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The Expanded Disability Status Scale Score and Demographic Indexes Are Correlated with the Severity of Cognitive Impairment in Multiple Sclerosis Patients

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Background and Purpose Cognitive impairment (CI) is a common symptom of multiple sclerosis (MS). Although demographic and clinical factors contribute to MS-dependent CI, previous findings have been inconsistent. This study aimed to identify the cognitive domains that are impaired in MS patients, and to determine the impacts of the Expanded Disability Status Scale (EDSS) score and other clinical and demographic factors on them domains.

Methods This study enrolled 115 MS patients. Cognitive performance was assessed using the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) battery. CI severity was assessed based on the number of impaired tasks in the MACFIMS battery, with impairment in two or more tasks defined as CI cases. Correlation analysis was used to determine whether factors including current age, age at disease onset, EDSS score, disease duration, relapse rate, and education level affect the severity of CI.

Results The scores on the Paced Auditory Serial Addition Test and Delis-Kaplan Executive Function System were the most and least affected, respectively. EDSS score (r=0.438, p<0.001), current age (r=0.393, p<0.001), and disease duration (r=0.486, p<0.001) were positively correlated with CI severity, whereas education level (r=-0.527, p<0.001) had a negative correlation with CI severity, and age at disease onset and relapse rate were not correlated with CI severity (r=0.150 and p=0.107, and r=0.052 and p=0.530, respectively). However, all variables (except EDSS score) significantly predicted CI severity in a multiple regression model (p<0.001, r=0.668).

Conclusions Information processing speed and working memory were the most commonly affected cognitive domains in the present MS patients. CI severity had strong positive correlations with current age, EDSS score, and disease duration, and a negative correlation with education level. The relapse rate and age at disease onset were not correlated with CI severity.

Key Words multiple sclerosis, neuropsychological assessment, cognitive impairment, MACFIMS.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) that damages the brain and spinal cord via various pathophysiological mechanisms. MS is the most common neurological complication in young adults, which affecting at least 2.5 million people worldwide up to 2018.[1] Disease symptoms vary with the location and extent of the damage in the CNS, which is the characteristic feature of MS.[2-5] Although cognitive impairment (CI) is a common symptom in MS, it is usually disregarded in clinical evaluations.[6,7] The CI frequency has been estimated to be between 40% and 70%.[8-12] Although CI is more common in progressive forms of the disease, it is also seen in the ear-

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ly stages of MS and clinically isolated syndrome (CIS). The common risk factors for CI in MS are physical disability as measured using the Expanded Disability Status Scale (EDSS), current age, sex, cognitive reserve, location and extent of pathological damage, affective disturbance, and genetic factors.[13-15]

While CI has been reported in MS for more than 160 years, a test for its evaluation has only been standardized over the last 2 decades.[16,17] The Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) is currently the gold standard for the cognitive assessment of MS patients.[18,19] The MACFIMS battery includes the following seven tests covering five cognitive domains: Controlled Oral Word Association (COWAT), Judgment of Line Orientation (JLO), second edition of the California Verbal Learning Test (CVLT-II), Brief Visuospatial Memory Test–Revised (BVMT-R), Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition Test (PASAT), and Delis-Kaplan Executive Function System (DKEFS). The information processing speed (IPS) and executive function are the most common cognitive domains reported. The frequency of impairment in the other cognitive domains has varied between studies due to the use of different methodologies and neuropsychological (NP) batteries.[19-22]

The clinical and demographic factors that impact on CI in MS remain controversial. There have been some reports of cognitive status being weakly related to EDSS score and disease duration,[23] but there have also been contradictory reports. The same is true for the relationship between relapse rate and patient age.[19,24-26] Studying CI in MS is essential for establishing better treatment plans. Recognition of the factors influencing CI is necessary for this purpose. Due to the discrepancies between the reports of CI in MS, further studies with a standardized battery are needed to reach a consensus. Also, the controversy about the impacts of demographic factors on the severity of CI makes further evaluations of these items necessary.

The present study assessed all cognitive domains of the MACFIMS battery when evaluating CI in patients. The following parameters were evaluated: current age, age at disease onset, disease duration, EDSS score, relapse rate, first clinical presentation, and education level.

METHODS

Participants

This study involved 118 MS patients in the MS clinic in the Tabriz University of Medical Science between October 1, 2018 and January 31, 2020. We randomly selected patients from those who were referred to the hospital clinic. Three patients who met the inclusion criteria were excluded due to fatigue and dissatisfaction during the middle portion of the test. The study was approved by the Ethics Committee of Tabriz University of Medical Sciences (Approval code: IR.TBZMED.REC.1397.791), and written informed consent was obtained from all of the patients before the study.

The McDonald (2017 revised) diagnostic criteria were used for detecting MS patients.[27] The included patients had no other neurological disease, a literacy level above ninth grade, were fluent in Persian, and were aged 18–60 years. The exclusion criteria were psychiatric disorders, major depressive disorder (assessed using the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders), learning disability, history of alcohol abuse, receiving corticosteroid pulse therapy or MS relapse within 12 weeks of the assessment, systemic disease or severe disability, presence of physical impairments that could interfere with NP testing, or presence of CIS. Depression was assessed using the Beck Depression Inventory Fast Screen questionnaire. All patients were receiving routine MS treatment, and we did not exclude patients based on their medications.

To ensure cross-cultural adaptation and normal range attainment, a previously validated Persian version of the MACFIMS battery was used.[28]

NP assessment using the MACFIMS battery

The MACFIMS battery is a sensitive and valid instrument for the routine NP assessment of MS patients.[19] The battery took about 90 minutes to administer and included the following tasks: CVLT-II to assess auditory or verbal episodic memory, SDMT to assess visual processing speed and working memory, PASAT to evaluate auditory processing speed and working memory, BVMT-R to assess visual or spatial episodic memory, COWAT to assess expressive language, DKEFS to assess executive function, and JLO to evaluate spatial processing. Impairment was defined as a score that was at least 1.5 SDs below the mean normative value for each cognitive test. The CI severity was assessed based on the number of impaired tasks in the MACFIMS battery. CI was defined as failure on two or more tasks of the MACFIMS battery.

Statistical analyses

Data were analyzed using SPSS statistical software (version 23.0, IBM Corp., Armonk, NY, USA). Descriptive data are presented using number (frequency) and mean±SD values. Spearman's rank correlation was applied for correlation analyses. Multiple regression analysis was used to test whether the investigated indexes can predict the severity of CI in a merged model. Student's *t*-test was applied to compare means between two groups. The Mann-Whitney used to compare

frequencies. Graphs were plotted using GraphPad Prism (version 6.01, GraphPad Inc., La Jolla, CA, USA). In all comparisons, $p<0.05$ was considered statistically significant.

RESULTS

Our study included 115 patients (35 males and 80 females) aged 34.13±9.80 years (range, 18–60 years) with an EDSS score of 2.00±1.94 (range, 0–7.5), a disease duration of 86.70±64.52 months (range, 8–264 months), and an education level of 13.40±2.63 years (range, 9–19 years). The 115 tested patients comprised 7 (6.1%) classified as primary-progressive multiple sclerosis (PPMS), 21 (18.26%) as secondary-progressive multiple sclerosis (SPMS), and 87 (75.65%) as relapsing-remitting multiple sclerosis (RRMS). The largest age group comprised patients aged 20–30 years. Table 1 lists the detailed demographic and basic clinical data of the included patients.

Outcome on NP tasks

The scores on CVLT-II, PASAT, SDMT, BVMT-R, COWAT, DKEFS, and JLO along with the corresponding normal cutoffs of the Iranian normative data are reported in Table 2. The mean score of all tasks differed significantly between CI patients and patients with no cognitive impairment (NCI) ($p<0.001$).

The overall prevalence of CI was 30.4%, and the frequency of impairment was significantly lower in the NCI group

Table 1. Detailed demographic and basic clinical data of the included multiple sclerosis cases

Parameter	All patients (*n*=115)	RRMS (*n*=87)	PPMS/SPMS (*n*=28)
Sex, male/female	35/80	26/65	9/15
Age, years	34.13±9.80	32.60±7.50	43.75±7.31
Age at onset, years	27.15±8.05	25.96±7.55	31.66±8.47
Disease duration, months	86.70±64.52	65.66±53.23	147.50±62.04
EDSS score	2.00±1.94	1.51±1.32	3.70±1.68
Education level, years	13.40±2.63	13.82±2.56	11.83±2.29
Relapse rate, %	3.10±2.71	2.33±2.42	4.08±3.89 (only SPMS)
BDI-FS, score	5.71±3.63	5.74±3.66	5.57±3.59
DMT			
HDHF	22 (19.13)	20 (89.98)	2 (7.14)
LDLF	10 (8.69)	10 (11.49)	0 (0)
Dimethyl fumarate	28 (24.34)	26 (29.88)	2 (7.14)
Fingolimod	17 (14.78)	11 (12.64)	6 (21.42)
Natalizumab	8 (6.95)	8 (9.19)	0 (0)
Rituximab	25 (21.73)	8 (9.19)	17 (60.71)
No DMT	5 (4.34)	4 (4.59)	1 (3.57)

Data are Mean±SD or *n* (%).
BDI-FS: Beck Depression Inventory Fast Screen, DMT: disease-modifying therapy, EDSS: Expanded Disability Status Scale, HDHF: high dose, high frequency, LDLF: low dose, low frequency, MS: multiple sclerosis, PPMS: primary-progressive multiple sclerosis, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary-progressive multiple sclerosis.

Table 2. Score on each task of MACFIMS and the cutoff of the normative data

Cognitive test	Cutoff[28]	All patients	CI	NCI	*p*
CVLT-II	42.62	50.37±11.73	8.80±2.88	12.76±2.20	<0.001
PASAT	33.71	37.06±11.67	26.60±12.39	41.65±7.79	<0.001
SDMT	30.86	45.92±14.06	32.60±8.10	51.75±12.00	<0.001
BVMT-R	13.94	23.74±9.04	14.00±8.58	28.01±5.08	<0.001
COWAT	15.38	29.95±11.49	21.65±9.51	33.58±10.37	<0.001
DKEFS	15.56	34.34±10.30	25.11±9.29	38.38±7.85	<0.001
JLO	15.12	20.41±5.54	15.68±5.45	22.48±4.15	<0.001

Data are mean±SD values. CI was defined as a score that was at least 1.5 SDs below the mean normative value for each cognitive test.
BVMT-R: Brief Visuospatial Memory Test-Revised, CI: cognitive impairment, COWAT: Controlled Oral Word Association Test, CVLT-II: second edition of the California Verbal Learning Test, DKEFS: Delis-Kaplan Executive Function System, JLO: Judgment of Line Orientation, MACFIMS: Minimal Assessment of Cognitive Function in Multiple Sclerosis, NCI: no cognitive impairment, PASAT: Paced Auditory Serial Addition Test, SDMT: Symbol Digit Modalities Test.

than the CI group for all MACFIMS tasks (all $p<0.01$). The tasks and domains with the greatest impairment were auditory processing speed and working memory as evaluated by PASAT (34.8%), followed by episodic memory (auditory or verbal) and learning as evaluated by CVLT-II (26.1%). The frequency of CI was 71.4% in PPMS, 70.6% in SPMS, and 19.8% in RRMS. The extent of the involved cognitive domains and the scores on CVLT-II, PASAT, SDMT, BVMT-R, COWAT, DKEFS, and JLO in RRMS, PPMS, and SPMS are reported in Table 3. The score on all tasks except JLO ($p=0.38$) differed significantly ($p<0.05$) among RRMS and the progressive forms of MS.

Correlations of demographic data with MAKFIMS-related tasks and CI severity

Spearman's analysis revealed that the EDSS score, disease duration, and the demographic parameters of current age, age at disease onset, relapse rate, and education level were significantly correlated with the outcomes of MACFIMS-related tasks. The detailed data are presented in Table 4. The

Table 3. Frequencies of impaired tasks and scores in MACFIMS tasks according to multiple sclerosis types

	Frequency of impairment			Score		
	PPMS (*n*=7)	SPMS (*n*=21)	RRMS (*n*=87)	RRMS	SPMS/PPMS	*p*
CI (multiple domains)	5 (71.4)	12 (70.6)	18 (19.8)			
CVLT-II	5 (71.4)	6 (35.3)	19 (20.9)	52.05±11.54	44.00±10.36	0.02
PASAT	5 (71.4)	10 (58.8)	25 (27.5)	38.63±10.91	31.12±12.75	0.05
SDMT	3 (42.9)	7 (41.2)	7 (7.7)	48.89±13.24	34.66±11.25	<0.01
BVMT-R	4 (57.1)	7 (41.2)	6 (6.6)	24.40±6.90	13.66±8.93	<0.01
COWAT	4 (57.1)	4 (23.5)	3 (3.3)	21.65±11.28	23.50±10.05	0.02
DKEFS	0 (0.0)	4 (23.5)	2 (2.2)	36.29±9.12	26.95±11.32	<0.01
JLO	3 (42.9)	6 (35.3)	12 (13.2)	20.96±5.05	18.33±6.82	0.38

Data are *n* (%) or mean±SD values.
BVMT-R: Brief Visuospatial Memory Test-Revised, CI: cognitive impairment, COWAT: Controlled Oral Word Association Test, CVLT-II: second edition of the California Verbal Learning Test, DKEFS: Delis-Kaplan Executive Function System, JLO: Judgment of Line Orientation, MACFIMS: Minimal Assessment of Cognitive Function in Multiple Sclerosis, NCI: no cognitive impairment, PASAT: Paced Auditory Serial Addition Test, PPMS: primary-progressive multiple sclerosis, RRMS: relapsing-remitting multiple sclerosis, SDMT: Symbol Digit Modalities Test, SPMS: secondary-progressive multiple sclerosis.

Table 4. Correlations of MACFIMS-related tasks with evaluated indexes

	CVLT-II	PASAT	SDMT	BVMT-R	COWAT	DKEFS	JLO
Current age							
r	-0.296**	-0.317**	-0.389**	-0.377**	-0.179	-0.302**	-0.215*
p	0.001	0.001	<0.001	<0.001	0.056	0.001	0.021
Age at onset							
r	-0.180	-0.160	-0.183*	-0.206*	-0.117	-0.124	-0.102
p	0.055	0.089	0.050	0.027	0.212	0.186	0.277
Education level							
r	0.291**	0.329**	0.407**	0.462**	0.515**	0.542**	0.447**
p	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
EDSS score							
r	-0.269**	-0.248**	-0.496**	-0.395**	-0.299**	-0.375**	-0.227*
p	0.004	0.008	<0.001	<0.001	0.001	<0.001	0.015
Disease duration							
r	-0.239*	-0.289**	-0.353**	-0.384**	-0.163	-0.357**	-0.244**
p	0.010	0.002	0.001	<0.001	0.081	<0.001	0.009
Relapse rate							
r	-0.002	-0.001	-0.048	0.011	0.001	-0.156	-0.100
p	0.984	0.995	0.614	0.909	0.995	0.096	0.287

Data are Spearman's *r* values.
*$p<0.05$, **$p<0.01$.
BVMT-R: Brief Visuospatial Memory Test-Revised, COWAT: Controlled Oral Word Association Test, CVLT-II: second edition of the California Verbal Learning Test, DKEFS: Delis-Kaplan Executive Function System, EDSS: Expanded Disability Status Scale, JLO: Judgment of Line Orientation, MACFIMS: Minimal Assessment of Cognitive Function in Multiple Sclerosis, PASAT: Paced Auditory Serial Addition Test, SDMT: Symbol Digit Modalities Test.

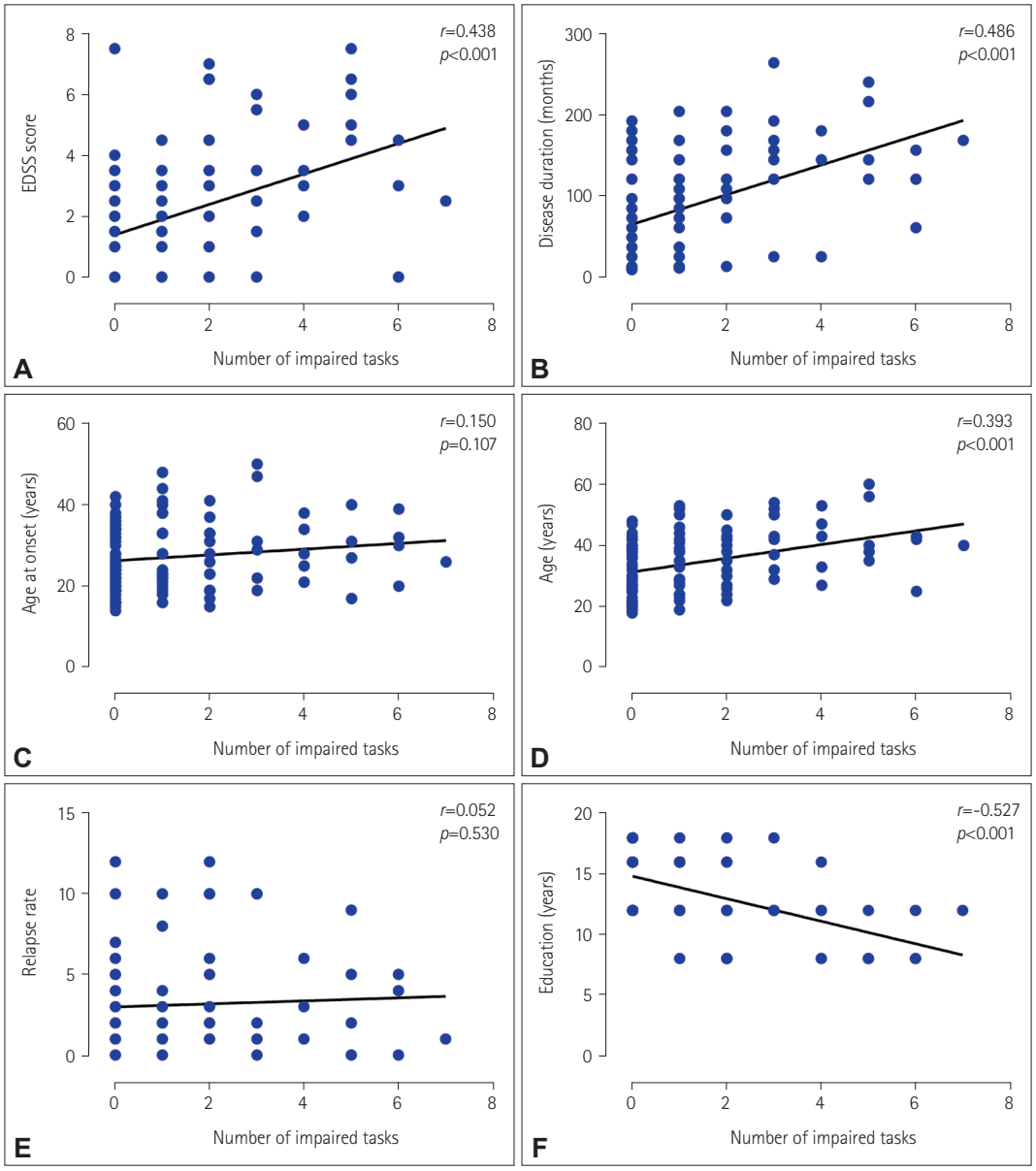

Fig. 1. Correlations between the severity of cognitive impairment (quantified as the number of impaired tasks) and Expanded Disability Status Scale (EDSS) score (A), disease duration (B), age at onset (C), current age (D), relapse rate (E), and education level (F).

age at disease onset only impacted the performance on SDMT and BVMT-R tasks. The relapse rate was not correlated with the impaired cognitive domains. Moreover, Spearman's analysis revealed correlations between increasing age and CI severity (defined as the number of tests failed) (r=0.393, p<0.001), disease duration (r=0.486, p<0.001), and EDSS score (r=0.438, p<0.001). The education level was negatively correlated with CI severity (r=-0.527, p<0.001) (Fig. 1), while CI severity was not correlated with the age at disease onset (r=0.150, p=0.107) or the relapse rate (r=0.052, p=0.530).

Multiple regression model indicated that current age, age at disease onset, EDSS score, disease duration, relapse rate, and education level predicted the CI severity [$F(5, 109)$=17.60, p<0.001, r=0.668]. All variables except the EDSS score contributed significantly to the prediction (p<0.01).

Demographic and basic clinical data differences between CI and NCI

As indicated in Table 5, the current age, disease duration, education level, relapse rate, and EDSS score differed significantly between the CI and NCI groups, whereas the age at disease onset did not. Patients in the CI group were significantly older (39.28±9.81 years) than those in the NCI group (31.88±8.82 years) (p<0.001). The disease duration in the CI group (130.28±65.21 months) was significantly longer than that in the NCI group (67.63±54.48 months) (p<0.001). Re-

Table 5. Demographic and basic clinical parameters in multiple sclerosis patients with and without CI

Parameter	CI (*n*=35, 30.4%)	NCI (*n*=80, 69.6%)	*p*
Current age, years	39.28±9.81	31.88±8.82	<0.001
Age at onset, years	28.68±8.68	26.53±7.76	0.190
Disease duration, months	130.28±65.21	67.63±54.48	<0.001
Education level, years	11.20±2.99	14.77±2.34	<0.001
EDSS score	3.44±2.17	1.37±1.45	<0.001
Relapse rate, %	3.88±3.39	2.78±2.31	0.040

Data are mean±SD values.
CI: cognitive impairment, EDSS: Expanded Disability Status Scale, NCI: no cognitive impairment.

garding the impact of disease severity on CI, the EDSS score was lower in the NCI group (1.37±1.45) than in the CI group (3.44±2.17) (p<0.01). Moreover, the relapse rate in the CI group (3.88±3.39%) was significantly higher than that in the NCI group (2.78±2.31%) (p<0.05). The results in Table 5 indicate that a lower literacy was associated with a larger number of impaired cognitive tasks (p<0.001).

DISCUSSION

CI significantly impacts the quality of life of MS patients, and the availability of accurate data is essential for setting up effective treatment plans. This study found that the rate of CI was about 30.4%. The frequency of impaired domains of MACFIMS-related cognitive tasks among MS patients was significantly higher in CI cases than in NCI cases. Moreover, the severity of CT was significantly correlated with current age, disease duration, education level, and EDSS score. Also, the EDSS score, disease duration, education level, relapse rate, and current age were higher in the CI group than the NCI group.

We found that the percentage of subjects with CI was highest in PPMS (71.4%), followed by SPMS (70.6%) and RRMS (19.8%). Different types of pathological process drive these different components of the disease, with PPMS being heralded by neurodegeneration that is often more closely linked to cognitive deficit.[29,30] The rate of CI is reportedly lower among RRMS and higher among the progressive forms of MS.[31-33]

There is controversy in the literature regarding the rate of CI in MS patients, with the reported overall rate ranging widely from about 20% to 70%. This variability could arise from methodological differences between studies such as in the CI definition criteria, study design, data sources, and NP tests.[23,34,35] Rao et al.[23] and Solari et al.[36] found that the rate was about 43%. Patti et al.[37] and Cáceres et al.[29] found that the frequency of CI using the Brief Repeatable Battery of Neuropsychological Tests was about 44%, and the mean disease duration in both studies was 8.6 years. Another study that applied the MACFIMS battery to 107 RRMS patients found that 65.4% of patients had impairment in at least in 1 test, and defined this as CI.[21] In contrast, in accordance with the research of Benedict et al.,[19] the present study defined impairment on two or more tests as CI. The rate of CI in our study based on the MACFIMS test of 30.4% is slightly lower than the rates found in population-based studies. This difference could be due to the lower mean age, higher education level, and shorter disease duration in our study.

The IPS and especially including the auditory processing speed and working memory as evaluated by PASAT were the most frequently impaired domains in all three clinical types. The results are supported by previous reports of the most affected cognitive domains being IPS, verbal/visuospatial memory, and executive function. It has been shown that the number of affected cognitive domains is larger in SPMS and PPMS than in RRMS.[38,39] Also, working memory, attention, executive function, and verbal episodic memory are affected more in the progressive subtypes of MS than in RRMS.[14,40-43]

The effect of disease duration on CI has been assessed in a small number of studies. The longitudinal study of Amato et al.[10,44] suggested that disease progression tends to extend the number of cognitive deficits. On the other hand, some cross-sectional studies have found only a weak correlation[45] or no correlation between disease duration and CI.[46,47] In our study, the disease duration had a significant positive correlation with CI severity, and the mean disease duration was significantly longer in the CI group than in the NCI group.

Very few studies have investigated the relationship between age and literacy with CI. There are some reports of significant correlations of older age and low education level with CI.[10,14,48] Ruano et al.[14] found that CI was significantly associated with age, disease duration, and EDSS score, but not with sex and education level. In our study, a lower level of literacy was correlated with a higher severity of CI. The literature contains strong evidence for an association between the disability level as measured by the EDSS score and CI,[10,14,23,29,32,48] and the present study found a positive correlation between EDSS score and CI severity.

Like most studies, the present study was subject to some limitations. First, we assessed mainly RRMS cases, with only about 20% of the patients having the progressive forms of MS. Second, the MACFIMS test is time-consuming, which restricted the size of the study population and hence also the statistical power of the evaluations; this characteristic would also restrict the ability to apply the battery in general clinical practice.

In conclusion, we found that the rate of CI was significant-

ly higher and that there were significantly more cognitive domains affected in the progressive forms of MS than in RRMS. The most commonly affected cognitive test was PASAT. A multiple regression model based on current age, age at disease onset, disease duration, relapse rate, and education level predicted CI in MS patients. A pairwise analysis demonstrated that CI severity is correlated with current age, EDSS score, disease duration, and education level, and so these items can be considered as risk/protective factors for CI in MS patients.

Author Contributions

Conceptualization: Mahnaz Talebi. Data curation: Negin Abbasi Garravnd. Formal analysis: Saeed Sadigh-Eteghad. Funding acquisition: Mahnaz Talebi. Investigation: Negin Abbasi Garravnd, Mahsa Feizollahi. Methodology: Saeed Sadigh-Eteghad. Project administration: Mahnaz Talebi. Resources: Saeed Sadigh-Eteghad. Software: Mahsa Feizollahi. Supervision: Mahnaz Talebi. Validation: Saeed Sadigh-Eteghad. Visualization: Mahsa Feizollahi. Writing—original draft: Mahnaz Talebi. Writing—review & editing: Saeed Sadigh-Eteghad.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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