CORRELATIONS BETWEEN ELECTROPHYSIOLOGICAL PARAMETERS AND COMPUTATIONAL GAIT ANALYSIS AT PATIENTS WITH MULTIPLE SCLEROSIS

DOCTORATE THESIS

RESUME

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PART I – KNOWLEDGE STAGE

1. MULTIPLE SCLEROSIS

The first chapter presents multiple sclerosis (MS) as a chronic, often progressive disease, characterized by inflammatory processes at the level of central nervous system, associated with demyelisation in axonal area.

Factors that have been involved in etiology and pathogenesis of MS are demographic, genetic, infectious and immunological. Neuropathogenesis MS of lesions is based on studies which showed four patterns of the disease (Lucchinetti C. et al., 2000; Ferguson B. et al., 1997).

The second part of the first chapter illustrates neurophysiologic characteristics of MS, which emphasize the fact that anomalies of nervous transmission involve a symptoms produced by the interruption of myelin layer. This will lead to a longitudinal distribution of the current flowing along internodes membrane, where Na channels register a low density (Frohman E.M. et al., 2003).

The last part of the first chapter presents MS clinical division into four patterns (Hufschmidt şi Lücking, 2002), as well as paraclinical evaluation focussing Nuclear Magnetic Resonance (MRI) (Francis G.S. et al., 1995; Frohman E.M. et al., 2003; Fazekas F. et al., 1999 Brück W. et al., 2001; Brex P.A. et al., 2002), visual evoked potentials, cephalorachidian liquid examination, blood tests and histopathology examinations. Assessment of disabilities benefit from specific tests for mobility, balance, posture and cognition.

2. NEUROPHYSIOLOGICAL ASSESSMENT

The second chapter of this paper brings forward classic and actual investigations of neurophysiologic evaluation, such as evoked potentials (EP) and tensiomyography (TMG).

EP are electrical manifestations of external stimuli reception and of central nervous system (CNS) responses released by these stimuli. Visual evoked potentials (VEP) represent the recording of bioelectrical activity in projection areas of occipital pole at the scalp level.

TMG is a relatively recent technique, which allows assessment of contractile properties of muscles by using an electrical stimulus placed on the highest zone of the muscle, generating an isometric contraction (Šimunic B., et al., 2005), whose parameters will be analyzed and statistically processed.

3. BIOMECHANICS OF HUMAN GAIT

The third chapter of this paper describes biomechanics of human gait, including an accurate analysis of gait and a thorough description of its stages. Normal gait characteristics depend on the
posture assessment in orthostatic position, which is given by the perfect symmetry and alignment of lower limb joints. The range of joint movements in neutral position offers practical applicability information relating to movement axes at the level of foot joints. The main pathologic types of gait are also depicted in this chapter, besides the latest data of interpreting and analyzing the kinematic and kinetic aspects of movement biomechanics.

**PART II – PERSONAL CONTRIBUTIONS**

**4. PURPOSE AND OBJECTIVES OF THE RESEARCH**

The main objective is identification of certain correlations between electrophysiological parameters obtained by TMG tests and VEP assessment, in association with biomechanical parameters got by computational gait analysis at patients with MS. Therefore, on the basis of our work, we proposed the following objectives:

- assessment of nervous transmission and muscular contraction in MS,
- gait analysis by using updated equipment,
- clinical implementation of certain methods which allow the improvement in data generating, standardizing, acquisition and analysis; identification of new research directions to facilitate diagnosis and objective monitoring of these patients.

**5. GROUPS AND METHODS**

**5.1. STUDIED GROUPS**

The research aimed to carry out prospective, randomized studies concerning the correlations between electrophysiological parameters and computational gait analysis at 20 patients suffering from MS, out of which 9 were males (45%) and 11 females (55%). There were selected the patients included in the category of certain clinical MS, conform to MS diagnosis and staging criteria (Hufschmidt A. and Lücking C. H., 2002).

The group was divided into two subgroups: subgroup A, consisting of 13 patients suffering from MS with clinically detectable gait disorders, and subgroup B, made up of 7 MS patients without clinically detectable gait disorders. Following biomechanical gait evaluation the patients belonging to both groups were divided into three categories: patients with normal symmetric gait, patients with abnormal symmetric gait and patients with asymmetric gait.

**5.2. METHODS USED IN THE RESEARCH**

Both patients suffering from MS and the subjects in the control group included in our research were tested by neurophysiologic evaluation methods such as VEP and TMG, and biomechanic
**analysis and gait evaluation** as well. **Statistical processing** aimed to determine both the existence of significant differences among certain results and the presence of some correlations between the parameters characterizing the studied groups.

6. RESULTS

6.1 RESULTS OF VEP ASSESSMENT

Concerning VEP testing, we focused on specific complex $N_{75}$, $P_{100}$, $N_{135-145}$, studying the latencies and durations of the waves.

Regarding latency of wave $N_{75}$, we registered a mean with values between 86,31ms and 90,86ms ± 8,48ms – 10,82ms, with interocular differences within physiologic limits. Analyzing latencies mean for the two MS subgroups, we realize they are higher at the subjects in subgroup B, comparatively with the patients in subgroup A. Wave $N_{75}$ duration in the group suffering from MS registered a mean varying between 26,84ms and 29,54ms ± 7,9 – 10,6ms. The high dispersion of the results led to significant statistic differences comparatively with the control group.

Wave $P_{100}$ latency has a mean value between 124,11ms and 128,14ms ± 15,35 – 17,81ms, registering thus a highly significant statistic difference comparatively with control group. We find the same aspect when comparing healthy subjects with the patients in subgroup A. Similar comparison for subgroup B is within the significance limit. Duration of $P_{100}$ registers mean values between 45,3ms and 50,9ms ± 11,12 – 17,82ms. While comparing with control group, there are no significant statistic differences for either MS subgroup.

Latency parameter of wave $N_{135-145}$ has mean values between 165,69ms and 175,38ms ± 11,38 – 30,07ms, outdoing maximum limit of physiologic lapse by far. Comparing with mean values of control group, we notice significant statistic differences only in the case of subgroup B. Wave $N_{135-145}$ duration has mean values between 44,62ms and 56,83ms ± 21,50 – 30,19ms at MS patients, without registering significant differences while comparing with control group.

Correlation of interocular differences of wave $N_{75}$ latencies (DIOL) presents values which outdo those of control group, both in the case of the whole group and of the two subgroups.

As far as waves $P_{100}$ and $N_{135-145}$ are concerned, we notice the same aspects, in contrast with DIOL in OL₅ and OR₅ derivations, which register significant differences at subgroup A.

6.2. RESULTS OBTAINED FOLLOWING TMG ASSESSMENT

Through tensiomyography testing we aimed to assess the parameters obtained at both muscular groups at the thigh and shank level.
Muscular displacement (Dm) has an average, normal value of 8,17mm. Dm analysis emphasizes low values at both A and B subgroups. This aspect is not registered in control group, which indicates the development of antero-posterior compensatory mechanisms at the patients suffering from MS.

Contraction time (Tc) is correlated with the type of muscular fibers, thus lower values indicate the predominance of Type II fast fibers. Tc normal average values are of 32,83ms, and analyzing Tc values indicated muscular fatigue at the level of femoral biceps and tibialis anterior.

Delay time (Td) registered high values at MS patients belonging to both subgroups, even higher at subgroup B; their correlation with Tc high values indicates muscular fatigue with deficiency in motor-unit recruitment, more severely in anterior tibial.

Relaxation time (Tr) presents higher values at the subjects in subgroup A, which are more pronounced in posterior muscular groups; there are also noticed high value differences between left and right lower limb.

Sustain time (Ts) shows major differences of mean values of shank muscles in subgroup A, comparatively with control group.

6.3. RESULTS OBTAINED THROUGH COMPUTATIONAL GAIT ANALYSIS

Gait biomechanics was assessed during all the three relevant gait stages. These gait stages require a motor order and a motor control, both depending on the way of muscular contraction and respectively, muscular control are inducted.

At the heel level, contact area presents similar tendencies of increased mean values in its two areas, whereas in the foot medial contact area increased in subgroup A.

Impulse emphasizes higher values in MS subgroups.

Pressure (Max. P) indicates different values in lower limbs of the patients suffering from MS; Force (max. F) also shows different values at MS patients.

Load rate and active contact area are tightly correlated with max P and max F.

6.4. CORRELATIONS OBTAINED FOLLOWING ASSESSED PARAMETERS EVALUATION

Our study assesses 166 parameters, respectively 36 parameters in VEP evaluation, 50 in TMG and 80 in gait analysis, both on a group of patients suffering from Ms and a control group. We focused on the correlation degree of the tested parameters, computing Pearson correlation coefficient among all the assessed parameters and presented a series of tables. Synthetizing, we found out 737 correlations between VEP and gait analysis parameters and TMG.
Analysing the number of VEP waves correlations with the other two tests, we can notice a 10% rise between correlated parameters $N_{75}$ and $P_{100}$, the parameters of wave $N_{135}$ registering the highest percent, of 40%. In conclusion, there is not a uniform distribution of the correlations of the three waves.

7. DISCUSSIONS

7.1. DISCUSSIONS ON THE RESULTS OBTAINED THROUGH VEP TESTING

VEP are not only the easiest and the most reproducible EP but, what is most important, there have been alterations in their characteristic parameters in more than 70% of MS patients - Gundogan et al., 2007, Naismith et al., 2009, Kolappan et al., 2009, Mozafari et al., 2010.

Interestingly, they had higher values of wave $N_{75}$ latency in subgroup B, comparatively with subgroup A. Concerning the duration of wave $N_{75}$, comparing the values registered in MS patients with those in control group obtained through Student test, there were no statistically significant values, probably due to the wide dissemination of the results.

Wave $P_{100}$, the most constant wave of specific complex, presented changes of analyzed parameters, mainly in latencies. Wave $P_{100}$ delays in subgroup B subjects are statistically significant in most recorded derivations, emphasizing EVP change both in patients with clinical symptoms and in those with subclinical lesions - Mizota et al., 2007; Turker et al., 2008; Lebrun et al., 2009.

Studying wave $N_{135}$ parameters we can notice few statistically significant differences of latencies values. Despite these aspects, subgroup B marked out high, or just statistically significant differences, in almost all recorded deviations (exception - Fz-Oz when stimulating OS). The values of wave $N_{135}$ do not differ from the control group, neither in the case of the whole group nor in the subgroups.

Analyzing DIOL we can notice that, despite the higher values than control group (except for wave $N_{135}$), there are statistically significant differences only in few cases owing to the fact all the patients in our group were MS diagnosed, and in this case ocular disorder is bilaterally advanced.

7.2. DISCUSSIONS ON THE RESULTS OBTAINED AT TMG TESTING

Gait biomechanical analyses and TMG provided us information of morpho-functional modifications in skeletal muscles of SM patients.

Compensatory mechanisms developed in consequence of nervous conduct involved, balance disorders based on structural and functional muscular changes pointed out by the way muscle tonus is distributed to lower limbs – the case of right femoral muscle (mRF), which has an increased muscle tonus.
In our study, Tc showed an increase of muscular fibres type I at mBF level owing to the increase of this parameter, which is also demonstrated in the studies carried out by Kent-Braun J. A., et al (1997). Muscular biopsy showed that in MS the percent of fibers type I increases and the percent of fibers type II decreases. The explanation of this configuration is the so-called ‘fiber effect’. In our case this effect allows a higher resistance during muscular fatigue, which can be quantified by TMG, eliminating thus the invasive and unpleasant character caused by muscular biopsy.

High values of Ts, clearly noticed in shank muscular groups, point out a continuous isometric muscular contraction due to structural changes of muscular fibers, trying to stimulate the mechanisms of muscular fibers type I development to increase resistance to muscular fatigue.

In conclusion, this type of evaluation is a non-invasive way for assessment the contractile characteristics of the skeletal muscle, without an integration of tendon properties, articular mechanics or conjunctive tissue in mechanic response to muscle deterioration caused by electrical stimulation.

7.3. DISCUSSIONS ON THE RESULTS OBTAINED THROUGH COMPUTATIONAL GAIT ANALYSIS

In this study we provide a biomechanical gait analysis taking into consideration the fact that kinetic gait analysis involves the forces developed during this functional activity.

Contact area analysis at the heel level indicates an increase tendency at the patients in subgroup A as a compensatory means of maintaining balance. A similar situation is at the level of heel medial. On the other hand, there is a functional deficit in ankle joint complex because the physiological orientation of vector forces is transmitted from shank to foot, this aspect was demonstrated by Houglum P. in 2005.

Impulse has higher values at MS group owing to deficit motor control noticed by Kelleher K.J. et al., (2010) who observes the decrease of plantar flexion and propulsion force while doing a dynamic EMG gait analysis.

Global analysis of max. P shows that there is a tendency to develop a higher pressure at the heel level because, reflexively, there is a trial to increase sustaining base. This aspect cannot be noticed in medial foot area where the pressure is lower at patients in MS subgroups comparatively with control group.

We also identified different max. F values between control group and MS subgroups, which were higher in subgroup B despite the fact that the patients in this group did not have gait disorders.

Load rate at MS subjects took place mainly at the heel level, asymmetrically right-left, which is in accordance with the evolution of force and pressure values.
We notice approximately the same value of active contact area at both MS subgroups, and a right-left asymmetry which is more pregnant at the patients in subgroup B at lateral heel area.

Analyzing plantar symmetry during gait we observe that most MS patients’ gait is symmetric but with normal load rate and distribution of pressure centre, which may be an indication of subsequent evolution of the patient from the point of view of MS impact on the functional deficit; that is why it is possible to organize an objective rehabilitation programme.

7.4. DISCUSSIONS ON CORRELATIONS OBTAINED BY ANALYZING TESTED PARAMETERS

We noticed the greater number of correlations between VEP parameters and those of gait analysis (410), probably owing to the fact that the latter had more parameters. The ratio direct/converse correlation is higher in VEP/TMG correlations (62%/38%) than VEP results in gait analysis (54%/46%).

Specialty literature has poor data on correlations between VEP and imagistic procedures – MRN, optic tomography - Gundogan et al., 2007; Frohman et al., 2008; Almarcegui et al., 2010; Naismith et al., 2009, as well as between EP and evaluation scales – EDSS- Leocani et al., 2006. The above-mentioned data emphasize VEP higher sensitivity comparatively with imagistic testing. These aspects show the originality of our study as, besides classic investigations in MS - VEP, we have used certain tests such as TMG and biomechanical gait analysis for the first time in our country.

8. CONCLUSIONS

1. The main objective of our complex study was the clinical implementation of new methods (TMG and computational gait analysis) besides classic ones (VEP), which certainly improves data gathering, standardization, acquisition and analysis. It also helps us identify new research directions on the basis of the studied correlations to better diagnose and issue evaluation programmes of demyelization disease evolution and to prescribe individual treatment.

2. We recorded high values of wave N75 latencies in subgroup A (84,65 ms - 89,94 ms) due to progressive evolution of demyelization lesions, including spinal nervous ax. The delays of wave P100, were statistically significant even at subjects without clinical gait disorders, emphasizing thus subclinical lesions of optic neuritis.

3. We obtained interesting data analyzing the parameters of wave N135-145, rooted in association cortical areas, and we noticed significant differences in latencies which were in greater number at the patients suffering from MS without clinical detectable gait than control group (values of p 0,004 - 0,037).
4. Regarding the duration of the three VEP waves, our study did not identify great differences between MS group and control group, which demonstrates that this parameter was not a predictive factor in disease evolution.

5. After analyzing Dm and Tr, we observed a higher muscle tonus in all muscular groups we tested, especially in gastrocnemian muscles, which explained the decrease in the foot motor control when reaching the ground during gait.

6. In our study, Tc - as TMG parameter – recorded higher values in posterior muscular group of the thigh (41.95 ms -mBF right) and anterior muscular group of the shank (54.93-60 ms) owing to the increase of muscular fibers type I and muscle fatigue.

7. TMG study identified a decrease in recruiting motor units, more pregnant in anterior muscular group of the shank, reflected in functional and coordination deficit of the foot during gait.

8. We noticed high Ts values in shank muscular groups (323.78 ms - mGL), which emphasized the trial to stimulate the tendency to increase compensatory mechanisms to maintain body balance.

9. Computational gait analysis showed an increase of contact area at patients with gait disorders (64.46-84.65 cm² – foot medial area), which corroborates with evolution of active contact area. These increases could be explained by the tendency of developing compensatory mechanisms to maintain body balance.

10. Biomechanical study showed that load rate and impulse had high values at MS subjects; MS subjects also displayed a clear right-left asymmetry during each gait stage owing to the decrease in propulsion force of the foot during gait.

11. Pressures and force tests revealed a predominant distribution at the level of lateral heel area. This can be explain because try to compensate the balance and orientation disorders of the ground reaction force in order to have a normal gait.

12. We analyzed biomechanical parameters objectively and we noticed that, although from clinical point of view the patients were divided into two subgroups – with and without gait disorders, yet there were subclinical disorders detectable only by kinetic analysis.

12. The characteristics of waves N75 and P100, rooted in cortical specific visual areas, correlated in similar number with TMG and gait parameters; the number of wave P100 correlations was higher (64%) than the number of wave N75 (51%), which can be explained by the high number of P100, parameters related to the parameters of the other two investigations.

14. We noticed the importance of wave N135-145, a wave which was less studied in specialty literature but which recorded the most correlations (299), revealing the development of interneuron
connections between association areas to substitute the lesions arising in specific zones, thus ensuring the running of a function also using information from the less damaged opposite area.

15. The great number of gait parameters was disclosed in direct correlation with latencies N\textsubscript{75} and P\textsubscript{100} at subgroup B, especially in toe 2-5 area. Converse correlations were noticed at the patients in the same subgroup, mainly in medial foot area.

16. As for the correlations of waves N\textsubscript{75} and P\textsubscript{100} latencies with TMG parameters, the subjects in subgroup B had a larger number of direct correlations as compared to the ones in subgroup A (with gait disorders). Among the studied muscles, we noticed that right femoral, anterior tibial and femoral biceps had a greater number of correlated parameters.

17. We have used original testing methods for the first time in our country such as tensiomyographic and computational gait analysis to explore MS patients, simultaneously completing an analysis by correlating the results of the three investigations to both create a new diagnosis algorithm and predict the evolution of balance and gait disorders at these patients.
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