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Clinical and Demographic Determinants of Cognitive Disorders in Multiple Sclerosis Patients

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Abstract - Multiple sclerosis (MS) is a chronic, inflammatory, (auto) immune disease of the central nervous system (CNS). The aim of the study was to determine the distribution of cognitive disorders in MS in relation to demographic parameters, degree of clinical disability and depression. The prospective study included 135 subjects with MS in the Clinic of Neurology of the University Clinical Center in Tuzla. The first group consisted of women (101 respondents) and the second of men (34 respondents). Clinical assessment instruments were: Expanded Disability Status Scale Score, Mini Mental Status, Beck Depression Scale, Battery of Cognitive Function Assessment Tests: Wechsler Intelligence Scale, Revised Beta Test, Raven Coloured Progressive Matrix, Wechsler Memory Verification Scale, Audio Memory Test learning, Rey-Osterriecht complex character test, verbal fluency test. There were no significant differences between the mentioned groups in age, level of education, duration of the disease, severity of disease symptoms or in the prevalence of certain forms of MS. Cognitive disorders are present in 40-60 % of subjects with MS. Visuospatial, visuoconstructive, visuoperceptive functions, mnestic functions were most affected in both groups of respondents. There was no difference in the level of depression in relation to sex. Poor results of cognitive parameters in 32.7 % can be considered the cause of high scores of EDSS in female patients and in 29.2 % in patients, which is not statistically significant. The correlation between depression and EDSS is positive but not statistically significant in both sexes. Cognitive disorders are heterogeneous regardless of sex. Cognitive impairment in MS patients is related to impairment of working ability and memory, executive functions and attention. Subjects with a more severe degree of clinical disability had poorer cognitive functions.

Key words: cognition; cognition disorders; multiple sclerosis

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Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, (auto) immune disease of the central nervous system (CNS) whose etiological background is not completely clear [1]. 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 [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].

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Cognitive functions are higher mental processes that encompass a number of different functions that Lezak 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 behaviours are the product of intermediate information processing in the neural networks of the associative cortex and limbic system [4].

Cognitive changes have been recognized as a dominant and debilitating symptom of MS, especially when it comes to memory deficits and information processing speed [5]. Cognitive impairment, along with fatigue, depression, and anxiety, has a negative impact on a patient's quality of life and can affect the ability to carry out daily activities [6,7]. The first cognitive symptoms may be subtle, noticed either by the patient himself or by a family member or colleague. Patients with MS may experience a wide range of symptoms of cognitive impairment that can vary over time, including: difficulties in planning, problem-solving, and impulse control; difficulty concentrating over a long period of time or performing multiple tasks can easily get distracted; memory problems; lack of visual recognition of objects or problems with navigating space and perception of depth; and slowed information processing. Things to recognize and address include: word-finding problems, memory problems, concentration problems, inability to understand what is being said and difficulties at work/school [8]. Previous research has established that severity cognitive impairment has a significant positive correlation with current age, EDSS score and disease duration, and a negative correlation with education level. Relapse rate and age at onset were not correlated with severity cognitive impairment [9].

The aim of the research was to determine the distribution of cognitive disorders in MS patients with reference to demographic parameters, degree of clinical disability and depression.

Subjects and Methods

The research was prospectively conducted at the University Clinical Center Tuzla, at the Clinic of Neurology during a period of 2.5 years. The prospective study included 135 subjects with MS. The first group consisted of women (101 respondents) and the second of men (34 respondents). Inclusion criterion was a definite diagnosis of MS, according to the McDonald criteria [10]. Participants were examined by a neurologist, and tests to assess cognitive functions were performed by a psychologist and a neurologist together.

Clinical assessment instruments were: Expanded Disability Status Scale Score (EDSS), Mini-mental state examination (MMSE), Beck Depression Scale (BDS) and a Battery of Cognitive Function Assessment Tests: Wechsler Intelligence Scale, Revised Beta Test, Raven Colored Progressive Matrix, Wechsler Memory Verification Scale, Audio Memory Test learning, Rey-Osterriecht complex character test, and verbal fluency test [11-22].

Statistical processing was performed in 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).

Results

A total of 135 respondents, 101 females and 34 males. In the mentioned two groups they were equal, there were no significant differences between them: in age, at the level of education, duration of the disease, severity of disease symptoms nor in the representation of certain forms of MS (Tables 1 and 2). Table 3 shows the differences in the scores of individual cognitive parameters. Statistically significantly higher results on Auditory Verbal Learning Test (AVLT) 6 and 7 were achieved by female patients. The results of the AVLT 6 and 7, i.e., attention, memory, and the ability to learn in the auditory-verbal domain were significantly higher in women. There were no significant differences in other domains of cognitive functions. There were no differences regarding the levels of depressive symptoms among the two groups of subjects (Table 4). The EDSS score has a significant negative cor-

Table 1. Demographic and clinical characteristics of the respondents

	Female n = 101	Male n = 34	T – test t value (p value)
Age in years	40.3 (20 – 58) ± 10.1	39.7 (23 – 61) ± 9.7	0.3227 (0.3737)
Education in years	12.3 (4 – 17) ± 2.4	12.2 (4 – 16) ± 2.8	0.0856 (0.4660)
EDSS	2.9 (0 – 8.5) ± 2.2	3.6 (1 – 8) ± 2.3	- 1.5337 (0.0637)
Duration of disease in years	4.7 (1 – 18) ± 4.4	5.0 (1 – 15) ± 4.0	- 0.3732 (0.3551)

T-test - test for 2 independent means; EDSS - extended scale of disability status in multiple sclerosis.

Table 2. Differences in the frequency of multiple sclerosis forms

	Female n = 101	Male n = 34	The chi-square (p value)
RRMS	93	28	2.5889 (0.1076)
SPMS	8	6	

RRMS - relapsing remitting form of multiple sclerosis; SPMS - secondary progressive form of multiple sclerosis.

Table 3. Cognitive condition in patients with multiple sclerosis

	Female n = 101	Male n = 34	T – test T value (p value)
MMSE	26.6 (17 – 30) ± 3.1	26.5 (17 – 30) ± 3.2	0.0568 (0.4774)
Wbac	8.4 (1 – 12) ± 2.5	8.3 (1 – 10) ± 2.2	0.3125 (0.3776)
WBc	10.8 (4 – 15) ± 2.0	10. 7 (7 – 15) ± 1.8	0.2949 (0.3843)
CPM	33.7 (22 – 36) ± 2.9	34.3 (26 – 36) ± 2.5	- 1.0454 (0.1489)
ß	7.9 (2 – 10) ± 2.2	7.4 (1 – 10) ± 2.7	1.0603 (0.1454)
WB mc	8.4 (2 – 13) ± 2.3	8 (4 – 12) ± 2.4	0.8537 (0.1974)
WB lm	7.2 (1 – 12) ± 2.6	6.6 (3 – 10) ± 2.4	1.1873 (0.1186)
AVLT 1-5	10.8 (4 – 15) ± 2.3	10.1 (5 – 15) ± 2.6	1.4301 (0.0775)
AVLT 6	8.3 (1 – 14) ± 3.1	6.7 (1 – 14) ± 3.2	2.4551 (0.0077)*
AVLT 7	8.1 (0 – 14) ± 3.2	6.5 (0 – 13) ± 3.5	2.4686 (0.0074)*
RCFT rc	29.6 (6 – 36) ± 7.8	28.7 (3 – 36) ± 9.6	0.5490 (0.2920)
RCFT vm	18.8 (2 – 31) ± 6.7	17.8 (0 – 29) ± 7.2	0.7345 (0.2320)
FAS	19.4 (5 – 42) ±6.2	18.9 (1 – 28) ± 6.1	0.4820 (0.3153)

MMSE - Mini-Mental State Examination; WBac - Wechsler Bellevue scale form II subtest: Assembling cubes; WBc - Wechsler Bellevue scale form II - subtest: CPM - Raven's Coloured Progressive Matrices; β - Revised Beta test maze; WB mc - Wechsler Bellevue scale form II - subtest: mental control; WB lm - Wechsler Bellevue scale form II – subtest: logical memory; AVLT - Auditory-verbal learning test; RCFT rc - Rey Complex Figure Test - recognition trial; RCFT vm - Rey Complex Figure Test - visual memory; FAS - FAS verbal fluency tests.

Table 4. Differences in the depressive symptoms in patients with multiple sclerosis

	Female n = 101	Male n = 34	T – test T value (p value)
Beck Depression Scale (BDI)	12 (0 – 37) ± 7.4	11.0 (1- 35) ± 8.3	0.6813 (0.2484)

relation with all cognitive function parameters in patients and with most cognitive parameters in MS patients (Tables 5 and 6).

The correlation of multiple linear regression between depression symptoms and EDSS scores in women with MS was positive, but not statistically significant (Figure 1). The multiple correlation coefficient (R) was 0.571514. This means that there is a moderate direct relationship between cognitive values and the observed EDSS. R square (R2) was equal to 0.326628. This means that predictors (cognitive values) explain 32.7 % of EDSS variance. The correlation of linear regression between depression symptoms and EDSS score in men with MS was positive, but not statistically significant (Figure 2). The multiple correlation coefficient (R) was 0.540239. This means that

Table 5. Correlation between EDSS and Cognitive condition in females with multiple sclerosis

	Female n = 101		r (p value)
MMSE	26.6 (17 – 30) ± 3.1	EDSS 2.9 (0 – 8.5) ± 2.2	- 0.5194 (<0.0001)*
Wbac	8.4 (1 – 12) ± 2.5		- 0.3882 (<0.0001)*
WBc	10.8 (4 – 15) ± 2.0		- 0.2979 (0.0025)*
CPM	33.7 (22 – 36) ± 2.9		- 0.3299 (0.0008)*
ß	7.9 (2 – 10) ± 2.2		- 0.3872 (<0.0001)*
WB mc	8.4 (2 – 13) ± 2.3		- 0.5862 (<0.0001)*
WB lm	7.2 (1 – 12) ± 2.6		- 0.2717 (0.0060)*
AVLT 1-5	10.8 (4 – 15) ± 2.3		- 0.3752 (0.0001)*
AVLT 6	8.3 (1 – 14) ± 3.1		- 0.3323 (0.0007)*
AVLT 7	8.1 (0 – 14) ± 3.2		- 0.3553 (0.0003)*
RCFT rc	29.6 (6 – 36) ± 7.8		- 0.4897 (<0.0001)*
RCFT vm	18.8 (2 – 31) ± 6.7		- 0.3765 (<0.0001)*
FAS	19.4 (5 – 42) ±6.2		- 0.3417 (0.0005)*

MMSE - Mini-Mental State Examination; WBac - Wechsler Bellevue scale form II subtest: Assembling cubes; WBc - Wechsler Bellevue scale form II subtest: CPM - Raven's Coloured Progressive Matrices; β - Revised Beta test maze; WB mc - Wechsler Bellevue scale form II subtest: mental control; WB lm - Wechsler Bellevue scale form II subtest: logical memory; AVLT - Auditory-verbal learning test; RCFT rc - Rey Complex Figure Test - recognition trial; RCFT vm - Rey Complex Figure Test - visual memory; FAS - FAS verbal fluency tests; EDSS - extended scale of disability status in multiple sclerosis; r - Pearson correlation coefficient.

Table 6. Correlation between EDSS and cognitive parameters in males with multiple sclerosis

	Male n = 34		r (p value)
MMSE	26.5 (17 – 30) ± 3.2	EDSS 3.6 (1 – 8) ± 2.3	- 0.4150 (0.0147)*
Wbac	8.3 (1 – 10) ± 2.2		- 0.5402 (0.0010)*
WBc	10. 7 (7 – 15) ± 1.8		- 0.0078 (0.9651)
CPM	34.3 (26 – 36) ± 2.5		- 0.3360 (0.0521)
ß	7.4 (1 – 10) ± 2.7		- 0.5314 (0.0012)*
WB mc	8 (4 – 12) ± 2.4		- 0.2486 (0.1562)
WB lm	6.6 (3 – 10) ± 2.4		- 0.3587 (0.0373)*
AVLT 1-5	10.1 (5 – 15) ± 2.6		- 0.3600 (0.0365)*
AVLT 6	6.7 (1 – 14) ± 3.2		- 0.4716 (0.0049)*
AVLT 7	6.5 (0 – 13) ± 3.5		- 0.3539 (0.0400)*
RCFT rc	28.7 (3 – 36) ± 9.6		- 0.3774 (0.0278)*
RCFT vm	17.8 (0 – 29) ± 7.2		- 0.2555 (0.1447)
FAS	18.9 (1 – 28) ± 6.1		- 0.4628 (0.0058)*

EDSS - extended scale of disability status in multiple sclerosis; MMSE - Mini-Mental State Examination; WBac - Wechsler Bellevue scale form II subtest: Assembling cubes; WBc - Wechsler Bellevue scale form II subtest: CPM - Raven's Coloured Progressive Matrices; β - Revised Beta test maze; WB mc - Wechsler Bellevue scale form II subtest: mental control; WB lm - Wechsler Bellevue scale form II subtest: logical memory; AVLT - Auditory-verbal learning test; RCFT rc - Rey Complex Figure Test - recognition trial; RCFT vm - Rey Complex Figure Test - visual memory; FAS - FAS verbal fluency tests; r - Pearson correlation coefficient.

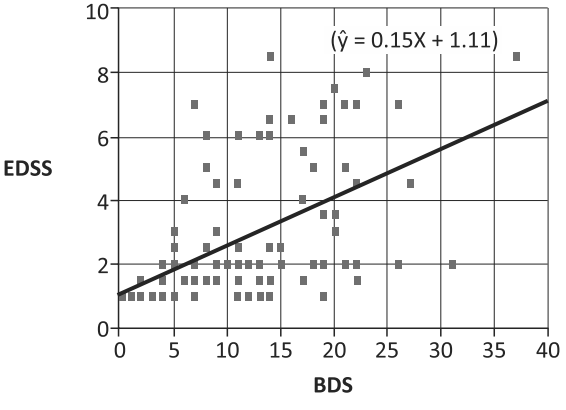

Figure 1. Linear regression correlation between EDSS and BDS in females with multiple sclerosis

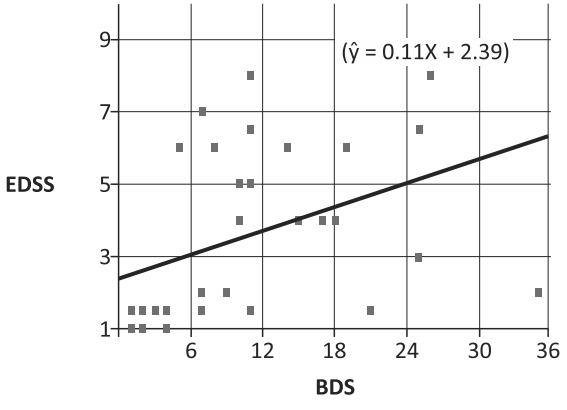

Figure 2. Linear regression correlation between EDSS and BDS in males with multiple sclerosis

there is a moderate direct relationship between cognitive values and the observed EDSS. R square (R2) was equal to 0.291858. This means that predictors (cognitive values) explain 29.2 % of EDSS variance. Poor results of cognitive parameters in 32.7 % can be considered the cause of high scores of EDSS in female patients and in 29.2% in men patients, which was not statistically significant

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 (75 %). Participants did not statistically differ in terms of sex (women 40.3 years, men 39.7 years). Result was shown in previous studies [23,24]. In this study, we had 89 % of participants with relapsing-remitting type (RRMS) and 11 % of participants with secondary progressive type (SPMS) of MS. According to neuropsychological assessment, the overall prevalence of cognitive dysfunction in our participants was 42 - 50 %. Cognitive changes were present in 40 to 70 % of patients, regardless of stage or type of MS. The main pattern of neurological disability in young and middle-aged people. They affect people with SPMS, which significantly affects their quality of life [25].

In our research a higher degree of cognitive impairment was found in secondary-progressive MS (64.5 %) compared to relapse-remitting MS (43 %). In the early stages of the disease, mnestic functions (learning process, short-term and long-term memory, short-term memory of visual material, verbal-logical memory) and attention are first impaired. In the advanced stages of the disease, there is a more pronounced impairment of mnestic functions, with worsening of visuoperceptive, visuoconstructive, and visuospatial processes, as well as executive functions. Poorer results were shown by respondents with longer duration of the disease (in 30 % of cases). Patients with newly diagnosed MS scored better on learning curves and executive functions. Abstract thinking and general intellectual ability were preserved. Dysfunctions in long-term memory, working memory, and abstract reasoning are common, and information processing speed is one of the primary cognitive impairments in MS, as found in the study Oreja-Guevara and associates. [25]. A study by Rahn and associates 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 [26]. A study by Papathanasiou and associates indicated 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) [27]. Study by Denney and associates also confirmed that cognitive deficits are more common and worse in chronic progressive MS and tend to worsen with disease progression [28]. Such results can be correlated with a study by Rao and associates who established that executive functions are impaired in 19 % of participants, although they are not observed in a higher percentage in the initial phase of the disease [29].

Papathanasiou and associates concluded that cognitive impairment occurs in almost all cognitive domains, with episodic memory, executive functions, and information processing speed being the most impaired, along with a gradual increase in frequency as the disease progresses [27]. 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 clinical isolated syndrome phase predict progression to MS, and cognitive status in MS predicts possible deposition of physical disability [27].

The correlation of multiple linear regression between depression and EDSS scores in women with MS was positive, but not statistically significant. The EDSS score has a significant negative correlation with all cognitive

function parameters in patients. Poor results of cognitive parameters in 32.7 % of patients can be considered the cause of high scores of EDSS in female patients and in 29.2 % in men patients, which was not statistically significant. In the study by Sadigh-Eteghad and associates authors observed that the severity of cognitive impairment had a strong positive correlation with the current age, EDSS score and duration of the disease, and a negative correlation with the level of education [9]. Relapse rate and age at disease onset were not correlated with severity of cognitive impairment. Ralph and associates found that the heterogeneity of neuropsychological presentation among MS patients reflects the influence of many factors, including sex, genetics, intelligence level, disease course, comorbid neuropsychiatric disease and health behaviours [30]. Male patients with early evidence of cerebral grey matter atrophy are most prone to impairment, while high premorbid intelligence improves neuropsychological prognosis.

Cognitive impairment in MS can occur at any time during the illness and are present in 40 - 60 % of patients- They are a major cause of disability. Risk factors for cognitive impairment are age, sex, phenotype and duration of disease, depression, level of education. Cognitive impairments are heterogeneous among subjects with MS, given that the sites of lesions differ among patients. The first cognitive symptoms may be subtle, noticed either by the patient himself or by a family member or colleague. Mnestic functions, attention disorders, short-term and long-term memory, nonverbal learning are the most impaired. Executive and intellectual functions are preserved in most participants. In this study, women were more represented than men, and the results of the auditory verbal learning, attention, memory and the ability to learn in the auditory-verbal domain were significantly higher in women. There were no significant differences in other cognitive domains. Poor results of cognitive parameters can be considered the cause of EDSS high scores in female patients compared to men. Monitoring cognitive functions can help determine disease activity. 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.

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Conflict of interest

None to declare.

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