ORIGINAL ARTICLE

COGNITIVE FUNCTIONS IN MULTIPLE SCLEROSIS PATIENTS DEPENDING ON THE DIFFERENT RISK FACTORS PRESENCE

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ABSTRACT

The aim: To clarify the influence of different risk factors on cognitive impairment (CI) in general and in separate domains and their association with MRI findings in patients with relapsing-remitting (RRMS) and progressive forms of multiple sclerosis (SPMS and PPMS).

Materials and methods: One hundred and thirty-seven participants with MS (102 females and 35 males) aged from 22 to 69 years were enrolled into this study. All patients completed the Montreal Cognitive Assessment (MoCA), Beck Depression Inventory (BDI), Hamilton Anxiety Rating Scale (HAM-A) and undergone MRI.

Results: According to MS phenotypes all participants were divided into two groups: patients with RRMS (n= 106) and with progressive phenotypes (n= 31). A significant positive correlation was present between MoCA and BDI scores in all participants (p= 0,0015). Presence of anxiety did not demonstrate any valid influence on cognitive performance, although severe anxiety was significantly more often found in subjects with progressive phenotypes in presence of brain atrophy (p= 0,0028). Patients with higher education had no CI more frequently compare to those without it (p= 0,0019), whereas, participants smoking cigarettes had higher prevalence of severe CI than non-smokers (p= 0,0061).

Conclusions: Among cognitive domains memory, visual-spatial and executive functions, abstract thinking were impaired the most in MS patients, though abstract thinking was more often affected in progressive forms. The results demonstrated that physical disability, depression and smoking negatively impacted cognitive performance, meanwhile presence of higher education demonstrated a favorable influence on cognition in MS patients.

KEY WORDS: multiple sclerosis, cognitive impairment, depression

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INTRODUCTION

Multiple sclerosis (MS) is an insidious chronic inflammatory autoimmune neurodegenerative disease of the central nervous system (CNS), which eventually leads to a severe long-term disability of a significant number of able-bodied population (2.8 million people worldwide) as a result of the neurological and motor deficit along with cognitive impairment (CI) and psycho-emotional disorders [1; 2; 3]. CI is a common socio-economically disabling feature of MS, prevailing in 40-65% of those patients, furthermore, CI can be present already on the early stages of the disease as well as predict the shift to the motor phase and future motor impairment [4; 5]. The factors influencing cognition still are not fully comprehended due to variety of controversial results of multiple studies. In particular, severity of CI is frequently correlated with age and physical disability [6], it also depends on the MS phenotype, age of the disease debut, education level, although one of the most debatable factors is the disease duration (DD) on account of the difficulty in determining the onset [7; 8]. Apart from those, some comorbidities, like anxiety or depression, can impact the severity of CI [4; 9]. While depression's impact on CI proves to be solid [10; 11], anxiety's influence according to various sources is still controversial [9; 12; 13]. Among the environmental factors, cognitive reserve (high IQ prior to the disease onset, presence of higher education, stimulating hobbies and speaking foreign language) demonstrates positive influence on cognitive performance in MS patients [14; 15], whereas, smoking cigarettes not only increases the frequency of relapses and hastens progression, but also contributes into CI deterioration [14; 16].

Conventional magnetic resonance imaging (MRI) of the brain and the spinal cord plays the crucial role for diagnostic (according to the 2017 reviewed McDonald criteria) and disease-modifying purposes since it corresponds to the observed clinical picture [17].

Nevertheless, the factors contributing to development and deterioration of CI in people suffering from MS are disputable and, therefore, still being studied in order to improve methods of treatment and rehabilitation.

THE AIM

To clarify the influence of different risk factors (smoking, physical disability, disease duration, anxiety, depression and level of education) on cognitive impairment (CI) in general and in separate domains and their association with MRI findings in patients with relapsing-remitting (RRMS) and progressive forms of multiple sclerosis (SPMS and PPMS).

MATERIALS AND METHODS

This study included one hundred and thirty-seven participants with MS (102 females and 35 males) aged from 22 to 69 years. Thus, all participants were divided into two groups: A – patients with RRMS (n= 106; 81 females and 25 males aged from 22 to 67 years, mean age: 41.8±10.7, disease duration (DD): 10.3±8.5 years) and B – the study subjects with progressive phenotypes (n= 31; 21 females and 10 males aged from 28 to 69 years, mean age: 47,2±13,6, DD: 16,6±12,5 years). The mean EDSS score in group A was 3,5±1,6, whereas in the group B it was 5,1±1,3. The study subjects were diagnosed RRMS, SPMS and PPMS according to McDonald's Criteria 2017 [17].

A medical history was obtained from each participant. The examination consisted of a standard clinical evaluation, neurological examination, the application of neuropsychological questionnaires, laboratory tests (complete blood count, biochemical parameters, TSH) and polymerase chain reaction test for Covid-19 (everyone had negative results). Every patient underwent MRI of the brain. The disability level in MS patients was evaluated by means of Kurtzke's Expanded Disability Status Scale (EDSS). Mild disability equals 1-3,5 points, moderate – 4-6 points and 6,5-8 stand for severe disability [18]. The Montreal Cognitive Assessment (MoCA) was applied to evaluate presence and severity of CI. The MoCA includes six subcategories according to the domains: memory (M), language (L), attention (A), abstract thinking (AT), visual-spatial and executive functions (VS/EF). The scale score was interpreted as: 30-26 points – no CI; 25-18 points – mild CI; <18 points – severe CI [19]. Beck Depression Inventory (BDI) was applied to screen for the presence and asses the severity of depression. This scale consists of 21 items that cover major depression symptoms according to diagnostic criteria listed in the Diagnostic and Statistical Manual for Mental Disorders. Each answer is scored from 0 to 3 points. Mean score 0–9 indicates absence of depression, 10–18 – mild depression, 19–29 – moderate depression and 30–63 – severe depression [20]. To measure the severity of perceived anxiety symptoms we used Hamilton Anxiety Rating Scale (HAM-A). The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where 0-13 – absence of anxiety, 14-17 indicates mild severity, 18–24 moderate severity and ≥ 25 severe anxiety [21].

The patients were excluded from the study in case they were younger than 18 years, had progressive forms of MS, exacerbation stage of MS, severe depression, pelvic disorders, pregnancy, also including participants treated with corticosteroids and INF-β, that could alter the study's parameters.

All study subjects provided written informed consent and the study was approved by the Institutional Ethics Committee.

The statistical data was processed by means of Graph Pad Prism version 9 and STATISTICA 12.5. 192.5. Student's t-test (t) was applied for evaluating credibility between mean quantitative positions of two samples. Proportions were compared using $\chi 2$. Relationships between different indicators were assessed using the Pearson's correlation coefficient (r) according to statistical distribution. A $p<0.05$ value was considered statistically significant.

RESULTS

Our patients had the following complaints: decreased memory, difficulties in verbalization (vocabulary), inability to concentrate, decreased occupational performance, fatigue, lack of energy during usual daily activities, presence of disturbing thoughts, mood swings, general weakness, fatigue and anxiety. Meanwhile, the neurological examination revealed pyramidal signs, presence of pathological reflexes, increased muscle tone (spastic type), coordination impairment (intention tremor, gait and truncal ataxia, missing the mark), brainstem disorders (vertigo, nausea, slight dysarthria) and sensory disorders (in particular, impaired vibration and proprioception sense, paresthesia, Lhermitte's sign) were revealed. Pyramidal disturbances (p= 0,0018), cerebellar dysfunction (p= 0,0439) and brainstem disorders (p= 0,0054) were observed more frequently in the group B.

In accordance with the results of the brain MRI, the majority of the study subjects had multifocal lesions in the white and gray matter, especially in periventricular, corpus callosum (CC), cortical (FL, TL, PL) areas, cerebellum and brainstem, presence of brain atrophy. Parietal (p= 0,0109) and occipital lobe (p= 0,0055) lesions, brain atrophy (p= 0,0008), combined lesions of frontal lobe with brain atrophy corpus callosum (p= 0,0021), combination of parietal lobe and corpus callosum lesions (p=0,0279) and simultaneously affected parietal lobe with brain atrophy (p= 0,0138) were found in the group B more often than in the group A.

The mean MoCA score in group A was 23,4±4,1, while in the group B – 22,67±3,67. Based on MoCA score, participants in these groups were divided into three subgroups: 1 – without CI (A1 – 40; B1 – 10), 2 – with moderate CI (A2 – 53; B2 – 19), 3 – with severe CI (A3 – 13; B3 – 2). There was no significant difference between the main groups. Moderate CI were found more frequently comparing to severe CI and absence of CI in the group A (p= <0,0001). And similarly, in the group B moderate CI were observed more often in comparison to severe and absence of CI (p= <0,0001) (Fig. 1).

In the group A the most frequently affected domain compare to the rest was M (69%) (p <0,0001), followed by VS/EF (58%) and AT (48%). As for the group B, the most common deteriorated cognitive domains were the same: M (77%) (p <0,0001), VS/EF and AT (both 68%). AT was present substantially more often in the group B compare to group A in case of TL lesion (p= 0,0024), CC lesion (p= 0,0219), simultaneous FL, TL and PL lesions (p= 0,0302). There were no difference concerning other cognitive domains between the two groups (Fig. 2).

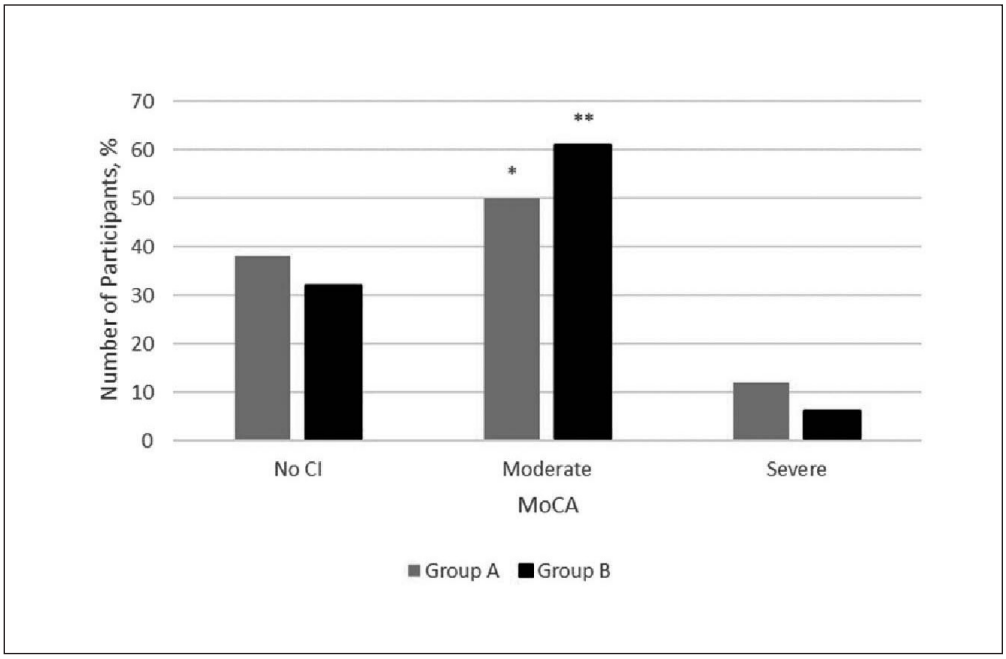

Fig. 1. Distribution of the Levels of CI in Both Study Groups.
* p= <0,0001
** p= <0,0001

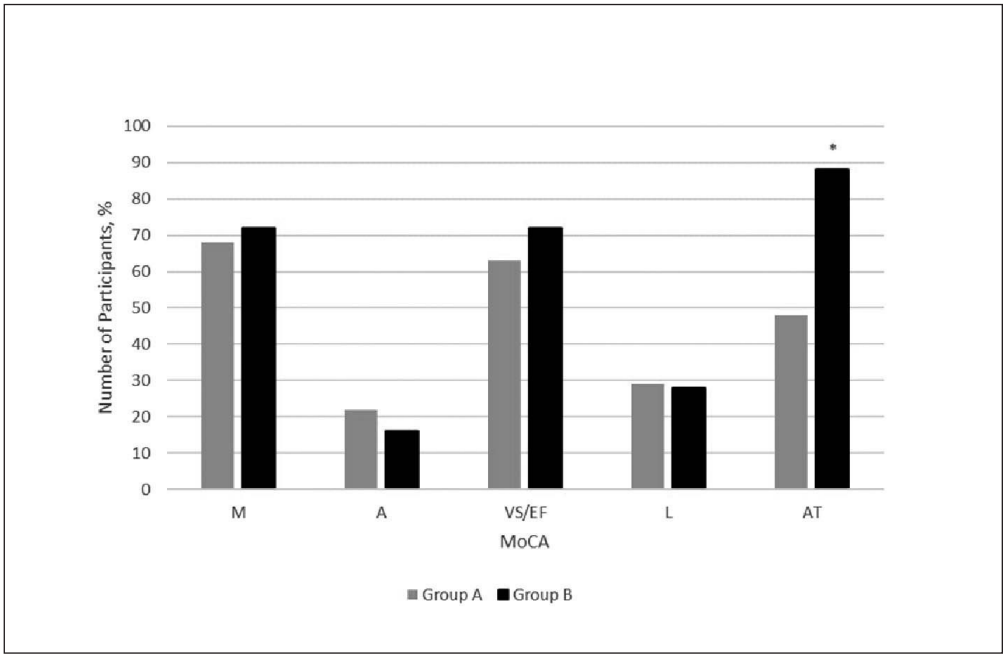

Fig. 2. Distribution of Affected Domains in Participants of Both Groups in Case of Lesion of Temporal Lobe.
*p= 0,0024

None of the groups demonstrated a connection between the severity of CI and DD (group A: p= 0,8210; group B: p= 0,4503).

The current study did not demonstrate a correlation between age and CI in both study groups (p= 0,3747). No connection between age and CI was observed in participants with RRMS (p= 0,7999), as well as in patients with progressive types of MS (p= 0,0639).

There was a significant correlation between CI and EDSS score (r= 0,2433, p= 0,0042) in all participants. A significant positive correlation between CI and EDSS score (r= 0,1999, p< 0,01) was detected in the group A (Fig. 3). The study subjects of the group B also show the strong positive correlation between CI and EDSS (r= 0,3941; p< 0,05) (Fig. 4).

The results of BDI revealed that, the participants had either no signs of depression or its presence of mild and moderate severity, as the severe level was not detected. In group A 52 (49%) patients had no signs of depression, 38 (36%) had mild depression, 16 (15%) had moderate. As for the group B: 11 (35%) had no depression, 16 (52%) – mild depression, 4 (13%) – moderate one.

A substantial positive correlation between severity of CI and depression's degree of manifestation was observed in all study subjects (r= 0,3038; p= 0,0015) (Fig.5). Significant positive correlation between CI and depression severity was found in patients of the group A (r= 0.3717, p= 0.0093), as well as in patients of the group B (r=0,4125; p=0,0211), indicating that CI can influence the depressive disorder and vice versa in all MS phenotypes.

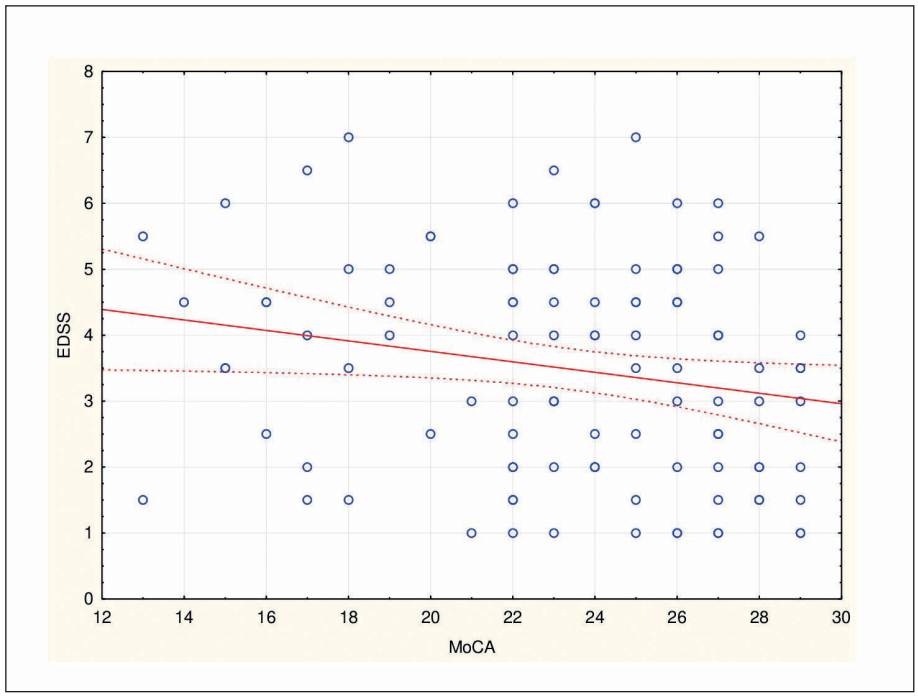

Fig. 3. The Correlation between CI and EDSS Scores in the group A.

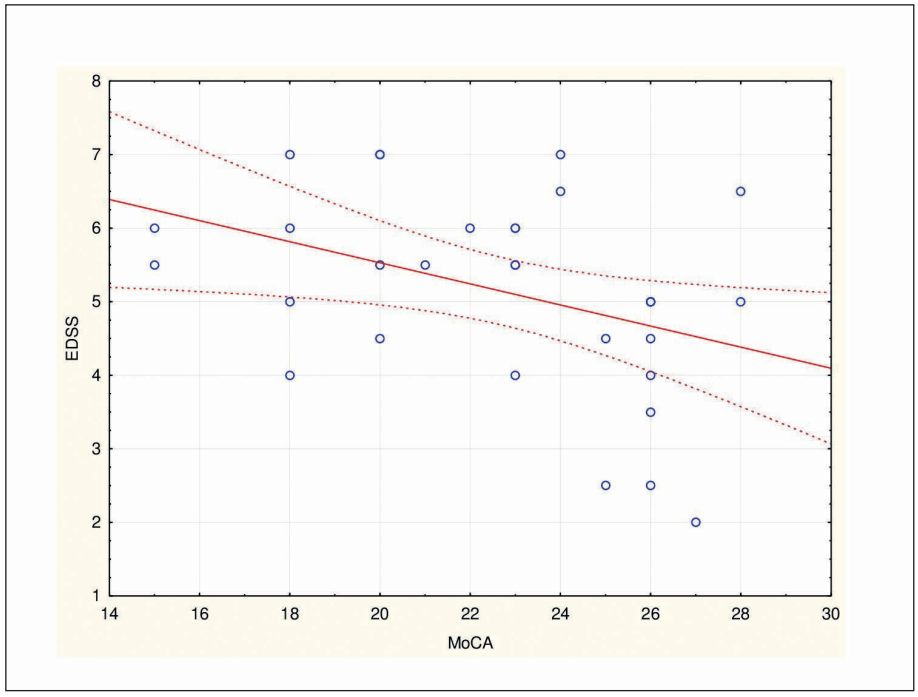

Fig. 4. The Correlation between CI and EDSS Scores in the group B.

In the group A mild depression was associated with lesions of CC (73%), FL (63%) and PL (52%), whereas, moderate was connected with lesions of FL, CC (both 75%) and BA (62%). Meanwhile, in the group B mild depression was detected most frequently in case of CC (87%), FL (75%), TL (69%) lesions and BA (69%), moderate depression was observed more often in patients with PL (75%) and CC (75%). Presence of BA in case of mild depression was significantly more frequent in the group B compare to the group A (p= 0,0035).

Among all study subjects 97 demonstrated the presence of anxiety. In 22 (23%) mild level of anxiety was observed, in 32 (33%) moderate and in 43 (44%) severe. FL was more frequently affected in cases of mild and moderate anxiety in comparison to severe (p= 0,0119) in all patients.

There was no correlation found between CI severity and the level of anxiety in the group A (p= 0,02537). In the group A 33 (31%) participants had no signs of anxiety, 16 (15%) – had mild, 24 (23%) – moderate and 33 (31%) had severe level of anxiety. Absence and severe level of anxiety appeared more often compare to mild and moderate (p= 0,0176) in the patients of the group A. Mild level of anxiety was associated with lesions of CC (81%), FL (75%), TL (62%) and PL (50%); moderate – with FL (79%), PL (67%), TL (50%) and CC (58%); severe anxiety – with lesions in

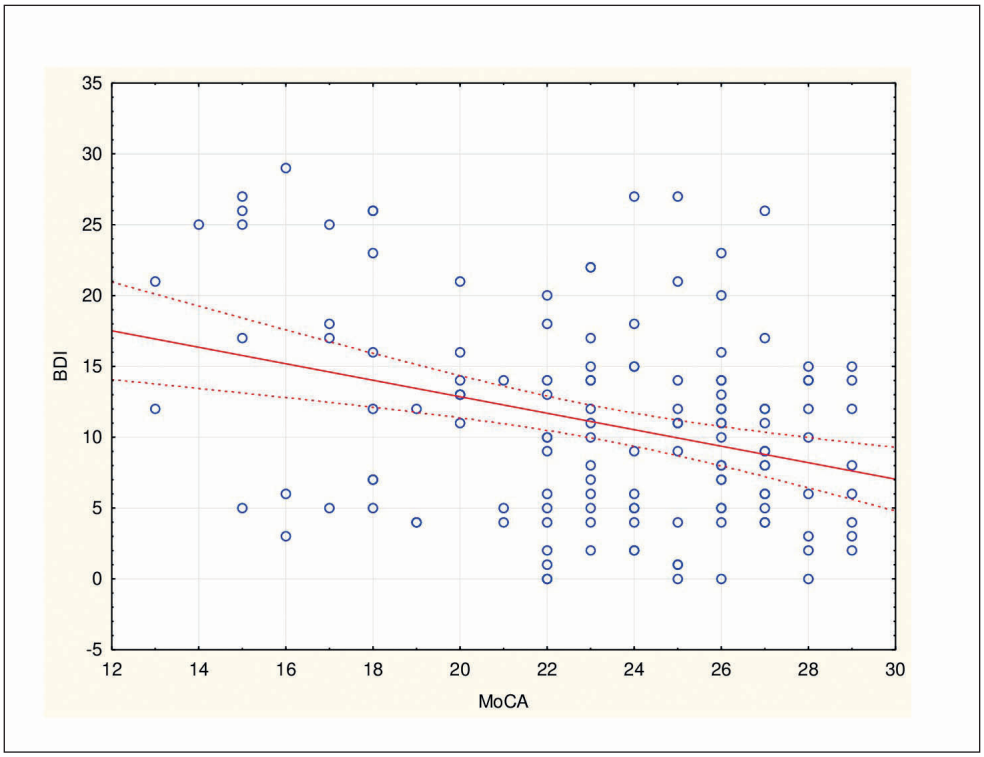

Fig. 5. The Correlation between MoCA and BDI Scores in All Participants.

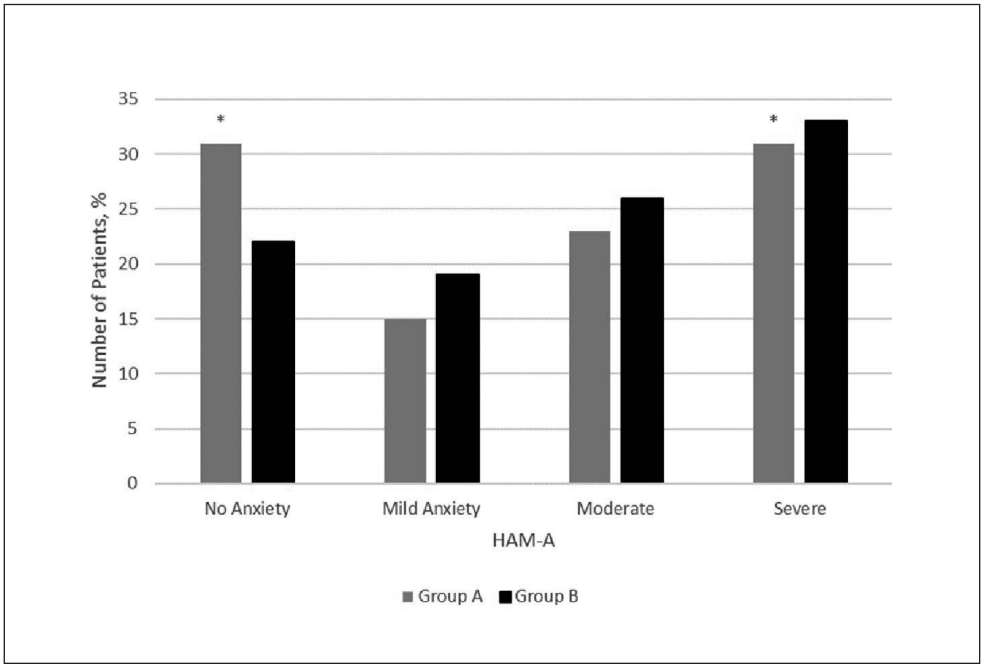

Fig. 6. The Severity of Anxiety in All Study Groups.

CC (72%), FL (51%), PL (48%), FL (45%). The group B did not demonstrate a correlation between the level of CI and anxiety severity (p= 0,9405) as well. Among the study subjects of this group 7 (22%) had no anxiety, 6 (19%) had mild, 8 (26%) – moderate and 10 (33%) – severe; there was no significant difference in frequency of axiety severity levels (p= 0,6810) (Fig. 6). Concerning this group, mild level was connected with lesions of FL (100%), CC (80%); moderate was predominantly due to lesions of FL (93%), CC (67%) and PL (67%); severe was associated with CC (80%), BA (80%), TL (60%) and FL (50%). BA was detected more frequently in the group B compare to the group A in case of severe anxiety (p= 0,0028).

The strong positive correlation between EDSS score and BDI score was observed in the group A (r= 0,4396; p= <0,0001). No such connection was observed in the group B (p= 0,2813; r= 0,1252).

Among all participants 72 had received a higher education, among which 35 did not demonstrate signs of a CI, 32 had moderate and 5 had severe. 65 of our study subjects did not have a higher education, 15 of whom had no CI, 32 had moderate and 18 had severe. Patients with MS and

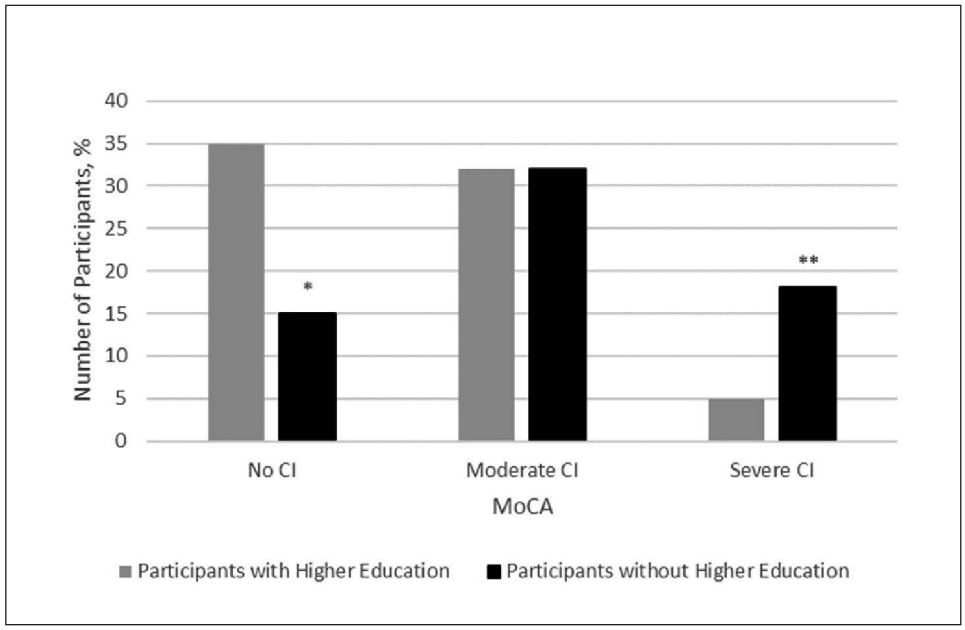

Fig. 7. The Distribution of Levels of Cognitive Impairment in All Participants Depending on the Presence of Higher Education.
* p= 0,0019
** p= 0,0012

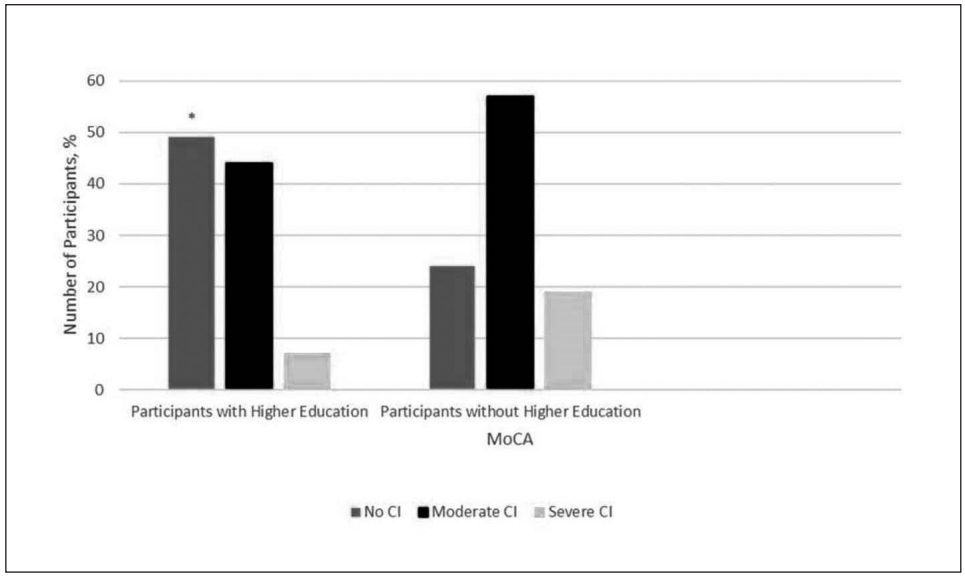

Fig. 8. Distribution of the CI Severity in the Group A Depending on the Presence of Higher Education
* p= 0,0066

higher education more frequently had no CI comparing to those without higher education (p= 0,0019), meanwhile higher frequency severe CI was observed in patients without higher education (p= 0,0012) (Fig.7).

In the group A 59 participants had higher education (29 did not have CI, 26 had moderate and 4 had severe) and 47 did not (11 had no signs of CI, 27 had moderate and 9 had severe). No CI was more frequently diagnosed in those patients of the group A with high education (p= 0,0066) (Fig. 8). 13 study subjects from the group B were with higher education (6 without CI, 7 with moderate, severe were not detected) and 18 were without (4 were without CI, 12 with moderate and 2 with severe). In the group B no connection was detected between CI severity and level of education.

30 of all patients were smoking cigarettes at the time of the study, 107 did not have the habit. Among smokers 26% had no CI, 40% had moderate CI and 34% had severe. In the non-smoking group 39% of the study subjects showed no signs of CI, 49 had moderate CI and 12% had severe. The severe CI prevailed in smokers compare to the non-smoking participants (p= 0,0061).

DISCUSSION

According to Brochet B. and Ruet A. preclinical forms and RRMS are characterized by the slowness of information processing speed and episodic verbal and visual-spatial memory deficits, that are more prominent than executive functions and verbal fluency impairment, meanwhile the progressive forms are characterized by information processing speed, attention, working memory, executive functions, and verbal episodic memory deterioration to the greater extent compare to the RRMS [7]. And similarly our study demonstrated that RRMS patients had impairment of memory, visual-spatial and executive functions, abstract thinking,

the same domains were the most frequently impaired in RRMS and progressive MS. Abstract thinking was affected more prominently in progressive forms than in RRMS in case of lesions of temporal lobe, corpus callosum and the simultaneously affected frontal, temporal and parietal lobes.

Several researches claimed that the duration of the disease impacts the cognitive functions [8], while others stated that it had no influence on cognitive performance [22]. In this study such connection was revealed only in RRMS phenotype, progressive forms did not demonstrate this kind of relation. Multiple studies proved that cognitive dysfunction is linked in direct ratio to a patient's age [6], however, the current research did not demonstrate any correlation between MoCA score and age. This could be explained by immense incidence of higher education (44%) and EDSS score lower than 6,5 (90%) in the study subjects, which would have a favorable influence on cognitive performance.

The physical disability, according to various researches, always had a strong influence on patients' mental status followed further deterioration in direct ratio, with seldom exceptions, and cognitive deficit was the credible predictor of the disability's onset [8; 22; 23] and vice versa, especially concerning the primary progressive phenotype [24], therefore, our study confirmed it demonstrating a strong correlation between severity of cognitive dysfunction and level of physical disability in both relapsing-remitting and progressive types of MS.

Depression, as the most widespread psychiatric disorder to be present in MS, was associated with lesions and atrophy in fronto-temporal and frontal lobes separately [25]. It was established that depression was impacting information processing speed, executive function, attention, motor functions and memory, but potentially could affect all cognitive domains [4; 26], although Whitehouse C. E. et al. [10] stated that MS participants of their study with depression had reduced cognitive performance, but the working memory was intact. Our study similarly confirmed that appearance of depression was connected to deterioration of the cognitive performance in relapsing-remitting and progressive forms, accordingly; also, it was more prominently associated with developed brain atrophy in participants of the group B.

According to various sources, anxiety in case of MS either was directly its symptom [27], or a comorbidity, or an adverse effect of some medications [3], ergo, it influenced cognitive and social performance [28; 29], mainly episodic memory and executive functions, but generally it was hard to separate anxiety's and depression's impact on cognition [4]. In this study anxiety's impact on cognition was not observed. Severe level of anxiety in patients with progressive phenotypes of MS was associated with presence of brain atrophy, as it was present significantly more frequently comparing to relapsing-remitting phenotype.

Concerning the environmental risk factors, several studies stated that smoking is a susceptible and prognostic risk factor for both physical disability and cognitive impairment as it had a great contribution to the processes of demyelination [14; 16], so our study confirmed smoking's impact on cognition, as it demonstrated higher incidence of severe cognitive deficit. Previous researches demonstrated a solid proof that cognitive reserve (high IQ score prior to MS debut, presence of higher education, speaking foreign language and stimulating hobbies) had favorable effect on MS patients' cognitive skills [14; 30], ergo, our study revealed higher prevalence of cases with intact cognition and substantially lower number of severe cognitive impairment in participants with higher education.

CONCLUSIONS

Cognitive impairment is the one of the common, yet disabling and socially disrupting, manifestations of MS. At the same time, it can be further deteriorated by progression of physical disability, presence of neuropsychological disorders and environmental factors, like lack of higher education and smoking cigarettes. Quite frequently complaints of poor cognitive performance are dismissed on the background of neurological deficit. Results of our study stress on the importance of a mandatory thorough screening of cognitive impairment, since cognitive performance can be reliably assessed, and management of risk factors in all MS patients from early stages in order to prevent further socio-economical maladjustment and disability of such patients and enroll them in adequate disease-modifying therapies.

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