

UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA
FACULTY OF MEDICINE

**THE STUDY OF NEUROPHYSIOLOGICAL
AND CEREBRAL VASCULAR PARAMETERS
TO A GROUP OF PATIENTS
WITH DEMYELINATING DISORDERS**

DOCTORATE THESIS

- ABSTRACT -

**SCIENTIFIC SUPERVISOR:
PROF. UNIV. DR. SIMONA GUSTI**

**PHD STUDENT:
DR. AURA COTEANU**

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CONTENTS

GENERAL PART - STATE OF KNOWLEDGE

1. Notions of Anatomy, Physiology and Cerebral Hemodynamics
2. Demyelinating disorders and multiple sclerosis
3. Particularities of neuroimaging and electrophysiological investigations in demyelinating disorders

SPECIAL PART –PERSONAL CONTRIBUTIONS

4. Material and Methods
5. Results
 - 5.1. Exploration results from the Extra-cranial Doppler
 - 5.2. Exploration results from the Trans-cranial Doppler
 - 5.3. Exploration results from the Trans-cranial Doppler - functional
 - 5.4. Results obtained from EEG
 - 5.5. Correlations between the parameters studied in the group with Clinically Isolated Syndrome
 - 5.6. Correlations between the parameters studied in the group with Multiple Sclerosis
6. Discussion
7. Conclusions
8. Bibliography

Key-words: demyelinating disorders, multiple sclerosis, Doppler ultrasonography, functional transcranial Doppler, cerebral hemodynamics, electroencephalography

Demyelinating diseases in neurology occupies a unique position due to the frequency and their tendency to fall ill young adults, to the diversity of events that put to a test even the most experienced clinicians and to the multiplicity of fundamental problems of neurobiology, immunology, virology and genetic which arise regarding their pathogenesis.

This paper tries to assess cerebral vascular changes that occur in the demyelinating diseases and to perform a correlation of various parameters obtained by non-invasive methods: Doppler ultrasound vascular exploration and electrophysiological investigations to determine, eventually, algorithm practices that can lead to the detection of correctable and treatable lesions of the cerebral vessels that provides drainage of the brain, and thus to be able to become a very useful tool, cost-effective, in the diagnosis and early treatment of demyelinating diseases, preventing their progression to major disabilities.

The thesis is divided into two parts: part general - current state of knowledge dedicated to the field concerned and part special dedicated to personal contributions.

Part general - Current state of knowledge

Chapter 1 presents the general concepts of anatomy and physiology of the cerebral circulation, both for cerebral arteries and cerebral veins. A special place is reserved to the feedback mechanisms at the level of the cerebral circulation and cerebral venous drainage concept.

Chapter 2 contains data about the current criteria for defining the demyelinating diseases. Also, it presents the significant progress that has appeared in last years regarding the understanding of the mechanisms involved in inflammation, demyelination and neurodegeneration that occurs in multiple sclerosis, as well as the concept of the *neurovascular unit*, relatively recently introduced in practice, which suggests a holistic approach of the vascular and neuronal lesions, indicating that the neural changes occur as a part of a complex response mechanism of the brain, blood vessels, and intercellular matrix.

Chapter 3 includes an overview of the features of neuroimaging and electrophysiological investigations in demyelinating diseases, out of these the magnetic resonance imaging and the study of the evoked potentials being a binding part of the positive diagnosis of these diseases and of the exclusion of other pathologies in the differential diagnosis.

The second part of the thesis, personal contributions, contains five chapters: materials and methods, results, discussion, conclusions and bibliography.

The purpose of this study is to establish a diagnostic algorithm for early detection and tracking the evolution of the patient with demyelinating disorders by noninvasive neurophysiological and cerebrovascular imaging investigations.

The objectives of this research were:

- Quantification of neurophysiological and cerebral vascular parameters (arterial and venous) in a group of patients with demyelinating disorders.
- Appreciation of the evolution of these parameters depending on the clinical form of the disease.
- Establishing correlations between the presence of cerebral venous changes, cerebral vaso-reactivity and certain electrophysiological patterns.

The observational study was performed, during 3 years, on a group of 45 patients (25 with Clinically Isolated Syndrome and 20 with multiple sclerosis). Data obtained on this lot were compared with those of a control group with similar demographic characteristics.

In **chapter 4** there are described the methods that used in the study, these including: clinical evaluation, laboratory evaluation, vascular evaluation and electrophysiological evaluation of the patient with demyelinating disorders.

The disability degree of the patients was assessed according to the Expanded Disability Status Scale (EDSS), which is a scale based on a neurological examination of eight functional systems.

There has been collected venous blood samples from the patients included in the studied groups, for the performance of blood counts and biochemical tests. Immunological investigations were carried out in order to the differential diagnosis of demyelinating diseases with autoimmune diseases or systemic.

The patients from the studied groups were examined in terms of vascular cerebral Doppler ultrasonography using an ultrasound Fukuda Denshi UF-850XTD equipped with a linear electronic probe FUT-LG-386-9A for the cervical vessels with selectable frequency 6.0/7, 5/9, 0 MHz and an electronic cardiovascular sector sound (phased array) with a selectable frequency 2.5/3.5/4.5 MHz.

For a better appreciation regarding the fundamental role of the dynamics of the thoracic muscle action over the venous flow, we proposed a new parameter: the ratio of maximum systolic velocity and resistance index (PSV/IR).

Electrophysiological evaluation was performed using electroencephalography EEG, using a multi-channel EP 28 MIZAR-LIGHT, the data obtained being managed by Galileo NT PMS software.

For statistic data analysis, I have used the Programme EPI Info2000 and SPSS, specialized in scientific statistic calculations. Registration and processing of patients data has been made in Excel, DATA ANALYSIS Module.

The personal results are presented in **Chapter 5**, grouping them as it follows: the results obtained from extra-cranial Doppler exploration of the internal jugular veins and vertebral veins, the results obtained from trans-cranial Doppler exploration of the deep middle cerebral veins and straight sinus, the results obtained from functional trans-cranial Doppler exploration, the results obtained from EEG. The studied correlations between parameters are then obtained on two groups of patients.

In **Chapter 6**, entitled discussions, results and correlations previously established are discussed making a comparison between groups of patients with clinically isolated syndrome and multiple sclerosis. The data obtained are compared with those of literature.

Noninvasive vascular exploration by ultrasonography, both at the cervical and intracranial level, allowed us to investigate a series of Doppler parameters in the attempt to establish what changes occur at the cerebral hemodynamics level to the patients with clinically isolated syndrome and to the patients with relapsing-remitting multiple sclerosis .

Chapter 7 presents the conclusions of this study:

1. The research was performed over a period of three years on a group of 45 patients with demyelinating diseases, out of which 25 patients (55.5%) were diagnosed with clinically isolated syndrome and 20 patients (44.5%) were diagnosed with multiple sclerosis relapsing-remitting form. Results of the study were compared with those from a control group of 30 clinically healthy persons of the same age group.

2. Mean age of patients with clinically isolated syndrome was 29.5 years (± 5.1), those with relapsing-remitting multiple sclerosis was 37.1 years (± 6.1) and those in the

control group was 34.4 (\pm 6.4), the groups being quite homogeneous from this point of view. In terms of distribution by ages, it showed that many patients are in the age group of 31-40 years, namely 25 patients (55.5%), this distribution changes between the two groups of patients; in the group of those with clinically isolated syndrome predominates the age group <30 years and in the group of patients with relapsing-remitting multiple sclerosis predominate the age group 31-40 years.

3. The group of patients was clinical and paraclinical evaluated complex and the degree of disability of patients was assessed according to the Expanded Disability Status Scale (EDSS). Cerebral perfusion was studied using non-invasive Doppler ultrasound exploring both extracranial and transcranial ultrasound with Fukuda Denshi UF-850XTD equipped with a linear electronic sound cervical vessels with selectable frequency 6.0 / 7.5 / 9.0 MHz and electronic sector sound (phased array) cardiovascular selectable frequency 2.5 / 3.5 / 4.5 MHz, we also investigated the changes that occur during performance of various tasks that stimulate certain brain areas by trans-cranial Doppler functional. Neurophysiological evaluation was performed with a multi-EP 28 EEG channels (broadband) MIZAR-LIGHT, the data obtained being managed by the Galileo NT PMS software (Patient Management System).

4. Extracranial and transcranial Doppler vascular exploration aimed to internal jugular veins, vertebral veins, deep middle cerebral veins, sinus straight, middle cerebral artery and posterior cerebral arteries. Significant changes were observed, statistically significant, different from control group in all two groups studied. The studied Doppler parameters appreciated the blood volume changes at the jugular vein level as response to the hydrostatic pressure changes caused by the different positions of the body, total venous blood flow in the cerebral circulation, impaired postural control jugular level, the presence of the blood reflux to the intracranial level, overloading that occurs in the venous return microcirculation and vaso-reactivity brain changes.

5. It has to be mentioned that the most significant changes of these parameters have been recorded at the patients with multiple sclerosis, comparing to controls, but significant changes have occurred in the group of patients with clinically isolated syndrome, too.

6. Exploration of extra-cranial Doppler, performed at the level of the jugular veins and vertebral veins, indicates that the presence of venous reflux in the internal jugular vein correlated with the negative flux difference is statistically significant comparing to controls.

7. Also, the other extra-cranial Doppler parameters showed significant changes, from a statistically point of view, in the group of patients with multiple sclerosis; it is worthy to note that the occurrence of the venous flow negative differences that reflect the importance of a "vascular pathways" in the appearance and evolution of the demyelinating diseases.

8. The changes of the report PSV/IR, a parameter introduced by us to better characterize the fundamental role of the thoracic muscle action over the venous flow, have validated this parameter as being important in differentiating the types of the demyelinating disorders.

9. The exploration TCD-f led to the conclusion that the changes presented in basal conditions is being maintained in the case of stimulation of some cerebral regions, existing differences with statistically significance between different types of clinically isolated syndromes, these changes might additional discrimination criteria between different types of clinically isolated syndrome, bringing, also, additional data in the understanding of the changes that occur in the brain.

10. The diffuse EEG changes routes were increased in patients with multiple sclerosis, although the response induced by light stimulation and the average frequency of the basic activity decreased in all groups studied. Thus, it has been noticed a decrease in alpha waves and a relative increase in theta waves. Focal changes and irritation, paroxysms of slow waves were more common in multiple sclerosis versus clinically isolated syndrome.

11. Note that there is a good correlation between the Doppler parameters determined at extracranial and intracranial level and the presence of theta waves and EEG changes which, in fact, it is translated into a deficiency of the coupling neuronal activation, given by the flow blood changes.

FINAL CONCLUSION

- The present research is extensive, complex, clinical and paraclinical, performed on a group of patients with clinically isolated syndrome and relapsing-remitting multiple sclerosis, using noninvasive methods of exploration: cerebral vascular ultrasound Doppler exploration, extracranial, transcranial and functional transcranial Doppler, electroencephalography, less mentioned in the literature.

- Using, within this study, a new vascular Doppler parameter (PSV/IR) which appreciates more the crucial role of dynamics chest muscle action on venous flow in the cerebral circulation is original, not mentioned in the literature.

- The correlation of parameter changes measured by extra and transcranial Doppler, including functional trans-cranial Doppler exploration and neuroelectrophysiological method, study that is not mentioned in the literature, led to interesting results and conclusions concerning the development of the vascular pattern in the pathogenesis of demyelinating diseases.

- The non-invasive methods of exploration have enabled the early detection of the changes from the arterial and venous circulation at patients with demyelinating disorders, these changes being as much serious as the number of relapses was higher.

- The exploration of the cerebral vascular Doppler ultrasound can detect correctable and treatable injuries that ensure drainage of cerebral veins, can become a very useful tool, cost-effective, in the early diagnosis of demyelinating disease, preventing their development to the emergence of major disability at young patients, which involves huge socio-economic costs.

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