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RESEARCH

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Evaluation of the determinants of cognitive dysfunction in patients with multiple sclerosis

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Abstract

Background: Cognitive dysfunction is common among patients with multiple sclerosis (MS); however, the determinants of cognitive dysfunction are still unknown. This study aimed to investigate the determinants of cognitive dysfunction in a relatively large sample of patients with MS for rapid screening.

Results: Fifty-three patients (33.6%) had cognitive dysfunction. According to the Wechsler Memory Scale, patients with relapsing-remitting MS (RRMS) and patients with progressive MS (PMS) had significantly lower scores than the control group. Patients with RRMS compared to the control group were 76.73 ± 8.50 versus 105.58 ± 8.71 ($P < 0.01$), and patients with PMS compared to the control group were 72.56 ± 6.44 versus 105.58 ± 8.71 ($P < 0.01$). In patients with RRMS, the factors affecting the emergence of cognitive dysfunction included disability, fatigue, depression, and duration of illness, whereas in patients with PMS, just the disability variable was related to the presence or absence of cognitive dysfunction.

Conclusions: Our findings showed that disability, fatigue, depression, and duration of illness were factors associated with cognitive dysfunction in patients with RRMS. Proper identification of these factors can be helpful in the screening of cognitive dysfunction in this population.

Keywords: Cognition, Multiple sclerosis, Neuropsychology, Memory

Background

Multiple sclerosis (MS) is a common disease in the central nervous system caused by the degeneration of myelin axons. This impairment can disturb the ability of some parts of the nervous system that are responsible for communication and create many physical and cognitive signs and symptoms [1, 2]. MS appears in several forms, and its symptoms emerge either as staged recurrence (in relapsing forms) or over time (in intermittent forms) [3]. This disease often appears at a young age, and its onset is usually between the ages of 20 and 40 [4].

Physicians are more inclined to examine the physical disabilities of MS; however, over the past few decades, there has been a lot of awareness regarding cognitive dysfunctions in patients with MS. The involvement of various cognitive domains such as memory, processing speed, attention, and executive function can develop in the early stages of the disease, and even despite the lack of progress of physical dysfunction, MS-induced cognitive dysfunctions can accelerate over time [4, 5].

Many hypotheses have been proposed regarding the factors affecting the development of MS-induced cognitive dysfunctions [6, 7]. For example, fatigue and depression in patients with MS are among the factors whose effects on cognitive function can often be discussed and challenged. Individuals with MS may experience extreme fatigue after performing cognitive tasks [4, 8]. Moreover, the type or stage of MS can create a variety of cognitive dysfunctions of varying severity [9]. Other factors such as anxiety, disability, education, and age are also among other areas of interest for researchers [10, 11]. Even gender may play a role in this issue. Some studies have shown that gender may affect cognitive function, and men with

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MS may exhibit poorer cognitive abilities, especially in auditory-verbal memory [12]. In contrast, another study showed that women had lower scores on cognitive tests (the Selective Reminding Test-Long Term Storage (SRT-LTS) and the Paced Auditory Serial Addition Test-3 (PASAT-3) than men [13]. If the factors affecting cognitive dysfunctions are identified, they can be treated using psychotherapy. In addition, cognition can be improved through rehabilitation and other treatments, but the choice of appropriate treatment depends on the proper diagnosis of the underlying cause of cognitive dysfunction [4].

Few studies have been performed on the determinants of cognitive dysfunction in patients with multiple sclerosis [4, 7, 14]. Most of the published studies were not performed on large samples of patients with MS, so there is limited research on large sample sizes to reach a consensus in this domain. This study aimed to investigate the determinants of cognitive dysfunctions in a relatively large sample of patients with MS for screening of these patients. In the present study, the authors hypothesized a relationship between the type of MS disease and cognitive dysfunction. Based on this, it was also assumed that there is a relationship between clinical and demographic factors affecting cognitive dysfunction and the type of multiple sclerosis.

Methods

This study investigated 186 patients with MS who were referred to the MS Clinic of Booali Hospital in Qazvin for follow-up and were under care in this clinic from April 2017 to January 2018. Concerning MS status, 32 patients (17.6%) were classified as individuals with progressive MS (PMS), and 150 patients (82.4%) were categorized as individuals with relapsing-remitting MS (RRMS). This study was performed according to the research priorities of Qazvin University of Medical Sciences, had no ethical problems, and was approved by the ethics committee of the university.

The inclusion criteria in this study included the diagnosis of MS by McDonald's revised diagnostic criteria [15], not having underlying diseases, not using psychotropic drugs, not having previous cognitive learning disabilities, not having serious vision and hearing problems, no previous history of psychiatric dysfunctions, complete familiarity with the Persian language, and no history of drug or alcohol use. Patients who did not have enough tendency and motivation to participate in the study were also excluded from the research. Of the 186 patients under study, 4 patients did not have the motivation to participate in the study, so they were excluded. To compare cognitive dysfunction between patients with MS and the general population, the assessment was performed in healthy individuals, as well. One hundred eighty-six healthy individuals were selected as the control group. These individuals were selected from the local community through advertising. All of them were Persian speakers, and 126 individuals (70%) were female. Control group participants were screened based on clinical interviews. The screening criteria in this study were the absence of neurological and psychiatric disorders and alcohol and drug abuse. In addition, those who had serious medical diseases such as diabetes and hypertension were also excluded from the study. It should be noted that 6 individuals in the control group did not have the motivation to participate in the study, so they were excluded.

Data collection method

The data for the present study can be classified into three general groups. The first group included data on demographic and clinical information, including age, gender, education level, and duration of illness. The second group involved cognitive data (Wechsler Memory Scale – 3rd Edition (WMS-III)), and the third group included the data related to the evaluation of neuropsychological status, including the Beck Depression and Anxiety Scales, the Fatigue Severity Scale (FSS), and the Expanded Disability Status Scale (EDSS).

Cognitive data

This study used the WMS-III to assess patients' cognitive function. Due to its characteristics, this scale is considered the main component of any complete cognitive assessment. This scale was designed for people 16–89 years of age and took 15–20 min to complete [16]. A study in Iran showed an internal consistency of 0.85 for the WMS-III subscales and Cronbach's alpha of 0.76 to 0.83 for the WMS-III indices [16]. According to the criteria in previous articles, in this study, we used a score lower than 70 on the WMS to indicate the presence of cognitive dysfunction.

The assessment of neuropsychological status

To evaluate the effect of fatigue severity on cognitive dysfunction stemmed from MS, the FSS was used [17]. This questionnaire consists of 9 items that examine the symptoms related to daily life activities such as physical function, work, and family and social life. Each item is scored on a 1- to 7-point scale and assesses fatigue in general. A score of 4 or higher indicates severe fatigue. A study by Shahvaroughi et al. investigated the reliability of the Persian version of the FSS in subjects with multiple sclerosis. All the participants found the FSS–P item precise in pilot testing. The intraclass correlation coefficient (ICC) was reported at 0.93 for the total score that showed high repeatability of (FSS), and Cronbach's

alpha was reported at 0.96 [18]. Mental health status was assessed using the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI). The reliability and validity of the Persian version of the questionnaire, which is a powerful tool for measuring depression and anxiety, have been determined in previous studies [19]. Finally, the disability status was assessed using the EDSS, which estimates the degree of disability in patients with MS [20]. Persian version of this scale is widely used in national and internal literature [20, 21].

Statistical analysis

After data collection, the results were analyzed using SPSS. The Kolmogorov-Smirnov test was used to check the normality of the data. Frequency and percentage were calculated for stratified variables, and mean and standard deviation were calculated for continuous variables. To consider the different characteristics of the disease, patients were divided into two subgroups: RRMS and PMS. These three groups (PMS, RRMS, and control) were compared according to clinical and demographic variables using the analysis of variance (ANOVA) test. Post hoc tests (Tukey tests) were also used, where appropriate. The chi-square test was used to compare the stratified variables, and the independent *t*-test and ANOVA test were used to compare the continuous variables. To determine the factors affecting the WMS-III test scores in patients with MS, a multiple regression analysis was performed to identify significant predictors of the sensitive cognitive dysfunction test in MS. Logistic regression analysis was used to determine the effect of significant demographic and clinical variables on cognitive dysfunctions. The logistic regression models used in this study were entry methods. Due to the different clinical features between RRMS and PMS, regression analysis was divided into two different analyses. A P value < 0.05 was utilized as the significance level.

Results

Among the patients referred to the clinic, 53 patients with MS (33.6%) had cognitive dysfunction, and 126 patients (64.7%) had no cognitive dysfunction. The demographic and clinical characteristics of participants in the PMS, RRMS, and control groups are shown in Table 1. The groups were different regarding education level (P < 0.001) so the education level of the PMS group was significantly lower than that of the control group ($F = 6.13$, $P < 0.001$). PMS and RRMS groups had more fatigue compared to the control group ($F = 49.02$, $P < 0.001$). Concerning depression, both PMS and RRMS groups were higher than the control group ($P < 0.001$). In addition, the mean depression of the PMS group was significantly higher than the RRMS group ($F = 6.13$, $P < 0.001$). Regarding other variables (gender, age, and anxiety), no significant differences were observed between the different groups ($P > 0.5$).

Concerning the WMS-III, patients with RRMS and PMS had significantly lower scores compared to the control group, as patients with RRMS compared to the control group were 76.73 ± 8.05 versus 105.58 ± 8.71 (P < 0.01), and patients with PMS compared to the control group were 72.56 ± 6.64 versus 105.58 ± 8.71 ($P < 0.01$). Moreover, patients with RRMS also had significantly lower WMS-III scores than those with PMS (72.56 ± 6.64 versus 76.73 ± 8.05, $P < 0.001$) (Fig. 1).

Regression analysis regarding the WMS-III score as the dependent variable showed that the significant predictors included education ($B = -0.95$, $P = 0.04$),

Table 1 The demographic and clinical characteristics of participants

Variable	PMS (32)	RRMS (150)	CONTROL (180)	*F* or *t* or *x2*	*P*-value
Gender				$x2 = 4.32$	0.11
Male	8 (25%)	30 (20%)	54 (30%)		
Female	24 (75%)	120 (80%)	126 (70%)		
Age (years)	39.62 ± 7.32	38.52 ± 7.40	38.60 ± 7.95	$F = 0.28$	0.75
Education (years)	9.25 ± 2.31	10.06 ± 2.02	10.65 ± 2.53	$F = 6.13^{\pi}$	0.002
Hospitalization duration (years)	5.50 ± 2.71	4.68 ± 2.84		$t = 1.49$	1.37
Disability	3.87 ± 2.29	2.60 ± 1.87		$t = 3.35$	0.001
Fatigue	39.50 ± 11.79	35.96 ± 13.73	24.13 ± 10.60	$F = 49.02^{\pi\text{Þ}}$	$P < 0.001$
Anxiety	13.81 ± 12.33	10.28 ± 8.27	10.06 ± 12.18	$F = 1.69$	0.185
Depression	41.56 ± 15.16	35.20 ± 13.23	27.33 ± 7.78	$F = 34.09^{\text{Ŧ}\pi\text{Þ}}$	$P < 0.001$

Ŧ PMS is significantly different from RRMS

π PMS is significantly different from the control group

Þ RRMS is significantly different from the control group

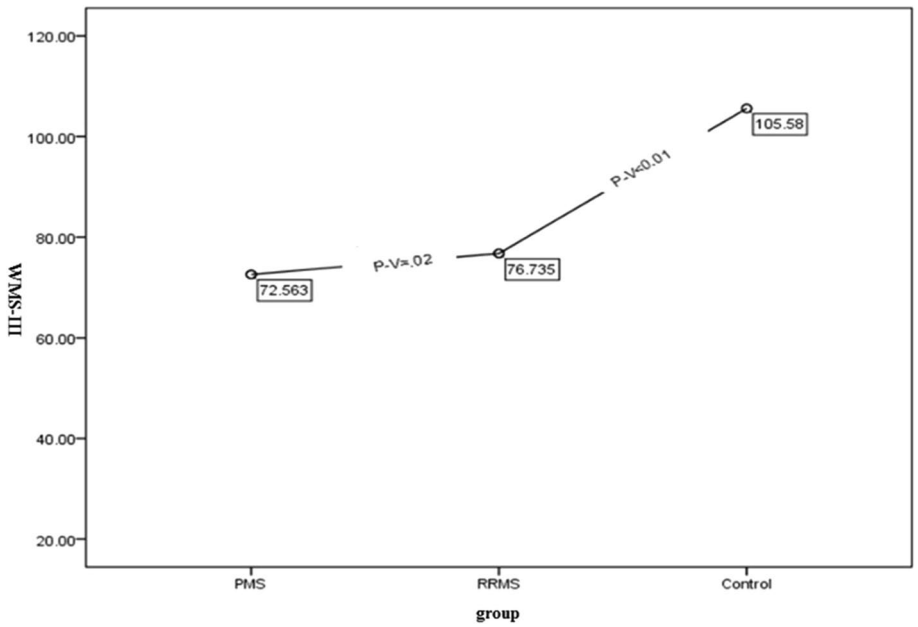

Fig. 1 Comparison of different groups in terms of WMS-III

disability ($B = -0.98$, $P = 0.04$), fatigue ($B = -0.34$, $P < 0.001$), depression ($B = -0.11$, $P = 0.015$), and duration of illness ($B = -0.04$, $P = 0.004$), with an adjusted $R^2 = 0.608$.

Table 2 presents the logistic regression analysis to determine the factors affecting cognitive dysfunctions in patients with RRMS. Among the potential predictors, the variables of disability, fatigue, depression, and duration of illness were associated with the presence or absence of cognitive dysfunctions in patients with MS. After adjusting the regression model by age, gender, and education, despite a slight change in the odds ratio of the mentioned variables, no significant difference was observed in their significance pattern.

Table 3 presents the logistic regression analysis to determine the factors affecting cognitive dysfunction in patients with PMS. After the entry of potential predictors into the regression model, only disability was related to the presence or absence of cognitive dysfunction. After adjusting the regression model by age, gender, and education, despite a slight change in the odds ratio of the mentioned variables, no significant difference was observed in their significance pattern.

Discussion

To date, most published studies on the factors affecting cognitive dysfunction in patients with MS have not included large samples of patients with this disease. This is one issue that has led to the lack of clear evidence in this regard [4, 7, 14]. In this study, a relatively large sample of patients with MS was examined concerning cognitive dysfunction and the factors affecting the presence of these dysfunctions. The results showed that among patients with MS, 53 patients (33.6%) had cognitive dysfunction. Studies have shown

Table 2 Logistic regression analysis to determine the factors affecting cognitive dysfunctions in patients with RRMS

Variable	*B*	*P*-value	Odds ratio (95% CI)	*B*	*P*-value	Odds ratio (95% CI)
	Cognitive dysfunction A			Cognitive dysfunction B		
Disability	0.31	0.01	1.36 (1.10–1.70)	0.344	0.004	1.41 (1.15–1.78)
Fatigue	0.06	$P < 0.001$	1.05 (1.03–1.10)	0.06	0.001	1.06 (1.02–1.09)
Depression	0.36	$P < 0.001$	1.43 (1.20–1.71)	0.36	$P < 0.001$	1.43 (1.19–1.73)
Duration of illness	0.27	$P < 0.001$	1.31 (1.14–1.51)	0.3	$P < 0.001$	1.35 (1.16–1.56)

A = Cognitive dysfunction without adjustment

B = Cognitive dysfunction with adjustment of age, gender, and education

Table 3 Logistic regression analysis to determine the factors affecting cognitive dysfunctions in patients with PMS

Variable	Cognitive dysfunction A		Odds ratio (95% CI)	Cognitive dysfunction B		Odds ratio (95% CI)
	B	*P*-value		*B*	*P*-value	
Disability	0.766	0.03	2.15 (1.04–4.41)	0.902	0.008	2.46 (1.26–4.80)
Fatigue	0.088	0.075	1.09 (0.99–1.14)	0.129	0.250	1.13 (0.91–1.41)
Depression	0.053	0.173	1.05 (0.97–1.13)	0.022	0.586	1.02 (0.94–1.10)
Duration of illness	0.318	0.058	1.37 (0.99–1.90)	0.324	0.137	1.38 (0.92–2.11)

A = Cognitive dysfunction without adjustment

B = Cognitive dysfunction with adjustment of age, gender, and education

that the prevalence rate of cognitive dysfunction in patients with MS varies between 30 and 70% [13]. Differences in the prevalence rate of cognitive dysfunction can be due to the different statistical populations in various studies. Another reason is that cognitive dysfunctions in this domain are not usually evaluated overall but are merely measured in various areas such as attention, processing speed, or information.

Since patients with MS are usually divided into two separate groups due to different clinical profiles [22], the analysis was performed accordingly. After comparing the three groups (PMS, RRMS, and control), the results showed that cognitive dysfunction was higher in patients with PMS compared to those with RRMS and the control group. In a study, Eijlers et al. also obtained similar results [7].

The comparisons between the three groups concerning demographic variables showed that patients in the PMS group had lower education levels than the control group. Regarding other demographic variables (age and gender), no significant difference was observed among the three groups. Regarding clinical variables, patients in the PMS and the RRMS groups had higher levels of fatigue and depression compared to the control group. Therefore, patients with PMS in this study had more clinical issues and more severe cognitive dysfunction. Additionally, a significant portion of the WMS-III score was related to education, fatigue, depression, and duration of illness. As expected, education level, fatigue, depression, and duration of illness had inverse relationships to the WMS-III score; however, age and gender had no significant relationship to WMS-III. In another study, Sandi et al. investigated demographic and clinical variables in patients with MS and the resultant cognitive dysfunction [23], showing that the difference between males and females was significant ($P < 0.001$). They found that except for gender, no significant predictor determines cognitive dysfunction in males. However, in females, both the EDSS and education level had decisive roles in the rate of cognitive dysfunction. In a study by Ruano et al., the effect of age on cognitive dysfunctions in the different groups of patients with MS was examined [24]. The results indicated that patients with severe cognitive dysfunction were older. However, this relationship was not statistically significant, and from this point of view, its results are in line with the present study. Studies performed on the relationship between demographic criteria and cognitive dysfunction in MS have discrepant results [25, 26]. Part of this discrepancy may be due to the small sample size or differences in the individuals under study. Examining the effects of demographic criteria such as age, gender, and education level can give us a more complete picture of the causes of cognitive dysfunction [4].

The results concerning the effect of depression on cognitive dysfunction are contradictory, although it is believed that healthy individuals with depression are prone to cognitive dysfunction [25]. Previous studies in this regard have shown no association between depression and decreased cognitive function in patients with MS [27]. However, in line with the present research, new studies have provided reasons to justify these findings [4, 28].

To investigate the role of each factor in the presence or absence of cognitive dysfunctions, logistic regression analysis was used. Because of the different clinical profiles of the two groups RRMS and PMS, the final analysis was performed for the two groups separately. Logistic regression analysis for the RRMS group showed that significant predictors for cognitive dysfunctions included disability, fatigue, depression, and duration of illness. Therefore, these variables can be used as a screening tool to screen cognitive dysfunctions in patients with MS. Interestingly, when we performed these analyses with PMS patients, the only significant variable in the model was disability that had no significant change after adjusting for age, gender, and education. Perhaps the reason is due to the different clinical profiles between the two groups. Research has shown that, regardless of disability and depression, among the symptoms of MS, fatigue is one of the

most common symptoms that has been reported in more than 90% of patients [29] and is considered the worst symptom occurring in more than two-thirds of individuals with MS [30]. Contrary to this study, the results of Morrow et al.'s study showed no association between fatigue and cognitive dysfunction in MS [31]. Perhaps one of the reasons for the non-significance of clinical variables in these studies is that they have serious methodological problems (drawbacks) such as a small statistical sample and the use of inappropriate tools.

The limitation of the current study is related to its design. This analysis is an observational study in which no neuroimaging or genetic analysis has been performed. Therefore, performing studies involving neuroimaging and genetic factors, along with demographic and clinical data, can be very valuable.

Conclusions

This study shows that the type of MS and its duration and the level of depression, fatigue, and disability are the underlying factors related to cognitive dysfunction in this population. Proper identification of these factors can be effective in the screening of cognitive dysfunction in patients with MS and also will be effective in choosing the appropriate treatment and thus, through screening, will facilitate the treatment process of patients.

Abbreviations

MS: Multiple sclerosis; WMS-III: Wechsler Memory Scale – 3rd Edition; FSS: Fatigue Severity Scale; EDSS: Expanded Disability Status Scale; RRMS: Patients with relapsing-remitting MS; PMS: Patients with progressive MS.

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Authors' contributions

AJ: methodology, visualization, conceptualization, investigation, software, data curation, and writing—original draft. AS: conceptualization, methodology, software, visualization, investigation, supervision. NB: writing—reviewing and editing. The authors read and approved the final manuscript.

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Availability of data and materials

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

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Qazvin University of Medical Sciences, and the participation of individuals was subject to written consent.

Consent for publication

Written informed consent was obtained from the patients for the publication of this information and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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References

1. Pulido-Valdeolivas I, Andorra M, Gomez-Andres D, Nakamura K, Alba-Arbalat S, Lampert EJ et al (2020) Retinal and brain damage during multiple sclerosis course: inflammatory activity is a key factor in the first 5 years. Sci Rep 10(1):13333
2. Ferraro D, Guicciardi C, De Biasi S, Pinti M, Bedin R, Camera V et al (2020) Plasma neurofilaments correlate with disability in progressive multiple sclerosis patients. Acta Neurol Scand 141(1):16–21
3. Zuroff LR, Benjamins JA, Bar-Or A, Lisak RP (2021) Inflammatory mechanisms underlying cortical injury in progressive multiple sclerosis. Neuroimmunol Neuroinflamm 8(1):111
4. Oh J, Vidal-Jordana A, Montalban X (2018) Multiple sclerosis: clinical aspects. Curr Opin Neurol 31(6):752–759
5. Hassani M, Nadi MA, Sajjadian I (2019) Examining the effectiveness of the cognitive-emotional-social working memory training intervention of on cognitive emotion regulation of 5th grade female elementary school students in Tehran. J Instruct Eval 12(47):39–66
6. Amato MP, Prestipino E, Bellinvia A, Niccolai C, Razzolini L, Pasto L et al (2019) Cognitive impairment in multiple sclerosis: an exploratory analysis of environmental and lifestyle risk factors. PLoS One 14(10):e0222929
7. Eijlers AJC, Meijer KA, van Geest Q, Geurts JJG, Schoonheim MM (2018) Determinants of cognitive impairment in patients with multiple sclerosis with and without atrophy. Radiology. 288(2):544–551
8. Golan D, Doniger GM, Wissemann K, Zarif M, Bumstead B, Buhse M et al (2018) The impact of subjective cognitive fatigue and depression on cognitive function in patients with multiple sclerosis. Mult Scler 24(2):196–204
9. Brochet B, Ruet A (2019) Cognitive impairment in multiple sclerosis with regards to disease duration and clinical phenotypes. Front Neurol 10:261
10. Marrie RA, Patel R, Figley CR, Kornelsen J, Bolton JM, Graff L et al (2019) Diabetes and anxiety adversely affect cognition in multiple sclerosis. Multiple Sclerosis Relat Disord 27:164–170
11. Hassanshahi E, Asadollahi Z, Azin H, Hassanshahi J, Hassanshahi A, Azin M (2020) Cognitive function in multiple sclerosis patients based on age, gender, and education level. Acta Medica Iranica 58(10):500-507.
12. Rosti-Otajarvi E, Mantynen A, Koivisto K, Huhtala H, Hamalainen P (2013) Patient-related factors may affect the outcome of neuropsychological rehabilitation in multiple sclerosis. J Neurol Sci 334(1-2):106–111
13. Borghi M, Cavallo M, Carletto S, Ostacoli L, Zuffranieri M, Picci RL et al (2013) Presence and significant determinants of cognitive impairment in a large sample of patients with multiple sclerosis. PLoS One 8(7):e69820
14. Oset M, Stasiolek M, Matysiak M (2020) Cognitive dysfunction in the early stages of multiple sclerosis-how much and how important? Curr Neurol Neurosci Rep 20(7):22
15. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M et al (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 69(2):292–302
16. Tavakoli M, Barekatain M, Doust HT, Molavi H, Nouri RK, Moradi A et al (2011) Cognitive impairments in patients with intractable temporal lobe epilepsy. J Res Med Sci 16(11):1466–1472
17. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD (1989) The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 46(10):1121–1123

18. A'zimiyan M, Fallah-Pour M, Karimlou M. (2010) Fatigue Severity Scale (FSS): evaluation of reliability of the Persian version among persons with multiple sclerosis. Archives of. Rehabilitation. 10(4):0
19. Javadi M, Jourabchi Z, Shafikhani AA, Tajik E (2017) Prevalence of depression and anxiety and their association with body mass index among high school students in Qazvin, Iran, 2013-2014. Electron Physician 9(6):4655–4660
20. Moghaddasi M, Hosseini Nasab A, Shirali A, Soltan SM (2011) Evaluation of relation between the retinal nerve fiber layer and Expanded Disability Status Scale (EDSS) in patients with relapsing-remitting form of multiple sclerosis referring to Rasool Akram Hospital. Razi J Med Sci 18(87):36–43
21. Khodaveisi M, Ashtarani F, Mahjub H (2018) Correlations between severity of disease and quality of life in patients with multiple sclerosis in Hamadan. Jundishapur J Chronic Dis Care 7(3):e67005.
22. Eshaghi A, Riyahi-Alam S, Roostaei T, Haeri G, Aghsaei A, Aidi MR et al (2012) Validity and reliability of a Persian translation of the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS). Clin Neuropsychol 26(6):975–984
23. Sandi D, Biernacki T, Szekeres D, Fuvesi J, Kincses ZT, Rozsa C et al (2017) Prevalence of cognitive impairment among Hungarian patients with relapsing-remitting multiple sclerosis and clinically isolated syndrome. Multiple Sclerosis Relat Disord 17:57–62
24. Ruano L, Portaccio E, Goretti B, Niccolai C, Severo M, Patti F et al (2017) Age and disability drive cognitive impairment in multiple sclerosis across disease subtypes. Mult Scler 23(9):1258–1267
25. Fraser C, Stark S (2003) Cognitive symptoms and correlates of physical disability in individuals with multiple sclerosis. J Neurosci Nurs 35(6):314–320
26. Slavkovic S, Lazic M, Honan C, Nad C, Brkic-Jovanovic N, Golubovic S (2019) Differentiation of cognitive deficit profiles in multiple sclerosis patients: latent profile analysis. Med Princ Pract 28(4):373–379
27. Winkelmann A, Engel C, Apel A, Zettl UK (2007) Cognitive impairment in multiple sclerosis. J Neurol 254 Suppl 2:II35–II42
28. Dobson R, Giovannoni G (2019) Multiple sclerosis - a review. Eur J Neurol 26(1):27–40
29. Comi G, Leocani L, Rossi P, Colombo B (2001) Physiopathology and treatment of fatigue in multiple sclerosis. J Neurol 248(3):174–179
30. Siegert RJ, Abernethy DA (2005) Depression in multiple sclerosis: a review. J Neurol Neurosurg Psychiatry 76(4):469–475
31. Morrow SA, Weinstock-Guttman B, Munschauer FE, Hojnacki D, Benedict RH (2009) Subjective fatigue is not associated with cognitive impairment in multiple sclerosis: cross-sectional and longitudinal analysis. Mult Scler 15(8):998–1005

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