Cognitive Function in Multiple Sclerosis Patients Based on Age, Gender, and Education Level

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Received: 14 Apr. 2020; Accepted: 26 Sep. 2020

Abstract- Multiple sclerosis (MS) is defined as an inflammatory, progressive, and autoimmune disease in the central nervous system, recognized by its subsequent demyelination and neurodegeneration. Cognitive disorders are among the most severe problems in patients with MS, affecting their personal and professional life. This study is aimed to evaluate memory and visual learning, visual processing speed, and spatial perception in MS patients based on age, gender, and level of education. This cross-sectional study was carried out on 42 MS patients (based on McDonald's criteria). The level of disability in patients was assessed using EDSS, and cognitive performance was evaluated by the use of judgment of line orientation (JLO), symbol digit modalities test (SDMT), and revised brief visuospatial memory test (BVMT-R). In this study, patients were within the age range of 20-51 years, 73.8% of which were female, and 61.9% had academic degrees. According to the classes of independent variables (gender, education level), no significant difference was observed in the mean scores of dependent variables (JLO, SDMT, and BVMR-T scores) ($P>0.05$). In addition, age as a confounding variable had no impact ($P>0.05$). In addition, gender and level of education had no significant interaction ($P>0.05$). According to the results of the study, age, gender, and education level had no significant effect on memory and visual learning, visual processing speed, and spatial perception.
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Acta Med Iran 2020;58(10):500-507.

Keywords: Multiple sclerosis; Judgment of line orientation (JLO); Brief visuospatial memory test-revised (BVMT-R); Symbol digit modalities test (SDMT); Cognitive function

Introduction

Multiple sclerosis (MS) is a chronic inflammatory, progressive, and autoimmune disease in the central nervous system (CNS) recognized by its subsequent demyelination and neurodegeneration (1). The disease symptoms depend on the myelin destruction location and the extent of the lesion (1). An estimated 2,500,000 in the world and 50,000 people in Iran have MS, and the prevalence rate of MS in Iran has been estimated at nine per 100,000 individuals (2,3). Studies showed that the number of MS patients has been increasing in recent years in Iran (4). The pathogenesis of MS is complex and multifaceted, and various factors are involved in the emergence of the disease, including immune system state, inheritance, and several environmental factors (5). Nevertheless, all of the above-said factors have to be proven yet, and MS has no clear etiology (6). In other words, MS has no definitive treatment (7,8), and the main goal of treatment is to reduce disability and delay maximum incapability (1).

Some of the most common symptoms of MS include

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sensory, motor, visual, intestine, bladder, cognitive, and emotional disorders (9). In this regard, cognitive disorders are among the most prevalent complications of the disease (10). With a prevalence of 50-70% among MS patients, cognitive dysfunction is related to memory, learning, information processing speed, visual-spatial perception, and performance (7,11). Cognitive domains most commonly impaired in MS are information processing speed and memory (12). These cognitive impairments begin at a high-speed level and affect patients' personal and professional life (13). Furthermore, the above mentioned cognitive impairments exacerbate disabilities in MS patients up to 43-70% (14). The emergence of cognitive disorders might be related to individual and clinical features (15) and could affect the personal and professional lives of individuals (13). Impaired cognitive performance is often determined by tests that measure attention, information processing speed, working memory, spatial and visual-spatial memory, and executive functions (16).

In research, a delay was found in the reaction time in MS patients, compared to normal people (17). Another study revealed problems in the processing speed in all cognitive domains, especially the memory of MS patients (18). Rao reported deficits in mental processing and memory in MS patients (19). In various studies, the relationship between cognitive disorders and some individual and clinical features has been assessed, some of which have yielded contradictory results (15,20,21). The present study was designed and conducted due to insufficient evidence of the relationship between age, gender, and level of education with cognitive disorders in MS patients.

Materials and Methods

This cross-sectional research was performed on 42 MS patients (31 females and 11 males) with a mean age of 30.53±7.27 years, who were referred to neurologic clinics in Kerman and Rafsanjan, Iran. Inclusion criteria were willingness to participate in the study, definitive diagnosis of MS via neurological examinations by a specialist, evaluation of medical files, and based on the McDonald Criteria for diagnosis of MS (22), experiencing at least one relapse in the past two years, and receiving a 0-3.5 score in expanded disability status scale (EDSS). On the other hand, exclusion criteria were brain-related diseases, such as stroke, history of brain injury, seizure, and intellectual disability. At first, the research objectives were explained to the participants, who filled a consent form and a demographic characteristics questionnaire (age, gender, and level of education). Afterward, a neurologist determined the level of disability in MS patients using EDSS (23).

The cognitive performance of MS patients was assessed using MACFIMS, the Farsi version of which has been validated by Eshaghi *et al*., (2012) (24). Among the cognitive tests, the researchers used three tests, which were symbol digit modalities test (SDMT), revised brief visuospatial memory test (BVMT-R), and judgment of line orientation (JLO). SDMT was applied to assess the visual processing speed and working memory of patients. This test encompasses nine pairs of numbers/symbols, and patients were asked to verbally express the numbers related to the target symbol in 90 seconds at the fastest pace possible. After that, the number of correct figures expressed in 90 seconds was recorded, and a score of 0-110 was allocated to each subject (25,26). The researchers also used BVMT-R, where patients were asked to present six abstract shapes in a 2x3 network. The participants were given 10 seconds to learn the shapes and their position. In addition, they were required to draw the shapes on a piece of paper using a pencil without a time limit. It is to be noted that the test was repeated three times (T1, T2, T3). Each drawing was allocated a score of 0, 1, or 2 based on the accuracy and positioning criteria of the six shapes (27). Moreover, processing ability and spatial-visual perception in patients were assessed using JLO, which involves displaying two lines with various angles to patients. There are 11 numbered lines at the bottom of the sheet creating a semicircle. According to the test, patients paired the angled lines with 11 numbered lines by expressing the number of lines. The test involved five practice tests and 30 main tests. The test had no time limit, and correct responses were recorded (28,29).

Statistical analysis

Demographic characteristics and test results were presented as mean±SD, except for educational level and gender, for which data were shown as n (%). In the study, the distribution of continuous variables was normal, and the Friedman test was carried out for other variables due to abnormal data. Moreover, the effects of gender and level of education on test data were evaluated using multivariate analyses of variance (MANOVA). In this analysis, JLO, Oral SDMT, Written SDMT, and Total Recall of BVMT were variables of task response, but age was a covariate. All statistical assessments were two-tailed, and $P<0.05$ was considered significant. Data were analyzed using SPSS (version 21, Chicago, IL, USA).

Results

Among the subjects, 73.8% were female, and 61.9% had academic degrees. In addition, the age range of patients was 20-51 years, and their mean age was reported as 30.53±7.37 years (Table 1). Moreover, Table one shows the range and mean scores obtained by MS patients in various aspects of JLO, SDMT, and BVMT-R.

Table two shows the results of spatial-visual perception and processing in MS patients using JLO. According to the table, the most and least correct responses were related to items six (97.6) and 27 (24.4).

Table 1. The descriptive data of the study

Variables		Number	Range	Mean ± SD
age (year)		42	20- 51	30.53 ± 7.27
MMSE		42	25 -30	29.52 ± 1.13
JLO		42	7-29	20.21 ± 5.35
SDMT	**Oral**	42	20-77	46.21 ± 12.43
	Written	42	16 -77	44.19± 12.40
BVMT-R	**Trial-1**	42	1-12	5.89 ± 2.63
	Trial-2	42	2- 12	8.81 ± 2.95
	Trial-3	42	3- 12	9.65 ± 2.80
	Total Recall	42	7- 36	24.36 ± 7.77
Education level	**Elementary n(%)**		3 (7.1)	
	High school n(%)		13 (31.0)	
	University/college n(%)		26 (61.9)	
Gender	**Male n(%)**		11(26.2)	
	Female n(%)		31 (73.8)	

Table 2. Results of the evaluation of spatial vision processing in MS patients using the judgment of line orientation test (JLO)

Test Items	Correct Answer	The number of correct answers to each item (%)
V1	5-10 HH	21 (51.2)
V2	2-11 MM	28 (68.3)
V3	1-2 LL	38 (92.7)
V4	1-7 HH	34 (82.9)
V5	6-7 HH	37 (90.2)
V6	5-6 LL	41 (97.6)
V7	4-5 HH	32 (78.0)
V8	1-3 MM	28 (68.3)
V9	5-11 MM	36 (87.8)
V10	1-10 HH	37 (90.2)
V11	1-7 MM	30 (73.2)
V12	2-6 HH	35 (85.4)
V13	7-9 MM	30 (73.2)
V14	2-5 HL	25 (61.0)
V15	1-9 LL	28 (68.3)
V16	7-8 MM	37 (90.2)
V17	3-5 HH	35 (85.4)
V18	10-11 MH	29 (70.7)
V19	1-4 MM	26 (63.4)
V20	3-11 LL	27 (65.9)
V21	6-10 LL	20 (48.8)
V22	2-9 LL	21 (51.2)
V23	3-8 HH	30 (73.2)
V24	9-11 HH	15 (36.6)
V25	3-4 LM	19 (46.3)
V26	8-9 LL	17 (41.5)
V27	8-11 HH	10 (24.4)
V28	7-10 HL	20 (48.8)
V29	3-10 HL	12 (29.3)
V30	5-8 HM	31 (75.6)

Table three shows the results of the evaluation of the learning and visual memory of MS patients applying BVMT-R. According to Friedman's test results, the frequency distribution of patients' responses varied in T1, T2, and T3 stages in every six drawings ($P<0.05$), and almost all six drawings of patients received a score of zero and two at T1 and T3 stages, respectively.

Table 3. Results of the evaluation of learning and visual memory of MS patients using brief visuospatial memory test-revised (BVMT-R)

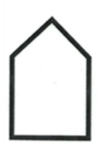
BVMT-R		Trial -1 N (%)	Trial-2 N (%)	Trial-3 N (%)	*P*
	**0**	9 (23.7)	4 (10.5)	3 (8.1)	
	1	10 (26.3)	8 (21.1)	5 (13.5)	0.003
	2	19 (50.5)	26 (68.4)	29 (78.4)	
	**0**	12 (31.6)	3 (7.9)	2 (5.4)	
	1	16 (42.1)	18 (47.4)	13 (35.1)	*P*<0.0001
	2	10 (26.3)	17 (44.7)	22 (59.5)	
	**0**	9 (23.7)	3 (7.9)	1 (2.7)	
	1	6 (15.8)	4 (10.5)	3 (8.1)	*P*<0.0001
	2	23 (60.5)	31 (81.6)	33 (89.2)	
	**0**	14 (36.8)	3 (7.9)	3 (8.1)	
	1	15 (39.5)	10 (26.3)	8 (21.6)	*P*<0.0001
	2	9 (23.7)	25 (65.8)	26 (70.3)	
	**0**	15 (39.5)	7 (18.4)	4 (10.8)	
	1	11 (28.9)	9 (23.7)	5 (11.9)	*P*<0.0001
	2	12 (28.6)	22 (57.9)	28 (66.7)	
	**0**	23 (60.5)	13 (34.2)	7 (16.7)	
	1	10 (26.3)	7 (18.4)	8 (19.0)	*P*<0.0001
	2	5 (13.2)	18 (47.4)	22 (52.4)	

Table 4 shows the mean and standard deviation of scores of JLO, SDMT, and BVMT in MS patients is based on gender and level of education. JLO, SDMT-oral, SDMT- written, and BVMT-total recall received the highest scores in MS patients, Men with the education of diploma, elementary school, a high school diploma, and elementary school degrees.

According to Table five, no significant difference was observed in the mean scores of any of the dependent variables (JLO, SDMT, BVMR-T) based on classes of independent variables (gender and level of education) ($P>0.05$).

According to Figure 1, age had no impact on the results as a confounding factor ($P>0.05$). Furthermore, gender and level of education had no significant interaction ($P>0.05$).

Table 4. Sample composition and scores for each subgroup

Gender	Education level	JLO Mean ± SD	SDMT oral Mean ± SD	SDMT Written Mean ± SD	BVMT-total recall Mean ± SD
	Elementary	16.00 ± 0.00	34.00 ± 0.00	40.00 ±0.00	7.00 ± 0.00
Female	**High school**	20.44 ± 5.59	43.55 ± 11.18	40.44 ± 7.93	23.22 ± 7.66
	University	18.35 ± 5.18	44.64 ± 11.76	43.58 ±14.51	25.41 ± 7.54
	Elementary	19.00 ± 0.00	56.00 ± 0.00	49.00 ±0.00	31.00 ± 0.00
Male	**High school**	26.00 ± 2.16	49.00 ± 2.94	50.00 ± 3.07	25.75 ± 4.03
	University	21.20 ± 1.92	43.40 ± 10.59	40.40 ±10.78	22.80 ± 9.73

Table 5. MANOVA results

Source of variation	Dependent Variable	d.f.	Mean square	F	*P*
Age	JLO	1	19.03	0.828	0.370
	ORAL	1	152.74	1.296	0.264
	WRITTEN	1	26.99	0.186	0.669
	Total Recall	1	22.91	0.385	0.540
Gender	JLO	1	53.39	2.32	0.138
	ORAL	1	286.86	2.43	0.129
	WRITTEN	1	84.42	0.582	0.451
	Total Recall	1	208.56	3.507	0.071
Education level	JLO	2	49.32	2.145	0.135
	ORAL	2	27.26	0.231	0.795
	WRITTEN	2	31.31	0.216	0.807
	Total Recall	2	33.47	0.563	0.575
gender× education level	JLO	2	8.632	0.375	0.690
	ORAL	2	151.075	1.282	0.292
	WRITTEN	2	133.378	0.920	0.410
	Total Recall	2	155.290	2.611	0.090

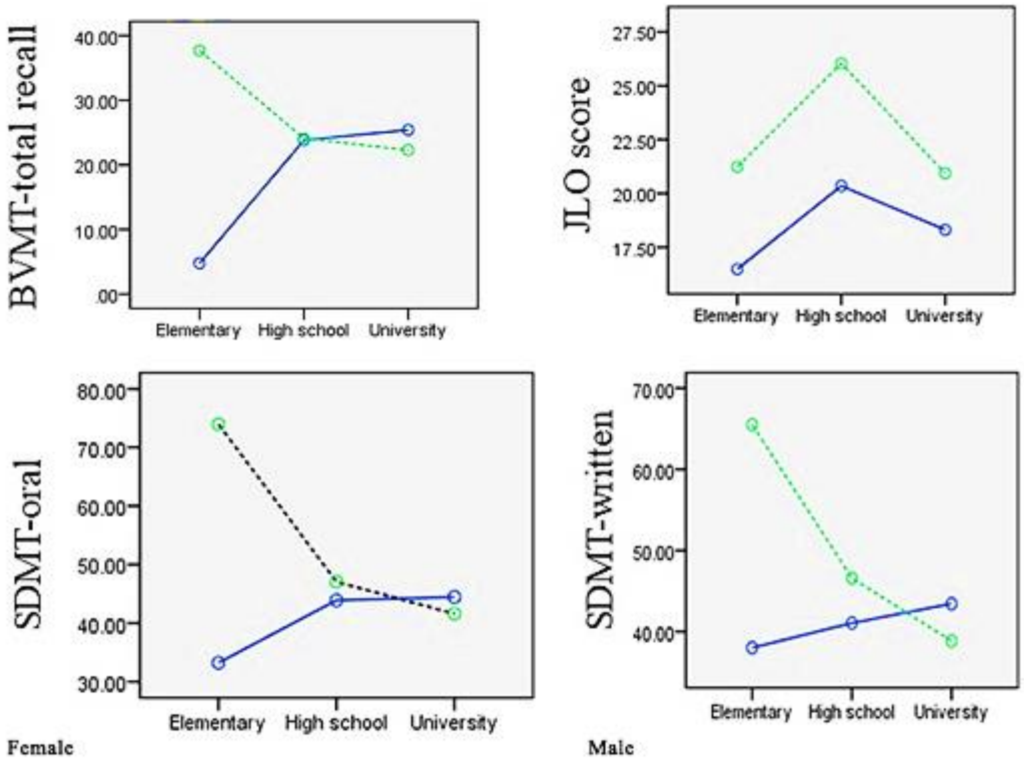


Figure 1. Means of JLO, ORAL, WRITTEN, and Total Recall according to gender and education. Age is estimated as a Covariate variable in the model 30.5541. There is no significant difference

Discussion

Given the fact that cognitive disorders are among the common problems in MS patients (10), the present study aimed to evaluate memory and visual learning, visual processing speed, and spatial processing and perception (as important cognitive branches) in MS patients based on age, gender and level of education (as important individual characteristics). While the psychological assessment of MS patients dates back more than 50 years (30), different studies have highlighted the role of neuropsychological assessment tools in recognition of these disorders (31). In line with the overall conclusion of the study by Vanotti S *et al.*, (2016) (32), where BVMT-

R and SDMT were used as reliable monitoring tools to identify MS patients with cognitive disorders, and since the impaired cognitive function is determined by tests that measure attention, information processing speed, spatial-visual memory and executive functions (16), we applied JLO, BVMT-R, and SDMT in the current research.

In the present study, age had no impact on cognitive functions, which is incongruent with the results obtained by Amato *et al*., (33), who reported a decrease in the cognitive level of subjects by aging. This lack of consistency between the results might be due to the age range of participants (20-50 years), and evaluation of higher ages might show a greater impact of age on the cognitive status of individuals. We observed that age had no effect on cognitive function as a confounding variable, which is inconsistent with the results obtained by Tam JW *et al*., (34), who marked a significant relationship between age and learning and memory based on BVMT-R and SDMT. This inconsistency between the results might be due to the age range in the current study (20-50 years). The findings of the present study are not in line with the results obtained by Pouramiri M *et al*., (35), who reported a significant association between age and executive functions. This lack of consistency might be due to differences in the type of cognitive test. Similarly, the findings of this study are inconsistent with the results obtained by Vanotti S *et al*., (36), who marked a significant correlation between age and the overall performance based on BICAMS. This inconsistency between the results might be due to different age ranges (18-60 years in the study by Vanotti S *et al*.,).

According to the results of the present study, gender had no significant impact on the cognitive function of the participants, which is congruent with the results obtained by Tam JW *et al*., (34), who did not consider gender as a predictive factor, Beyti *et al*., (37), who reported that gender was not a predictive factor at the cognitive level, and Pouramiri M *et al*., (35) and Vanotti S *et al*., (36), who observed no significant relationship between gender and cognitive and executive functions. On the other hand, our findings are inconsistent with the results obtained by Shaygannejhad *et al*., (15), who reported more cognitive complications in women compared to men. This inconsistency between the results might be due to the small sample size and low sensitivity of cognitive assessment tools. Similarly, our findings are inconsistent with the results obtained by Benedict *et al*., (10), who recognized the male gender as one of the risk factors for cognitive impairment in MS patients. This lack of consistency between the results might be due to different MS diseases, duration of disease, and type of cognitive test.

In the current research, level of education had no impact on the cognitive function of MS patients, which is in line with the results obtained by Maloni *et al*., (38), who expressed that level of education did not act as a predictor for cognitive dysfunction, and the results obtained by Pouramiri M *et al*., (35), who marked a lack of a significant association between level of education and cognitive performance. Nevertheless, the findings of this study are not in line with the results obtained by Shaygannejhad *et al*., (15), who posed a significant relationship between cognitive disorders and level of education. This inconsistency between the results might be due to different cognitive assessment tools since the level of education had an impact on some of the cognitive tools.

According to the results of the present study, level of education and gender had no significant effect on cognitive performance of MS patients, which is incongruent with the results obtained by Caparelli-Dáquer EM *et al*., (39), who reported that the highest scores on the correct answer to the JLO test were in men and in higher education groups. This lack of consistency between the results might be due to different sample populations and sizes.

Some of the limitations of the research included a small sample size, having a similar type of MS, and an age limit. In addition, disease duration, cultural factors, and lifestyle might have affected the results of cognitive tests.

It is recommended that future studies evaluate the effect of age, gender, level of education, and duration of disease on cognitive performance of MS patients and they should be assessed on larger sample sizes and the results should be compared to healthy individuals.

The results of SMDT, JLO, and BVMT-R were indicative of the lack of impact of age, gender, and level of education on cognitive performance of MS patients.

Acknowledgments

This study was financially supported by Rafsanjan University of Medical Sciences. Hereby, we express our gratitude to the participants for assisting us in performing the research.

References

1. Fletcher JM, Lalor SJ, Sweeney CM, Tubridy N, Mills KHG. T cells in multiple sclerosis and experimental autoimmune encephalomyelitis. Clin Exp Immunol

2010;162:1-11.
2. Eskandarieh S, Heydarpour P, Minagar A, Pourmand S, Sahraian MA. Multiple sclerosis epidemiology in east Asia, south east Asia and south Asia: a systematic review. Neuroepidemiology 2016;46:209-21.
3. Sahebi R, Amiri M, Jami MS. Multiple Sclerosis in Iran. Int J Epidemiol Res 2017;5:30-3.
4. Asgari A, Mehrabi F. Epidemiology of multiple sclerosis (MS) in military personnel: demographic study in Iran. Biomed Pharmacol J 2015;8:105-10.
5. Hauser SL, Oksenberg JR, Baranzini SE. Multiple sclerosis. In: Rosenberg RN, Pascual JM. Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease. 5th ed. Netherlands: Elsevier, 2015:1001-14.
6. Taylor BV. The major cause of multiple sclerosis is environmental: genetics has a minor role-Yes. Mult Scler J 2011;17:1171-3.
7. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. Lancet Neurol 2008;7:1139-51.
8. Lublin F, Miller A. Multiple sclerosis and other inflammatory demyelinating diseases of the central nervous system. Pocket Companion to Neurology in Clinical Practice. 5th ed. Philadelphia, PA: Butterworth-Heinemann Limited, 2008:1583-613.
9. Pakniya N, Bahmani B, Dadkhah A, Azimian M, Naghiyaee M, MasudiSani R. Effectiveness of Cognitive Existential Approach on Decreasing Demoralization in Women with Multiple Sclerosis. Iran Rehabil J 2015;13:28-33.
10. Benedict RH, Zivadinov R. Risk factors for and management of cognitive dysfunction in multiple sclerosis. Nat Rev Neurol 2011;7:332-42.
11. Patti F, Amato MP, Trojano M, Bastianello S, Tola MR, 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;15:779-88.
12. Sumowski JF, Benedict R, Enzinger C, Filippi M, Geurts JJ, Hamalainen P, et al, Cognition inmultiple sclerosis: State of the field and priorities for the future. Neurology 2018;90:278-88.
13. Rahn K, Slusher B, Kaplin A. Cognitive impairment in multiple sclerosis: a forgotten disability remembered. Cerebrum 2012;2012:14.
14. Kollndorfer K, Krajnik J, Woitek R, Freiherr J, Prayer D, Schöpf V. Altered likelihood of brain activation in attention and working memory networks in patients with multiple sclerosis: an ALE meta-analysis. Neurosci Biobehav Rev 2013;37:2699-708.
15. Shaygannejad V, Afshar H. The Frequency of Cognitive Dysfunction among Multiple Sclerosis Patients with Mild Physical Disability. J Isfahan Med Sch 2012;29:167.
16. Denney DR, Hughes AJ, Owens EM, Lynch SG. Deficits in planning time but not performance in patients with multiple sclerosis. Arch Clin Neuropsychol 2011;27:148-58.
17. Elsass P, Zeeberg I. Reaction time deficit in multiple sclerosis. Acta Neurol Scand 1983;68:257-61.
18. Kujala P, Portin R, Ruutiainen J. Memory deficits and early cognitive deterioration in MS. Acta Neurol Scand 1996;93:329-35.
19. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis.: I. Frequency, patterns , and prediction. Neurology 1991;41:685-91.
20. Evans DA, Beckett LA, Albert MS, Hebert LE, Scherr PA, Funkenstein HH, et al., Level of education and change in cognitive function in a community population of older persons. Ann epidemiol 1993;3:71-7.
21. Simioni S, Ruffieuxb C, Bruggimanna L, Annonia JM, Schluepa M. Cognition ,mood and fatigue in patients in the early stage of multiple sclerosis. Swiss Med Wkly 2007;137:496-501.
22. Williams MT, Tapos DO, Juhász C. Use of the 2010 McDonald criteria can facilitate early diagnosis of pediatric multiple sclerosis in a predominantly black cohort. Pediatr neurol 2014;51:826-30.
23. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444-52.
24. 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;26:975-84.
25. Morrow S, O'Connor PW, Polman CH, Goodman AD, Kappos L, et al. Evaluation of the symbol digit modalities test (SDMT) and MS neuropsychological screening questionnaire (MSNQ) in natalizumab-treated MS patients over 48 weeks. Mult Scler 2010;16:1385-92.
26. Smith A. Symbol digit modalities test (SDMT) manual (revised). Los Angeles: Western Psychological Services, 1982.
27. Benedict RH. Brief visuospatial memory test—revised. PAR: professional manual, 1997.
28. Benton AL, Sivan AB, Hamsher K, Varney NR, Spreen O. Contributions to neuropsychological assessment: A Clinical manual. USA: Oxford University Press, 1994.
29. Riva D, Benton A. Visuospatial judgment: A crossnational comparison. Cortex 1993;29:141-3.
30. Canter AH. Direct and indirect measures of psychological

deficit in multiple sclerosis: Part I. J Gen Psychol 1951;44:3-25.

31. Wilken J, Kane R, Sullivan CL, Wallin M, Usiskin JB, Quig ME, et al., The utility of computerized neuropsychological assessment of cognitive dysfunction in patients with relapsing-remitting multiple sclerosis. Mult Scler 2003;9:119-27.
32. Vanotti S, Smerbeck A, Rochester, NY, US, Benedict RHB, Caceres F. A new assessment tool for patients with multiple sclerosis from Spanish-speaking countries: validation of the Brief International Cognitive Assessment for MS (BICAMS) in Argentina. Clin Neuropsychol 2016; 30:1023-31.
33. Amato MP, Ponziani G, Siracusa G, Sorbi S. Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. Arch Neurol 2001;58:1602-6.
34. Tam JW, Schmitter-Edgecombe M. The role of processing speed in the Brief Visuospatial MemoryTest–revised. Clin Neuropsychol 2013;27:962-72.
35. Pouramiri M, Hossienzadeh S, Pishyareh E, Akbarfahimi N, Azimian M. Investigating the relationship between individual and clinical characteristics and Executive dysfunction of multiple sclerosis individuals. Arch Rehabilitation 2019;20:114-23.
36. Vanotti S, Smerbeck A, Eizaguirre MB, Saladino ML, Benedict RRH, Caceres FJ. BICAMS in the Argentine population: relationship with clinical and sociodemographic variables. Appl Neuropsychol Adult 2018;25:424-33.
37. Beatty WW, Goodkin DE, Hertsgaard D, Monson N. Clinical and demographic predictors of cognitive performance in multiple sclerosis: Do diagnostic type, disease duration, and disability matter? Arch Neurol 1990;47:305-8.
38. Maloni H. Cognitive impairment in multiple sclerosis. J Nurse Pract 2018;14:172-7.
39. Caparelli-Dáquer EM, Oliveira-Souza R, Moreira Filho PF. Judgment of line orientation depends on gender, education, and type of error. Brain Cogn 2009;69:116-20.