Prevalence of cognitive impairment among Hungarian patients with relapsing-remitting multiple sclerosis and clinically isolated syndrome

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Abstract

Background: Cognitive impairment (CI) is a frequent symptom of multiple sclerosis (MS); its prevalence is reported to be 43-70%. It is one of the most important determinants of MS patients' quality of life, as it is one of the main factors for MS patients becoming unemployed.

Aim: We aimed to determine the prevalence of CI among the relapsing-remitting MS (RRMS) and clinically isolated syndrome (CIS) patients in Hungary, to evaluate the predicting factors of CI and to assess the differences between sexes and patients with different educational levels.

Patients and methods: Five-hundred and fifty-three CIS and RRMS patients were enrolled to our study from three Hungarian MS centers. Age at screening, age at disease onset, disease duration, EDSS score, sex and educational levels were analyzed as socio-demographic factors. The BICAMS battery was used to assess their cognitive state, the BDI-II battery to assess depression. For statistical analysis, we utilized logistical regression, and used Fisher exact tests, chi-square tests and one-way ANOVA.

Results: The mean age of our patients was 44.93±11.69 years, mean age at disease onset was 31.95±10.01 years, the mean disease duration was 13.05±8.05 years and the median EDSS score 2.0 (Range: 6.5, IQR:2.0) points. Three-hundred and sixteen (57.1%) patients had CI. Sex, educational level and EDSS score proved to be significant predictors of CI (OR: 2.71, $p<0.001$; OR: 1.94, $p=0.023$; OR: 0.47, $p=0.003$ respectively). CI was significantly ($p<0.001$) more frequent among men (70.1%) than women (52.0%). We found, that educational level and EDSS score were only a significant predicting factor among women. Thus, the prevalence of CI among women with college or university degree was significantly ($p<0.001$) less common (39.4%) than women with 12-15 years of education (57.4%) and women without a high school degree (66.7%). Also, we found that among women with higher EDSS score than 2 points, the prevalence of CI is 69.9% as compared to women with EDSS score between 0-2 points, where the prevalence is 42.8% ($p<0.001$). No such differences were observed among man.

Discussion: Our prevalence data is similar to those reported in the literature (43-70%), and almost identical to the one assessment using the BICAMS battery. We found that men are more vulnerable to CI than women in MS, as was reported recently. We are the first to report however, that higher educational level and lower EDSS scores are only associated with better cognitive performance in women.

Keywords: cognitive impairment; multiple sclerosis; prevalence; BICAMS; Hungary

Introduction

Cognitive impairment (CI) is a frequent and substantial symptom of multiple sclerosis (MS); studies report its prevalence to be 43-70% (Chiaravalloti and DeLuca, 2008). CI has a serious negative impact on the patients' quality of life. Cognitively impaired patients are more likely to have reduced physical independence and competence in daily activities; to report impaired social lives and higher rates of divorce (DeLuca et al., 2015; Goverover et al., 2007; Rao et al., 1991b). Also it negatively affects the patients' coping mechanism, medical adherence and rehabilitation potential (Bruce et al., 2010; Ehrensperger et al., 2008; Langdon and Thompson, 1999). It is indicated to be the strongest predictor of MS patients' becoming unemployed (Krause et al., 2013; Morrow et al., 2010).

MS patients don't suffer from global impairment of cognitive functions: the most frequently affected domains are information processing speed, visuospatial memory and verbal memory (Langdon, 2011).

CI can appear at any stage of the disease, even as early as the clinically isolated syndrome (CIS) and radiologically isolated syndrome (RIS) stages and affects patients regardless of their age or physical state (Amato et al., 2012; Glanz et al., 2007). Studies report CI to be a progressive consequence of MS with very low chance of improvement once it occurs (DeLuca et al., 2015). There are very little, and also conflicting data about the effect of disease modifying therapies (DMTs) on cognition in MS (Mattioli et al., 2015; Sundgren et al., 2016). There is evidence that cognitive dysfunction can appear as acute relapse, as described by Morrow et al (Morrow et al., 2011). Also, MS may present with primarily cognitive dysfunction with minimal or no other neurological domains involved (Calabrese et al., 2015). Until now, no clinical characteristic was found to be predictive of developing or worsening cognitive impairment (Amato et al., 2001).

The best biomarkers for CI in MS are provided by magnetic resonance imaging (MRI) data. There are several studies indicating that CI correlates with global brain atrophy and regional atrophy in the cerebral cortex, hippocampal region, thalamus and the basal ganglia (Brass et al., 2006; DeLuca et al., 2015; Houtchens et al., 2007; Koenig et al., 2014; Morgen et al., 2006). Also the presence of gray matter lesions and the greater volume of white matter lesions – predominantly in the corpus callosum - are linked to the presence of cognitive impairment (Calabrese et al., 2007; Diker et al., 2016; Rossi et al., 2012). Furthermore, there are evidences provided by diffusion tensor imaging (DTI) studies, that disconnection resulting from diffuse and non-lesional white matter damage contribute to cognitive dysfunction in MS, as well as dysfunction in the default mode network (DMN) (Bonavita et al., 2011; Dineen et al., 2009; Paul, 2016; Rocca et al., 2010).

The large difference between the prevalence data are not surprising as the studies not only were conducted on different populations, but also used different methodology to determine cognitive dysfunction. Also, the screening of cognition can be very time-consuming and many times requires neuropsychologists and special tools. Therefore, a short, easily administered screening battery was needed in everyday practice. For this purpose, Langdon and colleagues created the "Brief International Cognitive Assessment for Multiple Sclerosis" (BICAMS) battery in 2011. The BICAMS is a short, easily administered, yet highly sensitive tool for measuring cognitive dysfunction in MS patients in the three most affected key areas: information processing speed, visuospatial memory and verbal memory (Langdon et al., 2012). It is comprised of three individual tests: the Symbol Digit Modalities Test (SDMT), a sensitive measuring tool for information processing speed, the first three

immediate recall trials of the Brief Visuospatial Memory Test Revised (BVMT-R), and the first five immediate recall trials of the California Verbal Learning Test (CVLT-II) (Langdon et al., 2012).

The objectives of the present evaluation were to determine the prevalence of CI among the RRMS/CIS patients in Hungary, to assess the predictors of cognitive dysfunction and to evaluate the possible differences between sexes and patients with different educational levels.

Patients and methods

Patients

We consecutively enrolled 553 (28 CIS and 525 RRMS) patients into our study beginning in February, 2014, until November, 2015. Four-hundred and four was treated at the multiple sclerosis outpatients' clinic of the Department of Neurology of the University of Szeged; 111 at the multiple sclerosis outpatients' clinic of the Jahn Ferenc Dél-Pest Hospital in Budapest and 38 at the multiple sclerosis outpatients' clinic of the Markhot Ferenc Hospital in Eger. One-hundred and fifty-seven patients were man, 396 women. They were classified into 3 categories depending on their educational level: the first group consisted of 123 patients, who had less than 12 years of education, indicating they did not obtain a high school degree; the second group, 209 patients either finished high school or after high school obtained some qualification but not a degree from college or university (12-15 years of education); the third group, 221 patients, had college or university level of graduation (16 or more years of education). Additionally, young patients currently enrolled to college or university were placed in the third group. Ninety patients received no disease modifying therapy (DMT); 169 patients received β-1-interferon (IFN), 129 patients glatiramer-acetate, 31 patients teriflunomide, 33 patients dimethyl-fumarate therapy; 56 patients were on natalizumab and 41 patients on fingolimod. Additionally, 1-1 patient was involved in the daclizumab, the LINGO-1 and the siponimod clinical trials.

All sociodemographic data on the patients including age, age at disease onset, disease duration and EDSS score were obtained from the Multiple Sclerosis Register in case of the center, or from the outpatient treatment reports.

We included patients into the evaluation, if:

1. Their age was 18 years or older.
2. The first language was Hungarian.
3. They were diagnosed with CIS or RRMS based on the revised McDonald's criteria (Polman et al., 2011).
4. They were in remission and did not receive steroid therapy for at least 30 days during the evaluation.
5. Their EDSS score ranged from 0-6.5.

We have excluded patients from the study:

1. With secondary (SPMS) or primary progressive (PPMS) course of the disease.
2. If they were undergoing acute infection or an acute relapse.
3. If they were diagnosed with psychiatric or personality disorder as these have a fairly large co-incidence with MS and can cause cognitive impairment (Marrie et al., 2015).
4. If they had a history of chronic alcoholism as it can also worsen the cognitive state (Bernardin et al., 2014).
5. If they had a history of drug abuse or dependence (Worley et al., 2014).

Methods

We evaluated the patients' cognitive state with the Hungarian version of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) questionnaire (Sandi et al., 2015). As no consensual threshold on CI for BICAMS has been proposed yet, we used the thresholds given in the manuals of the separate tests (-1.5 standard deviation [SD] below the average for SDMT; T-score 40 or below for BVMT-R and CVLT-II). We identified patients as cognitively impaired whom had abnormal scores on one or more tests, a criterion proposed by Dusankova et al. in 2012 in their own BICAMS validation process (Dusankova et al., 2012).

Depression can seriously worsen the cognitive function of patients; therefore, its evaluation is very important to get a clear picture on the patients' cognitive state. We used the Beck Depression Inventory (BDI-II) to assess depression in our group of patients (Beck, 1996). All patients with a score of 13 or above were classified as depressed.

Statistical analysis

We utilized univariate logistic regression model to assess the predictors of CI. To assess the differences in the cognitive state and depression between the sexes and patients with different levels of education, we used Fisher's exact test and chi-square tests, for assessing the differences between key clinical and demographic factors (age, age at disease onset, disease duration, EDSS score) we utilized one-way ANOVA.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Ethics approval for this research was obtained from the Ethics Committee of the University of Szeged (authorization number 127/2013).

Results

All 553 patients have been tested with the BICAMS battery while we have data on 437 patients' BDI scores. The difference is due to either the patient did not fully complete the BDI questionnaire hence their score could not be reliably calculated or the patient did not consent to complete the BDI questionnaire.

Demographics and clinical data

The mean age of our patients was 44.93±11.69 years, mean age at disease onset was 31.95±10.01 years, the mean disease duration was 13.05±8.05 years and the median EDSS score 2.0 (Range: 6.5, IQR:2.0) points. One-hundred and sixteen patients of the 437 (26.5%) were depressed, and only 17 (4%) patients fell into the "severe" category.

Table 1 shows the key clinical and demographic data on the sexes. There was no significant difference between the sexes in the rate of patients with different educational levels, disease duration, EDSS score and the rate of depression. Yet the men were approximately 4.5 years younger than the women and 3.5 years younger at the onset of MS. These differences however are not considered to be clinically relevant (Table 1). Table 2 shows the demographic data on the different clinical forms. As expected, CIS patients have a considerably shorter disease duration and lower EDSS score as compared to RRMS patients. (Table 2).

Table 1: The comparison of clinical and demographic data of the male and female participants

Clinical and demographic data		Man	Women	Difference (p)
Age (+SD)		40.83 (±11.35)	45.24 (±11.49)	4.39 (p<0.001)*
Age at disease onset (+SD)		29.59 (±9.58)	32.88 (±9.91)	3.29 (p<0.001)*
Disease duration (+SD)		12.21 (±8.06)	13.35 (±8.00)	1.14 (p=0.132)
Median EDSS (Range; IQR)		2.0 (6.5; 2.0)	2.0 (6.5; 2.0)	0.0 (p=0.436)
Education	<12 years	42 (26.8%)	81 (20.5%)	p=0.254
	12-15 years	54 (34.4%)	155 (39.1%)	
	≥16 years	61 (38.9%)	160 (40.4%)	
Depression	Present	31 (23.8%)	85 (27.7%)	3.9% (p=0.477)
	Not present	99 (76.2%)	222 (72.3%)	

SD, Standard deviation; IQR, Interquartile range

**Table 2: The comparison of clinical and demographic data of the CIS and RRMS participants**

Clinical and demographic data		CIS	RRMS	Difference (p)
Age (+SD)		42.46 (±12.09)	44.91 (±11.65)	2.45 (p=0.308)
Age at disease onset (+SD)		35.82 (±12.20)	31.74 (±9.75)	4.08 (p<0.037)*
Disease duration (+SD)		5.44 (±4.94)	13.71 (±8.14)	8.27 (p<0.001)*
Median EDSS (Range; IQR)		0.0 (2.0; 1.5)	2.0 (6.5; 2.0)	2.0 (p<0.001)*
Depression	Present	6 (17.8%)	110 (27.1%)	9.3% (p=0.231)
	Not present	22 (82.2%)	299 (72.9%)	

CIS, clinically isolated syndrome; RRMS, relapsing-remitting multiple sclerosis; SD, Standard deviation; IQR, Interquartile range

Prevalence of cognitive impairment

Three-hundred and sixteen (57.1%) of our patients had some level of CI. Two-hundred and thirty-one patients (41.7%) had impaired SDMT scores, 210 patients (38.0%) had impaired BVMT-R scores and 75 patients (13.6%) had impaired CVLT-II results. Ninety-one patients (16.5%) had impaired scores solely on the SDMT screening, 66 patients (11.8%) only on the BVMT-R questionnaire, and 6 patients (1.1%) only on the CVLT-II assessment. Eighty-four patients (15.2%) performed impaired on both the SDMT and the BVMT-R tests, 9 (1.6%) patients on both the SDMT and CVLT-II tests, and 13 patients (2.4%) on both the BVMT-R and the CVLT-II screenings. Forty-seven patients (8.5%) had impaired scores on all three batteries (Figure 1). There was no difference between cognitively impaired and unimpaired patients regarding the clinical and demographic data. Of our CIS patients, 7 (25.0%) had some level of CI as compared to the 309 (58.8%) of the RRMS patients. This difference is significant (p=0.001).

Figure 1: The rate of cognitive impairment among Hungarian patients with multiple sclerosis in the different subtests of the BICAMS battery
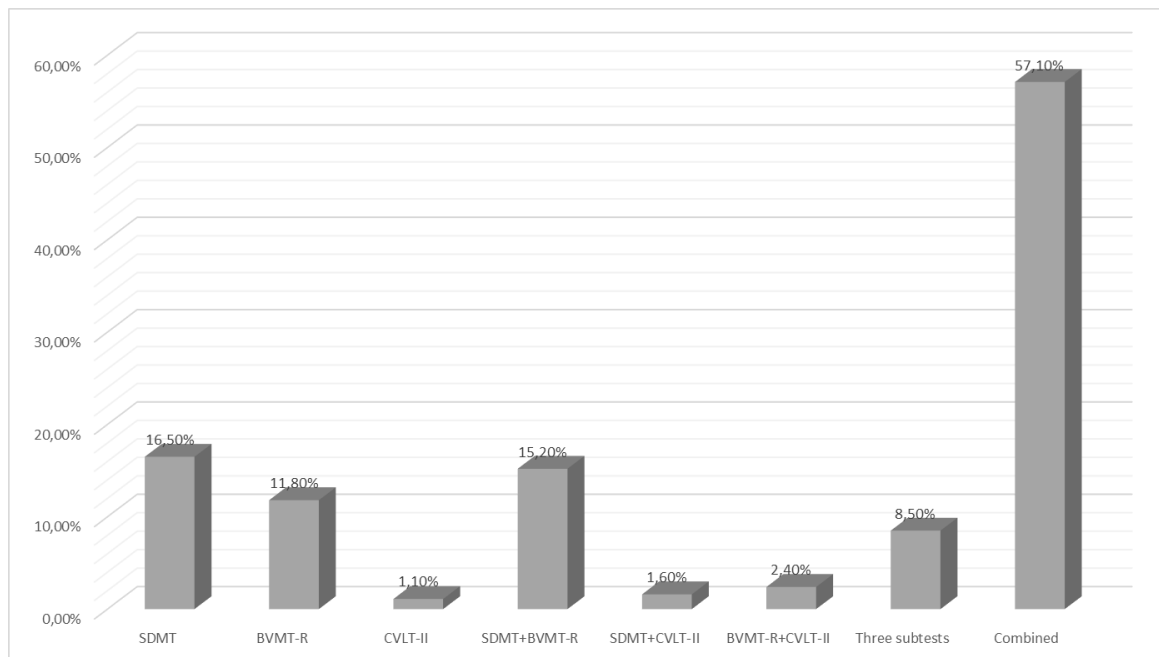
SDMT, Symbol Digit Modalities Test; BVMT-R, Brief Visuospatial Memory Test Revised; CVLT-II, California Verbal Learning Test 2nd Edition

We performed a univariate logistic regression analysis to assess the possible predictors of CI. Of the evaluated clinical and demographic parameters, disease duration, age, age at disease onset, receiving DMTs and depression did not predict CI; however, sex, educational level and EDSS score were significant predictors (Table 3). The dichotomization of EDSS score was based on the median EDSS level, similarly as in the survey done by Patti et al (Patti et al., 2015). Men had almost threefold risk to develop CI than women, people without a high school degree developed a twofold higher chance of CI than people with college and university degree. Also, people with low EDSS scores (0-2 points) have approximately half the risk than people with higher EDSS scores.

Table 3: Univariate logistic regression analysis of the predictors of cognitive impairment

Predictor		OR	95%CI	p-value
Sex	Man	2,71	1.66-4.41	<0.001
	Women	1,00		
Education	<12 years	1,94	1.10-3.42	0.023
	12-15 years	1,32	0.81-2.13	0.261
	≥16 years	1,00		
EDSS	0-2 points	0,47	0.29-0.77	0.003
	>2 points	1,00		

OR, odds ratio; 95%CI, 95% confidence interval; EDSS, Expanded Disability Status Scale.

Considering the differences between the sexes, 70.1% of the man had some level of CI, while 52.0% of the women suffered from cognitive dysfunction. This difference is statistically significant (p<0.001). Men had a higher rate of abnormal scores in all three subtests of the BICAMS battery than women (SDMT: 55.4% vs. 36.4%, BVMT-R: 48.4% vs. 33.8%, CVLT-II: 21.7% vs. 10.4%; p<0.001). The prevalence of CI among patients without high school degree was 68.3%, among patients with 12-15 years of education 60.8% and among patients with college or university degree was 48.0%, which significantly differed from the other two categories (p=0.001). Patients had a significantly higher rate of impaired scores on both the SDMT (53.7%, 41.6%, 35.3%; p=0.004) and the BVMT-R (48.0%, 39.7%, 30.8%; p=0.006) assessments as the educational levels lowered, but there was no significant difference between the groups in the CVLT-II assessment (17.1%, 14.8%, 10.4%; p=0.178). Considering EDSS score, 49.7% of patients with EDSS scores between 0-2 points had CI, while 72.9% of those, who had higher EDSS scores (p<0.001). Patients with higher EDSS scores performed worse on all BICAMS subtests, than patients with lower EDSS score (SDMT: 55.2% vs. 35.4%, BVMT-R: 53.1% vs. 31.1%, CVLT-II: 20.3% vs. 10.2%; p<0.001).

We combined the predictors, and assessed both sexes with logistic regression analysis. It revealed that beside their sex, there is no other significant predictor of CI for man. The prevalence of CI did not significantly differ in any educational groups, or the groups based on EDSS scores. The only significant difference was in the BVMT-R performance of different EDSS categories (Table 4). However, among women, we found that both the educational categories and the EDSS score is a significant predictor of CI. Women with 12-15 years of education had an OR of 1.79 (95%CI: 1.10-2.92; p=0.021), while women without high school degree an even higher, OR of 2.46 (95%CI: 1.34-4.52; p=0.004) as compared to women with a college or university degree. Regarding EDSS score, women with EDSS scores between 0-2 points had an OR of 0.40 (95%CI: 0.24-0.65; p<0.001) as compared to women with higher EDSS scores. This is reflected in the prevalence of CI: the higher the education, the lower the prevalence of CI is (66.7% for women without a high school degree, 57.4% for women with 12-15 years of education and 39.4% for women with college or university degree; p<0.001); while the prevalence of CI is 42.8% among women with EDSS scores between 0-2 points and 69.9% with higher EDSS scores (p<0.001). Women with higher EDSS performed worse an all three BICAMS subtests, while women with higher education performed significantly better on SDMT and BVMT-R assessments, but not on the CVLT-II screening (Table 5).

Table 4: The rate of cognitive impairment among man with different educational levels, different EDSS score categories. Both the combined prevalence and the prevalence on the individual subtests of BICAMS are shown.

Predictor		All domain	*p-value*	SDMT	*p-value*	BVMT-R	*p-value*	CVLT-II	*p-value*
Education	<12 years	71.4%	0.949	64.3%	0.227	47.6%	0.687	19.0%	0.641
	12-15 years	68.5%		57.4%		44.4%		25.9%	
	≥16 years	70.5%		47.5%		52.5%		19.7%	
EDSS	0-2 points	66.7%	0.098	53.8%	0.405	40.9%	0.012*	19.4%	0.422
	>2 points	79.7%		61.0%		62.7%		25.4%	

EDSS, Expanded Disability Status Scale; SDMT, Symbol Digit Modalities Test; BVMT-R, Brief Visuospatial Memory Test Revised; CVLT-II, California Verbal Learning Test 2nd Edition
*significant on the level of p<0.05

Table 5: The rate of cognitive impairment among woman with different educational levels, different EDSS score categories. Both the combined prevalence and the prevalence on the individual subtests of BICAMS are shown.

Predictor		All domain	*p-value*	SDMT	*p-value*	BVMT-R	*p-value*	CVLT-II	*p-value*
Education	<12 years	66.7%	<0.001	48.1%	0.030	48.1%	<0.001	16.0%	0.083
	12-15 years	57.4%		36.1%		38.1%		11.0%	
	≥16 years	39.4%		30.6%		22.5%		6.9%	
EDSS	0-2 points	42.8%	<0.001	27.9%	<0.001	27.1%	<0.001	6.6%	0.001
	>2 points	69.9%		52.6%		48.9%		18.0%	

EDSS, Expanded Disability Status Scale; SDMT, Symbol Digit Modalities Test; BVMT-R, Brief Visuospatial Memory Test Revised; CVLT-II, California Verbal Learning Test 2nd Edition

Discussion

The prevalence of CI is 43-70% among patients with MS according to different studies dedicated to the topic (Chiaravalloti and DeLuca, 2008). As these evaluations were conducted with very different methodologies, these great differences between the results are not surprising: some assessments were conducted by assessing one domain only (with SDMT for example), other studies used complex neuropsychological examinations such as Rao's Brief Repeatable Battery (Morrow et al., 2010; Rao et al., 1991a). Until 2011, there wasn't any consensual, easily administered and scored, yet sensitive method to measure cognitive dysfunction in patients with MS. This changed with the introduction of the BICAMS battery by Langdon et al (Langdon et al., 2012). To our best knowledge, there has been only one prevalence data published to date, using the BICAMS battery: Dusankova et al found the prevalence of CI in the Czech MS population to be 55% in 2012 (Dusankova et al., 2012). We found the prevalence of CI to be 57.1% in Hungary, which is very similar to their findings, and well within the wide range of results published in other evaluations. Yet, our examination was carried out in an almost double-sized, homogenous population in contrast to the Czech assessment in which PPMS and SPMS patients also participated. As we know that CI occurs more often in the progressive forms of the disease, we hypothesize that our almost identical prevalence data is due to the larger, homogenous sample-size and would have been even higher if progressive patients were to be included. Yet, as to date, we only have therapy for RRMS, we believe that the appearance of CI in RRMS patients can have therapeutic consequences in the near future.

We detected that information processing speed is the most vulnerable cognitive domain in Hungarian MS patients (41.7%), followed by visuospatial memory (37.8%). Verbal memory seems to be less affected than the other two domains (13.6%). These results are not surprising as other studies demonstrated similar tendencies to various degrees (Chiaravalloti and DeLuca, 2008).

We found sex, education and EDSS score to be significant predictors of CI. This is in agreement with previous studies (Amato et al., 2006; Bonnet et al., 2006; DeLuca et al., 2015). We found no association between age at onset, disease duration and cognitive dysfunction. Earlier assessments were controversial on this matter: some studies found association with these factors, most, on the other hand, did not (Amato et al., 2012; DeLuca et al., 2015; Patti et al., 2015). This can partially be explained by the different sample sizes and methodologies of these assessments, but this should be evaluated further to get a clear picture. Also, we note, that the dichotomization of the EDSS score at the low level of 2 points might seem to be strange. Yet, we chose the median EDSS level for the differentiation, like the earlier study in Italy (Patti et al., 2015). In 2013, it was shown that in Csongrád-County, Hungary, 92% of RRMS patients have an EDSS score between 0-4 points, with a mean EDSS score of approximately 2 points, so our results are completely in line with this earlier report and warrant the choice of dichotomization at our chosen level (Zsiros et al., 2014). Our results imply that not the disease duration, rather the activity of the disease might be an important factor in developing CI, yet this is merely a speculative explanation and should be evaluated further in the future. Depression was not a significant factor, despite that it is linked to CI. Yet, it was also established, that mainly moderate to severe levels of depression have a significant impact on cognitive functioning (Siegert and Abernethy, 2005). In our sample, the majority of depressed patients fell into the mild category, so this might explain our results. In our assessment, men were more vulnerable to cognitive dysfunction (70.1%) than women (52.0%). Men showed higher prevalence rate of cognitive dysfunction in all three subtests of the BICAMS battery than women. Yet, there were no other significant predictors for cognitive dysfunction for men. There are only a

few studies that assessed sex differences in MS patients, and however they showed similar differences in prevalence, to our best knowledge, no other study found that education and EDSS are restricted to women as a predicting factor (DeLuca et al., 2015; Patti et al., 2015).

The reason behind sex differences in cognitive functions is not well understood. Certain kind of genetic variables were assessed as factors in developing more serious cognitive dysfunction. It was established that the more frequent presence of the Apo-E ε4 allele in men led to more severe CI as compared to women (Savettieri et al., 2004). Also the role of sex hormones was implied: in particular, the possible protective effect of estrogens on cognitive function can partly explain these differences, as this protective effect has been already reported in other neurodegenerative conditions, most notably in Alzheimer's and Parkinson's disease (Bove et al., 2014; Miller and Cronin-Golomb, 2010). Though, as we did not evaluate the genetic polymorphisms of our patients, these are merely speculative explanations, thus these differences can warrant further investigation into the link between genetics and cognitive functions. Our results also show that among women, the prevalence of CI is significantly lower among the highly educated and patients with lower EDSS scores. These findings are in line with previous assessments that showed EDSS might be a predictor of CI and also that higher cognitive reserve associated with higher educational levels is a protective factor against cognitive decline (Amato et al., 2006; Sumowski et al., 2014; Whalley et al., 2004). Yet, to our best knowledge, no assessment found that this only occurs in women. The reason behind this surprising finding can be partly explained by MRI assessments. It was demonstrated that MS patients suffer a faster rate of brain atrophy: and not only was the global atrophy rate higher, but several different structures (hippocampus, thalamus, basal ganglia) associated with memory show a higher rate of atrophy (Brass et al., 2006; DeLuca et al., 2015; Houtchens et al., 2007; Koenig et al., 2014; Morgen et al., 2006). Also, Király et al showed that brain atrophy is faster in healthy men than in healthy women (Kiraly et al., 2015). It is possible, that the accelerated atrophy in MS patients combined with the already faster atrophy rate in men results in the faster disappearance of cognitive reserve thus eliminating it as a protective factor. An important factor to consider can be, that male sex itself was shown to be a predictor for worse prognosis in MS patients (Weinshenker et al., 1991). Seemingly, this applies to the cognitive domain as well.

The prevalence of CI among CIS patients was 25.0%, similarly to earlier reported findings (Hyncicova et al., 2017). Sadly, as we could only recruit 28 patients with CIS to our study, we could not make a similar, in depth analysis of the differences created by other factors as with our RRMS patients, due to the low number of participants in that group. Also, the problem caused by the low number of patients is apparent in the difference between their age at disease onset: it was almost 4 years higher than in RRMS patients, yet otherwise the disease duration was much shorter and the EDSS scores much lower, as expected. As sadly, many of the younger CIS patients declined to participate in the study, this difference is mainly caused by these biases.

As conclusion, we can state that CI is a frequent yet under-diagnosed symptom of MS. Man are more susceptible to cognitive decline than women are. While higher education and lower EDSS scores seems to be a protective factor in women, apparently, it is not in men. This is possibly caused by the faster elimination of cognitive reserve by a higher rate of brain atrophy in men. To our best knowledge, we are the first to demonstrate this kind of difference between sexes in MS patients. We confirmed a fairly high prevalence of CI among CIS and RRMS patients who were young, active and in relatively good physical condition. This shows that despite a patient may seem to be symptom-free during a physical examination, the disease can still be active. Therefore, we believe

that the routine screening of the cognitive state and the detection of CI is highly important because it can help to decide on the best therapy for MS patients.

The limitation of our study lies in its design: it is an epidemiological survey with no neuroimaging or genetical analysis included, therefore the explanation of the demonstrated differences and results are hypothetical. Possibly more in depth psychological assessments should be considered to assess the sex differences further. The next stages of this evaluation should be the inclusion of neuroimaging and possibly genetic factors to analyze beside the clinical and demographic data, as well as the follow-up of the patients in longer, longitudinal studies.

Conflict of Interest

The Authors declare that there is no conflict of interest.

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