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ORIGINAL PAPER

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Cognitive Impairment in Multiple Sclerosis: Relation to Disability, Duration and Type of Disease

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ABSTRACT

Background: Cognitive dysfunctions are often presented as a symptom in multiple sclerosis which is associated with both structural and functional impairments of neuronal networks in the brain. **Objective:** The aim of the study was to evaluate the influence of disability, duration and type of disease on cognitive functions in multiple sclerosis patients. **Methods:** This study included 60 MS patients treated at the Department of Neurology, Clinical Center University of Sarajevo. Inclusion criteria were clinically definite diagnosis of multiple sclerosis, 18 years of age or older and were able to give written informed consent. Cognitive function was evaluated by the Montreal Cognitive Assessment (MoCa) screening test. Mann-Whitney and Kruskal-Wallis test were used for comparisons between clinical characteristics and MoCa test scores. **Results:** Out of 63.33% of patients had EDSS \leq 4.5. Disease lasted longer than 10 years in 30% of patients. 80% had relapsing-remitting MS and 20% had secondary progressive MS. 84.2% of patients with EDSS \leq 4.5 had cognitive dysfunction. Higher disability ($\rho=0,306$, $p<0,05$), progressive type of disease ($\rho=0,377$, $p<0,01$) and longer disease duration ($\rho=0,282$, $p<0,05$) were associated with worse overall cognitive functions. Level of disability showed statistical significant correlation with the executive functions and language domains of cognition ($p<0.01$). Longer disease duration was significant correlated with executive functions ($p<0,01$) and language domains ($p<0,01$), while progressive type of disease was significant correlated only with executive func-

tions domain ($p<0,01$). MoCa score variables did not show a statistically significant difference in relation to the number of relapses per year and the use of immunotherapy. Statistically significant negative correlation was obtained between executive functions domain and level of disability, disease duration and progressive type of disease, while language domain significantly correlated only with disability level and progressive type of disease. **Conclusion:** High percentage of MS patients has cognitive impairment. Patients with higher disability were presented with lower cognitive abilities, especially in executive functions and language domains. Higher frequency of cognitive impairment were presented in progressive forms of disease and longer disease duration with strong influence on executive functions domains of cognition.

Keywords: Multiple sclerosis, cognitive functions, clinical characteristics.

1. BACKGROUND

Cognitive impairment (CI) is often presented in multiple sclerosis (MS), with frequency between 40% and 70% of subcortical types reported by epidemiological studies (1, 2). Multiple sclerosis as chronic and progressive inflammatory, immunomediated disease of the central nervous system (CNS) is characterized by great clinical heterogeneity with no valid multidimensional measure covering all aspects of disease (3). It is a complex disease that may be presented by different neurological symptoms causing impairment of physical, psychological and cognitive functions.

Remission of cognitive symptoms is not common, and cognitive decline may indicate progressive disease despite stable physical symptoms (4). Sustained attention, speed of information processing, abstract reasoning, executive functions, and long-term verbal and visual memory are the most frequently affected cognitive functions in MS patients (5). Previous studies reported that disability and disease duration did not have an influence on the results of the neuropsychological functions tests in multiple sclerosis by more than 10% to 15% (6). These results could have been explained by heterogeneity in investigated samples and methodologies that has been used. On the contrary, some studies suggest existing correlation between disability and cognitive status in MS (7, 8). However, underlying MS pathology includes focal demyelination and neurodegeneration in different regions of central nervous system such as the cerebral white matter, hippocampus, cortical and deep gray matter, that are anatomically or functionally related to the both physical and cognitive functioning (9-11). Recent studies presented that cognitive dysfunctions in MS are associated with both structural injury and functional impairment of neuronal networks in the brain (12). Cortical functions such as aphasia or negligence are not frequently involved (13). Although cognitive impairment is usually presented in advanced disease stages, it may occur at any time during disease even as the first manifestation of the disease (14). MS-related cognitive decline may also be related to disease duration (15). Many studies showed that existing cognitive impairment progresses over time (16, 17). On the other side, some studies showed that cognitive impairment is barely correlated with disease duration (18). These results could be explained by different level of disability in patients with the same disease duration and also by difficulties in precise determination of onset of the disease. It is proved that cognitive dysfunctions may be presented in the subclinical radiologically isolated syndrome, clinically isolated syndrome, and all phases of clinical MS. Progressive forms of MS are more often presented with cognitive dysfunction, especially with severe forms than relapsing MS. It is also discussed that immunomodulatory drugs have a beneficial effect on MS cognitive functions (19). CI also has a prognostic value in evaluation of transition to progressive phase of disease (16, 20). It is known that some specific cognitive performances are influenced at different stages of disease such as processing speed and executive functions at the very early stage of the disease (17). Verbal and visual memory in the relapsing-remitting MS are mostly affected (21). A more frequent and severe all types of cognitive dysfunctions are presented in a chronic progressive MS (22). The results of this study are expected to help in early detection of factors influencing cognitive impairment in multiple sclerosis patients.

2. OBJECTIVE

The aim of the study is to investigate the relationship of different cognitive functions domains with disability, disease duration and type of multiple sclerosis.

3. PATIENTS AND METHODS

This study included 60 patients with multiple sclerosis treated in the hospital and through the multiple sclerosis counseling center at the Department of Neurology, Clinical Center University of Sarajevo. Patients included in the study satisfied the following criteria: clinically definite diagnosis of multiple sclerosis, 18 years of age or older and were able to give written informed consent. Exclusion criteria were age younger than 18, patients with an unconfirmed diagnosis of multiple sclerosis, and those who provided incomplete data or refused to cooperate. This was an independent, observational, cross-sectional study. Discipline for Science and Teaching, Organizational Unit for Science, Teaching and Clinical Trials of the Clinical Center of the University of Sarajevo gave consent to conduct research and access to data from the Clinic for Neurology KCUS (number: 45-30-5-6187/22). Each patient gave informed written consent to use the results obtained for publication before enrollment.

Each respondent was asked to fill out a questionnaire which includes sociodemographic data and clinical data. For evaluation of cognitive functions, we used the Bosnian version of Montreal Cognitive Assessment (MoCa) screening test (24). MoCa is a rapid screening instrument for mild cognitive dysfunction based on testing eight cognitive functions (visuospatial/executive skills, naming, memory, attention, language, abstract thinking, delayed recall/MIS and orientation). The maximum score is 30, and based on the score, patients are divided into the following groups: 26-30 normal cognitive status, 18-25 mild cognitive impairment, 10-17 moderate cognitive impairment, < 9 severe cognitive impairment.

Statistical analysis

Statistical data processing was done using the computer program Excel (Microsoft Office Excel 2010) and the SPSS computer program for statistical analysis (SPSS—Statistical Package for Social Sciences), version 22.0. The data were processed using standard statistical methods and presented in the form of tables and charts. Mann-Witney and Kruskal Wallis tests were used for comparisons between clinical characteristics and MoCa scores.

4. RESULTS

Out of 63.33% of patients had EDSS \leq 4.5. Disease lasted longer than 10 years in 30% of patients. 80% had relapsing-remitting MS and 20% had secondary progressive MS. 78.33% had less than or equal to 2 relapses per year, and 45% of them used immunotherapy. 84.2% of patients with EDSS \leq 4.5 had cognitive dysfunction. 68.4% of them have mild, 15.8% had moderate and none had severe cognitive dysfunction. Higher disability ($\rho=0,306$, $p<0,05$), progressive type of disease ($\rho=0,377$, $p<0,01$) and longer disease duration ($\rho=0,282$, $p<0,05$) were associated with worse overall cognitive functions. Level of disability showed statistical significant correlation with the executive functions and language domains of cognition ($p<0,01$) (Table 1). Longer disease duration was significant correlated with executive functions ($p<0,01$) and language domains ($p<0,01$),

while progressive type of disease was significant correlated only with executive functions domain ($p < 0,01$). The median values of MoCa score variables did not show a statistically significant difference in relation to the number of relapses per year and the use of immunotherapy. Correspondingly, the investigation obtained a statistically significant negative correlation between executive functions domain and level of disability, disease duration and progressive type of disease, while language domain significantly correlated only with disability level and progressive type of disease (Table 2).

5. DISCUSSION

High percentage of patients in our study had cognitive impairment including the group of patients with lower level of disability. This is similar to the results of the study that investigated cognitive impairment in relapsing-remitting multiple sclerosis patients with very mild clinical disability, showing that more than 50 % of patient with mild disability have cognitive dysfunction (24). These results confirm that cognitive dysfunction are present also in early disease stages. The highest influence of disability on cognitive functions, in our study, was found within language and executive domains. Executive functions are cognitive processes that include planning, decision making, problem solving, action sequencing, task assignment and organization (25).

According to the previous results executive functions and verbal memory could be impaired even before the onset of significant disability and can remain stable in patients with mild disability (24). Information processing speed and visual memory are relatively preserved in patients with no disability and tend to deteriorate with the progression of disability level (24).

Another study showed that MS patients with lower disability has mostly fronto-subcortical type of cognitive impairment especially in memory, decision-making, working memory, planning and goal-oriented behavior domains (26). This type of impairment is found to be in correlation with structural and functional disorganization in frontolateral areas of fronto-subcortical brain regions (26). These areas are especially linked to executive cognitive dysfunction, including planning, inhibitory control, strategy development, cognitive flexibility and working memory (27).

Unfortunately, executive dysfunctions are often unrecognized because patients rarely complain about these problems by themselves. Importance for recognition of these problems is even bigger since executive function impairment significantly lower patient's quality of life and their everyday life functioning (28). One study showed that MS patients with higher level of disability

presented more impairment in language domains and also attention, memory, information processing speed, and to a lesser extent task switching for executive functions (19). Level of disability influenced negatively the overall cognitive functions in our study which is in correlation with the results of previous studies that used different neuropsychological batteries (4, 8, 24, 29-34). Cognitive impairment might be present at any time of disease course. Some studies investigate neuropsychological performances in patients with clinical isolated syndrome (CIS) and found out presence of cognitive impairments (35,36). Cognitive dysfunctions were

MoCa domains *	EDSS** (25 th -75 th percentile)		P
Executive functions	<=4,5	4 (2-4)	< 0,01
	> 4,5	1 (0-3,25)	
Naming	<=4,5	3 (3-3)	0,873
	> 4,5	3 (3-3)	
Attention	<=4,5	5 (5-6)	0,413
	> 4,5	5 (5-6)	
Language	<=4,5	2 (2-2)	< 0,01
	> 4,5	1 (0,75-2)	
Abstraction	<=4,5	1 (1-1,25)	0,868
	> 4,5	1 (1-2)	
Delayed recall	<=4,5	1,5 (0-2)	0,174
	> 4,5	0 (0-2,25)	
Orientation	<=4,5	6 (6-6)	0,935
	> 4,5	6 (6-6)	

Table 1. MoCA* domains scores according to disability level (EDSS score). * Montreal Cognitive Assessment ; ** Expanded Disability Status Scale, MoCA domains * EDSS** Disease duration Disease type**

MoCA domains *	EDSS**	Disease duration (years)	Disease type
Executive functions	Rho	- 0,376	- 0,329
	p	< 0,01	< 0,5
Naming	Rho	0,058	- 0,005
	p	0,661	0,068
Attention	Rho	0,028	0,077
	p	0,830	0,557
Language	Rho	- 0,463	- 0,238
	p	< 0,01	0,067
Abstraction	Rho	- 0,046	- 0,056
	p	0,725	0,668
Delayed recall	Rho	- 0,185	- 0,186
	p	0,157	0,155
Orientation	Rho	- 0,004	- 0,087
	p	0,975	0,551

Table 2. MoCA* domains scores according to disability level (EDSS score), disease duration and disease type. * Montreal Cognitive Assessment ; ** Expanded Disability Status Scale**

also found in many studies in recently diagnosed MS patients (37,38). Also, cognitive impairment was found in patients with mild or no disability in early stages of multiple sclerosis (39,40). It was showed that patients with chronic progressive or secondary progressive MS had more cognitive dysfunctions than patients with relapsing-remitting MS (41,42). In our study patients with progressive type of disease were presented with lower scores of cognitive impairment especially in executive functions domain. One study also showed that patients with SPMS had lower cognitive functions especially considering executive functions, attention, memory and language, information-processing speed, in comparison to the patients with RRMS (19).

A study that investigated cognitive impairment in secondary progressive multiple sclerosis also presented that the profile of cognitive impairment was different in the progressive forms with greater impairment of executive functions, information processing speed, verbal memory, and working memory (43). Similar results were found in another study showing that patients with progressive MS had more significant cognitive decline than patients with RRMS (44). A higher frequency of cognitive impairment in secondary progressive forms might be linked not only to a longer duration of disease but also to the progressive phenotype of disease (43). This could be explained by the neuro-pathological mechanisms specific to progressive forms, including involvement of the cortex and the neurodegeneration presented by brain atrophy (45). However, progressive type of disease is related to the higher extent of brain volume loss which leads to cognitive impairment (46).

One study also showed that MS patients who experienced frequent relapses had significant impairment in attention, memory, and language (19). In our study number of relapses had no impact on cognitive functions at any domain. Disease duration, in this study, had significant impact on cognitive functions, mostly executive function, suggesting that cognitive deficits getting worse as the disease progresses. Probably, accumulation of disability, the progression of both gray matter and white matter pathology and loss of brain volume have the impact on these results. Similar results were found in a study that investigated cognitive function in MS patients (30). Disease duration also affected the cognitive performance especially in memory and language in a study that investigated clinical predictors of cognitive impairment in MS patients (19). Previous studies found a weak or no correlation between cognition and disease duration (6,41,47). Another studies that used different neuropsychological tests demonstrated worsening of cognitive functions over years (31, 48, 49).

6. CONCLUSION

This study confirmed high prevalence of cognitive dysfunctions in multiple sclerosis patients. Patients with higher disability were presented with lower cognitive abilities, especially in executive functions and language domains. Higher frequency of cognitive impairment were found in progressive forms of disease and longer

disease duration. All modalities of cognitions were affected. Strong influence of clinical parameters of disease on executive functions domains of cognition highlights importance of early detection of executive functions problem using more specific neuropsychological tests

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