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THE CLINICAL - IMAGISTIC STUDY OF MULTIPLE SCLEROSIS

ABSTRACT

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A. THE COMMON PART

1. EMBRYOLOGY DEVELOPMENT OF WHITE MATTER

This chapter alludes to the myelination of nerve fibers and to the elements that participate in the development of the myelin sheath in both central nervous system and in the periphery.

It deals with data about the development and organization of the myelin sheath, myelin formation mechanisms in the CNS and PNS, an under-chapter referring to the biochemical composition of myelin.

2. THE ANATOMY OF WHITE MATTER

This chapter refers to the anatomical features of the brain and spinal white matter. Myelinated fibers existing in the cerebral white matter may be classified by origin and termination, but also after their functions: projection fibers, fiber associations and corners. The white matter of the spinal cord consists of neuronal myelinated extensions (axons), which in the spinal cord occupy the superficial region as opposed to the gray matter, placed under the form of cords (anterior, posterior and lateral).

3. ETIOPATHOGENIC AND CLINICAL ASPECTS IN MULTIPLE SCLEROSIS

In this chapter is presented data on the etiopathogenesis of multiple sclerosis, although the impugned pathogenic factor is not known, several hypotheses were developed: virus-induced demyelination, defect metabolic, autoimmune hypothesis may impose the establishment of two factors: triggers that induce an antigenic stimulus specific and/or unspecific and factors involved in the maintenance and organization of the autoimmune process.

This chapter displays the main clinical manifestations, atypical clinical manifestations in MS and differential diagnosis, based on the clinical aspects, MRI and the parameters of cerebrospinal fluid.

4. THE LABORATORY ASPECTS IN MULTIPLE SCLEROSIS

In this chapter are presented the current methods used in exploring MS, offering a detailed presentation of each method: magnetic resonance imaging, computed tomography, evoked potentials, cerebrospinal fluid.
5. MATERIAL AND METHOD

5.1 Modeling study and the characteristics of the studied population The survey was performed during 2007-2010, the investigated group included 30 patients with relapsing-remitting multiple sclerosis, the selection of the patients was realized taking into consideration the inclusion and exclusion criteria. The studied group was monitored clinical-imaging study in three stages at an interval of 6 months.

Analyzing the distribution of patients by gender, it revealed a predominance of females, 63.33% and 33.66% male, medium age being of 32.83 years, age range being between 21-43 years.

Analyzing group in terms of duration of illness, we observed that it was $4.89 \pm 2.31$ years, the value at male patients being lower ($3.88 \pm 2.36$) compared to female patients ($5.09 \pm 1.99$).

5.2 THE METODS OF STUDY

5.2.1 Complete clinical examination was performed to all patients of the studied group, including the anamnesis and clinical examination with appliances and systems. Neurological examination included the normal assessment methodology of clinical specialty. For estimating the degree of disability, and the clinical assessment we used the Expanded Disability Status Scale (EDSS) and Multiple sclerosis Functional Composite (MSFC).

EDSS remains the most often used scale for assessing overall disability of MS patients being possible an evaluation at various clinical levels. EDSS quantifies pyramidal, cerebellar, the brain stem, sensorial, bowel and bladder, visual and cognitive functions.

MSFC represents a multidimensional score based on the complex measurement of the neurological dysfunction in MS on three clinical dimensions: upper limb function test using nine-hole peg test (9HPT); lower limb function using 25-foot timed walk test (TWT); cognitive function using Paced Auditory Serial Addition Test (PASAT).
5.2.2 The laboratory examination included: complete blood counts (CBC), ESR, glycemia, urea, creatinine, transaminase levels, urinary tests. Biological and biochemical exploration are not to be neglected, in our case they don't have a significant contribution, only a general role in monitoring therapy.

5.2.3 The electrocardiogram and blood pressure were performed on all patients, noting the presence/absence of the sinusal rhythm, the presence of the cardiac arrhythmia, the lead disturbances, the ischaemic modifications, the presence of the Q waves; it also determined systolic and diastolic blood pressure.

5.2.4 Computer tomography (CT) Although it is not a method used in monitoring patients with MS, it was proved in some cases to be very useful for guiding early diagnosis and admission to a correct differential diagnosis (revealed the presence of suggestive lesions of other diseases).

5.2.5 Magnetic resonance imaging (MRI) MRI is the imaging method of choice, non-invasive, mapping the internal structure of the central nervous system. Imaging modality is useful in supporting diagnosis and good clinical correlation imaging MS.

MRI criteria have been developed to identify MRI features of MS increased sensitivity, thus emphasizing the importance of MRI in the demonstration of lesions disseminated in time and space, while allowing the expression of early diagnosis. In this study we evaluated the correlations between the lesions shown on T$_1$, T$_1$-postGd and T$_2$ sequences with clinical disability with the purposes of highlighting some MRI parameters related to the evolution of the disease.

5.2.6 Methods of statistical analysis For the statistical analysis we used SPSS 17 and Epi Info2000 programs, specialized in scientific statistical calculations. The recording and processing of the patients’ data was performed using Excel program, Data Analysis module.

6. RESULTS

6.1 Results on clinical features of study group The primary clinical evaluation performed and quantified of the lot, based on functional scores used in the final composition EDSS, reveals 13.3% of asymptomatic patients, 26.6% monosimptomatics and 60% plurisimptomatics.
Initial clinical evaluation revealed impairment measured by EDSS score shown that 70% of patients pyramidal functions were affected, the brain stem to 36.6% of patients, cerebellar in 26.6% of patients, sensitive to 33.3% of patients, visual to 16.6% of patients, sphincter to 6.66% of patients. Analyzing the relationship between changes in EDSS between the II and III presentation of the studied group, we found a strong relationship, Pearson correlation index being $r = 0.98$.

Clinical evaluation quantified using MSFC score after calculating the Z score for each test component for each patient, had an average value of 0.07 at baseline, 0.13 at the second assessment and 0.16 in the final evaluation.

Correlations between EDSS and MSFC, as well as between EDSS and MSFC components highlight during the study a significant correlation between EDSS and 9HPT, TWT, whereas the data obtained for the PASAT test reveals a negative correlation, as this test indicates that additional information provides understanding the patient's clinical status.

The average correlations between EDSS and TWT are due the fact that patients included in the group during the study had no EDSS values above 4 which would have determined difficulties in assessing ambulatory capacity.

In terms of clinical development for the entire duration of the study, the global analysis of clinical parameters EDSS and MSFC showed an insignificant correlation, $r = -0.32$, although during the study there was a tight connection between different components of the MSFC and EDSS test.

6.2 Results on imaging parameters regarding the studied group Visual imaging analysis of the supratentorial lesions, showed 90% of the patients had periventricular lesions, 73.3% juxtacortical, 60% corpus callosum and 43.3% at the capsular level. At the infratentorial level, were placed at 30% of patients in the cerebellum, and at 19.9% at brainstem.

6.3 Results on the relationship between imagistical and clinical parameters Analyzing the correlation between $T_2$ lesions and clinical parameters we obtained a medium correlation ($r = 0.30$) between $T_2$ lesions and EDSS shown on the duration of the study (most patients presenting EDSS score between 1-1.5 for a number of lesions between 8-16), however, we obtained a significant relationship ($p <0.005$) between imaging changes and MSFC.

The relationship between the number of new or enlarged lesions shown on the $T_2$ sequence and EDSS changes throughout the study, we obtained an average
correlation \( (r = 0.52) \) between imaging changes and disease progression, but the relationship between \( T_2 \)-lesions and clinical relapse was weak on the full duration of the study \( (r = 0.15) \).

In terms of the relationship between \( T_1 \) lesions and clinical parameters, we’ve got a strong correlation between lesions shown on \( T_1 \) sequences and clinical parameters, EDSS \( (r = 0.62) \) and MSFC, particularly for components 9HPT \( (r = 0.74) \) and TWT \( (r = 0.82) \).

We obtained an average correlation between active lesions \( (T_1\text{-Gd}) \) and clinical relapses \( (r = 0.42) \), thus patients with a higher number of lesions have more clinical relapses, but the relationship between \( T_1 \) lesions and clinical relapses was weak on the full study duration \( (r = 0.24) \).

Analyzing the relationship between the lesions identified on \( T_2 \) and \( T_1\text{-Gd} \) sequences, we obtained an average correlation, the different behavior of the lesions being explained by the fact that \( T_2 \) lesions have no corresponding \( T_1 \) lesions.

7. DISCUSSIONS

7.1 Discussion on the clinical features of study group
Clinical evaluation revealed impairment measured by EDSS score pyramid functions in most patients, EDSS changes throughout the study being 1.54, EDSS is therefore less sensitive to the inter-rater changes.

Correlations between EDSS and MSFC, and between EDSS and MSFC components during the study showed a strong correlation between EDSS and 9HPT, TWT, but results obtained for the PASAT test reveal the negative correlation, which shows the fact that the evaluation size of the PASAT test is not captured by the EDSS score.

7.2 Discussions on the imaging features of study group
Analyzing the correlation between \( T_2 \) lesions and clinical parameters we obtained an average correlation between \( T_2 \) lesions and EDSS during the study, instead we got a moderate correlation between imaging parameters and 9HPT and TWT components. Regarding the relationship between \( T_2 \) lesions and clinical relapses we obtained a weak correlation during the whole study.
In terms of the relationship between T₁ lesions and clinical parameters we obtained a strong correlation between the lesions shown on T₁ sequences and clinical parameters, EDSS and MSFC, especially for 9HPT and TWT components.

We obtained an average correlation between active lesions and clinical relapses as well as between lesions shown on T₂ and T₁-Gd sequences.

8. CONCLUSIONS

1. Multiple sclerosis is a neuroimmune disease, presenting a great heterogeneity in terms of the clinical evolution, neuroimaging and response to therapy.
2. Disability that this condition may produce in the age group affected is a major cause of disability, although morbidity through MS is not very high.
3. The group of patients consisted of 30 patients diagnosed with RRMS, of whom 21 women (63.33%) and 11 men (33.66%) aged 21-43 years.
4. In my study for quantifying the degree of disability and assessment of clinical course we used the EDSS and MSFC.
5. EDSS represents the most used scale in assessing the global disability of patients. EDSS scale has the advantage of being widely known, but it is difficult to use in practice between different evaluators.
6. MSFC represents a multidimensional score based on the complex measurement of the neurological dysfunction in MS on three clinical dimensions: upper limb function, lower limb function and cognitive function.
7. During the clinical analysis with EDSS, we noticed that most MS patients showed impaired pyramidal function, closely followed by the sensitive events and the brainstem.
8. In terms of EDSS score we found significant differences between evaluations, EDSS changes throughout the study was of 1.54, suggesting the fact that EDSS adds quantitative information, being less sensitive to the inter-rater changes.
9. Regarding MSFC scores during the study, we observed a clinical impairment regarding the components 9HPT TWT, instead for the PASAT test we recorded a slight decrease at the final assessment.
10. Correlations between EDSS and MSFC, and EDSS and MSFC components during the study highlighted a good correlation between EDSS and 9HPT, TWT, instead the data obtained for the PASAT test reveal a weak correlation, proving the
The fact that the evaluation dimensions of PASAT test are not comprised in the EDSS score.

11. We noted an average correlation between the lesions shown on T2 sequences and EDSS throughout the study. Regarding the relationship between new or enlarged T2 lesions, we obtained a moderate correlation, instead analyzing the relationship with clinical relapse, it was a weak one. This is probably related to the relatively short duration of the study, the small number of patients with RRMS that I had (a relatively clinically stable group), and to the difficulties of analyzing the differences in size of the lesions.

12. Correlations between T2 lesions and TWT, 9HPT components of the MSFC test for the entire duration of the study showed a strong correlation, having with positive direction, so a higher load being associated with a higher score on the test 9HPT, TWT and a decreased PASAT score (p <0.001).

13. Analyzing the relationship between T1 lesions and clinical parameters we obtained a strong correlation between lesions on T1 sequences and clinical parameters (p <0.001), T1 sequence may have implications on the direct result of patients in clinical practice.

14. On patients belonging to the group we obtained an average correlation between the lesions identified on T2 and T1-Gd sequences, different behavior is explained by the fact that many T2 lesions have no correspondent in T1 lesions.

Finally, it may be considered that the deem T1 sequence represents a sensitive marker in assessing the clinical evolution, T1-Gd having a predictive value regarding the short term disability.

Regarding T2 sequence, we can deem the high number of lesions related to an MSFC score low, highlighted on short-term (non-linear relationship), could have predictive value on long-term disease progression, sustaining a linear relationship between these parameters. In this case, the study should be extended to a greater number of patients and over a longer period of timer period of time to verify these preliminary data.

**Key words:** Multiple Sclerosis, Expanded Disability Status Scale, Multiple Sclerosis Functional Composite, Magnetic resonance imaging.
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