brain, the patient has such clinical symptoms as impaired vision, decreased cognitive abilities, impaired motor function and excessive fatigue [1, 3]. These signs and symptoms significantly affect patients' quality of life and their ability to participate in society [3, 6]. Clinical manifestations of MS are different in each patients, thus, the progression of the disease is difficult to predict [3]. However, changes in the myelin protein, which is lost over time due to the activation of the immune system, can be observed in the early stages of the disease even before the appearance of clinical neurological symptoms [3, 4]. Without early application of disease-modifying therapy, many people experience permanent loss of work capacity and social life due to progression [3]. Such a result requires the establishment of additional biomarkers regarding the period of the disease and its progression [3].

The application of biomarkers includes the use of diagnostic tools, such as the classification of the degree of disease, which will indicate the prognosis of the disease, as well as the prediction and monitoring of the clinical response to some appointment [3]. Currently, there are few biomarkers for the clinical assessment of MS [3, 7]. The distinction between relapsing-remitting (RRMS) and progressive types of MS — disease stages with markedly different mechanisms of action [3, 4] — is based almost exclusively on clinical features, and few reliable biomarkers of disease progression have been established to aid in the management of prescribed treatment [2, 7]. In some works, it is claimed that TMS can also become a marker of progression for MS [3]. TMS has the potential to be less expensive and less invasive than other techniques used in the clinical approach to MS [3, 8]. The unique ability of TMS to investigate corticomotor inhibition and excitability in real time may be useful for a better understanding of the pathophysiology of MS [3]. Very few scientific studies have combined TMS and clinical assessment of MS [3, 9]. TMS as a marker of MS progression is a progressive direction of research in the spectrum of demyelinating diseases.

Aim of the study: to describe the difference of TMS indicators among patients with different courses of MS, to assess the degree of disability of a MS patients using MEP through TMS studies and to investigate the relationship between EDS scores and MEP parameters.

Materials and methods

We examined 130 patients with MS in the Department of Nervous Diseases in Vinnytsia National Pirogov Memorial Medical University. Patients were divided into 2 groups regarding to the disease course. 1st group included patients with relapsing-remitting MS — (RRMS), 2nd group — progressive MS (primary progressive MS (PPMS)+secondary progressive MS (SPMS). Diagnosis of MS was confirmed according to the McDonald criteria 2017. A neurological examination and assessment of disability status were performed using the Kurtzke Expanded Disability Status Scale (EDSS) [10, 11], which is used to assess the degree of disability in MS. The scale ranges from 0 (normal) to 10 (death due to MS) on a 20-point scale (in 0.5-point increments). An EDSS of 1.0–4.0 refers to fully ambulatory settlements, and EDSS steps 5.0–9.5 are described as a reduction in mobility [10, 12]. 96 patients with MS from observed cohort underwent transcranial magnetic stimulation (TMS) by paired cortical stimulation. Puls-

es were delivered using a 90-mm circular stimulator coil (serial 0543, Denmark) placed tangentially to the scalp (handle pointing back) and connected to a MagPro R30 stimulator (The Tonica Electronics A/S, Lucernemarken 15, DK-3520 Farum, Denmark). An electromyography (EMG) device (Neuro-EMG-Micro, 8-channel electromyography, model SN 1150SA, Ukraine) was used to record the signal from the abductor major muscle of the dominant upper limb by surface electrodes of the disc in the tendon. During the examination, the patient was asked to sit comfortably with relaxed arms. First, the stimulation threshold was searched, after which subthreshold and suprathreshold (15–20%) stimuli were given, to each of which a reproducible response was obtained. MEPs with the smallest delay and the largest amplitude were evaluated each at 2, 3, 12, 15 second. The parameters evaluated were the following: motor threshold (MT) in rest, cortical motor evoke potential (MEP), motor evoked potential amplitude (MEP). The research was conducted according to the principles of the Helsinki Declaration of the World Medical Association «Ethical Principles of Medical Research with the participation of a person as an object of research». Statistical data was analyzed by SPSS statistics program, version 26.0.0 with elements of descriptive statistical methods, assessment of reliability according to the Student`s criterion, Spearman's rank correlation. The level of significance was taken to be equal to 0.05.

Results and discussion

130 patients were divided into 2 groups with RRMS (n=98) and PMS (n=32). Among this cohort 96 patients agreed to be examined by paired cortical stimulation. Demographics is demonstrated in Table 1. The majority of patients with MS were females. Generally, it is well-known fact that women suffer more than men in occurence of MS [1]. Regarding the MS type, RRMS was predominant that is confirmed in literature as the most common type of MS [1]. In group of RRMS EDSS accounted for 3.5±0.85 points that meaned for the patients to be fully ambulatory. Mean EDSS of PMS accounted for 5.56±1.11. This result showed that progressive course caused decreased mobility of patients to compare with relapsing-remitting type. In our study the minimum of EDSS was — 2.0 points, the maximum one — 7.0 that showed wide range of motor abilities and level of disabilities.

Table 1 Demographics of observed MS patients

Demographic data	RRMS		PMS (PPMS+SPMS)	
Age	32.38±7.06		51.75±3.53 46.25±7.45	
Gender	Male	Female	Male	Female
	33.6% (n=33)	66.3% (n=65)	33.3% (n=8)	66.6% (n=16)
Disease duration	6.39±4.08		15.22±9.63	

RRMS — relapsing-remitting multiple sclerosis; PMS — progressive multiple sclerosis; PPMS — primary progressive multiple sclerosis; SPMS — secondary progressive multiple sclerosis.

We analysed mean±SD data among 96 patients that agreed to proceed with proposed TMS protocol. MT accounted for 43.79±9.17%, cortical MEP — 1.9±1.63 mV. MEP amplitude was counted on response of 2 (MEP1), 3 (MEP2), 12 (MEP3) and 15 second (MEP4). MEP1 indicated 1,06±1,10; MEP2 — 1.43±1.40, MEP3 — 3.10±2.36, MEP4 — 4.20±2.88 mV.

We analysed MT and MEP amplitude according to the EDSS. Patients were divided into 2 groups: EDSS 2.0–4.0 that indicated fully ambulatory patients; EDSS 4.5–7.0 that indicated restricted ambulance in daily living. The cortical MEP was measured by delivering a single supra-threshold stimulus (typically 120% of MT) over the motor cortex and recording from a peripheral muscle. Cortical MEP is measured by applying a single suprathreshold stimulus (120% of MT) over the motor cortex and recording the response from the abductor major muscle of the dominant hand. Data with compared results between groups described at Table 2.

Cortical MEP in group with lower EDSS accounted for 2.13±1.7 mV, in group with higher EDSS — 1.09±0.99. The difference of MT between group with lower and higher EDSS is statistically significant. Simpson et al [13] described in their review that lower MT could be possibly showing a researcher that corticospinal connections are stronger. This conception confirmed that high EDSS indicates the failure in corticospinal connections. It can be seen from Table 2 that in both groups pattern of recording of MEP amplitude through different timeframes is saved — amplitude as raised as the time of recording increased. Although, it is worth admitting that MEP amplitude was decreased in group with higher EDSS. However, in our study there were not found statistically significant correlation (r=–0.16; p=0.09), there are studies that confirmed described connection. Vucic et al. [14] in their study confirmed significant negative correlation between disability (EDSS) and MEP amplitude and a significant positive correlation between EDSS and resting motor threshold.

Table 2 Transcranial magnetic stimulation parameters in patients with MS and different EDSS

TMS parameters	EDSS		p-value
	2.0–4.0 (n=75)	4.5–7.0 (n=21)	
MT (%)	42.64±9.95	48.28±12.23	0.03
MEP1 (mV)	1.26±1.17	0.34±0.24	0.12
MEP2 (mV)	1.68±1.48	0.5±0.32	0.76
MEP3 (mV)	3.55±2.39	1.53±1.33	0.67
MEP4 (mV)	4.8±2.89	2.13±1.58	0.97

TMS — transcranial magnetic stimulation; EDSS — expanded disability status scale; MT — a motor threshold; MEP — motor evoke potential.

Next step in our study was to compare TMS parameters between RRMS and PMS. Cortical MEP accounted for RRMS group — 2.04±1.73 mV; PMS group showed 1.38±1.05 mV. TMS parameters of RRMS cohort (n=76) described below: MT — 41.98±8.75%; MEP1 — 1.17±1.16; MEP2 — 1.57±1.48; MEP3 — 3.35±2.41; MEP4 — 4.47±2.84 mV. TMS parameters of patients with PMS (n=20) showed the next data: MT — 50.65±12.36%; MEP1 — 0.64±0.73; MEP2 — 0.87±0.88; MEP3 — 2.18±1.95; MEP4 — 3.22±2.88 mV. We found similar pattern of parameters to compare with EDSS divided groups. However, when data was divided into MS types, significant negative correlation was found in group of PMS between EDSS and MEP amplitude 1 (r=–0.43, p=0.018), MEP2 (r=–0.45; p=0.072), MEP 3 (r=–0.41; p=0.05), MEP 4 (r=–0.51; p=0.018). Significant correlation between EDSS and MT was described by Mori et al. [15] among group of RRMS patients. In study done by Conte et al. [16] founded in patients with SPMS that their MEP were lower in comparison with PPMS and control group and significant correlation between EDSS and MEP.

It would be useful to note that the progressive disability in PMS, such as PPMS and SPMS, is the result of cerebral and especially cortical degeneration, not just inflammatory demyelination, and that the process of degeneration is better reflected in functional neurophysiological measures, such as TMS, particularly paired stimulation, while the demyelination process is easier to see with MRI changes [13].

Conclusion

In our study we used TMS as a tool to indicate MS progression. We compared patients with MS according to the MS course and EDSS. We received a difference in TMS parameters that showed decreased conduction of impulses through corticospinal tract. The statistically significant difference was found between group with lower and higher EDSS that confirmed that ambulatory patients still have better connection of piramidal tract and lower MT in comparison with group of patients with restricted mobility. Although there were not significant correlation in RRMS group, in case of PMS was found significant negative correlation between EDSS and MEP amplitude. Thus, it is worth saying that TMS might be used as a predictive tool in MS progression, especially in differentiation of possible degeneration process and nor only inflammation.

Perspective of future research

It is an unmet need to find reasonable biomarkers to predict MS progression among different populations of MS patients. TMS might be an useful tool in perspective to conform primary or secondary progression of MS. The direction of future research could involve investigation of both sides of the body, not only dominant one that we used in this study. Also, it would be useful to compare data between upper and lower limbs especially in patients with impaired walking.

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Роль транскраніальної магнітної стимуляції у прогнозі множинного розсіяного склерозу

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Анотація. ***Мета.*** Дослідження описує різницю між показниками транскраніальної магнітної стимуляції (ТМС) у пацієнтів із різним перебігом розсіяного склерозу (РС) і розширеною шкалою статусу інвалідності (Expanded Disability Status Scale — EDSS), використання моторних викликаних потенціалів (МВП) і моторного порогу (МП) при парній ТМС. ***Об'єкт і методи дослідження.*** 130 хворих на РС неврологічно обстежено за EDSS. ТМС проводили 96 пацієнтам з РС. Інвентар ТМС включав магнітну котушку 90 мм, яка підключена до машини стимулятора ТМС. Імпульси від великого відвідного м'яза домінантної верхньої кінцівки реєстрували електроміографічним приладом. Параметри ТМС включали МП, кортикальний МВП і МВП, записаний через 2, 3, 12 і 15 с після доставленого стимулу. ***Результати.*** Порівняння між групами з різним балом EDSS показало суттєву різницю МП: вищий бал за EDSS зумовлював вищий МТ. При розподілі даних за типами РС виявлено достовірну негативну кореляцію в групі прогресуючого РС між показником EDSS та амплітудою МВП 1 (r=–0,43; p=0,018), МВП2 (r=–0,45; p=0,072), МВП3 (r=–0,41; p=0,05), МВП4 (r=–0,51; p=0,018). ***Висновок.*** Зв'язок між балом за EDSS, перебігом захворювання та електрофізіологічними параметрами ТМС може бути корисним у використанні парної ТМС як інструменту для демонстрації кортикальної дегенерації. Це перспективний напрям у майбутніх дослідженнях пошуку додаткового біомаркеру для прогнозування РС.

Ключові слова: розсіяний склероз, транскраніальна магнітна стимуляція, нейрофізіологія, діагностика, демієлінізаційне захворювання центральної нервової системи, біомаркер розсіяного склерозу.

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Надійшла до редакції/Received: 22.11.2023

Прийнято до друку/Accepted: 13.12.2023