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Cognitive Disorders in Patients with Multiple Sclerosis

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ABSTRACT

Introduction: Multiple sclerosis (MS) is a chronic, inflammatory, (auto) immune disease of the central nervous system (CNS). Cognitive disorders are found in over 50% of patients. **Aim:** The aim of the study was to determine the distribution of cognitive disorders in people with MS. **Methods:** The prospective study included 135 respondents with MS and 50 healthy respondents. The respondents were divided into three groups: the first group consisted of 85 respondents where the disease lasted longer than one year, the second group consisted of 50 respondents with newly diagnosed MS, the third group consisted of 50 healthy respondents. Clinical assessment instruments were: Extended Disability Score in Multiple Sclerosis Patients, Mini Mental Status, Battery of Tests to Assess Cognitive Functions: Wechsler Intelligence Scale, Revised Beta Test, Raven Colored Progressive Matrices, Wechsler Memory Scale, Rey Audio Verbal Learning Test -Osterriecht's complex character test, verbal fluency test. **Results:** Cognitive disorders were present in 40-60% of respondents with MS. Visuospatial, visuoconstructive and visuoperceptive functions are worse in the first group. Mnestic functions (learning process, short-term and long-term memory, recollection, verbal-logical memory) were most affected in both groups of respondents, ranging from 30-60%. Poorer cognitive domains are in the first groups of respondents. Immediate working process memory (current learning), memory, attention, short-term and logical memory is worse in the examinees of the first group. At the beginning of the disease, 16% had verbal fluency difficulties, and as the disease progresses, the difficulties become more pronounced. **Conclusion:** Cognitive disorders are heterogeneous, they can be noticed in the early stages of the disease. They refer to impairments of working memory, executive functions and attention, while global intellectual efficiency is later reduced.

Key words: multiple sclerosis, cognition, neurology.

1. INTRODUCTION

Cervical Multiple sclerosis (MS) is a chronic, inflammatory, (auto) immune disease of the central nervous system (CNS) whose etiological background is not completely clear. The disease is characterized by decay of the myelin sheath, axons, as well as oligodendroglia. As a consequence, scars with a diverse spectrum of symptoms and signs of the disease remain at the site of decay (1). The cause of the disease is unknown, but the most common view is that it is a disease that is a combination of genetic predisposition and deregulation in the immune system, influenced by various risk factors from the environment (2). MS occurs more frequently in women than in men in a ratio of 2.3–3.5: 1 and this ratio has been rising in recent decades (3). Clinically, the dissemination of lesions in time and space is characteristic of this disease. The clinical course of the disease is different and determines the form of MS. The most common is the relapsing-remitting form of MS, which often turns into a secondary-progressive form. There are also primarily progressive as well as relapsing-progressive forms of MS. Symptoms most commonly (85-90%) occur in seizures (exacerbation or remission) or slowly progress over time (4).

Cognitive functions are higher mental processes that encompass a number of different functions that Lezak (5) divides into the following subgroups: receptive functions, memory and learning, thinking, and expressive functions. Thinking, language functions, selective attention, memory, and all forms of cognitive activities and behaviors are the product of intermediate information processing in the neural

networks of the associative cortex and limbic system (6). Evaluation of cognitive functions includes the degree and quality of their impairment, the influence of dysfunction on behavior in general and the analysis of the neuroanatomic substrate. Cognitive disorders are heterogeneous, but recent studies suggest that there is a definite pattern of MS-related cognitive disorders (7).

2. AIM

The aim of the study was to determine the distribution of cognitive disorders in people with MS.

3. PATIENTS AND METHODS

The research was prospectively conducted at the University Clinical Center Tuzla, at the Clinic of Neurology for a period of 2.5 years. The sample included 135 participants with MS and 50 healthy subjects. Participants were divided into three groups: the first (I) group consisted of 85 patients with MS disease lasting more than one year, the second (II) group consisted of 50 patients diagnosed with newly diagnosed MS (disease lasting no longer than one year), the third (III) the group consisted of 50 healthy participants adapted to the experimental groups according to age, gender and education. The selection of participants was done consecutively. Including the criteria for the first group of participants were definitely diagnosed with MS according to the valid McDonald criteria and performed magnetic resonance imaging (MR) of the brain no more than one year before the date of the first test. For the second group including criteria are the existence of a diagnosis of newly diagnosed MS according to the revised McDonald criteria from 2011 (8). Including the criterion for the third group are subjects who have no symptoms and signs of neurological diseases, nor cognitive disorders previously medically documented. Excluding criteria for the first and second groups are associated with diseases and injuries of the brain and spinal cord (injuries, metabolic disorders, epilepsy, vascular lesions). Demographic data (age, gender, level of education) were analyzed for each participants who met the criteria for inclusion in the study. Each patient diagnosed with MS had one brain MRI finding at the first test, from which the number of visible lesions was registered.

The clinical assessment instruments were: Expanded Disability Status Scale (EDSS) (9); Mini Mental Status (MMSE) (10); Tests to assess cognitive functions: Wechsler intelligence scale WB-II (11), Revised Beta test (12), Raven's colored progressive matrices - Intellectual ability test (13), Wechsler memory scale (14), Audio verbal learning test (AVLT) 15,16), Rey-Osterriecht complex character test - RCFT (15), Verbal fluency test - FAS (19, 20).

Participants were examined by a neurologist, and tests to assess cognitive functions were performed by a psychologist and a neurologist together.

Participants from all three groups underwent basic testing and control testing for all groups of participants was performed one year after the primary testing.

Statistical processing was performed in SPSS ver. 13 or SPSS 17.0 (Chicago, IL, USA). To assess the statistical significance of the differences in the results obtained, we used: Mann Whitney U test, Wilcoxon, Hi-square test. The correlation of variables, scales, scores, and domains was examined by regression and correlation analysis (Spearman's correlation coefficient).

	First testing			Second testing	
	Control group	MS > 1 year.	MS de novo	Control group	MS > 1 year.
Number of participants	50	85	50	50	80
RRMS	0	71	50	0	66
SPMS	0	14	0	0	14
Year	38 ± 5.8	42 ± 9.3	37.5 ± 10.8	39 ± 5.8	43 ± 9.3
Gender (♀/♂)	35 / 15	60 / 25	41 / 9	35 / 15	59 / 21
Education (year)	16 ± 1.8	12 ± 2.5	12 ± 2.4	16 ± 1.8	12 ± 2.5
EDSS	0	2.5 ± 2.3	1.9 ± 1.8	0	3 ± 2.6
Length of disease	0	6 ± 4.0	< 1	0	7 ± 4.0

Table 1. Demographic and clinical characteristics of all subjects (Control and both study groups). MS - Multiple sclerosis; RRMS-relapsing-remitting multiple sclerosis; SPMS-secondary-progressive multiple sclerosis; EDSS - Extended Disability Status Scale (Kurtzke's Standardized Extended Disability Status Scale).

4. RESULTS

Demographic and clinical characteristics of the participants are shown in Table 1.

The distribution of cognitive impairments in multiple sclerosis patients is shown in Table 2 after initial testing and in Table 3 one year later.

A group of healthy respondents had normal cognitive functions according to the results of the tests used.

Abstract thinking and general intellectual functioning preserved in both groups of respondents. By measuring educational, nonverbal function, ie understanding complex situations, function to find meaning in events, function to perceive and think, we found that 96.5% of respondents in the first group and 94% of respondents in the second group have regular functioning (Raven's colored matrices-CPM). Earlier engrams of memory remain preserved.

Participants of the first group, however, have slightly worse visuospatial, visuoconstructive and visuoperceptive functions compared to the second group of participants (27% on the cube subtest and 35.29% of the first group on the subtest show pathological values). Deviations in this test are seen in individuals with posterior right-sided lesions, and deviations can also be found in anterior and left-sided lesions.

Spatial function and executive function measured by the test Revised Beta-subtest maze was in the first group of participants neat in 79%, and in the second group 86% of participants had neat values. Similar results were obtained through the verbal fluency test (FAS) as one of the indicators of executive functions (72% had a normal FAS in the first group and 84% in the second group). These tests are mainly an indicator of the preservation of the frontal lobes, as well as how much insight a person has into their condition.

Short-term and long-term verbal learning, new learning

	First testing (n = 85)			Second testing (n = 80)	
	Test	Normal	Below average	Pathological	Normal	Below average
The first group (the disease lasts more than a year)	W k	58.82	14.12	27.06	62.50	15.00
	W zp	38.82	54.12	7.06	32.50	61.25
	CPM	96.47	2.35	1.18	92.50	0.00
	B	65.88	12.94	21.18	71.25	10.00
	W np	38.82	32.94	28.24	28.75	38.75
	W lp	41.18	10.59	48.24	41.25	15.00
	AVLT 1-5	49.41	21.18	29.41	42.50	21.25
	AVLT 6	22.35	20.00	57.65	21.25	23.75
	AVLT 7	21.18	17.65	61.18	21.25	20.00
	RCFT Rt	56.47	8.24	35.29	58.75	5.00
	RCFT vp	36.47	9.41	54.12	36.25	16.25
	FAS	65.88	5.88	28.24	71.25	7.50
		First testing (n = 50)			Second testing (n = 45)	
	Test	Uredan	Below average	Pathological	Uredan	Below average
The second group (newly diagnosed pac.)	W k	80.00	8.00	12.00	77.78	13.33
	W zp	44.00	46.00	10.00	28.89	64.44
	CPM	94.00	4.00	2.00	95.56	4.44
	B	80.00	6.00	14.00	82.22	8.89
	W np	50.00	36.00	14.00	44.44	31.11
	W lp	46.00	16.00	38.00	42.22	20.00
	AVLT 1-5	54.00	22.00	24.00	42.22	33.33
	AVLT 6	26.00	26.00	48.00	24.44	28.89
	AVLT 7	28.00	32.00	40.00	17.78	28.89
	RCFT Rt	74.00	12.00	14.00	75.56	4.44
	RCFT vp	48.00	10.00	42.00	53.33	13.33
	FAS	76.00	8.00	16.00	71.11	15.56

Table 2. Distribution of cognitive disorders in two study groups in the first and second testing.. W k - Wechsler IQ scale; W zp - Wechsler intelligence scale-subtest common concepts; CPM - Raven colored progressive matrices - CPM; β - Test Revised beta maze; W np - Wechsler memory scale - numerical memory; W lp - Wechsler memory scale - logical memory; AVLT A1-A5 test; AVLT A6 test; AVLT A7 test; RCFT Rt - Rey test of the complex character RCFT; RCFT vp - RCFT visual memory recall; FAS verbal fluency test; Rho - Sperman rank correlation coefficient.

ability, learning strategies, and sensitivity to proactive and retroactive inhibition are assessed by audioverbal learning and verbal material memory tests. Immediate working process memory (current learning), attention and short-term memory (Wechsler memory scales subtest memory numbers) are impaired in 28.2% of respondents in the first group, and in 16% of respondents in the second group. Logical memory (Wechsler memory scale subtest logical memory) was impaired in the first group of participants in 48.2% and in the second group of 38% of participants. Direct memory of verbal unrelated material on the learning curve (AVLT A1-A5) shows that about 30% of participants in both groups have a pathological score. Short-term memory (A6) is significantly impaired in both groups of participants, in the first group 57% of participants and in the second group 48% have impaired short-term verbal memory. Both groups of participants show long-term memory impairment (forgetting verbal material-A7), in the first group 61% and in the second group 40% of participants showed signs of forgetting. Significant impairments were noticed in the non-verbal recall tests (RCFT Rey test recall) and they refer to direct visual recall, perceptual-analytical and organizational ability, which is impaired in the first group of participants in 54% and in the second group in 42% of participants.

Verbal fluency in organic brain damage, in this case due to demyelinating lesions, was in the first group of participants impairment in 28.2%, and in the second group in 16% of participants.

Participants of the first and second groups show statistically significant deviations in all psychological tests in relation to the control group of healthy people, who showed normal scores.

The results show that MMSE is not a sufficiently sensitive method for assessing cognitive functions in MS patients. In the first and second groups of participants showed orderly values in over 85% of participants. Using a specific neuropsychological battery of tests, significant deviations are obtained (mnestic functions, long-term memory and recollection, logical memory and attention are most affected), while intellectual functions, executive functions and short-term working process memory showed a high percentage of preservation.

5. DISCUSSION

Multiple sclerosis is a neurodegenerative progressive disorder that affects younger adults in the most productive age, women get sick more often. In this study, women were more represented than men in both groups (70.5% in the first group and 82% in the second group). The average age of the participants in the first group was 42.0 +/- 9.3 years, and in the second group 37.5 +/- 10.8 years. Result was shown in pervious studies (2, 21, 22). The control group (gender and age distribution) was adjusted to the demographic parameters of the first and second groups. The third group (healthy control group) had 70% women, and the mean age was 38.0 +/- 5.8. In the study, we had 82% of participants with relapsing-remitting type and 18% of participants with secondary-progressive type of disease.

According to previous studies, cognitive disorders have been observed in 45-60% of MS patients (7). By neuropsychological assessment, the overall prevalence of cognitive dysfunction in our participants was 50% in patients in the first group and 42% in patients in the second group (newly diagnosed MS), which is consistent with the estimated

prevalence of previous studies ranging from 40% to 70% (24). Cognitive dysfunction in the group RRMS (N = 66) was found in 43% of participants, and in SPMS (N = 14) in 64.5% of participants. A Greek study by Papathanasiou et al (24) indicates that cognitive dysfunction is found in RRMS (N = 50) in 38% of participants, but participants in the group with SPMS (N = 30) have poorer cognitive status (80% of them had some form of cognitive dysfunction). A study by Denney et al (25) also confirms that cognitive deficits are more common and worse in chronic progressive MS and tend to worsen with disease progression.

In both groups of our participants in both tests we found that general intellectual abilities, nonverbal intelligence and executive functions remain preserved, especially at the beginning of the disease (total impaired executive functions in 17% of respondents in both groups). Such results are correlated with the study of Rao et al. (26) who found that executive functions were impaired in a total of 19% of participants, and in the initial phase of the disease are not observed in a higher percentage.

Visuospatial, visuoconstructive and visuoperceptive functions were better preserved in the second group of participants (88% of subjects showed normal results). Slightly worse were the participants of the first group, 30% of them showed difficulties in visuospatial, visuoscostructive and visuoperceptive functions.

Attention and short-term memory assessed by the subtest numerical memory shows that the participants of the second group have slightly worse attention (the subtest numerical memory has a pathological score in 28.24% of participants in the first group and in 14% of participants in the second group). A study by Rahn et al. (23) described similar results that people with MS may have impaired attention, impaired concentration, difficulty with tasks that require continuous attention, unable to remember the data needed to complete the task, and distraction.

Mnestic functions (learning process, short-term and long-term memory, memory-short-term memory of visual material, verbal-logical memory) were most affected in both groups of participants with slightly worse cognitive domains in the first group of participants. Participants of the second group showed better results in learning curves compared to the first group of participants. The process of verbal learning is more impaired in subjects where the disease lasts longer (28% of subjects in the first group and in 14% of participants in the second group show a pathological score on the learning scale). Both groups of participants show poor results in short-term and long-term memory, with a slightly worse score in those where the disease lasts longer. In the first group of participants, logical memory was impaired in 48.2% and in the second group in 38% of participants.

Papathanasiou et al (25) concluded that cognitive impairment occurs in almost all researched domains, with episodic memory, executive functions, and information

		First testing (n = 85)			Second testing (n = 80)	
The first group (the disease lasts more than a year)	Test	Physical dimension-Rho (...p)	Mental dimension Rho (...p)	Total score Rho (...p)	Physical dimension-Rho (...p)	Mental dimension Rho (...p)
	MMSE	0.5062**	0.4392**	0.4832**	0.4282**	0.4472**
	W k	0.4405**	0.3509**	0.4046**	0.4292**	0.3464**
	W zp	0.3352**	0.2936**	0.3256**	0.4244**	0.4220**
	CPM	0.3947**	0.3325**	0.3775**	0.5009**	0.4556**
	B	0.3678**	0.2993**	0.3383**	0.4304**	0.3424**
	W np	0.2922**	0.1392	0.2058*	0.3765**	0.3711**
	W lp	0.3770**	0.3187**	0.3471**	0.3208**	0.3150**
	AVLT 1-5	0.4424**	0.3757**	0.4265**	0.2808*	0.3019**
	AVLT 6	0.4302**	0.3205**	0.4029**	0.2913**	0.3098**
	AVLT 7	0.4095**	0.2985**	0.3739**	0.2279*	0.2524*
	RCFT Rt	0.3590**	0.2356*	0.2882**	0.5302**	0.5085**
	RCFT vp	0.3931**	0.3215**	0.3655**	0.4435**	0.4398**
	FAS	0.3685**	0.3398**	0.3675**	0.3051**	0.3057**
		First testing (n = 50)			Second testing (n = 45)	
The second group (newly diagnosed pac.)	Test	Physical dimension-Rho (...p)	Mental dimension Rho (...p)	Total score Rho (...p)	Physical dimension-Rho (...p)	Mental dimension Rho (...p)
	MMSE	0.3233*	0.3814**	0.3588*	0.5319*	0.6108**
	W k	0.3821**	0.3883**	0.3892**	0.2722	0.3341*
	W zp	0.3237*	0.3791**	0.3628*	0.3693*	0.4002**
	CPM	0.3644*	0.3628*	0.3707**	0.2752	0.3367*
	B	0.1792	0.1868	0.2007	0.2902	0.2918
	W np	0.2789	0.3125*	0.3095*	0.3158*	0.4036**
	W lp	0.3810**	0.3495*	0.3829**	0.2738	0.3267*
	AVLT 1-5	0.3451*	0.3228*	0.3432*	0.3974**	0.4725**
	AVLT 6	0.4134**	0.4140**	0.4345**	0.3496*	0.4140**
	AVLT 7	0.4054**	0.4340**	0.4376**	0.3299*	0.3896**
	RCFT Rt	0.3838**	0.4232**	0.4280**	0.3168*	0.4542**
	RCFT vp	0.3018*	0.3741**	0.3530*	0.2997*	0.4432**
	FAS	0.3373*	0.4103**	0.3722**	0.3861**	0.4527**

Table 3. Correlation of SF 36 with the results of psychological tests of two study groups in the first and second testing. . SF 36 - General generic questionnaire for measuring quality of life (short form 36); MMSE - mini - mental status questionnaire; W k - Wechsler IQ-subtest cube; W zp - Wechsler IQ-subtest common terms; CPM - Raven colored progressive matrices - CPM; β - Test Revised beta maze; W np - Wechsler memory scale - numerical memory; W lp - Wechsler memory scale - logical memory; AVLT A1-A5 test; AVLT A6 test; AVLT A7 test; RCFT Rt - Rey test of the complex character RCFT; RCFT vp - RCFT visual memory recall; FAS test; Rho - Sperman rank correlation coefficient; * - possibility of random error of two-way tested hypothesis ($p < 0.05$); ** - possibility of random difference of bidirectional tested hypothesis ($p < 0.01$).

processing speed being the most impaired, with a gradual increase in frequency as the disease progresses. Cognitive status is associated with the duration of the disease, physical disability, and it is important to note that cognition can predict future disease progression such as e.g. cognitive states in the CIS phase predict progression to MS, and cognitive status in MS predicts possible deposition of physical disability (25).

6. CONCLUSION

Cognitive disorders are present in 40-60% of subjects with MS. Mnestic functions, attention disorders, short-term and long-term memory, non-verbal learning are the most impaired, with poorer results in patients with a longer duration of the disease. Executive and intellectual functions in most participants are preserved. The increase in neuropsychological research, combined with the development of neuroimaging technologies, provides knowledge about neurocognitive disorders in patients with MS and draws the attention of the scientific and professional public to the importance of assessing cognitive functions for the outcome of treatment of patients..

- **Declaration of Patient Consent:** The authors certify that they obtained all appropriate patient consent forms.
- **Author's contribution:** All author gave substantial contributions to the conception or design of the work in acquisition, analysis, or interpretation of data for the work. Author had a part in article preparing for drafting or revising it critically for important intellectual content, and gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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