Spectrum of Cognitive Impairment in Patients with Multiple Sclerosis

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Abstract

Introduction. *Cognitive impairment (CI) is a common manifestation of multiple sclerosis (MS), which significantly affects patients' daily life and professional activity. Despite the development of methods to screen MS patients for CI, data on its prevalence in the Russian population are still lacking.*
Aim*: to comprehensively assess cognitive functions in patients with different types of MS.*
Materials and methods. *The study included MS patients who did not have any other possible causes of CI and no diseases or conditions that confounded this assessment. CI was determined using the Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS) test battery and the Stroop test as a decrease in the scores below the mean by at least 1.5 standard deviations. CI was subjectively assessed using the Perceived Deficit Questionnaire; fatigue was subjectively assessed using the Modified Fatigue Impact Scale (MFIS). The Mann–Whitney test and Fisher's exact test were used for comparison, and the Spearman test was used to evaluate correlations.*
Results. *We evaluated 77 MS patients (30 men; age 40 [30; 48] years; 47 with relapsing-remitting MS, 30 with progressive MS). CI incidence was 23.4% in patients with relapsing-remitting MS and 77% in patients with progressive MS, while multi-domain CI was statistically significantly more common in patients with progressive MS. Impairment of processing speed was the most common. Patients with relapsing-remitting MS and CI were statistically significantly older and had longer disease duration than those without CI. There was a statistically significant correlation of subjective CI severity with MFIS scores but not with testing results.*
Conclusion. *CI incidence in MS patients was relatively high with greater severity and involvement of more domains in patients with progressive MS. No correlation was found between subjective and objective CI assessment results, which may suggest that patients underestimated their deficit.*

Keywords: *multiple sclerosis; cognitive impairment; fatigue; cognitive test batteries*

Ethics approval. All patients provided their voluntary informed consent to participate in the study. The study protocol was approved by the Ethics Committee of Research Center of Neurology (Protocol 1-7/23, dated 25 January 2023).

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Спектр когнитивных нарушений у пациентов с рассеянным склерозом

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Аннотация

Введение. *Когнитивные нарушения (КН) являются распространённым проявлением рассеянного склероза (РС), значимо влияющим на повседневную и профессиональную активность пациентов. Несмотря на развитие методик скрининговой оценки КН при РС, сохраняется недостаток данных об их распространённости в российской популяции.*

Цель *исследования – комплексная оценка когнитивных функций у пациентов с разными типами течения РС.*

Материалы и методы. *В исследование включены пациенты с РС, не имеющие иных возможных причин развития КН и заболеваний или состояний, затрудняющих тестирование. КН определяли с помощью батареи тестов Brief International Cognitive Assessment in Multiple Sclerosis и теста Струпа как снижение показателей ниже среднего на 1,5 и более стандартных отклонения. Субъективную оценку КН проводили с помощью опросника Perceived Deficit Questionnaire, утомления – шкалы Modified Fatigue Impact Scale (MFIS). Для сравнения использовали критерий Манна–Уитни и точный критерий Фишера, для оценки корреляций – критерий Спирмена.*

Результаты. *Обследованы 77 пациентов с РС (30 мужчин, возраст 40 [30; 48] лет, 47 – с ремиттирующим РС, 30 – с прогрессирующим РС). Частота КН у пациентов с ремиттирующим РС составила 23,4%, с прогрессирующим РС – 77%, при этом у пациентов с прогрессирующим РС статистически значимо чаще встречались мультидоменные КН. Наиболее часто регистрировались нарушения скорости обработки информации. Пациенты с ремиттирующим РС и КН были статистически значимо старше и имели бóльшую длительность заболевания по сравнению с пациентами без КН. Субъективная выраженность КН статистически значимо коррелировала с показателями MFIS, но не с результатами тестирования.*

Заключение. *Показана достаточно высокая частота КН у пациентов с РС, при этом бóльшая выраженность и вовлечение большего числа доменов наблюдались при прогрессирующем РС. Обнаружено отсутствие корреляции субъективной и объективной оценки КН, что может свидетельствовать о недооценке пациентами дефицита.*

Ключевые слова: *рассеянный склероз; когнитивные нарушения; утомление; батареи когнитивных тестов*

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Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system with a relatively high prevalence. MS prevalence is estimated to be 2 to 165 cases per 100 thousand population in different geographical areas [1] and 50 to 80 cases per 100 thousand population in Russia [2, 3]. Depending on MS type, activity, and duration, neuroinflammation or degeneration mechanisms can predominate in its pathogenesis [4–6]. Despite significant development of treatment options for MS and improvement in its course, disability due to MS remains high [7, 8]. Affecting mostly patients of young or middle age, MS significantly worsens their professional and daily activities and decreases their quality of life [9].

Cognitive impairment (CI) in MS patients is quite challenging to diagnose, often ignored by patients themselves, and, therefore, often classified as a "hidden" MS symptom [10, 11]. In the Expanded Disability Status Scale (EDSS), the assessment of cognitive functions is limited to the subjective impression of the assessor, so CI is often not taken into account when disease activity is assessed, although its detection can further increase the sensitivity of relapse detection [12]. CI can also be a marker of aggressive disease [13].

Possible mechanisms underlying CI in MS patients include demyelination and gray matter atrophy. Several authors suggested that CI in MS patients can result from neuronal network disruption due to white matter lesions [14]. An important role in CI pathogenesis can be attributed to the atrophy of the gray matter in the thalamus, basal ganglia, hippocampal cortex, several areas of the cerebral cortex, and cerebellum [15, 16].

In recent years, increasing attention has been paid to studying cognitive functions using specialized scales and questionnaires, such as screening assessment tools and expanded neuropsychological test batteries. Most common screening tools include Symbol-Digit Modalities Test (SDMT) and its modifications, Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS) battery, and more detailed ones such as Brief Repeatable Battery of Neuropsychological tests in multiple sclerosis (BRB-N), Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS), Battery Evaluating Cognitive Functions in Multiple Sclerosis (BCcogSEP), etc. [17]. Several questionnaires have been developed to subjectively assess cognitive functions, such as Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) [18] and Perceived Deficit Questionnaire (PDQ). It is assumed that screening tools can be used in all MS patients to assess them for CI and its changes over time, while expanded scales are feasible for selected groups of patients, in particular, those who have complaints of cognitive decline, or when CI is detected using screening tools [19].

Both overall incidence and phenotype of CI depend on the MS type. For instance, mild single-domain verbal memory/semantic fluency CI is more typical for relapsing-remitting MS (RRMS). Patients with progressive MS (PMS) more often have multi-domain CI or severe attention/executive CI [20]. However, data on incidence of CI in different domains depending on MS type remain inconsistent [21].

Study aim. This study aimed to comprehensively assess cognitive functions in patients with different types of MS.

Materials and methods

This cross-sectional study involved MS patients who received inpatient treatment at Research Center of Neurology (Moscow, Russia) from 2021 to 2024. The study was approved by the Ethics Committee of Research Center of Neurology (Protocol 1-7/23 dated 25 January 2023) and was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria:
- voluntary informed consent to participate in the study;
- age over 18 years;
- MS diagnosis confirmed according to the McDonald criteria, 2017.

Exclusion criteria:
- Diagnosed diseases or conditions that can be associated with CI (such as concomitant neurological disorders that result in deterioration of cognitive functions; clinically significant depression; use of medications with a known effect on cognitive functions; alcohol or drug abuse).
- Diagnosed diseases or conditions that can confound cognitive test results (uncorrectable visual or hearing impairment, severe dysarthria, tremor in the dominant hand, paresis in the dominant hand with a decrease in muscle strength corresponding to a decrease by up to MRC Weakness Scale score 2 or lower).
- Diagnosed severe medical or neurological concomitant conditions.

An MS relapse (clinical manifestations or disease activity detected using contrast-enhanced MRI) was not an exclusion criterion for the study.

Once the patients signed the informed consent form, demographic data, general and medical history were recorded, severity of neurological deficit was assessed using the EDSS scale, and severity of depression was assessed using the corresponding subscale of the Hospital Anxiety and Depression Scale. Severity of subjective cognitive impairment was assessed using the PDQ questionnaire; fatigue was assessed using the Russian version of the Modified Fatigue Impact Scale (MFIS) [22]. Objective assessment of CI was performed using the Russian version

of BICAMS test battery [23], which included the following tests [24, 25]:

- *SDMT*, which assesses processing speed. Individuals tested should quickly pair geometric shapes to one of nine numbers, based on a provided key, for 90 seconds. The outcome is total number of correctly paired shapes. To prevent upper motor extremity weakness from confounding the written version of this test, the oral version is used, when the patient calls the numbers out loud, and the assessor writes them down under the corresponding symbols.
- *Californian Verbal Learning Test – Second Edition (CVLT-II)*, which assesses short-term verbal memory and learning. The BICAMS battery allows 5 consecutive trials, which test immediate recall. The researcher reads a list of 16 words from 4 semantic groups to the patient, who should memorize them and recall in any order immediately after their presentation. The presentation is repeated 5 times, and the final score is the total number of items recalled over 5 trials.
- *The Brief Visuospatial Memory Test – Revised (BVMT-R)*, a test for non-verbal visual memory and learning. As with CVLT-II, only trials that test immediate recall are evaluated. Individuals tested are asked to study a figure with six geometric shapes for 10 seconds. The figure is removed and the participant is asked to accurately draw as many of the geometric shapes as they can remember, while simultaneously placing them in the correct location on the page. The three learning trials are scored based on accuracy (1 point) of each shape and location (1 point). A total score is derived from summing up the total number points across all three learning trials.

Since PMS patients often have impairment of executive functions, the BICAMS battery was supplemented with a Russian verbal version of *the Stroop test* to assess inhibition. The test consists of 3 parts: in part 1, the participant reads a sequence of color names (red, blue, yellow, and green) printed in black ink; in part 2, a sequence of hexagons printed in the same ink is presented, and the participant names the color of the geometric shapes. In part 3, the participant is given a card with color names written in an incongruent ink colour. The participant should voice the ink colours, ignoring the written word. Only part 3 is used to evaluate executive functions; the number of correct responses in 45 seconds is recorded [26].

In this study, the patient was considered to have CI if at least one cognitive test from the BICAMS battery or the Stroop test differed by at least 1.5 standard deviations from the mean cut scores [25, 26]. These cut scores have the highest sensitivity and adequately high specificity [26]. Therefore, processing speed impairment was recorded if SDMT score decreased to 44 or less (sensitivity 0.95; specificity 0.848), verbal memory impairment was recorded if CVLT-II score decreased to 39 or less (sensitivity 0.93; specificity 0.875), and spatial memory

Table 1. Characteristics of RRMS and PMS patients

Parameter		RRMS (n = 47)	PMS (n = 30)	p_{unc}	p_{corr}
Gender (M : F)		14 : 33	16 : 14	0,055	
Age		34 [27; 42]	47 [40; 58]	**< 0,001**	
Higher education		27	18	1,0	
Disease duration, months		22 [9; 60]	156 [75; 204]	**< 0,001**	
Relapse		45	14	–	
EDSS		3 [2,5; 3,5]	6 [4,5; 6,0]	**< 0,001**	
DMT use (yes : no)		11 : 36	15 : 14	**0,014**	
SDMT	test results	52 [49,00; 58,00]	38 [31,00; 46,75]	**< 0,001**	**< 0,001**
	number of patients with CI	7	20	**< 0,001**	**< 0,001**
CVLT-II	test results	55 [50,25; 61,00]	45 [38,25; 50,75]	**< 0,001**	**< 0,001**
	number of patients with CI	2	9	**0,003**	**0,015**
BVMT-R	test results	25 [21,50; 28,50]	23 [15,75; 26,00]	**0,022**	0,11
	number of patients with CI	7	9	0,15	0,6
Stroop test	test results	43 [38,50; 49,50]	34 [26,25; 39,75]	**< 0,001**	**< 0,001**
	number of patients with CI	1	10	**< 0,001**	**< 0,001**
Number of patients with CI	total	11	23	**< 0,001**	**< 0,001**
	single-domain CI	7	9	0,15	0,6
	CI in ≥ 2 domains	4	14	**< 0,001**	**< 0,001**
PDQ		17 [10; 29]	26 [15; 34]	0,311	1,0
MFIS	total score	27 [7,0; 45,0]	80 [61,5; 104,5]	**0,002**	**0,01**
	cognitive function subscale	12 [5,75; 17,00]	15 [7,25; 21,25]	0,475	1,0

Note. p_{unc}, significance level without correction; p_{corr}, significance level with Bonferroni correction for multiple comparisons. DMTs, disease-modifying therapies.

impairment was recorded if BVMT-R score decreased to 17 or less (sensitivity 0.946; specificity 0.933) [25]. A score of 30 and lower was used as a cut score for the Stroop test [26].

Descriptive statistics were calculated using IBM SPSS Statistics v. 27. Distribution of data was not normal (Shapiro–Wilk test; $p < 0.05$), so non-parametric statistical methods were used for analysis. Cognitive test scores and questionnaire data were compared between the groups using the Mann-Whitney test; differences in CI incidence were assessed using Fisher's exact test; correlations were assessed using the Spearman coefficient. Differences were considered statistically significant if $p < 0.05$. Adjustment for multiple comparisons was performed using the Bonferroni correction.

Results

The study included 77 MS patients (30 men, age 40 [30; 48] years) (hereinafter data are presented as Me [Q1; Q3]); of those, 47 patients had RRMS and 30 patients had PMS (26 secondary progressive MS, 4 primary progressive MS). Clinical and demographic characteristics and cognitive test results are shown in Table 1.

CI was observed in 11 (23.4%) RRMS patients; of those, 7 patients had single-domain CI, and 2 patients each had CI in 2 and 3 domains, respectively. It should be noted that RRMS patients with multi-domain CI had MS relapse at the time of inclusion in the study and did not receive DMTs, and in patients with 3-domain CI, MS duration was more than 7 years. In PMS patients, CI was reported in 23 (77%) patients, with 9 of them having single-domain CI, 6 CI in 2 domains, 5 in 3 domains, and 3 in 4 domains. Overall incidence of CI and multi-domain CI in PMS patients was statistically significantly higher than in RRMS patients (Fisher's exact test, $p < 0.001$) with no statistically significant differences in incidence of single-domain CI (Table 1).

RRMS and PMS patients did not have any statistically significant differences in gender or education level but differed in age and MS severity (Mann–Whitney test, $p < 0.001$), as well as frequency of DMT use (Fisher exact test, $p < 0.05$; Table 1). When RRMS and PMS patients were compared, statistically significant differences were found in SDMT, CVLT-II, BVMT-R, and Stroop test scores with no statistically differences in PDQ and cognitive fatigue scores. After Bonferroni correction for multiple comparisons, all differences remained statistically significant except for BVMT-R scores. When the incidence of CI in different domains was compared, statistically significant differences were also shown for SDMT, CVLT-II, and Stroop test (Fisher's exact test, $p < 0.05$).

Considering statistically significant differences between the RRMS and PMS patients in their age, MS duration and severity, we also evaluated a relationship between cognitive test results and these parameters using the non-parametric Spearman coefficient. Mean negative statistically significant correlations were shown for SDMT with age, for SDMT and

Table 2. Correlations between test parameters and questionnaires

Parameter		Age	Duration	EDSS	PDQ	MFIS	$MFIS_{cogn}$
SDMT	ρ	**–0,402**	**–0,554**	**–0,618**	–0,087	–0,270	–0,111
	p	**< 0,001**	**< 0,001**	**< 0,001**	0,459	0,020	0,911
CVLT-II	ρ	–0,272	**–0,471**	**–0,509**	–0,225	–0,371	–0,257
	p	0,017	**< 0,001**	**< 0,001**	0,054	0,001	0,027
BVMT-R	ρ	–0,339	–0,334	–0,260	–0,092	–0,200	–0,077
	p	0,003	0,003	0,023	0,437	0,087	0,514
Stroop test	ρ	–0,286	–0,255	**–0,544**	–0,149	–0,278	–0,193
	p	0,012	0,026	**< 0,001**	0,204	0,017	0,099
PDQ	ρ	0,002	0,097	0,198	–	**0,726**	**0,828**
	p	0,985	0,415	0,091	–	**< 0,001**	**< 0,001**

Note. *p*, significance level; ρ, Spearman correlation coefficient. $MFIS_{cogn}$, Modified Fatigue Impact Scale, Cognitive Subscale.

CVLT-II with disease duration, and for SDMT, CVLT-II, and Stroop test with MS severity according to EDSS (Table 2).

Differences in cognitive test results and questionnaire scores were evaluated in patients who used and did not use DMTs at the time of inclusion in the study. No statistically significant differences were found for subjective CI severity and fatigue in the total population and separate subsets.

We evaluated differences between patients with or without CI in subsets of RRMS and PMS patients by their age, MS duration and severity. RRMS patients with CI were statistically significantly older than those without CI (Mann–Whitney test, $p = 0.010$) and had more severe disease ($p = 0.043$), while no statistically significant differences were found in disease duration. There were no statistically significant differences in patients' age, MS duration or severity in PMS patients.

We also evaluated a correlation of subjective CI severity with cognitive test results and fatigue score (total score and cognitive fatigue score). When the relationship between cognitive test results and total PDQ score was evaluated, no statistically significant correlations were found. In contrast, the assessment of fatigue (general and cognitive) had a statistically significant strong correlation with the subjective CI severity according to PDQ. We also assessed a relationship between overall fatigue and cognitive fatigue scores with cognitive test results. However, only a moderate statistically significant negative correlation was shown between the total fatigue score and CVLT-II results (Table 2).

Discussion

CI was observed in approximately a quarter of RRMS patients, while in PMS patients its incidence was significantly higher (i.e. 77%). CI severity was also higher in PMS patients; however, this may be partly explained by the older age and MS duration in patients in this group. CI spectrum was different: RRMS patients had single-domain CIs, most often decreased processing speed or visuospatial memory, while PMS patients more often had multi-domain CIs. In PMS patients, a decrease in processing speed was also predominantly observed; impairments in other domains were less common and had a similar incidence. No statistically significant correlation was shown for subjective CI and fatigue assessment with cognitive test results regardless of the MS type.

CI incidence in RRMS patients in our study (23.4%) was consistent with some previous studies [27, 28]. In contrast, other authors showed a higher incidence of CI, i.e. 30–45% [29–31]. It should be noted that among RRMS patients in our study patients with MS relapse predominated, while in several studies in RRMS patients with a similar or higher CI incidence, patients were in remission [27, 30, 31], or in other studies MS activity was not specified [28, 29]. Since patients during relapses were shown to have a higher severity of CI [32, 33], this inconsistency requires further investigation.

The incidence of CI in PMS patients in our study was generally consistent with literature data [21, 31]. The differences in CI spectrum in RRMS and PMS patients were consistent with previous data summarized in a review by B. Brochet et al. [21]. The higher incidence of single-domain CI in RRMS patients and multi-domain CI in PMS patients is consistent with a large study by E. De Meo et al. [20], where patients with early RRMS most often had mild single-domain impairment in verbal memory/semantic fluency. In our group, impairment of processing speed was the most common among single-domain CIs. On the other hand, the highest incidence of impairment in processing speed in our study is consistent with the pre-viously proposed model of cognitive impairment, according to which the earliest impairment is seen in proces-sing speed, followed by impairment in visuospatial cognition, verbal cognition, working memory/attention, and executive functions [34].

An association of CI and patients' age, MS severity and duration found in our study was also shown in previous studies [21, 31, 35]. Evidence remains conflicting as to whether MS type is an independent risk factor for CI or whether patients' age and disease severity contribute more to the differences [29, 31]. Although a meta-analysis by N.C. Landmeyer et al. [36] showed that cognitive function parameters improved in patients receiving DMTs, we did not detect any statistically significant differences between patients who received DMTs and those who did not. This may be related to the high proportion of patients with early RRMS who started their DMTs recently.

Along with previous studies, we did not found any statistically significant correlation between subjective CI severity and objective test results [37]. Severity of subjective CI was previously shown to be more influenced by depression and fatigue [38], which is consistent with our results. The statistically significant moderate correlation of the overall fatigue score with CVLT-II verbal memory test results is similar to the results of a study that showed a relationship between BICAMS battery scores and subjective fatigue, in which fatigue had the most significant effect on CVLT-II scores [39]. Consistent with another recent study, we found a correlation between cognitive fatigue with subjective CI but not with objective test data [40].

Limitations of our study include small sample size and relatively high heterogeneity of patients; however, our results reliably showed the incidence of CI in real-world clinical practice when assessed using standardized screening tools. In addition, the use of cut scores for determination of CI may be considered as an important limitation of the study, and therefore, in future studies, it may be advisable to

assess the reliability of CI determination using other normal values for the Russian-speaking population, such as those based on regression. Finally, further studies would be useful to investigate changes in CI depending on disease activity, assess other cognitive domains, and compare patients with benign and highly active MS.

To summarize, our study was the first to provide a comprehensive assessment of CI prevalence in patients with different types of MS and different MS activity using the standardized Russian version of the BICAMS test battery and the Stroop test. Clinical and demographic differences between patients with CI and intact cognitive functions were also assessed. A relationship between subjective CI severity with both cognitive test results and fatigue severity was evaluated for the first time in the Russian-speaking population.

Conclusion

When cognitive functions were assessed in patients with different MS types using standardized test batteries, CI was shown to be a rather common symptom in patients with different MS types, with processing speed being affected most frequently. CI is associated with both clinical and demographic characteristics of patients (age, MS severity and duration) and with its type; PMS patients had higher severity of CI and impairment in several cognitive domains. No significant correlation was found between subjective CI assessment results and testing results, which suggests that patients underestimated their deficit. Therefore, CI is a rather common manifestation of MS, and its identification requires the active use of standardized test batteries for the objective assessment of CI in clinical practice.

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