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COGNITIVE PERFORMANCE AND QUALITY OF LIFE IN PATIENTS WITH MULTIPLE SCLEROSIS

Aida Šehanović, Dževdet Smajlović, Emir Tupković, Omer Ć. Ibrahimagić, Suljo Kunić, Zikrija Dostović, Emina Zoletić, Zejneba Pašić

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COGNITIVE PERFORMANCE AND QUALITY OF LIFE IN PATIENTS WITH MULTIPLE SCLEROSIS
Authors:
Aida Šehanović 1,2*, Dževdet Smajlović 1,2, Emir Tupković 2,3, Omer Ć. Ibrahimagić 1,2, Suljo Kunić 2,3, Zikrija Dostović 1,2, Emina Zoletić 4, Zejneba Pašić 1,2

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Introduction: Multiple sclerosis is a chronic, inflammatory, (auto) immune disease of the central nervous system. Cognitive impairment and the presence of depressive symptoms affect the quality of life. The aim was to determine the impact of cognitive disorders and depression on quality of life in patients with multiple sclerosis. Methods: The prospective study included 135 sick and 50 healthy subjects. Participants were divided into three groups: the first group consisted of 85 participants whose illness lasted longer than one year, the second group consisted of 50 participants with a newly diagnosed disease, the third group consisted of 50 healthy participants. Clinical assessment instruments were: Extended Disability Score in Multiple Sclerosis Patients, Mini Mental Status, Beck Depression Scale, Battery Tests for Cognitive Function Assessment: Wechsler Intelligence Scale, Revised Beta Test, Raven Colored Progressive Matrices, Wechsler Memory Test audio verbal learning, the Rey-Osterriecht complex character test, the Verbal Fluency Test, and the SF-36 quality of life assessment scale. Results: Cognitive disorders were present in 40-60% of participants with MS. Visuospatial, visuoconstructive and visuoperceptive functions are worse in the first group. Mnestic functions are most affected. Immediate working process 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 disorders, and as the disease progresses, the disorders become more pronounced. Conclusion: Cognitive disorders in MS patients are heterogeneous. They refer to impairments of working ability and memory, executive functions and attention, while global intellectual efficiency is later reduced. Quality of life is related to overall cognitive performance and shows a greater association with the degree of adaptation to the disease than with its symptoms.

Key words: multiple sclerosis, cognitive disorders, quality of life

Affiliations:

1 Department of Neurology, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina,

2 Faculty of Medicine , University of Tuzla, Tuzla, Bosnia and Herzegovina,

3 Department of Neurology, Primary Health Center Tuzla, Tuzla, Bosnia and Herzegovina, 4 Research Centre of Epidemiology and Statistics, Sorbonne Paris Cité, Paris, France

Corresponding author:
Aida Šehanović,
E-mail: aida.sehanovic@gmail.com

INTRODUCTION

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 [1]. The cause of the disease is unknown, but the most widespread view is that it is a disease that is a combination of genetic predisposition and deregulation in the immune system, with the influence of 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 on the rise in recent decades [3]. New epidemiological studies suggest a geographical distribution of the so-called risk zones for MS: with a very high prevalence> 170/100. 000, with a high prevalence of 70-169 / 100,000, with a medium prevalence of 38-69 / 100,000, with a low prevalence of 13-37 / 100,000 and with a very low prevalence of more than 13 / 100,000 [4]. 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 often (85-90%) occur in attacks (exacerbation or remission) or slowly progressively over time [5]. Cognitive functions are higher mental processes that encompass a number of different functions that Lezak [6] 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 behaviour are the product of intermediary information processing in the neural networks of the associative cortex and limbic system [7]. Cognitive disorders are heterogeneous, but recent studies suggest that there is a definite pattern of MS-related cognitive disorders. They mainly refer to impairments of working ability and short-term memory, executive functions and attention, while global intellectual efficiency was later reduced [8]. The World Health Organization (WHO) has given the following definition:

"Quality of life (QC) is an individual perception of patients' position in life, in terms of the cultural and value system in which they live and in relation to their goals, expectations, standards and occupations" [9] . At least four dimensions must be included in the monitoring of QoL: physical, functional, mental and social. The physical dimension of health suggests primarily a link between disease, treatment, and symptom. Functional health includes self-care, mobility and level of physical activity, as well as playing different roles in the family or at work. Cognitive functioning, emotional status and a general understanding of health, well-being, life satisfaction and happiness, are the central components of the psychic area of QOL. Social functioning includes the assessment of qualitative and quantitative aspects of social contacts and interaction [10].

PARTICIPANTS AND METHODS

The research was prospectively conducted at the University Clinical Center Tuzla, in the Clinic of Neurology for a period of 2.5 years. The sample included 135 subjects with MS and 50 healthy participants. Participants were divided into three groups: the first (I) group consisted of 85 patients where MS disease lasted longer than one year, the second (II) group consisted of 50 patients diagnosed with newly diagnosed MS (disease does not last 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 [11]. Including the criterion for the third group are participants 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 participant who met the criteria for inclusion in the study. Each patient diagnosed with MS had one brain MRI finding at the first test. The instruments of clinical assessment were: Extended Disability Status Scale EDSS [12]; Mini Mental Status (MMSE) [13]; SF-36 score [14]. Tests to assess cognitive functions: Wechsler Intelligence Scale WB-II [15], Revised Beta Test [16], Raven's Colored Progressive Matrices - Intellectual Ability Test [17], Wechsler Memory Scale [18], Audio Verbal Learning Test (AVLT) [19, 20], Rey-Osterriecht complex character test - RCFT [21,22]. Verbal fluency test - FAS [23, 24]. 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 test and Hi-square test. The association of variables, scales, scores, and domains was examined by Spearman's rank correlation test.

RESULTS

Demographic and clinical characteristics of all three groups of participants are shown in Table 1. The first group of participants consisted of patients diagnosed with MS for more than one year, 85 of them. There were 60 women (70.5%) and 25 men (29.5%) . The mean age of the participants was 42.0 +/- 9.3 years. The second group of participants included patients with newly diagnosed MS. It included 50 participants, 41 were women (82%) and 9 were men (18%). The mean age of participants with newly diagnosed MS was 37.5 +/- 10.8 years. The group of healthy participants (control group) had harmonized demographic characteristics with the study participants of the first two groups. We had 82% of participants with relapsing-remitting type and 18% of participants with secondary-progressive type of disease.

Tabela 1. Demographic and clinical characteristics of all subjects (Control and both study groups)

	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

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).

The distribution of cognitive disorders in patients with multiple sclerosis is shown in Table 2 in two study groups of participants (first and second group) after initial testing and one year later.

Tabela 2. Distribution of cognitive disorders in two study groups in the first and second testing.

		First testing (n = 85)			***Second testing (n = 80)***	
	Test	**Uredan**	**Below average**	**Pathological**	**Uredan**	**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

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.

A group of healthy participants had normal cognitive functions according to the results of the tests used. 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. Abstract thinking and general intellectual ability preserved in both groups of diseased participants. Participants of the first group have slightly worse visuospatial, visuoconstructive and visuoperceptive abilities 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). Spatial ability and executive function (response planning, serial organization and behavioral inhibition and fine oculomotor coordination) measured by the test Revised Beta-subtest labyrinth was neat in the first group of participants 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% of participants had an orderly FAS in the first group and 84% in the second group). Immediate working process memory (current learning), attention and short-term memory (Wechsler memory scales subtest memory numbers) were impaired in 28.2% of participants in the first group, and in 16% of participants 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 deviations 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, is in the first group of participants impairment in 28.2%, and in the second group in 16% of participants. This finding fits in well with the maze subtest, given that verbal fluency is partly an indicator of executive function. 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 (most affected are mnestic functions, long-term memory and recollection, logical memory and attention, while intellectual abilities, executive functions and short-term working process memory showed a high percentage of preservation).

		First testing (n = 85)			***Second testing (n = 80)***	
The first group (the disease lasts more than a year)	**Test**	**Physical dimensionRho(... p)**	**Mental dimension Rho(... p)**	**Total score Rho(... p)**	**Physical dimensionRho(... 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 dimensionRho(... p)**	**Mental dimension Rho(... p)**	**Total score Rho(... p)**	**Physical dimensionRho(... 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**

*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).*

For both study groups in the first and second testing, Table 3 shows the correlation of SF 36 results (physical and mental dimensions as well as the overall quality of life score) with MMSE and 12 psychological tests (Wechsler IQ scale, Wechsler intelligence scale. common terms, Raven coloured progressive matrices-CPM, Revised beta maze test, Wechsler memory scale-numerical memory, Wechsler memory scale-logical memory, AVLT A1-A5 test, AVLT A6 test, AVLT A7 test, Reka R complex test visual memory and recall, FAS test). In the first group of participants, the physical, mental dimension and the overall quality of life score of the first group of participants in the first and second tests correlated significantly positively with MMSE. The physical dimension of the quality of life of this group of participants at the first test significantly correlates with all psychological tests used. The mental dimension of quality of life as well as the overall quality of life score of the first group of participants in the first test significantly correlates with all psychological tests used except the Wechsler memory scale - numerical memory. The results show that patients with poorer MMSE and those with poorer cognitive functions have a poorer quality of life. In the participants of the second group, after the first and second tests, the physical, mental dimension of quality of life as well as the overall SF-36 score in both tests positively significantly correlated with MMSE. The physical dimension of quality of life of the second group of participants in the first test significantly correlates with all used psychological tests except β-test (revised beta maze) and Wechsler memory scale - numerical memory, and in the second test significantly correlates with all used psychological tests except Wechsler intelligence scale - cube subtest, Raven's coloured progressive matrices -CPM, β-test (revised beta maze) and Wechsler memory scale - logical memory. The mental dimension as well as the overall quality of life score of the second group of participants in the first and second testing significantly correlates with all psychological tests used except the β-test (revised beta maze). Given that the Revised beta subtest maze test is mainly an indicator of executive (executive) functions and nonverbal intelligence, which remain preserved at the beginning of the disease, it explains that these cognitive impairments do not affect the quality of life of participants at the beginning of the disease.

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. This result correlates with the results in other studies [3, 4, 25]. The control group (gender, age distribution, education) was adjusted to the demographic parameters of the first and second groups. The third group (healthy control group) had a female 70%, and the mean age was 38.0 +/- 5.8. In this study, we had 82% of participants with relapsing-remitting type and 18% of participants with secondary-progressive type of disease, in correlation with other studies [25, 26]. According to previous studies, cognitive disorders have been observed in 45-60% of MS patients. Already in the early stages of the disease, they lead to impaired working ability, long-term memory, executive functions and attention, while global intellectual efficiency is later reduced [8, 28]. By neuropsychological assessment, the overall prevalence of cognitive dysfunction in our participants is 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% [27]. In both groups of our participants in both tests, we found that averall general intellectual abilities, more precisely nonverbal intelligence, and executive functions were preserved, especially at the onset of the disease. These results are correlated with the study of Rao et al. 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 [29]. Visuospatial, visuoconstructive and visuoperceptive functions are worse in the first group of participants, 30% of them showed difficulties in these functions. The process of attention and short-term memory assessed by the subtest numerical memory shows that the subjects of the second group have slightly worse attention. Deficiency tests can detect deficiencies in patients with mild to moderate cognitive impairment. A study by Rahn et al [30] 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. Better results on the learning curves were shown by the participants of the second group. The process of verbal learning is more impaired in participants where the disease lasts longer. 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. Papathanassiou et al [27] concluded that cognitive impairment occurs in almost all researched domains, with episodic memory, executive functions, and information processing speed being 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 [28]. The results of previous studies [26, 29] showed the relative preservation of speech at the beginning of the disease, and we obtained similar results in our participants. At the beginning of the disease (in the second group of respondents, 16% had verbal fluency disorders), and as the disease progresses, the disorders become more pronounced (28% of respondents in the first group showed a pathological finding). Quality of life is a multidimensional concept that connects physical, social, psychological and emotional functioning. Health assessment based on patient responses through a 36-question questionnaire from the health profile (SF-36) was mostly used in medical studies. The SF-

36 questionnaire simply highlights the areas of health affected by the disease, and can reveal how patients cope with the disease. Cognitive impairments with their reflection significantly affect the quality of life and social-emotional functioning. Using a battery of cognitive tests, it was determined that the physical, mental dimension as well as the overall quality of life score of the second group of participants in the first and second tests do not show a significant correlation with the Revised beta-subtest maze test, and significantly correlate with other tests. Executive (executive) functions and non-verbal intelligence remain preserved and do not affect the quality of life of the examinee at the beginning of the disease. According to a study by Rao et al. (1991) executive functions are impaired in total in 19% of participants, and in the initial phase of the disease they are not observed in a higher percentage [29]. The physical, mental dimension and the overall quality of life score of the first group of participants in the first and second tests correlated significantly positively with MMSE. The physical dimension of the quality of life of this group of participants at the first test significantly correlates with all psychological tests used. The mental dimension of quality of life as well as the overall quality of life score of the first group of participants in the first test significantly correlates with all psychological tests used except the Wechsler memory scale - numerical memory. All dimensions as well as the overall quality of life score of the first group of participants in the second test significantly correlated with all psychological tests used. The results show that patients with a poorer MMSE and those with poorer cognitive functions have poorer quality of life (physical, mental dimension and overall quality of life). Cognitive dysfunctions reduce physical independence and social activities, competence in daily activities, personal and social independence, adherence to therapeutic protocols , potential rehabilitation, traffic safety. Patients with cognitive impairment are more likely to be unemployed, while employed patients are more cognitively preserved [27].

CONCLUSION

Cognitive disorders are present in 40-60% of participants 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 growth of 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.

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