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Original article

COGNITIVE IMPAIRMENT IN DIFFERENT CLINICAL FORMS OF MULTIPLE SCLEROSIS

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ABSTRACT:

Purpose: The aim of the study is to investigate cognitive impairment (CI) in patients with different clinical forms of Multiple Sclerosis (MS) and to propose a suitable cognitive evaluation based on available tools for diagnosis and monitoring purposes.

Materials and Methods: The following tests were used**:** Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test-Revised (BVMT-R), Expanded Disability Status Scale (EDSS) and Magnetic Resonance Tomography 1.5T (MRT) in 60 consecutive patients; 22 were with first demyelination episode and 38 with MS. The control group of 40 healthy persons matched for sex, age and years of education. The follow-up period is three years.

Results: The average screening values of PASAT, SDMT, BVSMT-R are considerably lower ($p<0.05$) in MS patients compared to the controls and CIS patients. Point's number in the progressive forms in comparison with RRMS is reliably smaller. There was no significant difference in results between SPMS and PPMS patients at screening ($p>0.05$). In the 3rd year, there is a significant cognitive progression in all studied groups and for all tests ($p<0.05$).

Conclusion: The use of a neuropsychological screening test is a valuable method for registering CI in patients with relapsing-remitting course, as well as in patients with a progressive course of the disease. We recommend the SDMT for screening annual follow-up because it is easy to apply, validate and reliably report the progression of CI. In patients with visual disturbances and with arm weakness, it is better to use PASAT, taking into account the level of education and depression.

Keywords: Multiple Sclerosis, clinically isolated syndrome, cognitive impairment,

INTRODUCTION

Multiple sclerosis (MS) is a chronic, autoimmune, inflammatory and neurodegenerative disease of the central nervous system resulting in young people's invalidity [1]. Its symptoms vary in type and time sequence. They depend on the plaques localization in the cerebrum and spinal cord ÌcDonald WI, et al. [2]. MS is a very complex disease, and it would be good to have objective risk markers to identify MS patients at risk of developing CI before it manifests. Though frequently neglected, CI affects 45-70% of patients during the disease's development, and it has a serious impact on their social activity, family life, employability, and general well-being [3, 4].

Cognitive impairments are caused by complex neuroanatomic and pathophysiologic fundaments. The most frequently affected cognitive domains are information processing speed, complex attention, working memory, visuospatial ability, and executive functions, with a predominance of dysexecutive disorders in the progressive forms of MS and an amnestic profile in relapsing-remitting [4, 5, 6]. Clinically, the affected disorders are manifested by depression, euphoria, nervousness, irritability, sleeping disorders and apathy. Cognition in the various MS forms is impacted by the disease duration and age (pathology accumulation) and by the type of clinical phenotype [7, 8].

METHODOLOGY AND METHODS:

Goal: The aim of the study is to investigate cognitive impairment (CI) in patients with different clinical forms of Multiple Sclerosis (MS) and to propose a suitable cognitive evaluation based on available tools for diagnosis and monitoring purposes.

During the period 2016-2019, the diagnostics, clinical and neuropsychological tests, and patient monitoring were done in the Neurological Unit of MHAT - Pleven city. Sixty consecutively enrolled patients after prior-signed informed consent; 22 had the first demyelination episode, and 38 had different clinical forms of MS. Neuropsychological tests were conducted with 40 healthy persons cor-

responding in age, education and sex (average age 32.4 ± 11.03), 21(52.5%) of them were female patients.

The clinical method that applied the validation scale for reporting general functional deficit in compliance with Kurtzke et al. (1983) - Expanded Disability Status Scale (EDSS).

The cognitive skills of patients were assessed with the Paced Auditory Serial Additional Test (PASAT), Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test-Revised (BVMT-R). All these tests have been administered in compliance with standardized manuals for their application [5, 6]. At the beginning of the third year, these tests were also conducted.

The PASAT 3" is used as a multi-domain measure. Single digits are presented every 3 s, and the patient must add each new digit to the one immediately prior to it.

SDMT - in this test, the patients are shown a visual key that matches numbers and symbols on the top of a sheet. Then, they must specify the correct number for each of the symbols presented as fast and as accurately as they can during 90 s.

The BVSMT-R assesses visual learning and memory. The protocol suggested includes only the first three recall trials.

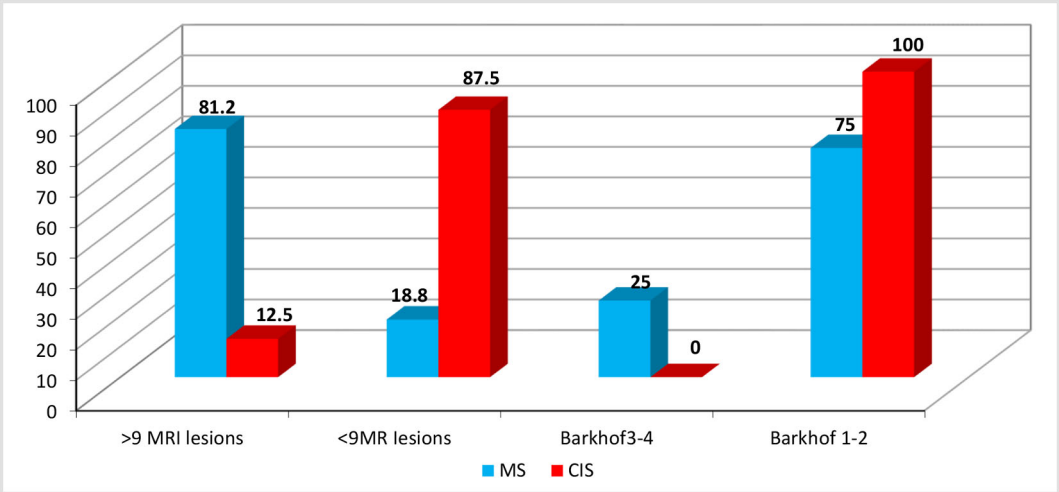
Neuroimaging Method. All patients had a magnetic-resonance tomography (MRT) at baseline, and in patients with a first demyelinating episode annual follow-up, applying contrast substance Omniscan in compliance with Barkof F, et al. [9] with equipment (Siemens Medical Systems), capacity 1,5 T and validated Polman protocols [10].

Statistical Analysis. The study data are presented as average values (X) ± standard error of the average value (SE). Differences between the studied groups are analyzed with ANOVA; in case of statistically significant differences and parametric data distribution, post hoc analysis applies the method for least significant differences (LSD). In the case of non-parametric distribution was done Kruskal-Wallis test. Correlations between the surveyed indices are estimated in compliance with the Pierson method. Significance level $p<0.05$ was accepted for all tests. For statistical data processing, applied the SPSS program for Windows, version 15.

RESULTS:

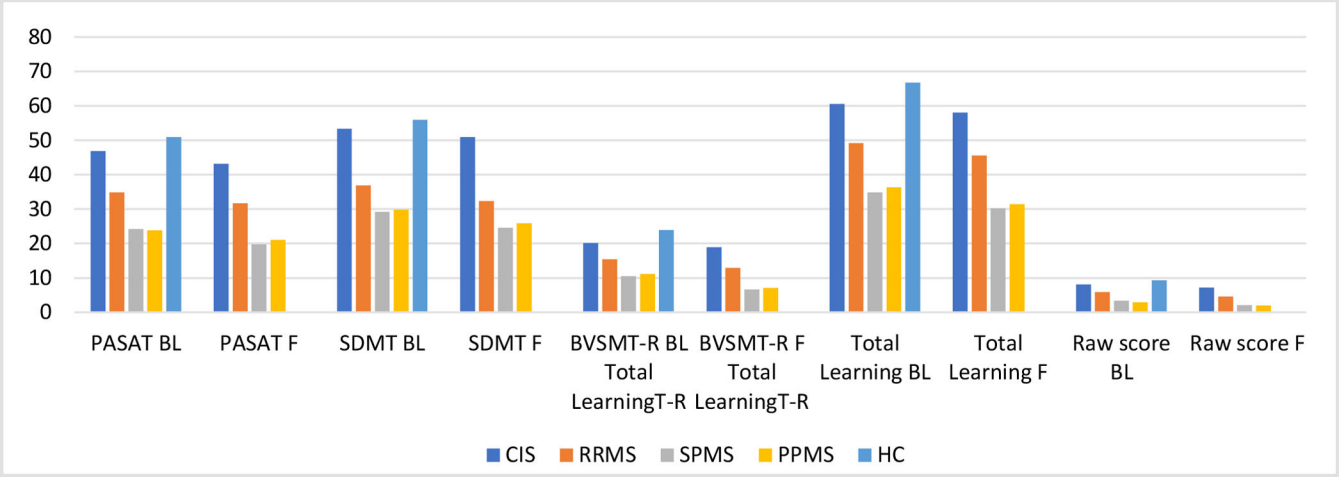
Of the initially included 60 patients, of which 22 with CIS and 38 with different clinical forms of MS, during the follow-up period, based on MRT criteria and EDSS assessment, from of these 22, CIS actually remained 8 (5 female patients, the average age 30.8 ± 8.2 (16 - 48); and 14 patients fulfilled the McDonald WI et al. 2010 criteria for MS (during the first year – 6 patients, within the monitoring period – 8 patients. MRT results demonstrate that the CIS group significantly prevailed ($p<0.05$) in the patients with less than 9 lesions (1-2 Barkhof criteria) (Figure 1). In the third year, the number of patients with MS according to the clinical course was: Relapsing-remitting form (RRMS) - 32, (female patients 19 (38.9 ± 8.3), with Secondary-Progressive SPMS – 14, (7 female patients, 40.6 ± 9.8), Primary-Progressive (PPMS) - 6, (3 female patients 45.4 ± 10.2).

Fig. 1. Percentage distribution of MS and CIS patients in compliance with a number of MRT lesions and the number of fulfilled MRT criteria.



The average screening values of PASAT, SDMT, BVSMT-R are considerably lower ($p<0.05$) in MS patients compared to the controls and CIS patients (Figure 2). Point's number in the progressive forms in comparison with RRMS is reliably smaller. There was no significant difference in results between SPMS and PPMS patients. In the 3rd year, there is a significant cognitive progression in all studied groups and for all tests ($p<0.05$) (Figure 2).

Fig. 2. Comparison of cognitive test scores in different forms of MS at baseline and follow-up period



HC-healthy controls; CIS-clinically isolated syndrome; RR-relapsing-remitting, PP-primary-progressive, SP-secondary-progressive; PASAT-Paced Auditory Serial Additional Test; BVSMT-R-Brief Visuospatial Memory Test-Revised; SDMT-Symbol Digit Modalities Test, BDI-II; BL-baseline, F-follow-up

PASAT results correlate negatively with age (r=-0.38; p=0.03), EDSS (r=-0.42; p=0.01), MRT lesion number (r=0.41, p=0.01), while in CIS patients - with covered criteria number of Barkof (r=-0.30; p=0.04), as well. A moderate positive correlation was found between SDMT results and MRT lesion number (r=0.64, p=0.0001), age (r=-0.42; p=001), EDSS (r=-0.40; p=0.02), covered criteria number of Barkof (r=0.31, p=0.04). BVMT-R correlated negatively with EDSS positively with MRT lesion number.

DISCUSSION:

MS results in motor, sensory, visual and neuropsychiatric symptoms that could appear independently [8]. Cognitive impairment can be present even in the initial stages of the disease. The most common disorders are related to abstract perception, short-term memory, attention and processing speed of information. The different course of the disease is certainly reflected in a different way in the cognitive abilities of the patients. The level of education should always be taken into account because MS patients with a high educational level in the initial phases of the disease have similar neuropsychological results compared to healthy controls. In general, MS patients with a relapsing-remitting course of the disease have better cognitive abilities compared to those with a progressive course of the disease [5, 11]. Data analysis demonstrates that in SPMS and PPMS patients, there is a broad spectrum of more pronounced cognitive deficits in memory and executive functions compared to the RRMS patients for more of the tests and damaged domains. This result coincides with what other researchers established as well [12, 13]. This suggests that in the cognitive patients' profile, an important role is played not only by the disease duration and age but also by the clinical phenotype, probably due to specific pathological mechanism [4, 8]. We did not establish a significant difference between SPMS and PPMS patients like [11], in contrast to the studies of big groups that found more serious deficits with PASAT in SPMS patients compared to PPMS patients [14].

In our study at year 3, the results were significantly lower in both tests, but the deterioration in the PASAT was more pronounced, which is consistent with the results of other authors [11]. As shown by our results and those of other researchers [15], the level of education and the affective state (anxiety, depression, motivation) show a significant influence on the total number of PASAT score, so it is difficult to report a clinically significant progression because there is no generally accepted limit point [15]. Our BVMT-R results confirm what was found by other researchers [16] that BVSMT-R has shown a greater discriminative validity and sensitivity for visuospatial memory, with the advantage that it does not require specialized material and has no ceiling effect, although the functionality of the upper limbs may influence its outcomes [16].

Thus, we confirm in our study that using SDMT has significant advantages. Takes 3-5 min, is easily reproducible, does not require specific neuropsychological training for its administration, test result correlates with CI, MRÒ and patient functional status [8].

Comparing the tests that, after three years, estimate the cognitive functions of the analyzed patients points out better results in PASAT, SDMT, BVSMT-R for patients with less number of attacks compared to the patients having more aggressive disease development. In addition, in T1-weighted MRT, the extent of cortical atrophy corresponds to the degree of cognitive deficit present. This means that both white matter and gray matter may account for cognitive decline in MS patients [17]. This probably happens because of the lower number of MRT lesions and the lack of cortex atrophy in these patients. Because of the same reason, patients with PPMS form are more preserved cognitively compared to the ones with secondary progradient MS form.

Cognitive and affective disorders (depression, dys-

phoria) have an unfavourable effect on family life, professional skills, management of real-life situations and reflect on the life quality of MS patients, and very often, they are the reason for employability loss [18].

The advantage of this study is coverage of the whole spectrum of MS patients from the first demyelination episode, relapsing-remitting to the progressive forms (SPMS and PPMS) and the monitoring period. In CIS patients, the correlation of cognitive changes with clinical symptoms and MRT finding is also valuable. Another strength of the study is that the cognitive tests were performed by the same blinded rater over a 3-year period. A disadvantage is that the number of patients studied is relatively small, and the impact of disease-modifying treatment on cognitive assessment was not taken into account.

CONCLUSION:

The use of a neuropsychological screening test is a valuable method for registering CI in patients with relapsing-remitting course, as well as in patients with a progressive course of the disease. We recommend the SDMT for screening annual follow-up because it is easy to apply, validate and reliably report the progression of CI. In patients with visual disturbances and with arm weakness, it is better to use PASAT, taking into account the level of education and depression.

Cognitive test application in patients with first demyelination event can be used as an additional method for complex risk estimation for conversion of CIS patients.

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