Correlation between neuromuscular assessment and evoked potential in the prediction of the multiple sclerosis evolution

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Abstract: Background: Multiple sclerosis (MS) is characterized by a great heterogeneity of both its clinical course and the aspect of the lesions. The main purpose of this study is to evaluate the neuromuscular disorders in MS using electrophysiological parameters, in order to enable the rehabilitation physician to set the goals of a prophylactic intervention. The major research question addressed here is to identify the correlations between the electrophysiological parameters obtained by tensiomyographic (TMG) and visual evoked potential (VEP) testing in patients with MS, and to clinically apply these results in prevention and rehabilitation of motor disorders. The alteration of muscular structure and function affects the postural control. Research method: The group of subjects consisted of 40 MS patients, aged 38.15±11.19 years, without clinically detectable gait disorders. The neurophysiological assessment methods used were the visual evoked potentials (VEP) and tensiomyography (TMG). In addition, the clinical and functional assessments were performed by clinical examination and evaluation of the Expanded Disability Status Scale (EDSS) score and spasticity. Results: We found that there is a strong correlation between the values of the neuromuscular parameters, which reflect the intramuscular conduction, and the characteristics of the P100 wave. At the level of the tibialis anterior muscle (TA), the P100 has an increased latency, which is pathognomonic for MS, and this is directly correlated with an increased levels of displacement (Dm) and a decreased contraction time (Tc). We also investigated some of the muscles belonging to the posterior compartment of the lower leg, namely the medial gastrocnemius (mGM) and the lateral gastrocnemius (mGL). We observed, both in the mGM and mTA, the same significant correlation between the Tc and Dm on the one hand and the P100 wave on the other hand, this correlation being stronger for Dm. These analyses determined the most significant parameters having a diagnostic value, which may reveal changes in a preclinical stage. Conclusions: Exploring MS patients by these two methods of evaluation and correlating the results of these investigations created the basis of a new algorithm for diagnosing and predicting possible motor disorders in these subjects and also set the goals for a rehabilitation program. By identifying the correlations between the TMG and the VEP early on, we can implement precocious rehabilitation program with the purpose of preventing or limiting the gait and balance disorders that may occur in time in patients with MS.

Keywords: Multiple sclerosis, tensiomyography, visual evoked potentials, neurophysiology, assessment

Introduction

Multiple sclerosis (MS) is one of the most frequently diagnosed neurologic disease in younger people and involve major disabilities due to the central nervous system (CNS) injury. The most important characteristic of MS is repetitive inflammation and demyelination of the CNS structures. Ethopathogenic and clinical complexity as treatments need to have a very deep evaluation of neuromuscular function. MS is characterized by recurrent neurological events [1] (clinical relapses), attributed to multifocal lesions of the CNS [2]. The symptomatology and duration of the disease suggest the correct diagnosis in most cases. The MS symptoms can be mild or severe, of long or short duration and can occur in various combinations, depending on the affected area of the CNS [3].
The alteration of muscular structure and function, due to neurological disorders, is a particular aspect of MS, because the muscle system activity is control through sensorial inputs generated at the higher level of CNS; therefore, any variation of the muscle tonus or muscle contraction (e.g., weakness) disturbs the postural control. The skeletal muscle includes two types of muscle fibres (type I and type IIa and IIb), as well as two types of motor units (MU) (x). During muscle contraction, the MUs are progressively recruited according to the muscle activity. Both the structure of muscle fibres and the recruitment of MUs influence the muscle force. Muscle force depends on the number, the type of motor units and the frequency of muscle stimuli. The type II MUs generates more muscle force than type I fibres, due to a larger volume of muscle fibres.

The neurophysiological aspects of MS are linked to molecular and electrophysiological changes which are responsible for nerve conduction in the demyelinating axons. The speed of the nerve conduction is proportional to the nerve fiber diameter in normal axons, but not in the MS demyelinating axons [4]. For this reason, one of the consequences of the demyelinating process is an alteration of the muscle con traction and therefore a disturbance of the gait which early on may have undetectable clinical manifestations.

The aim of this study is to determine whether, in patients with MS, there is a correlation between neuromuscular parameter values, obtained by tensiomyographic (TMG) testing and electrophysiological parameter values, obtained by VEP.

The objectives of this study are to evaluate the effect of damaged nerve conduction in conjunction with intramuscular conduction as a result of muscle stimulation and onset of isometric contractions in MS, and to identify correlations between the electrophysiological parameters studied by two methods, the TMG and the VEP.

The goal of this study is to develop and implement a conceptual model of medical data acquisition and analysis, which will make possible an early diagnosis of neuromuscular disorders affecting the gait. For this reason, this study investigated whether there is any correlation between TMG parameters and VEP parameters (like the P100 wave). The pathogenic mechanism of MS involves the demyelination of nerve cells. This affect the muscle contraction and therefore the motor activity (e.g., gait). In this research we performed an early evaluation of the CNS and muscle alterations, and showed that there is a correlation between these two changes with the purpose of predicting the evolution of motor activity (e.g., gait), even in the absence of gait disorders, using classical and new methods (VEP/TMG). This will allow an early diagnosis and the implementation of a preventive rehabilitation program for each patient. A positive correlation between the TMG and VEP will also give us information about the severity of CNS and muscle disorders (muscle contractile properties), at a stage when the changes have a limited clinical expression.

The tensiomyography (TMG) is an assessment method used to monitor transverse muscle belly displacement under isometric conditions. TMG is a non-invasive method that determines the presence of a certain type of muscle fibers and also diagnoses various muscular statuses/conditions (fatigue, stress influence on the body, etc.). The diagnosis of a functional muscular symmetry as presented by studies of [5-8], either temporal or morphological, and the evaluation of muscular synchronization, and fast detection of an infra-clinical lesion of the muscle in situ (less than 5 minutes).

TMG also demonstrates a connection between the contraction time of the entire muscle and its composition (the percentage of the slow-twitch muscle fibers, determined histochemically).

Muscle weakness, along with muscle spasticity, are common in MS and this could be assess by TMG. Since the TMG response reflects the level of motor unit (MU) activation [9], measuring muscle fatigue is possible.

Regarding the muscle changes, the previous studies found that contraction properties of spastic muscle could be evaluated using the tensiomyographic method before and after the treatment of spastic muscles with BTX-A [10].

The VEP is a specific evaluation method for MS because a latency of VEP waves is present in more than 80% of MS patients and correlates...
well with optic neuritis, which is quite common in MS. In this context, the changes of the $P_{100}$ wave are: an increase of the latency, a significant difference between left and right and a decrease of the amplitude. At present, there are not so many studies regarding the correlation between VEP parameters and other evaluation methods. Finding that such a correlation exists could offer precocious information about the locomotor disorders and therefore the possibility of prevention by rehabilitation. Prior studies [11-13] that examined the VEPs in MS found that the $P_{100}$ wave in MS patients had prolonged latencies and reduced amplitudes, and that these characteristics were related to motor and visual dysfunction. A similar pattern of the $P_{100}$ responses was reported in moderately and severely fatigued MS subjects, in a recent study [14]. VEPs have also been reported to predict MS disability [12, 13]. These studies indicate that the VEP can be a very useful tool for optic nerve assessment and the surveillance of disease progression in MS.

In this context, the existence of a correlation between the TMG parameters and the VEP is very important [15-19].

**Materials and methods**

This research was carried out in compliance with the principles of ethics covered by the Declaration of Helsinki and the Law No. 206/2004 and it was approved by the Ethics Committee of the University of Craiova - the Research Center for Human Body Motricity (REB-870-14). All participants acknowledged their willingness to take part in the study by signing a written informed consent document.

**Subjects**

The group of subjects consisted of 40 MS patients (25 women and 15 men), with no clinically detectable gait disorders. The average age of the patients was 38.15±11.19 years. The inclusion criteria for this study were the following: patients who met the clinical and paraclinical diagnostic criteria for MS, were able to ambulate and also were members of the National Association of MS. Thus, according to MS diagnosis and staging criteria proposed by [20], the patients selected were included in a clinically defined MS category, namely patients with two flares and a clinical picture of two separate lesions, patients with a clinical picture of one lesion and another subclinical lesion (as evidenced by neurophysiological or neuroimaging explorations) and patients with primary progressive multiple sclerosis (PPMS), with ≥1 year of disease progression, brain dissemination in space, and clinical certainty of MS. In order to select the patient who will participate in our study, we used the following criteria: McDonald criteria, age >18 years, Expanded Disability Status Scale (EDSS) scale score 0-8, one of the follow symptoms-sensitive disorders, ataxia, chronic fatigue, but no other motor disorders like gait disturbance.

**Study design**

This is a cross-sectional study.

First, we performed a clinical and functional assessment, evaluating spasticity (Ashworth scale average score 1), pain (Visual Analogue Scale-VAS, average score 2), muscle force (scale 0-5, average value 3), postural control (Tinetti, score 14/16) and balance (Berg scale, average value 52). We also used the EDSS/Kurtzke (Kurtzke Expanded Disability Status Scale) method in order to quantify disability in multiple sclerosis.

It is known that the EDSS scale does not have a linear correspondence with clinical disorders in many cases. That’s why we placed a great emphasis on the clinical qualitative observation of gait.

The neurophysiologic assessment methods used were represented by the visual evoked potentials (VEP) [11] and tensiomyography (TMG) [12-14].

**Assessment methods**

The visual evoked potential (VEP) is composed of a specific three-phase response: $N_{75}$, $P_{100}$ and $N_{135}$, the most characteristic component being the broad positive $P_{100}$ wave.

The stimulation was performed after a short recording of a spontaneous electroencephalogram (EEG) and an isoelectric line was obtained by mediation. The stimulation was carried out by computer using a reversal pattern matrix with yellow and green LEDs. To register the VEP, we applied the method of visual stimulation using an area of yellow-green LED, which can
respond very quickly to ON/OFF commands (nanosecond calibration). The subjects were placed as comfortably as possible on a chair in a sound proof room. Their visual stimulus was presented at a fixed distance, on the LED matrix, which has a red point. The stimulator did not produce noise, which could generate an auditory stimulation. The room was poorly lit to facilitate eye adaptation, especially when there was a longer interval between the stimuli. Visual acuity was of utmost importance in the stimulation pattern, since the patient had to focus on the image in order to see it clearly. The stimulation rate was of 1-2 seconds and the field stimulation was “Full-Field”. The stimulation is monocular and alternative. The patients wore glasses.

**Technique for the collection and amplification of bio-potentials:** The bio-potentials collection was carried out using metal electrodes specific to electro-encephalogram. The electrode-patient interface was well degreased and cleaned using alight abrasive. The electrode paste utilized reduced the contact impedance to 3000-7000 ohmi and did not contain irritants. The electrodes were placed in accordance with the International 10-20 System using a simplified installation.

**The system to highlight VEP:** The system used to obtain VEP was in everyday use in the laboratory of functional explorations of the Department of Physiology. Stimulation was performed by a special device, which was able to emit flashes of light or a pattern reversal with vertical bars. To have the best response time and a low remanence, the stimulation device was equipped with electroluminescent diodes.

The device was triggered by a computer that ran the entire process of highlighting the VEP macular complex.

The EEG was collected using an industrial EEG. This device was connected to an analog/digital device, which was able to achieve a conversion of 12 bits at a maximum sampling frequency of 100 KHz. The analog numerical acquisition pattern used was PCL 818, with numerical digital input/outputs (I/O). To improve the memory transfer rate, this pattern was directly transferred to the computer memory. The computer used was a PC AT 486DX at 33 MHz.

In order to record the potential differences, we used an Ag electrode (first leg), which was coated in a cloth bag, soaked in a sodium chloride solution to reduce contact resistance. The other two legs had a supporting role and consisted of an insulating material, ensuring verticality of the first leg. The electrode was fixed on the scalp with rubber bands forming a headset that could be easily mounted on the patient’s head.

The patients were required to focus on a fixed point (red point) during the recording and they were allowed to rest after each stimulation session.

The biopotentials were amplified using a polygraph (R611) manufactured by Beckman.

To determine the evoked response, the latency and duration of waves N75, P_{100}, N135 were evaluated, but only the P_{100} wave parameters were statistically analyzed and interpreted, since this wave changes significantly in MS.

**The tensiomyography (TMG)** was the method employed for neuromuscular exploration.

The protocol of TMG is presented below.

Tensiomyography (TMG) evaluates the morpho-functional potential of the muscle and allows the detection of the muscular response to electrical stimulation. It measures transverse muscle belly displacement under isometric conditions. The method was developed in the Laboratory for Bioelectromagnetics (LBM) of the Faculty of Electrical Engineering, at the University of Ljubljana, Slovenia. The muscle belly displacement (enlargement) during contraction is observed and monitored. Valenčič and Knez demonstrated that TMG method provides valuable data regarding the contractile properties of muscle [5].

The displacement sensor is positioned perpendicularly to the tangential plane, on the largest area, above the muscle belly. The TMG method has been evaluated histochemical. There was a high positive correlation (r = 0.93) between the percentage of type I muscle fibers and contraction time for nine selected skeletal muscles [21]. Through this method we can appreciate the ratio between type I (fatigue-resistant) and type II (white, fast-twitch, with low resistance to
fatigue) muscular fibers (the phenomenon of fatigue appears before the completion of the electrical stimulation process). In order to complete the data collected from the clinical and paraclinical examination, we used the TMG as an evaluation method for determining the muscular fatigue and skeletal muscle composition in MS patients; the TMG was also necessary to establish the connection between the structure and morphofunctional properties of the muscle on the one hand, and its functional potential on the other. The evaluation of muscular fatigue can be performed using an intermittent electrical stimulation of the muscle. This stimulation was carried out with a TMG-S1 electrostimulator (Furlan & Co., Ltd.), using 5/5 cm Platinum-type electrodes, under increasing electrical current intensities (10 to 65 mA), the duration of the stimulation being one millisecond. An isometric contraction was produced as a result of the electrical stimulation. The detection of the muscular response to the electrical stimulus was performed using a G40, RLS Inc. sensor, which was placed perpendicularly to the muscle surface, in the area where the muscular geography is well displayed (this can be more precisely determined if the subject is requested to perform an isotonic contraction, if a muscle strength higher than 2 is possible). The sensor placed at this level exerted a 0.7 N/mm² pressure on the contact surface. This pressure is called pretension [14] and its role is to increase the response to the applied electrical stimulus. Because of the electrical stimulation, a transversal movement of the muscular fibers will occur and the sensor will record this. The amplitude of this transversal movement is proportional to the muscular force and the percentage of type I muscle fibers, which enables us, together with the data obtained from the other parameter, to evaluate the muscle fatigue and transmission speed. The measurement of the muscular response, and the data storage and analysis was carried out using a dedicated TMG software.

**Signal recording**

The TMG signals were transmitted to a Matlab Compiler Toolbox at a frequency of 1 kHz. Two supra-maximal responses were stored and then the average was calculated. The supra-maximal stimulation proposed by [12] is considered to correspond to a minimal stimulation and generates a maximal amplitude of the muscular deformation, recorded as Dm.
The investigation was performed on the lower leg muscles, namely the lateral gastrocnemius (mGL), medial gastrocnemius (mGM) and tibialis anterior (mTA) and was carried out as follows:

- For the lateral gastrocnemius (mGL) and medial gastrocnemius (mGM) evaluation, the subject was placed in a prone position with support for the anterior regions of the ankle. The point with the highest lateral contraction amplitude in this position was determined through plantar flexion against resistance (Figures 1 and 2).

- For the tibialis anterior (mTA) evaluation, the subject was placed in a supine position. The point with the highest lateral contraction amplitude was determined through dorsal flexion of the leg against resistance (Figure 3).

We specified that the sensor which recorded the muscular response to stimulation was attached to the point with the highest lateral contraction amplitude, and the electrodes were placed on both sides of the sensor.

The parameters evaluated through TMG were:

- The contraction time (Tc) - the time interval between the moment when the muscular contraction reaches 10% and the moment when it reaches 90% of the maximum (ms). The values of the contraction time depended on the percent of fast and slow twitch fibers [14] in the studied muscle. Thus, these values decreased in muscles with high percentage of type II fibers and increased in muscles with low percentage of type II fibers and high percentage of type I fibers.

- The amplitude of muscular displacement in the transverse direction - Dm (mm) - is a parameter which was also correlated with Tc values and depended on the flexibility of muscular tissue. Therefore, Dm values increased when explosive force was developed and thus the movement amplitude was higher, and decreased in the presence of a high muscle tonus.

- The delay time (Td) - the period of time between the moment of stimulation and the moment when we obtained 10% of the muscular contraction (ms).

- The sustain time (Ts) - the period of time between the moment when the muscular contraction is 50% and the moment when the relaxation reaches 50% (ms).

- The relaxation time (Tr) - the time interval between the moment when the relaxation is 50% and the moment when the relaxation is 90% (ms).
Tensiomyography (TMG) is a non-invasive, selective and reliable approach to measure skeletal muscle contractile parameters [22]. Among them, the contraction time (Tc) of muscles in vivo appeared to correlate with the proportion of type I fibers measured in seven cadaver muscles [23, 24]. Subsequently, Šimunič et al. [25] measured TMG parameters and performed a biopsy to determine the Myosin I (MHC-I) proportion of the vastus lateralis (VL) in adults. The data were used to build a multiple regression model that estimates the VL MHC-1 proportion from three predictors (Tc, delay time - Td, and half-relaxation time - Tr), which were derived from the TMG response. This model gave a 6.08% standard error of the estimate and explained over 87% of MHC-1 proportion variance. The Tc, a main predictor that explains 77% of MHC-1 proportion variance, is dependent on the rate of Ca^{2+} release from the sarcoplasmic reticulum. A more important factor, however, is the cross-bridge kinetics as the changes in Ca^{2+} in the cell are much faster than the Tc (Westerblad et al., 1993). The cross-bridge kinetics of a cell, as reflected by the shortening velocity and force-velocity relationship, are largely determined by the MHC isoform composition of the fiber [26].

TMG is sensitive to track changes in skeletal muscle contractile properties [exercise-induced muscle damage (EIMD) alterations in contractile properties] during an eccentric exercise [27]. Hunter, under well controlled conditions, observed the association between EIMD markers and skeletal muscle contractile properties extracted by TMG and found a decrease in the Dm and an increase in the Tc during EIMD [27]. This may be due to a greater recruitment of type II muscle fibers in the high-intensity eccentric exercise that is commonly used in controlled EIMD studies. Furthermore, the type II fibers have been found to be more susceptible to disruption compared to the type I, indicating that athletes with greater proportion of type II muscle fibers might also exert a higher EIMD response in other models used for inducing EIMD response [28].

### Statistical patterns

Statistical data processing and graphics were carried out using general mathematical software packages (Microsoft Excel) or statistics-specific (academic use package, MINITAB15 or the package distributed by the WHO, EPI2000).

Microsoft Excel calculations and statistical analyzes were performed using predefined functions, Data Analysis module as well as XLSTAT and WINSTAT suites.

The recorded values were processed statistically to define certain characteristics of parameters (variables). Statistical processing established both the existence of significant differences between certain sets of values and the correlations between parameters that characterize the studied group.

### Results and discussion

We present here only the important aspects of clinical and functional evaluation regarding the distribution of MS stages (Figure 4) and the results of scale EDSS/Kurtzke assessment (Figure 5). The EDSS/Kurtzke scale shows an average score of 3.27±0.15.

In studying VEP wave characteristics, we recorded the latency and duration of the $P_{100}$ wave and then we processed them statistically. The $P_{100}$ wave, the most visible and constant

### Table 1. Latencies and average periods of $P_{100}$ (ms) wave

<table>
<thead>
<tr>
<th>Stimulation right eye</th>
<th>Stimulation left eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fz-OL5</td>
<td>Fz-Oz</td>
</tr>
<tr>
<td>Fz-OR5</td>
<td>Fz-OL5</td>
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<td>Fz-Oz</td>
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**LATENCY**

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<th>Fz-OL5</th>
<th>Fz-Oz</th>
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<td>5.00</td>
<td>4.00</td>
<td>5.00</td>
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<tr>
<td>Average</td>
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<td>134.50</td>
<td>131.01</td>
<td>126.0</td>
<td>122.1</td>
<td>123.8</td>
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<tr>
<td>Std dev</td>
<td>22.7</td>
<td>20.2</td>
<td>18.70</td>
<td>15.7</td>
<td>16.1</td>
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<tr>
<td>Min</td>
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<td>113.9</td>
<td>103.70</td>
<td>109.8</td>
<td>107.8</td>
<td>109.8</td>
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<tr>
<td>Max</td>
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<td>159.1</td>
<td>148.87</td>
<td>146.8</td>
<td>147.8</td>
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**PERIOD**

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<th>Fz-OR5</th>
<th>Fz-OL5</th>
<th>Fz-Oz</th>
<th>Fz-OR5</th>
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</thead>
<tbody>
<tr>
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<td>5.00</td>
<td>5.00</td>
<td>4.00</td>
<td>5.00</td>
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<td>Average</td>
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<td>56.47</td>
<td>48.2</td>
<td>51.3</td>
<td>57.4</td>
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</tbody>
</table>

Legend: std. dev-standard deviation. Fz-OL5-freqency, lateral deviation eye. Fz-frequency, Z deviation. $P_{100}$-latncey 90-100 ms, wave.
wave of the primary complex, has a value of latency averaging 132.6 ms in the right eye and 123.6 ms in the left eye (Table 1). Regarding the wavelength duration, the average recorded value was 46.33 ms (45.3 ms in the right eye and 46.55 ms in the left eye) (Table 1).

The TMG recordings were performed on all lower limb muscles, but this paper presents only the values of the TMG parameters (Dm, Tc, Td, Tr, Ts) obtained from muscles belonging to the lower leg (mGM, mGL and mTA), Table 2.

Correlations obtained by analyzing VEP and TMG results

For the muscles that were studied, we determined 40 direct and 5 indirect correlations between the TMG parameters and the $P_{100}$ wave latency and 16 direct and 19 indirect correlations between the TMG parameters and the $P_{100}$ wave length (Figures 6 and 7).

We noticed that in the tibialis anterior muscle (mTA) the $P_{100}$ wave, which is pathognomonic for MS, has an increased latency and is directly correlated with increased levels of the Dm and decreased Tc values. This means that intramuscular conduction velocity decreases, although the displacement amplitude remains constant or increases.

Analyzing the ratio between direct and indirect correlations in the same muscle group, we found that the TMG neuromuscular parameters and the $P_{100}$ wave have the same sense of variation (based on Pearson coefficient). Furthermore, we observed (Table 3) that this tendency is reversed for the Td, which shows that when $P_{100}$ wave latency increases the recruitment of motor units decreases.

We also investigated some of the muscles belonging to the posterior compartment of the lower leg, namely the medial gastrocnemius (mGM) and lateral gastrocnemius (mGL). We observed, both in the mGM and mTA, the same significant correlation between the Tc and the Dm on the one hand and the $P_{100}$ wave on the other hand, the correlation between the Dm and the $P_{100}$ wave being stronger, especially for the left lower limb. The mGL investigations showed similar results.

In MS patients without gait disorders, the $P_{100}$ wave delays values differ significantly statistically, in most derivations recorded, underlying VEP change both in the patients with clinically symptoms and in those with sub-clinical
lesions. The studies of [29-31] indicate an increase in $P_{100}$ wave latency. $P_{100}$ wave periods varied statistically in significantly.

The TMG analysis of the posterior muscular compartment of the lower leg showed similar values of the Dm form GL, somewhat lower in the left leg, which allowed us to conclude that the balance and motor control disorders developed in MS induced structural asymmetrical changes in the muscles, due to differential mechanical application, right-left, generated by the alteration of equilibrium and probably muscle fatigue. The decrease in the Dm is dependent on an increased muscle tone. In the mGM we saw a reversal of this situation, namely extremely low values of the Dm, which probably is the consequence of a compensatory mechanism. This observation, extracted by TMG, completes the muscle biopsy studies conducted in the mTA, whereby the presence of atrophy and increased muscle tone in the gastrocnemius, were thought to have been processes specific to hemiplegia findings in study of [32].

In the mTA, we observed that the Dm had elevated values in MS patients, superior to those recorded in the gastrocnemius, which indicates the presence of allow muscle tonus than in the posterior region of the calf, perhaps with the purpose of preserving the ankle kinetics, an important item in gait initiation. In gastrocnemius muscles, Tc values were lower with increasing Typell fibers, an aspect emphasized by [32] and explained by changes of enzymes, growth which can also be explained by the decrease tendency in cross-sectional area was observed by Kent-Braun J. et al. [33] in Typell fibers in MS and correlated with the Type II fiber atrophy.

This increase can be regarded, probably, as a compensatory reflex mechanism caused by structural changes.

In them TA, the Tc values were high, suggesting an increased percentage of Type I fibers, the consequence of an adaptive process to a pathological condition.
The recruitment of motor units was assessed using the Td parameter, a decrease of the delay time indicating a very poor-recruitment of motor units in them TA.

We observed a direct correlation between the P100 wave characteristics, namely latency and duration, and the TMG parameters in the tested muscles. The patients in the studied group having a large number of correlations in the analyzed muscle groups.

VEP and TMG parameters analysis revealed specific aspects consistent with the data in the literature. These analyses disclosed the most important and significant parameters with diagnostic value, which could detect precocious modifications without clinical expression.

It is necessary to specify the parameters and correlations to provide a high degree of simultaneous predictability in the modification of the applied test characteristics.

Analyzing Table 3 we see that there is approximately the same number of correlations for the parameters Td, Ts and Tr, without a significant relationship.

Moreover, development of the two parameters indicates a low muscle tonus while keeping elasticity. On the other hand, these correlations will allow the setting and monitoring of the left-right muscle balance and implicit, the dynamic equilibrium disorders, even in the absence of clinically detectable gait disorders.

These correlations suggest the presence of certain conduction abnormalities in the peripheral nervous system of the lower limb induced by the demyelination process.

There are few materials in the topic-specific literature regarding the correlations between VEP and various imaging techniques [magnetic resonance imaging (MRI), optical coherencemography], presented in the studies of [34], as well as between VEP and assessment scales-EDSS, investigated by [35]. The above-mentioned data emphasize a greater sensitivity of VEP in comparison with imaging techniques.

These facts support our original study, by joining classic investigation in MS-VEP-the tests that TMG performed for the first time in our country, (these test are performed internationally, especially in trauma recovery, neurological

<table>
<thead>
<tr>
<th>Muscle Parameters</th>
<th>Direct correlations with latency</th>
<th>Indirect correlations with latency</th>
<th>Direct correlations with wave period</th>
<th>Indirect correlations with wave period</th>
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<tr>
<td>mTA</td>
<td>Tc 1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dm 7</td>
<td>-</td>
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<td></td>
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<td>2</td>
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<td></td>
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<tr>
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Legend: mGM medial gastrocnemius. lGL lateral gastrocnemius. mTA tibialis anterior. Tc-contraction tim; Dm - displacement; Td - delay time; Ts - sustain time; Tr - relax time.

Therefore, TMG allowed us by employing two of its parameters, namely the Tc and the Dm, to achieve correlations with the P100 wave, which will enable a prediction about changes in muscle structure and CNS before gait disorders become clinically detectable due to the fact that VEP implementation and P100 wave analysis representearly diagnostic tools in MS.

This wave represents a diagnosis tool that paralleled the trends of the Tc and Dm parameters; its dynamic indicates an increase in the percentage of Type I fibers, justified by the need to counteract muscle fatigue.
recovery and sports performance). In order to improve the health and quality of life in patients with demyelinating disease, it is necessary to complete the VEP testing after photo stress studies with multifocal VEP and to increase the number of subjects in the studied lots.

The tables show the data about the values of TMG and VEP parameters and also the correlations (both direct and indirect) between these two categories of parameters, in order to emphasize the role of both methods in predicting the muscle disease progression based on the neurophysiological disorders produced by the nerve conduction alteration. For this reason we chose only some of TMG and VEP parameters, although we analyzed more parameters in our study.

Conclusions

There are delays in $P_{100}$ wave of more than 90-100 ms, that were statistically significant, even in subjects who, clinically, do not show abnormal gait, thus emphasizing subclinical optic neuritis lesions.

The tensiomyographic analysis, which includes measurement of the muscle movement amplitude and relaxation time showed an increased muscle tonus in the gastrocnemius muscles, which explains the reduction of the leg motor control during gait in the heel attack phase. An increase of the muscle tonus in the mGM and mGL suggests a decreased muscle contraction in the anterior compartment of the lower leg, which is responsible for a limited dorsiflexion in the moment of a heel attack. This aspect could be predicted by the TMG evaluation of the gastrocnemius muscles, long before the clinical gait disorders become visible.

In our study, the contraction time (a TMG parameter), recorded high values in anterior calf muscle group (54.93 to 60 ms) and correlated with an increase in the type I muscle fibers and muscle fatigue.

The TMG study identifies a more severe reduction in motor unit recruitment in the anterior calf muscle group, which resulted in a functional deficit and a poor coordination of the foot during gait.

We found increased values of the sustain time (Ts) in the calf muscle groups, which means that there is an attempt from the part of the body to stimulate the growth of the type I muscle fibers as a way of counteracting the muscle fatigue.

The $P_{100}$ wave characteristics were correlated with a significant number of TMG parameters.

Exploring MS patients by these two methods of investigation, classical and VEP, and correlating the results of these investigations help created a new algorithm for diagnosing and predicting the gait disorder progression.

By identifying the correlation between the TMG and VEP from the very beginning, we can implement rehabilitation programs in the early stages of the disease in order to prevent or limit the gait and balance disorders that may occur in time in patients with MS.

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Disclosure of conflict of interest

None.

Abbreviations

TMG, tensiomyography; VEP, visual evoked potential; mGM, medial gastrocnemius muscle; mGL, lateral gastrocnemius muscle; mTA, tibialis anterior muscle; Dm, displacement; Tc, contraction time; Td, dealy time; Tr, relax time; Ts, sustain time; MS, multiple sclerosis; MRI, magnetic resonance investigation; CNS, central nervous system; EDSS, Expanded Disability Status Scale; EEG, electroencephalography.

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Prediction of multiple sclerosis evolution


