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Predominant domains and associated demographic and clinical characteristics in multiple sclerosis-related cognitive impairment in mildly disabled patients

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Abstract

Background: Cognitive impairment (CI) is a common finding in multiple sclerosis (MS); however, there is a limited information about its prevalence in mildly disabled cases. We aimed to determine the most affected domains, and also the relation between the demographic factors and cognitive outcomes in mildly disabled relapsing–remitting MS (RRMS).

Results: Ninety-one mildly disabled RRMS patients with expanded disability status scale (EDSS) < 4 and literacy level above 9 years, were recruited. Based on Minimal Assessment of Cognitive Function in MS (MACFIMS) battery, CI was observed in 19.8% of the patients while 40.60% of the patients had at least one failure in cognitive tests. The most common impaired cognitive domain was information processing speed and working memory (27.5%). There was no significant difference between men and women in terms of CI in our sample (p-values > 0.05). Disease duration ($p = 0.01$), EDSS ($p = 0.01$), and education ($p < 0.01$) were significantly different between CI and non-CI patients, while age ($p = 0.72$), sex ($p = 0.50$), diagnostic gap ($p = 0.89$), and frequency of relapses ($p = 0.22$), did not differ considerably.

Conclusions: RRMS patients experience some degrees of CI that may present even before the onset of remarkable physical disability; nevertheless, a higher EDSS score and longer disease duration increases the risk of CI. These findings suggest routine cognitive assessment of MS patients.

Keywords: Multiple sclerosis, Neuropsychological assessment, Cognitive impairment, MACFIMS, Relapsing–remitting multiple sclerosis

Background

Cognitive impairment (CI) can present in all stages of multiple sclerosis (MS) [1, 2]. MS-related CI affects 40–60% of patients [3] and it is one of the leading causes of disability in these patients [4, 5]. The reported prevalence of MS-related CI in hospital-based studies is different from population-based ones [6–8]. Also, it greatly varies between different types of MS and it is more frequent in progressive forms of the disease [6, 9–11].

The reported prevalence of CI in relapsing–remitting multiple sclerosis (RRMS) varies from 10.5% to 50% [12–17]. This variety is probably due to the different neuropsychological (NP) batteries, applied cut-off values, patients' demographic characteristics, and also the stage of the disease. All cognitive domains may be impaired in RRMS patients, but based on previous studies, information processing speed (IPS), working memory, and learning memory are the most affected cognitive domains [18–21].

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There are limited studies about the prevalence of CI in mildly disabled MS patients. Significant impairment was observed in learning, visual, and long-term verbal memory, and information process speed in a sample of Spanish RRMS patients with Expanded Disability Status Scale (EDSS) < 4 [22]. Also, a study has reported a higher prevalence of isolated verbal fluency impairment in early RRMS patients (disease duration < 3 years) compared to a healthy control group [23]. A study of 92 Italian RRMS patients with EDSS scores ≤ 2.5, found that 51.1% of MS patients have CI with primary involvement of prefrontal cognitive functions [24]. Severe impairment of visual IPS and attention as well as moderate impairment in sustained attention and complex IPS has been stated in a sample of mildly disabled RRMS patients [25].

Information about the impact of demographic factors on MS-related CI is contradictory. Some reports have indicated that there is a relationship between CI and disease duration [26, 27], while others have not reported such a relation [28, 29]. The same is true of the EDSS so that there are reports of a correlation between CI and EDSS [6, 27, 30], but some have reported the opposite [31]. There are limited studies about the correlation between the frequency of relapses and the diagnostic gap with MS-related CI.

In this study, we aimed to determine the prevalence of CI and impaired cognitive domains in mildly disabled RRMS patients. Also, we investigated the impact of demographic factors including the disease duration, EDSS, frequency of relapses, and diagnostic gap on cognitive outcomes of MS patients.

Methods

This study was performed on adult patients (age ≥ 18) with a definite diagnosis of RRMS (McDonald 2017 revised diagnostic criteria) [32], literacy level above 9 years, and mild level of disability (EDSS < 4). Participants were recruited from 1 October 2019 to 1 April 2021 through the outpatient services of the MS clinic at Tabriz University of Medical Science (TUOMS). The study protocol was reviewed and approved by the Ethics Committee of TUOMS (Approval No. IR.TBZMED.REC.1397.791). Written informed consent was obtained from all patients before study entry. Exclusion criteria were relapsing of the disease or corticosteroid treatment in the last 3 months; psychiatric disorders; major depressive disorder (Diagnostic and Statistical Manual of Mental Disorders [DSM-5] criteria) [33]; neurological disorders other than MS; brain injuries; using psychoactive drugs like anticholinergics, anti-epileptic drugs, or antidepressant drugs; a systemic disease that could influence cognitive function; learning disabilities; history of alcohol abuse; the presence of physical impairments that could interfere with NP assessment; clinically isolated syndrome (CIS); and progressive forms of MS.

All patients underwent the neurological examination and a validated Persian version of minimal assessment of cognitive function in multiple sclerosis (MACFIMS) battery was performed to assess the cognitive outcomes [34, 35]. Depression was assessed using the validated Persian version of the Beck Depression Inventory-Fast Screen (BDI-FS) questionnaire [36, 37].

MACFIMS battery consists of the following seven NP tests covering the five cognitive domains: (1) California Verbal Learning Test, Second Edition (CVLT-II) to assess auditory/verbal episodic memory, with immediate recall (IR) and delayed recall (DR) components; (2) Symbol Digit Modalities Test (SDMT) to assess visual processing speed and working memory; (3) Paced Auditory Serial Addition Test (PASAT) to assess auditory processing speed and working memory; (4) Controlled Oral Word Association Test (COWAT) to assess expressive language; (5) Judgment of Line Orientation (JLO) to assess spatial processing; (6) Brief Visuospatial Memory Test-Revised (BVMT-R) to assess visuospatial episodic memory with IR and DR components, and (7) Delis–Kaplan Executive Function System Sorting (DKEFS) to assess executive function [38]. It takes approximately 90 min to complete the battery.

A trained psychologist under the supervision of an expert neurologist administered this battery to each participant. Impairment in each test of the battery was defined as ≤ 1.5 standard scores below the mean normative values for each cognitive task [35]. Overall CI was defined as the failure on at least two tests of the MACFIMS battery. Based on CI patients were separated into 2 groups of CI and non-CI. All NP tests were performed on all patients in the evening and in a quiet room. Before cognitive testing, the EDSS score was assessed by a neurologist. the Beck Depression Inventory-Fast Screen (BDI-FS) was completed by a psychologist.

Disease duration assessed from the onset of symptoms indicating MS. The diagnostic gap was calculated from the beginning of the symptoms, which indicates MS, to the time of definite diagnosis by a neurologist. Education levels are divided into four groups of < 12 (9–12 years of education), diploma (complete 12 years of education), university (12–16 years of education), and higher education (> 16 years of education). Also, patients were divided into 5 age groups: ≤ 20, 21–30, 31–40, 41–50, and 51–60.

Data were analyzed using SPSS statistical software (2015; Version 23.0. Armonk, NY, USA). Descriptive data were presented using frequencies (and percentages) and mean ± standard deviation (SD). The Student's t-test or Mann–Whitney U test was applied to compare the parametric data between two groups, based on the

normality of distribution which was assessed by the Kolmogorov–Smirnov test. For comparing the non-parametric variables Chi-square test was utilized. The Spearman correlation was utilized for assessing the correlations and multivariate logistic regressions were performed to identify the associated factors of CI. In all comparisons, $p<0.05$ was considered statistically significant and 95% levels of confidence of intervals was observed.

Results

Ninety-one RRMS patients including 65 women and 26 men were involved in this study. Table 1 shows the demographic characteristics of the patients. The sex ratio was not significantly different between the two groups ($p=0.504$). Patients with CI were slightly older than cognitively normal patients, but this difference was not significant ($p>0.05$). For assessment of the impact of age on CI, we also divided patients into five age groups. In the patients under 20 years old, we had no case of CI. As patients got older, CI increased and reached its peak at 51–60 age group.

Compared to the cognitively normal group, the mean EDSS score was significantly higher in the CI group ($p=0.014$). The detailed percentage of CI in each EDSS score is presented in Fig. 1. In our sample, 50% of patients with EDSS score 3 or 3.5 had CI. The diagnostic gap and the frequency of relapses were not significantly different between the two groups. The mean disease duration in the CI group was significantly longer than the cognitively normal group ($p=0.014$).

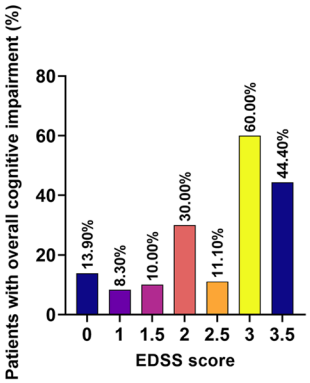

Fig. 1 The proportion of patients with cognitive impairment, based on the expanded disability status scale (EDSS)

Table 1 Demographic and clinical characteristics of the participants

Parameters		Overall (n = 91)	MS with CI (n = 18)	MS without CI (n = 73)	*p* value
Age		31.60 ± 8.64	34.88 ± 9.42	30.79 ± 8.31	0.72
Age groups	≤ 20	7 (7.7%)	0 (0%)	7 (100%)	0.39
	21–30	43 (47.3%)	7 (16.27%)	36 (83.72%)	
	31–40	28 (30.8%)	7 (25.00%)	21 (75.00%)	
	41–50	11 (12.1%)	3 (27.27%)	8 (72.72%)	
	51–60	2 (2.2%)	1 (50.00%)	1 (50.00%)	
Sex (male:female)		26:65	4:14	22:51	0.50
EDSS		1.29 ± 1.27	1.94 ± 1.48	1.13 ± 1.17	**0.01***
Disease duration (months)		70.67 ± 55.18	98.66 ± 55.15	63.76 ± 53.32	**0.01***
Diagnostic gap (months)		5.25 ± 11.23	5.55 ± 8.03	5.17 ± 11.93	0.89
Frequency of relapse		2.84 ± 2.29	3.44 ± 2.72	2.69 ± 2.17	0.22
BDI-FS score		4.76 ± 3.95	5.33 ± 3.91	4.63 ± 3.97	0.50
Education		14.05 ± 2.60	14.61 ± 2.27	11.77 ± 2.66	**< 0.01***
Education groups	< 12	7 (7.7%)	6 (85.7%)	1 (14.3%)	**< 0.01***
	12	33 (36.3%)	9 (27.3%)	24 (72.7%)	
	12–16	39 (42.9%)	2 (5.1%)	37 (94.9%)	
	> 16	12 (13.2%)	1 (8.3%)	11 (91.7%)	
Disease-modifying drugs	Dimethyl fumarate	26 (28.6%)	3 (11.5%)	23 (88.5%)	**0.02***
	Rituximab	9 (9.9%)	5 (55.6%)	4 (44.4%)	
	Interferon beta-1	30 (33.0%)	26 (86.7%)	4 (13.3%)	
	Natalizumab	8 (8.8%)	8 (100%)	0 (0%)	
	Fingolimod	13 (14.3%)	7 (53.8%)	6 (46.2%)	
	No drug for MS	5 (5.5%)	4 (80.0%)	1 (20.0%)	

SD standard deviation, *MS* multiple sclerosis, *CI* cognitive impairment, *EDSS* expanded disability status scale, *BDI-FS* beck depression inventory-fast screen

The mean of the education years was significantly different between the two groups ($p < 0.01$). In patients with a low level of literacy, the frequency of CI was higher. Six of the seven patients with less than 12 literacy levels had CI. In contrast, only one in 12 patients with literacy levels above 16, had CI. There was a significant difference between the CI and non-CI groups in terms of disease-modifying drugs ($p = 0.02$).

The most frequently impaired cognitive domains were IPS and working memory that assessed by PASAT (27.5%). The least impaired cognitive domain was the executive function that was assessed by DKEFS with two participants involved (2.2%). In women, the most common impaired cognitive domains were IPS and working memory, and the least impaired cognitive domains were expressive language and executive function. In men, the most common impaired cognitive domains were auditory/verbal episodic memory. The SDMT, BVMT-R Total, BVMT.R Delay, and DKEFS tasks did not show any impairment in men (Table 2). There was no significant difference between men and women in terms of CI in our sample (p-values > 0.05).

Overall CI is defined as the failure on at least two tasks of the MACFIMS battery. Eighteen patients (19.8%) had CI criteria (Fig. 2). The prevalence of CI in men and women was 15.4% and 21.5%, respectively. According to our assessment, 54 patients (59.3%) were within normal limits on all the cognitive function tests.

Based on multivariate analysis, EDSS (OR 1.643; 95% confidence intervals: 1.086–2.485) predicted an increased risk of CI in mildly disabled RRMS patients. The literacy level (OR 0.594; 95% confidence intervals: 0.448–0.789) had a protective effect against CI. Disease duration although increases the risk of CI ($p = 0.02$) (Table 3).

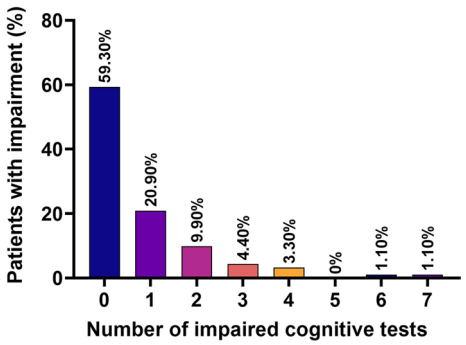

Fig. 2 The proportion of patients with the number of impaired cognitive tests, based on scores for Minimal Assessment of Cognitive Function in multiple sclerosis (MACFIMS) battery. Impairment in each test is defined as ≤ 1.5 standard deviations below the normative values

Figure 3 presents the correlations between demographic characteristics and cognitive scores of the MACFIMS battery. The literacy levels of the patients were significantly correlated to the all of the tests of the battery (p-values < 0.01). Except for COWAT ($p = 0.54$), there were a significant negative correlation between disease duration and all of the subtests of the MACFIMS battery (p-values < 0.01). Age was also negatively correlated to PASAT ($p < 0.01$), SDMT ($p < 0.01$), BVMT.R total ($p < 0.01$), and BVMT.R ($p = 0.02$) scores of the patients.

Table 2 Mean scores of each MACFIMS test, cut-off values and number of patients with impairment

Cognitive test	Cut-off values	Patients (mean ± SD)	Impaired test			
			Overall	Male	Female	*p*-value
CVLT-II T	42.62	52.05 ± 11.54	19 (20.9%)	5 (19.2%)	14 (21.5%)	0.80
CVLT-II. D	8.71	11.98 ± 2.88	10 (11.0%)	2 (7.7%)	8 (12.3%)	0.52
PASAT	33.71	38.63 ± 10.91	25 (27.5%)	4 (15.4%)	21 (32.3%)	0.10
SDMT	30.86	48.89 ± 13.24	7 (7.7%)	0 (0%)	7 (10.8%)	0.08
BVMT-R Total	13.94	26.40 ± 6.99	6 (6.6%)	0 (0%)	6 (9.2%)	0.10
BVMT.R D	5.45	10.56 ± 2.30	4 (4.4%)	0 (0%)	4 (6.2%)	0.19
COWAT	15.38	31.65 ± 11.28	3 (3.3%)	1 (3.8%)	2 (3.1%)	0.85
DKEFS	15.56	36.29 ± 9.12	2 (2.2%)	0 (0%)	2 (3.1%)	0.36
JLO	15.12	20.96 ± 5.05	12 (13.2%)	3 (11.5%)	9 (13.8%)	0.76
Failure in at least 1 task			37 (40.65%)	8 (21.6%)	29 (78.4%)	0.22
Failure in ≥ 2 (overall CI)			18 (19.78%)	4 (15.4%)	14 (21.5%)	0.50

Impairment was defined as ≤ − 1.5 standard deviations from the mean normative values for each cognitive test in the Iranian general population

SD standard deviation, *MACFIMS* minimal assessment of cognitive function in multiple sclerosis, *CI* cognitive impairment, *BVMT-R* brief visuospatial memory test-revised, *COWAT* controlled oral word association test, *CVLT-II* California Verbal Learning Test, Second Edition, *D-KEFS* Delis–Kaplan Executive Function System, *JLO* Judgment of Line Orientation, *PASAT* Paced Auditory Serial Addition Test, *SDMT* symbol digit modalities test, *CVLT-II T* CVLT-II total learning, *CVLT-II. D* CVLT-II delayed recall, *BVMT.R D* BVMT-R delayed recall

Table 3 Multivariate analysis of associated factors for MS-related cognitive impairment

Parameters	B	OR	95% CI		*p* value
			Lower	Upper	
Literacy level	− 0.521	0.594	0.448	0.789	**< 0.01***
Age	0.054	1.055	0.994	1.119	0.07
Disease duration	0.011	1.011	1.002	1.020	**0.02***
Frequency of relapse	0.125	1.133	0.926	0.926	0.22
Diagnostic gap	0.003	1.003	0.959	1.049	0.89
EDSS	0.496	1.643	1.086	2.485	**0.01***
Sex	0.412	1.510	0.446	5.106	0.50

EDSS expanded disability status scale, *OR* odds ratio, *CI* confidence interval

The level of physical disability, assessed by the EDSS score, had significant associations with SDMT ($p < 0.01$), BVMT.R total ($p = 0.03$) test and diagnostic gap was negatively correlated to SDMT ($p = 0.01$), BVMT.R total ($p = 0.02$), COWAT ($p < 0.01$), and DKEFS ($p = 0.03$).

Discussion

In this study, we evaluated the impaired cognitive domains in mildly disabled RRMS patients using the MACFIMS battery. Also, we determined the impact of demographic and clinical factors on cognitive outcomes in this group of patients. Based on our assessment, the prevalence of CI was 19.8% in RRMS patients with an EDSS < 4. There was a significant association between disease duration, education level, and EDSS with MS-related CI, but sex, age, diagnostic gap, and the frequency of relapse did not affect this outcome. We observed a significant difference between CI and non-CI patients in terms of disease-modifying drugs, which could be because of the small number of participants in each group. We also found that the literacy level, disease duration, age, EDSS, and diagnostic gap were significantly correlated to some cognitive scores of the patients in our sample.

The prevalence of MS-related CI in our study was lower than the reported rate in previous studies. This may be due to the diversity of NP batteries, demographic characteristics, and methodology between studies. Our patients had a mild disability with a mean EDSS score of 1.29 ± 1.27. The EDSS score in most previous studies was ≥ 6.0 [6, 39, 40]. The patients' age and disease duration were also considerably shorter in our study compared with previous studies [11, 39, 41, 42]. Also, in several reports, patients with a single impaired cognitive task were considered as CI, while we defined patients with at least two impaired cognitive tasks as overall CI [43].

Most studies included patients with a progressive form of the disease [40, 42, 44]. According to reports, CI is more prevalent in primary and secondary progressive MS compared with RRMS [30, 42]. Similar to our results, in a study on RRMS patients with a mean EDSS score of 1.9, CI was reported in 22% of the cases based on three impaired cognitive tests of the Rao's battery [45]. In another study on clinically isolated syndrome or newly diagnosed MS patients with a mean EDSS score of 1.3, CI was seen in 20% of patients based on two NP tests impaired [46].

Of the assessed cognitive domains, IPS especially auditory-component and working memory were the most frequently impaired cognitive domains in our sample. These results are supported by previous literature, in which the most frequently impaired cognitive domains were IPS, verbal/visuospatial memory, and executive functions [41, 47–49]. The most frequently involved task in our study was PASAT, whereas in the mentioned study it was SDMT [41]. Both tasks evaluate the processing speed but the auditory-component of processing speed evaluates by PAST, whereas, visual component evaluates by SDMT.

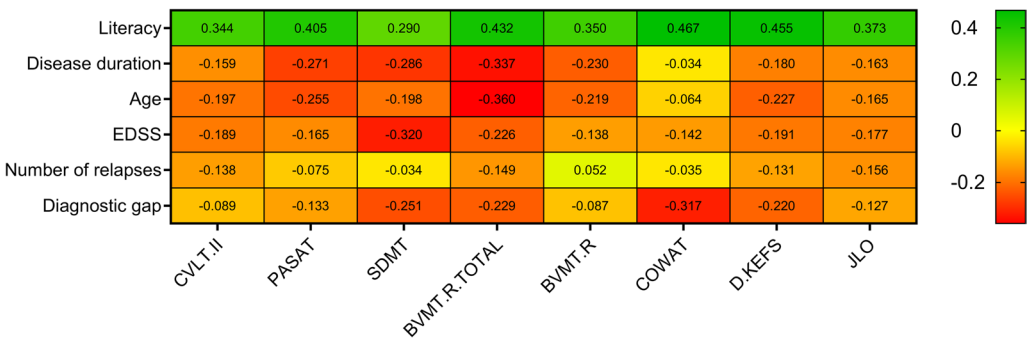

Fig. 3 The correlations between demographic characteristics and cognitive scores. The number inside each cell is "*r*" for Spearman's Rho

In the present study, the number of impaired cognitive domains in men was lower than in women. In male cases, the tasks of SDMT, BVMT, and DKEFS did not show impairment, but in the women, all tasks were affected. The limited number of male cases can be a reason for this finding. Episodic memory (auditory/verbal) was the most frequently impaired cognitive domain in men while processing speed and working memory were the most frequently impaired domains in women. Assessing gender differences in cognitive function is a controversial concept [50], which should be assessed in future studies.

In this study, the EDSS score in the CI group was significantly higher than the cognitively normal group, and it was found that the EDSS score can predict the risk of MS-related CI. These findings are supported by previous studies in which there is an association between the disability level and MS-related CI [5, 40]. Vice versa, in our results, a high education level had a protective effect against CI; while regression analysis showed a low predictor effect of older age on MS-related CI. Sex, frequency of relapse, and the diagnostic gap did not have a predictive effect on MS-related CI. Patti and colleagues in a study found that age is a significant predictor of MS-related CI, but they did not find significant associations between MS-related CI and education level [45]. On the other hand, Sartori and colleagues showed a significant correlation between older age and low level of education with MS-related CI [51].

It is suggested that MS-related CI could be a factor associated with worse outcomes in subsequent stages of MS [52]. Previous studies found that using screening methods with low sensitivity, such as Mini-Mental State Exam (MMSE) and Montreal Cognitive Assessment (MoCA), leads to a lack of diagnosis and treatment of MS-related CI [34, 53–55]. Also, cognitive assessment of patients with MACFIMS battery, as the gold standard method [35], is a time-consuming process and needs an appropriate cooperation of the patients. Studies suggested computer-based assessments such as Cambridge Neuropsychological Test Automated Battery (CANTAB) as an alternative method of CI screening in MS patients [49], but still, there is a need for developing new fast screening methods, with enough specificity for timely diagnosis and interventions to the prevention of the future possible consequences.

Conclusion

This study indicates that even among mildly disabled cases, RRMS patients experience some degrees of CI that may present even before the onset of remarkable physical disability which suggests routine cognitive assessment of MS patients. We also observed a difference between male and female cases in terms of most affected cognitive domains, but the overall sex differences in CI were not statistically significant. A higher EDSS score increases the risk of CI, whereas a higher level of education has a protective effect against it. Literacy level, disease duration, age, EDSS, and diagnostic gap are significantly correlated to cognitive scores of RRMS patients. There is a need for future well-designed studies with a larger sample of MS patients with mild levels of disability to validate these findings.

Abbreviations

CI: Cognitive impairment; MS: Multiple sclerosis; RRMS: Relapsing–remitting multiple sclerosis; NP: Neuropsychological; IPS: Information processing speed; EDSS: Expanded Disability Status Scale; TUOMS: Tabriz University of Medical Science; DSM IV: Diagnostic and Statistical Manual of Mental Disorders criteria; CIS: Clinically isolated syndrome; MACFIMS: Minimal Assessment of Cognitive Function in Multiple Sclerosis; BVMT-R: Brief Visuospatial Memory Test-Revised; COWAT: Controlled Oral Word Association Test; CVLT-II: California Verbal Learning Test, Second Edition; D-KEFS: Delis–Kaplan Executive Function System; JLO: Judgment of Line Orientation; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modalities Test; CVLT-II T: CVLT-II total learning; CVLT-II. D: CVLT-II delayed recall; BVMT.R D: BVMT-R delayed recall; BDI-FS: Beck depression inventory-fast screen; FSS: Fatigue severity scale; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Exam.

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None.

Author contributions

MT*: investigation; methodology; resources; roles/writing—review and editing; supervision; validation; SS-E and MT: investigation; resources; AN: methodology; resources; writing—original draft. FZ: resources; roles/writing—review and editing. All authors have read and approved the final version of the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol is reviewed and approved by the Ethics Committee of Tabriz University of Medical Science (7 March 2018, Approval No. IR.TBZMED.REC.1397.791). All methods were performed in accordance with the Helsinki declaration. Written informed consent was obtained from all patients before study entry.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflicting interests to disclose.

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References

1. Benedict RHB, Amato MP, DeLuca J, Geurts JJG. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. Lancet Neurol. 2020;19(10):860–71.
2. Benedict RHB. Cognition in multiple sclerosis: charcot was right. Lancet Neurol. 2020;19(10):810.
3. DeLuca GC, Yates RL, Beale H, Morrow SA. Cognitive impairment in multiple sclerosis: clinical, radiologic and pathologic insights. Brain Pathol. 2015;25(1):79–98.
4. Feuillet L, Reuter F, Audoin B, Malikova I, Barrau K, Cherif AA, et al. Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. Mult Scler. 2007;13(1):124–7.
5. Amato MP, Zipoli V, Portaccio E. Multiple sclerosis-related cognitive changes: a review of cross-sectional and longitudinal studies. J Neurol Sci. 2006;245(1–2):41–6.
6. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology. 1991;41(5):685–91.
7. McIntosh-Michaelis SA, Roberts MH, Wilkinson SM, Diamond ID, McLellan DL, Martin JP, et al. The prevalence of cognitive impairment in a community survey of multiple sclerosis. Br J Clin Psychol. 1991;30(4):333–48.
8. Reuter F, Zaaraoui W, Crespy L, Faivre A, Rico A, Malikova I, et al. Frequency of cognitive impairment dramatically increases during the first 5 years of multiple sclerosis. J Neurol Neurosurg Psychiatry. 2011;82(10):1157–9.
9. Wishart H, Sharpe D. Neuropsychological aspects of multiple sclerosis: a quantitative review. J Clin Exp Neuropsychol. 1997;19(6):810–24.
10. Francis PL, Jakubovic R, O'Connor P, Zhang L, Eilaghi A, Lee L, et al. Robust perfusion deficits in cognitively impaired patients with secondary-progressive multiple sclerosis. AJNR Am J Neuroradiol. 2013;34(1):62–7.
11. Potagas C, Giogkaraki E, Koutsis G, Mandellos D, Tsirempolou E, Sfagos C, et al. Cognitive impairment in different MS subtypes and clinically isolated syndromes. J Neurol Sci. 2008;267(1–2):100–6.
12. Patti F, Nicoletti A, Messina S, Bruno E, Fermo SL, Quattrocchi G, et al. Prevalence and incidence of cognitive impairment in multiple sclerosis: a population-based survey in Catania, Sicily. J Neurol. 2015;262(4):923–30.
13. Deloire MS, Salort E, Bonnet M, Arimone Y, Boudineau M, Amieva H, et al. Cognitive impairment as marker of diffuse brain abnormalities in early relapsing remitting multiple sclerosis. J Neurol Neurosurg Psychiatry. 2005;76(4):519–26.
14. Nocentini U, Pasqualetti P, Bonavita S, Buccafusca M, De Caro MF, Farina D, et al. Cognitive dysfunction in patients with relapsing–remitting multiple sclerosis. Mult Scler. 2006;12(1):77–87.
15. Prakash RS, Snook EM, Lewis JM, Motl RW, Kramer AF. Cognitive impairments in relapsing–remitting multiple sclerosis: a meta-analysis. Mult Scler. 2008;14(9):1250–61.
16. Heaton RK, Nelson LM, Thompson DS, Burks JS, Franklin GM. Neuropsychological findings in relapsing–remitting and chronic-progressive multiple sclerosis. J Consult Clin Psychol. 1985;53(1):103–10.
17. Amato MP, Ponziani G, Siracusa G, Sorbi S. Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. Arch Neurol. 2001;58(10):1602–6.
18. Langdon DW. Cognition in multiple sclerosis. Curr Opin Neurol. 2011;24(3):244–9.
19. Van Schependom J, D'Hooghe MB, Cleynhens K, D'Hooge M, Haelewyck MC, De Keyser J, et al. Reduced information processing speed as primum movens for cognitive decline in MS. Mult Scler. 2015;21(1):83–91.
20. Fischer JS. Cognitive impairment in multiple sclerosis. Handbook of multiple sclerosis: CRC Press; 2001. p. 250–73.
21. Sadigh-Eteghad S, Abbasi Garravnd N, Feizollahi M, Talebi M. The expanded disability status scale score and demographic indexes are correlated with the severity of cognitive impairment in multiple sclerosis patients. J Clin Neurol. 2021;17(1):113–20.
22. Santiago Rolanía O, Guàrdia Olmos J, Arbizu UT. Neuropsychology of mildly disabled patients with relapsing–remitting multiple sclerosis. Psicothema. 2006;18(1):84–7.
23. Brissart H, Morele E, Baumann C, Perf ML, Leininger M, Taillemite L, et al. Cognitive impairment among different clinical courses of multiple sclerosis. Neurol Res. 2013;35(8):867–72.
24. Migliore S, Ghazaryan A, Simonelli I, Pasqualetti P, Squitieri F, Curcio G, et al. Cognitive impairment in relapsing–remitting multiple sclerosis patients with very mild clinical disability. Behav Neurol. 2017;2017:7404289.
25. Edgar C, Jongen PJ, Sanders E, Sindic C, Goffette S, Dupuis M, et al. Cognitive performance in relapsing remitting multiple sclerosis: a longitudinal study in daily practice using a brief computerized cognitive battery. BMC Neurol. 2011;11:68.
26. Achiron A, Polliack M, Rao SM, Barak Y, Lavie M, Appelboim N, et al. Cognitive patterns and progression in multiple sclerosis: construction and validation of percentile curves. J Neurol Neurosurg Psychiatry. 2005;76(5):744–9.
27. Schwid SR, Goodman AD, Weinstein A, McDermott MP, Johnson KP. Cognitive function in relapsing multiple sclerosis: minimal changes in a 10-year clinical trial. J Neurol Sci. 2007;255(1–2):57–63.
28. Patti F, Failla G, Ciancio MR, L'Episcopo MR, Reggio A. Neuropsychological, neuroradiological and clinical findings in multiple sclerosis. A 3 year follow-up study. Eur J Neurol. 1998;5(3):283–6.
29. Mariani C, Farina E, Cappa SF, Anzola GP, Faglia L, Bevilacqua L, et al. Neuropsychological assessment in multiple sclerosis: a follow-up study with magnetic resonance imaging. J Neurol. 1991;238(7):395–400.
30. Huijbregts SC, Kalkers NF, de Sonneville LM, de Groot V, Polman CH. Cognitive impairment and decline in different MS subtypes. J Neurol Sci. 2006;245(1–2):187–94.
31. Rogers JM, Panegyres PK. Cognitive impairment in multiple sclerosis: evidence-based analysis and recommendations. J Clin Neurosci. 2007;14(10):919–27.
32. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–73.
33. Association AP, Association AP. Diagnostic and statistical manual of mental disorders: DSM-5. Washington, DC: American Psychiatric Association; 2013.
34. Benedict RH, Cookfair D, Gavett R, Gunther M, Munschauer F, Garg N, et al. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). J Int Neuropsychol Soc. 2006;12(4):549–58.
35. Eshaghi A, Riyahi-Alam S, Roostaei T, Haeri G, Aghsaei A, Aidi MR, et al. Validity and reliability of a Persian translation of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). Clin Neuropsychol. 2012;26(6):975–84.
36. Benedict RH, Fishman I, McClellan MM, Bakshi R, Weinstock-Guttman B. Validity of the Beck Depression Inventory-Fast Screen in multiple sclerosis. Mult Scler. 2003;9(4):393–6.
37. Ghassemzadeh H, Mojtabai R, Karamghadiri N, Ebrahimkhani N. Psychometric properties of a Persian-language version of the Beck Depression Inventory-Second edition: BDI-II-PERSIAN. Depress Anxiety. 2005;21(4):185–92.
38. Elwood RW. The California verbal learning test: psychometric characteristics and clinical application. Neuropsychol Rev. 1995;5(3):173–201.
39. Benedict RH, Bruce J, Dwyer MG, Weinstock-Guttman B, Tjoa C, Tavazzi E, et al. Diffusion-weighted imaging predicts cognitive impairment in multiple sclerosis. Mult Scler. 2007;13(6):722–30.
40. Sepulcre J, Vanotti S, Hernández R, Sandoval G, Cáceres F, Garcea O, et al. Cognitive impairment in patients with multiple sclerosis using the brief repeatable battery-neuropsychology test. Mult Scler. 2006;12(2):187–95.
41. DiGiuseppe G, Blair M, Morrow SA. Short report: prevalence of cognitive impairment in newly diagnosed relapsing–remitting multiple sclerosis. Int J MS Care. 2018;20(4):153–7.
42. Cáceres F, Vanotti S, Rao S. Epidemiological characteristics of cognitive impairment of multiple sclerosis patients in a Latin American country. J Clin Exp Neuropsychol. 2011;33(10):1094–8.
43. Calabrese M, Agosta F, Rinaldi F, Mattisi I, Grossi P, Favaretto A, et al. Cortical lesions and atrophy associated with cognitive impairment in relapsing–remitting multiple sclerosis. Arch Neurol. 2009;66(9):1144–50.
44. Savettieri G, Messina D, Andreoli V, Bonavita S, Caltagirone C, Cittadella R, et al. Gender-related effect of clinical and genetic variables on the cognitive impairment in multiple sclerosis. J Neurol. 2004;251(10):1208–14.

45. Patti F, Amato MP, Trojano M, Bastianello S, Tola MR, Goretti B, et al. Cognitive impairment and its relation with disease measures in mildly disabled patients with relapsing–remitting multiple sclerosis: baseline results from the Cognitive Impairment in Multiple Sclerosis (COGIMUS) study. Mult Scler. 2009;15(7):779–88.
46. Glanz BI, Holland CM, Gauthier SA, Amunwa EL, Liptak Z, Houtchens MK, et al. Cognitive dysfunction in patients with clinically isolated syndromes or newly diagnosed multiple sclerosis. Mult Scler. 2007;13(8):1004–10.
47. Archibald CJ, Fisk JD. Information processing efficiency in patients with multiple sclerosis. J Clin Exp Neuropsychol. 2000;22(5):686–701.
48. Demaree HA, DeLuca J, Gaudino EA, Diamond BJ. Speed of information processing as a key deficit in multiple sclerosis: implications for rehabilitation. J Neurol Neurosurg Psychiatry. 1999;67(5):661–3.
49. Talebi M, Majdi A, Kamari F, Sadigh-Eteghad S. The Cambridge neuropsychological test automated battery (CANTAB) versus the minimal assessment of cognitive function in multiple sclerosis (MACFIMS) for the assessment of cognitive function in patients with multiple sclerosis. Mult Scler Relat Disord. 2020;43: 102172.
50. Abraham A. Gender and creativity: an overview of psychological and neuroscientific literature. Brain Imaging Behav. 2016;10(2):609–18.
51. Sartori E, Edan G. Assessment of cognitive dysfunction in multiple sclerosis. J Neurol Sci. 2006;245(1–2):169–75.
52. Oset M, Stasiolek M, Matysiak M. Cognitive dysfunction in the early stages of multiple sclerosis-how much and how important? Curr Neurol Neurosci Rep. 2020;20(7):22.
53. Swirsky-Sacchetti T, Field HL, Mitchell DR, Seward J, Lublin FD, Knobler RL, et al. The sensitivity of the mini-mental state exam in the white matter dementia of multiple sclerosis. J Clin Psychol. 1992;48(6):779–86.
54. Scherer P. Cognitive screening in multiple sclerosis. J Neurol. 2007;254(Suppl 2):li26–9.
55. Benedict RH, Fischer JS, Archibald CJ, Arnett PA, Beatty WW, Bobholz J, et al. Minimal neuropsychological assessment of MS patients: a consensus approach. Clin Neuropsychol. 2002;16(3):381–97.

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