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Analysis of neuromuscular parameters in patients with multiple sclerosis and gait disorders

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Abstract

Gait is a motor activity that requires understanding the dynamics and functional anatomical elements that make possible its cyclical conduct. Patients with multiple sclerosis record impaired balance and gait due to the process of demyelination, disorders that can be estimated by quantifying neuromuscular and cortical parameters. The aim of this paper is to present both an analysis of these parameters in the thigh muscles and an evaluation of cortical parameters obtained by visual evoked potentials (VEP). *Patients and Methods*: The study was conducted on a group of 13 patients (mean age 38 years) with multiple sclerosis (MS), who had clinically detectable gait disturbance. Evaluation methods used were tensiomyography (TMG) and VEP, the monitored parameters were: contraction time (Tc), stance time (Ts), displacement (Dm), if TMG in the two muscle groups of the thigh (biceps femoris and right femoris), and if VEP the assessed waves were N_{75}, P_{100}, $N_{135\text{-}145}$. *Results*: There were estimated the average values of latency and duration of the three analyzed waves in VEP, the values of wave $N_{135\text{-}145}$ were far higher than physiological values. In terms of TMG values, they results indicate the existence of a clear right–left functional asymmetry. *Discussion and Conclusions*: Analyzing these results, we note an increase in the muscular tone of the groups studied, a functional asymmetry agonist/antagonist, low speed response to stimulus. Regarding VEP wave parameters, we find significant variations of these waves' latencies, particularly of P_{100} wave, while the duration of these waves did not register significant figures. In conclusion, we can emphasize a change in muscle structure with predominantly type I muscular fibers and inter-neuronal connections between areas of the association to substitute the lesions occurred in specific areas.

Keywords: gait, visual evoked potentials, tensiomyography.

Introduction

Locomotion assessment requires knowledge and understanding of locomotion dynamics and control mechanisms, aspects incompletely elucidated [1].

Gait is a cyclic locomotor movement, which is achieved by successively moving a leg before the other. One of the gait characteristics is the continual support of the body on the ground, either on foot or on both feet. Unilateral stance takes five times longer than bilateral stance: thus, within one hour we lean 50 minutes in a foot. During unilateral support, the lower limb, which supports the body weight, is called the stance member and the other lower limb is called the swing member [2].

During a gait cycle, there are two main phases: the stance phase and the swing phase. Simultaneous action of the two legs is carried out so as to share responsibility for the body weight support when both feet are in contact with the ground (namely, the body support is completed by both legs).

In multiple sclerosis (MS), there are identified certain symptoms of motor disorders (spasticity secondary muscular cramps) affecting autonomous muscles (urinary, bowel, sexual dysfunctions); symptoms characteristic to spinal cord damage may also be present: decreased limb strength to paresis especially in lower limbs, mono-, hemi- and paraparesis, myoclonus, exaggerated tendon reflexes, presence of pathological reflexes – positive Babinski, lack of abdominal cutaneous reflexes, pyramid hypertonia, cerebellar symptoms (Charcot triad, consisting of dysarthria, ataxia, cerebellar tremor); gait disorders, dysmetria, nystagmus; incoordination, which can either lead to ataxia or occur only as "clumsy" movements, spastic-ataxic gait [3].

Disordered, dys-synergic gait is specific to MS and it is characterized either by unequal steps on a hypotonic or hypertonic background or asymmetric gait due to muscle fatigue and lack of motor control [4].

The purpose of this research is the assessment of correlations between parameters of neuromuscular muscle of the thigh and visual evoked potentials (VEP) in a group of MS patients presenting clinically detectable abnormal gait.

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Patients and Methods

The study group consisted of 13 MS patients, seven men and six women, with clinically detectable gait disorders. The patients were selected conform to specific inclusion and exclusion criteria. Inclusion criteria were: clinical diagnosis of MS and a certain clinical picture of a MRI lesion. Exclusion criteria were: patients who were in gait impossibility, having experienced more than two relapses and incomplete anamnesis. Average age 38 years, mean duration of disease was of 10 years. In terms of clinical-functional gait symmetry, two patients show a normal, symmetric gait, seven patients have abnormal gait and four patients asymmetric gait (Figure 1).

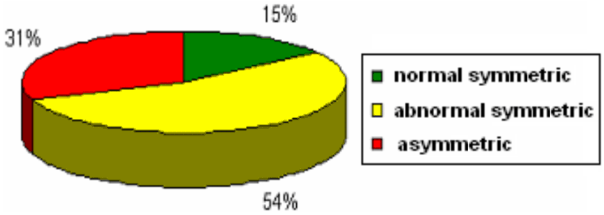

Figure 1 – ***Distribution of patients depending on gait symmetry.***

The evaluation methods used included VEP and tensiomyography (TMG).

Visual stimulation was performed with a matrix of yellow-green LED, which can respond very quickly to ON/OFF command (order of nanoseconds) [5]. In order to stimulate the patient, he is seated, as comfortable as possible, in a chair in a soundproof room. He is presented with a visual stimulus fixed at a certain distance on the LED matrix. It is important that the stimulator may not produce any noise, which could generate an auditory stimulation. In the room, there may be a low light background to facilitate the adaptation of the eye, when the interval between the stimulations is long. Of particular importance in the stimulation pattern is visual acuity, the patient should focus on the image to see it very clearly. Parameters characterizing the visual stimulation are: the rate of stimulation, intensity, contrast, size of the stimulation area, orientation pattern. The rate of stimulation is of 1–2 seconds. Bio-potentials collection is made using metallic electrodes, specific to electroencephalography. Placing electrodes shall be in accordance with the 10–20 International System, using a simplified installation device. The system used to obtain VEP is in current use of laboratory of functional exploration of the Department of Physiology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania. Stimulation was performed by a special device capable of emitting light flash or reversal pattern with vertical bars. To have the best response time and the lowest remanence, the stimulation device was made of light emitting diodes.

The device is controlled by a computer, which runs the entire process of highlighting the macular complex of VEP.

EEG is collected using an EEG industrial device.

Tensiomyography is a method that allows the assessment of contractile properties of striated skeletal muscle The equipment used to record TMG parameters consists of: electrical stimulator TMG-S1 (Furlan Co. & Ltd.), bipolar surface electrode Platinum 5/5 cm type, displacement sensor G40, RLS Inc.; PC for data collection and processing, equipped with dedicated software type TMG 100.

This method allows both the assessment of the contraction capacity of the studied muscles by shortening it and of the rate of shortening during muscle contraction produced by electrical stimulation. The method consists of applying an electrical stimulus whose intensity increases progressively (single stimulus) and registering a contractile response through a transducer. Electrical stimulation is in the proximal point of muscle insertion and the contractile response is registered by means of a transducer that is applied to the motor point of the muscle.

The necessary stimulation is performed by surface electrodes at certain intensities, gradually increasing from 10 mA to an intensity that determines the maximal response, highlighted by the morphology of the contraction–relaxation curve. Stimulation is given by successive pulses, its duration being of 0.1 ms for each stimulus. Frequency of stimulation: 5–25 Hz, voltage 40–50 V. Total stimulation time interval is of 10 s. The stimulation electrodes are placed symmetrically in relation to the displacement sensor: the anode is situated distally and the cathode is proximally, at about 20–50 mm from the measuring point (the location of the sensor). This stimulation causes an isometric contraction.

Detection of muscle response to electrical stimulus is performed using a G40 sensor, RLS Inc., which incorporates a spring developing a force of 0.17 N/mm and is placed at right angles to the surface of the muscle, in the muscular area where the relief is very well highlighted (this relief can be determined more accurately if the subject is required to perform an isotonic contraction when/if the muscle strength is higher than 2). Following electrical stimulation, there will be a transverse displacement of muscle fibers, which is recorded by the sensor.

The amplitude of this transverse displacement is proportional to muscular force developed during isometric contraction and with the percentage of type I muscle fibers, which allows, together with data provided by other parameters, evaluation of muscle fatigue and intramuscular conduction velocity. Measurement of muscle response and storage, data analysis was performed using a TMG software.

The muscle groups assessed were: right femoris (mRF) and biceps femoris (mBF), and TMG parameters analyzed were: latency (Td), contraction time (Tc), stance time (Ts), relaxation time (Tr), muscle amplitude in transverse displacement (Dm) (26, 104) [6, 7]. Among these specific parameters, we will focus on Tc, Ts and Dm to assess the impact on the knee during gait control in conjunction with the VEP.

Results

This technique and the method of signal averaging allow the extraction of VEP components from the "random noise" of the electroencephalogram, mainly the specific complex N_{75} P_{100} $N_{135\text{-}145}$. Studying the characteristic parameters of the three waveforms, we recorded the wave latencies and durations, which proved to be the most illustrative parameters, and used them in our statistical processing.

The VEP test results are given in Tables 1 and 2. As far as N_{75} wave is concerned, we notice a latency with an average value ranged between 84.65 ms and 89.94 ms. The interocular differences were within physiological limits, under 7 ms, the maximum permissible value. Analyzing the values recorded in the subjects with MS, with abnormal gait, we found out that the mean latency is higher in the patients without gait disorders compared to those with gait disorders. Taking into account the great data dispersion, we determined no statistically significant difference between MS patients and the healthy ones.

Table 1 – ***Values of average latency for N_{75}, P_{100}, $N_{135\text{-}145}$ waves [ms]***

Waves	Values	Stimulation right eye			Stimulation left eye		
		Fz-OL5	*Fz-Oz*	*Fz-OR5*	*Fz-OL5*	*Fz-Oz*	*Fz-OR5*
N_{75} wave [ms]	No.	9.00	9.00	10.00	9.00	11.00	10.00
	Mean	88.75	84.65	84.70	89.32	88.76	89.94
	Std. dev.	8.64	8.65	9.52	10.59	7.00	9.02
	Min.	73.92	74.95	66.74	74.95	77.00	78.03
	Max.	99.59	103.70	98.56	104.72	99.59	104.72
P_{100} wave [ms]	No.	12.00	12.00	11.00	12.00	12.00	12.00
	Mean	121.15	119.78	122.55	128.85	126.54	128.94
	Std. dev.	15.25	15.34	15.17	18.26	15.55	15.93
	Min.	99.59	98.56	91.38	107.80	110.88	106.78
	Max.	155.03	154.00	155.03	165.30	162.22	163.24
$N_{135\text{-}145}$ wave [ms]	No.	9.00	10.00	7.00	8.00	9.00	9.00
	Mean	166.67	169.61	174.98	165.17	166.67	165.30
	Std. dev.	26.64	35.90	33.96	19.67	14.90	13.22
	Min.	130.39	128.34	143.74	146.82	149.90	148.87
	Max.	219.71	237.17	245.38	205.34	189.94	191.99

Table 2 – ***Values of average time of N_{75}, P_{100}, $N_{135\text{-}145}$ waves [ms]***

Waves	Values	Stimulation right eye			Stimulation left eye		
		Fz-OL5	*Fz-Oz*	*Fz-OR5*	*Fz-OL5*	*Fz-Oz*	*Fz-OR5*
N_{75} wave [ms]	No.	9	9	10	9	11	10
	Mean	25.78111	26.35111	25.46	31.82556	28.93273	27.925
	Std. dev.	8.749176	11.60472	9.331099	9.267829	12.60597	7.288204
	Min.	17.45	13.35	18.48	22.59	17.45	15.4
	Max.	41.07	47.23	45.17	52.36	61.6	39.01
P_{100} wave [ms]	No.	12	12	11	12	12	12
	Mean	47.39833	50.30583	51.52091	45.94333	47.9975	46.88417
	Std. dev.	19.48955	17.21262	17.13203	18.32659	13.2722	18.00881
	Min.	21.56	24.64	32.85	26.69	25.67	28.75
	Max.	96.51	95.48	85.22	88.3	78.03	95.48
$N_{135\text{-}145}$ wave [ms]	No.	9	10	7	8	9	9
	Mean	48.59667	57.084	53.82714	49.79375	44.71778	39.69778
	Std. dev.	21.05502	33.46841	28.92298	23.90541	24.71011	26.47723
	Min.	22.59	24.64	13.35	20.53	14.37	15.4
	Max.	77	132.44	102.67	91.38	89.32	93.43

For P_{100} wave, the average means of latency were between 119.78 ms and 128.94 ms. In terms of latency, P_{100} wave, which is the most visible and steady wave of the primary complex, records a highly significant statistical difference compared to the group without gait disorders. The same aspect is seen when comparing healthy subjects with the patients with gait disorders.

In the case of wave $N_{135\text{-}145}$ the mean value ranged between 165.17 ms and 174.98 ms, far exceeding the upper limit of the physiological range. Concerning the third component of the specific complex, $N_{135\text{-}145}$ wave, the average latency values greatly exceeded the maximum physiological range. There were statistically significant differences in the average means between the patients without gait disorders and MS patients.

Regarding the mean values of time duration, they varied: between 25.46 ms and 31.82556 ms for N_{75} wave. The high dispersion of the values resulted in statistically significant differences between the patients without gait disturbance and the MS patients; the same differences were recorded while comparing the values obtained in the healthy subjects without gait disorders.

Regarding the mean values of time duration, they varied: between 45.94333 and 51.52091 ms for P_{100}. The other parameter analyzed, the waveform length, is comparable with the lot of the healthy subjects, without providing any data to show statistically significant differences for the group of MS subjects.

Regarding the mean values of time duration, they varied: between 39.69778 and 57.084 ms for $N_{135\text{-}145}$ wave.

The length of $N_{135\text{-}145}$ waveform – its average values are between 44.62 and 56.83 ± 21.50 ms – was of 30. 19 ms in the group of MS patients; there was no statistically significant difference when comparing these patients with the healthy ones. The same results were obtained when comparing the subjects with gait disorders, with or without asymmetry, with the group of healthy subjects. Analysis of VEP parameters recorded in the patients with multiple sclerosis also includes the correlation of interocular differences in our study, particularly when analyzing the waveforms latency. For instance, in the case of N_{75} wave, the interocular differences of the waveform latencies (DIOL) had values that exceed both the values recorded in the healthy subjects involved in the study, and in the two groups of subjects with MS, who had gait disorders with or without asymmetry in the left lateral bypass (OL5).

Analysis of TMG parameters shows that the normal mean value Dm is 8.17 mm and the values recorded in the MS patients are shown in Table 3. For Tc normal, the average values are 32.83 ms and the values determined in the assessed group are shown in Table 4. For Ts, the average values 146.8 ms for mRF and 183.1 ms for mBF are normal and the values of investigated patients are shown in Table 5.

Table 3 – ***Average values of Dm for the assessed muscles [mm]***

Dm	m.B.F.		m.R.F.	
	Right	***Left***	***Right***	***Left***
Mean	5.53	4.37	3.59	3.21
Std. dev.	3.64	3.90	2.08	2.60
Min.	-1.00	-1.00	1.10	-0.20
Max.	10.90	9.50	7.70	7.60
No. val.	13.00	13.00	13.00	13.00

Table 4 – ***Average values of Tc for the assessed muscles [ms]***

Tc	m.B.F.		m.R.F.	
	Right	***Left***	***Right***	***Left***
Mean	37.58	26.39	24.88	24.42
Std. dev.	17.83	17.43	5.38	8.34
Min.	-1.00	-1.00	17.10	10.90
Max.	72.40	46.30	36.40	39.10
No. val.	13.00	13.00	13.00	13.00

Table 5 – ***Average values of Ts [ms] for the assessed muscles***

Ts	m.B.F.		m.R.F.	
	Right	***Left***	***Right***	***Left***
Mean	214.62	231.34	132.57	136.32
Std. dev.	95.61	218.56	67.05	85.13
Min.	-1.00	-1.00	41.50	42.10
Max.	440.30	838.90	260.20	392.70
No. val.	13.00	13.00	13.00	13.00

Analyzing the results recorded by TMG, we notice that in the posterior region of the thigh, mBF records right-left functional asymmetry, with higher values in the right lower limb. In the rectus femoris (mRF), we notice significant differences between the group of healthy subjects, whose mean values are 6.59 mm in the right lower limb and 6.79 mm in the left lower limb, comparatively to MS patients, whose values are 3.59 mm in the right lower limb and 3.21 mm in the left lower limb, respectively 3.17 mm in the right lower limb and 2.80 mm in the left lower limb. Therefore, there is a functional asymmetry with higher values in the left lower limb, but with no significant differences between the two categories of subjects.

Muscular displacement (Dm) records highly significant values of mRF, bilaterally in the healthy subjects comparatively to the MS patients. In the posterior region of the thigh, we notice significant values in the group of healthy subjects in comparison with MS patients, particularly in the left lower limb. Compared to the average mean, we notice that in the mRF the average values of the MS group are much lower than the values of the healthy group. Also, the maximum values are below normal figures, while the minimum values can reach zero, meaning that there are patients who do not respond to muscular stimulation. The low values of Dm show an increased muscle tone.

In the posterior region of the thigh and calf, we notice that the low values of Dm in mBF are recorded in MS subjects with gait disturbance, which means that they show a much-increased muscle tone, but there is a maximum response to stimulation. This aspect can be corroborated with the results obtained when analyzing mRF and, probably, the high increase in mRF tone is caused by the need to develop a different gait pattern, which can benefit from the knee stability. This gait pattern must have been the result of balance disorders. Analyzing Tc, we notice certain average values with significantly higher Tc values, which means there is a definite fatigue of the muscles of the right lower limb. These values are correlated with Dm evolution, which is low (<8 mm), meaning an increased muscle tone. We find Tc values, which are lower than the minimum normal values, meaning an increase in the percentage of type II fibers.

Analyzing the Ts values, we determine that this parameter has higher values in subjects with MS and gait disturbance, which means that there is a muscular contraction caused by the alteration of the structural configuration of the muscle, consistent with the increased muscle tone.

Discussion

Analyzing the results obtained by TMG, we note that mBF records sharp left and right functional asymmetry, with high values of Dm. Regarding the same muscle group, Tc is found significantly increased, especially in the right limb, which means a severe muscle fatigue and an increased muscle tone, as well as a small intramuscular speed [8]. Assessment of Ts values shows high values in mBF, indicating a constant contraction due to the changing of the structural configuration of the muscle in accordance with the increase of muscle tone [9]. Regarding mRF, we notice a functional asymmetry with higher values in the left lower limb due to the decrease in Dm values; the average values are low and the minimum values reach 0, which means that stimulation causes no muscle response but an increased muscle tone. Tc records lower values than normal ones, and intramuscular conduction velocity indicates lower values in the right limb, which is consistent with functional right-left asymmetry [10, 11]. Ts analyzed in terms of values shows increased values in the left lower limb, which is also correlated with the above-mentioned parameters, supporting the functional asymmetry.

The results obtained by VEP assessment show an increase in N_{75} wave latencies, which is correlated with an expansion of demyelinating lesions and spinal nerve lesions [12, 13]. Statistically, regarding the length of N_{75} a wave, there is recorded no significant result. In P_{100} wave, we notice a latency prolongation, which is the main aspect of the VEP changes. The values of P_{100} wave durations are statistically insignificant. The latency of $N_{135-145}$ wave records statistically significant differences, there is probably an activation of several cortical areas during stimulation. Similar to the other two waves, $N_{135-145}$ wave duration has no statistically significant values [14].

By calculating the correlation coefficients between the VEP and TMG, we notice the existence of both direct and inverse correlations, predominantly direct correlations, between N_{75} and P_{100} waves and TMG parameters, while between $N_{135-145}$ and TMG parameters there are predominantly reverse correlations [15, 16]. This means that there is an activation of neuronal plasticity [17] processes that contribute to the definition of a particular profile of $N_{135-145}$ wave.

Calculating the correlation coefficients between the results of VEP tests [18] and the data obtained by tensiomiography led and highlighted the existence of certain direct and inverse correlations between the above-mentioned elements. Therefore, calculating the Pearson's correlation coefficient allowed the finding of 737 correlations, out of which 424 were direct correlations and 313 indirect ones. Correlation analysis was deepened by determining the number of VEP parameters correlated with the parameters of the other two tests. The characteristics of the waveforms N_{75} and P_{100}, originating from the specific visual cortical areas [19], were correlated in comparable number with TMG parameters (89 and 121 – TMG). As we can easily see, the number of correlations specific to P_{100} wave is higher than that of the N_{75} wave, which can be explained by the increased number of parameters of the waveform P_{100}, correlated with the parameters of the other two investigations. We can also notice the predominance of the direct correlations on the reverse correlations in both VEP waveforms and the other two tests, especially in correlation with TMG and P_{100} wave.

On the other hand, we did not expect that most of the correlations (40%) were recorded in $N_{135-145}$ wave, a waveform generated by cortical association areas, which was less studied due to its unsteady nature and characteristics [20]. This aspect points to important changes in interneuronal connections [21] in the association areas to replace the damage occurred in specific areas. Thus, a certain function deployment is restored, using information from a controlateral area, considered less affected. The correlations of N_{135} wave with TMG parameters and gait parameters have special features compared to other waveforms of VEP specific complex. That is why, the inverse correlations with TMG exceed the direct correlations and the ration direct/reverse correlations of VEP with TMG and gait is in a perfect balance.

Taking into consideration all the above-mentioned aspects, we underline the existence of certain processes of neural plasticity, which clearly picture a particular profile of the waveform N_{135} and it is, therefore, an item of real interest for our study and future scientific trials. The specialty literature is very poor in studying the correlation between VEP and imagistic procedures – nuclear magnetic resonance, optical coherence tomography [16, 22–25]. The previously mentioned data focus on the greater sensitivity of the VEP *versus* imagistic testing.

Conclusions

Summarizing the results obtained by the two types of investigations, we note that increased values of N_{75} wave latency are closely linked to the progressive development of demyelinating lesions, including spinal and nervous area. Regarding the duration time of the three waves assessed in our study, this does not seem to be a predictive factor in disease progression. In TMG parameters, the increased values of Tc in the posterior thigh muscles correlate with the increase in the percentage of type I muscle fibers and muscle fatigue installation. We have to note the importance of $N_{135-145}$ wave, less studied so far, which indicates the development of inter-neuronal connections between associated areas, to substitute the lesions occurred in specific areas. Correlations between VEP and TMG parameters are significant for P_{100} wave.

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Author contribution

All authors have contributed equally to this study.

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