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The association between body mass index, demographic and clinical characteristics with cognitive performance in patients with neuromyelitis optica spectrum disorder

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Nasim Rezaeimanesh, Roghayyeh Saeedi, Mohammad Ali Sahraian, Fereshteh Ghadiri, Abdorreza Naser Moghadasi

Multiple Sclerosis Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran

Keywords
Neuromyelitis Optica; Cognition; Body Mass Index; Demography

Abstract

Background: Cognitive dysfunction is one of the problems that patients with neuromyelitis optica spectrum disorder (NMOSD) suffer from. We aimed to assess the association between demographic and clinical features as well as body mass index (BMI) and cognitive function in patients with NMOSD.

Methods: A cross-sectional study was performed on 41 patients with definite diagnosis of NMOSD. Serum status of neuromyelitis optica immunoglobulin G (NMO-IgG) was determined using enzyme-linked immunosorbent assay (ELISA) method. Cognitive function was assessed by Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) battery which is validated for Persian people before and North American Adult Reading Test (NAART).

Results: The mean score of NAART test was higher in participants with normal weight compared with overweight patients (40.47 ± 3.51 vs. 36.00 ± 5.74, P = 0.02). Current age was negatively correlated with Delis-Kaplan Executive Function System (D-KEFS)-Sorting (P = 0.05, r = -0.30). The correlation of duration of disease and cognitive performance was not significant (P > 0.05). Higher physical disability based on Expanded Disability Status Scale (EDSS) was correlated with lower results in Brief Visuospatial Memory Test-Revised (BVMT-R) (P < 0.01, r = -0.50), California Verbal Learning Test-second edition (CVLT-II)-Delayed Recall (P = 0.02, r = -0.35), and Symbol Digit Modalities Test (SDMT) (P = 0.03, r = -0.33) subtests of MACFIMS. Annual relapse rate

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Corresponding Author: Abdorreza Naser Moghadasi
Email: abdorrezamoghadasi@gmail.com

was indirectly correlated with CVLT-II (P = 0.03, r = -0.34) and CVLT-II-Delayed Recall (P = 0.01, r = -0.38). Male participants obtained better scores in Paced Auditory Serial Addition Test (PASAT) subtest (P = 0.05). NMO-IgG seropositive patients had poorer performance in terms of CVLT-II-Delayed Recall, Controlled Oral Word Association Test (COWAT), and D-KEFS-Descriptive (P < 0.05). Participants with bachelor and master education degrees showed significantly better results compared to those with high school degree (P < 0.05).

Conclusion: Investigating the clinical and demographic factors affecting cognitive impairment can increase the awareness of health care providers for early diagnosis of cognitive impairment in patients with NMOSD and increase the quality of health services.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease with inflammatory characteristics.[1] The autoimmunity in NMOSD refers to presence of antibodies against aquaporin-4 (AQP4-Ab) water channel mainly on astrocytes in spinal cord and optic nerves which results in motor and vision dysfunction.[2] The prevalence of NMOSD based on 2015 criteria has been reported between 0.7 to 10 person per 100000 subjects in the different populations worldwide.[2,3] In 2019, the point prevalence of NMOSD was calculated as 1.31 per 100000 person in Tehran, the capital city of Iran.[4]

It seems that inflammation has a potential role in NMOSD pathogenesis. Elevated level of interleukin (IL)-2, IL-6, IL-17, tumor necrosis factor alpha (TNFα), interferon-γ (INF-γ), and T helper (Th)-2, and Th-17 related cytokines is reported in patients with NMOSD.[5,6]

Cognitive dysfunction is one of the problems that patients with NMOSD suffer from. Impairment in memory, language, information processing speed, attention, and executive function test is reported in patients with NMOSD.[7] In a recently published systematic review, the pooled prevalence of cognitive impairment in patients with NMOSD has been estimated as 44%.[8] NMOSD mostly involves young population, so that the mean age of onset in 2019 report in Tehran was 30.03 years old.[4] Due to higher incidence of NMOSD in young people, cognitive dysfunction in this patients could affect various aspects of patients' individual and social lives.

It seems that seropositive and seronegative NMOSD patients are different in terms of clinical manifestation.[9] But until now, there is no study on the cognitive difference between them in human.[10] Some evidence indicates the relationship between neuromyelitis optica immunoglobulin G (NMO-IgG) presence and cognitive dysfunction in mice.[11,12] Saji et al. investigated the correlation between demographic and clinical characteristics and cognitive performance in NMOSD and reported the negative effect of age on cognition.[13] Some other investigations highlighted the negative association of disease duration and level of physical disability with cognitive performance, while the higher level of education was associated with better scores in neuropsychological test.[10]

The result of investigation shows controversy in the association between body mass index (BMI) and cognitive impairment.[14] A meta-analysis in 2020 mentioned that underweight or obesity in midlife and underweight in late-life were associated with 1.39, 1.31, and 1.64-fold increase in cognitive impairment and dementia. Overweight and obesity in late-life was related to 21% and 25% decreased risk. On the other hand, dose-response meta-analysis showed the significantly higher risk of all-cause dementia (ACD), Alzheimer's disease (AD), and vascular dementia (VaD) in people with BMI more than 29, 30, and 32 kg/m^2.[14] Owji et al. in 2019 investigated the association between BMI and cognitive function in patients with relapsing-remitting multiple sclerosis (RRMS). The results of this study proposed indirect correlation between BMI and cognitive function.[15]

Based on our knowledge, there is not any study on the association between BMI, NMO-IgG status, and cognitive function in patients with NMOSD, and data on the effects of demographic and clinical features on cognition are limited. Therefore, we aimed to examine these associations in a cross-sectional study.

Materials and Methods

Participants: A cross-sectional study was conducted in NMOSD specialist clinic of Sina Hospital, Tehran. All participants had definite diagnosis of NMOSD by an expert neurologist using 2015 international consensus diagnostic criteria for NMOSD.[3] Participants were involved in the study if they considered inclusion criteria including: A) age of 18-60 years, B) not having any neurological disorders other than NMOSD or any major psychological disorders, C) not having any underlying chronic diseases such as chronic liver, kidney, cardiovascular, etc. diseases, D) not being on any special regimen such as weight loss, vegetarian, etc. diets, E) not being pregnant or

breastfeeding, F) no NMOSD relapse in the past month, G) not receiving corticosteroid in the past month, and H) not having any diseases which could affect cognitive function.

Ethical approval: The study protocol was approved at the Ethical Committee of National Institute for Medical Research Development (IRB number: IR.NIMAD.REC.1398.159).

The study aims and protocols were explained for all participants and informed consents were taken from all of them before data collection.

Data collection: Demographic data including age, gender, and level of education were obtained during interview. NMOSD clinical data including disease duration, disability degree based on the Expanded Disability Status Scale (EDSS), annual relapse, and NMOSD medication were collected from medical records of patients. Serum status of NMO-IgG for all participants was determined using the enzyme-linked immunosorbent assay (ELISA) method in the same lab.

Weight was assessed with minimal clothing by a Seca digital scale (Seca, Hamburg, Germany) in "kg" with accuracy of 100 g. Height was measured barefoot using a tape meter and reported in "m" with 0.5 cm accuracy. BMI was calculated according to weight (kg)/height^2 (m^2) and was categorized based on World Health Organization (WHO) standard classification as underweight (BMI < 18.5), normal weight (18.5 ≤ BMI < 25), overweight (25 ≤ BMI < 30), category I obesity (30 ≤ BMI < 35), and category II obesity (BMI ≥ 35).[16]

For evaluating cognitive function in participants with NMOSD, the Persian translation of Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS), which is reliable and valid for Iranian patients, and North American Adult Reading Test (NAART) as a reliable and valid measure of verbal intelligence were administered.[17,18] MACFIMS test consists of ten subtests including the California Verbal Learning Test-second edition (CVLT-II) which consists of five learning trials with 16 words, the Paced Auditory Serial Addition Test (PASAT) which is auditory working memory test, Symbol Digit Modalities Test (SDMT) for visual processing speed evaluation, Brief Visuospatial Memory Test-Revised (BVMT-R) for evaluation of memory, Controlled Oral Word Association Test (COWAT) for testing verbal fluency, the Delis-Kaplan Executive Function System (D-KEFS) Sorting Test for evaluating executive function, and the Judgment of Line Orientation Test (JLO) for assessing spatial processing. All cognitive tests for all patients were applied by an expert psychologist in the same visit of participants which BMI data were collected.

Data analysis was performed using SPSS software (version 24, IBM Corporation, Armonk, NY, USA). Data normality was checked using Kolmogorov-Smirnov test. Quantitative variables were presented as mean ± standard deviation (SD) and qualitative variables as number and percentage. There were no participants in underweight group. The normal weight category of BMI was considered as reference category and the difference between cognitive test scores between normal weight and the other groups was assessed by independent samples t-test. Pearson correlation was applied to assess the correlation between cognitive test scores and quantitative variables. In case of qualitative variables, independent samples t-test or one-way analysis of variance (ANOVA) was used based on the number of categories. P-value < 0.05 was considered as significant in the present study.

Results

Table 1 describes demographic and clinical data of participants with NMOSD.

Table 1. Demographic and clinical characteristics of participants with neuromyelitis optica spectrum disorder (NMOSD)

Variables	Value
Age (year)	36.15 ± 9.74
Gender	
Men	7 (17.1)
Women	34 (82.9)
Level of education	
High school	7 (17.1)
Diploma	14 (34.1)
Associate's degree	5 (12.2)
Bachelor's degree	12 (29.3)
Master's degree	3 (7.3)
PhD	0 (0)
BMI (kg/m^2)	26.19 ± 5.43
Duration of disease (year)	3.98 ± 3.62
EDSS	2.65 ± 1.82
Treatment	
Rituximab	21 (51.2)
Azaram	18 (43.9)
Mycophenolate mofetil	2 (4.9)
Rate of relapse (per year)	3.08 ± 1.63
NMO-IgG	
Positive	18 (43.9)
Negative	23 (56.1)

Data are presented as mean ± standard deviation (SD) or number and percentage

BMI: Body mass index; EDSS: Expanded Disability Status Scale; NMO-IgG: Neuromyelitis optica immunoglobulin G

Totally, 41 patients with NMOSD were included in the study. The mean ± SD of age was 36.15 ± 9.74 years and 34 (82.9%) of them were women. Diploma was the most prevalent level of education [14 (34.1%) subjects] following by bachelor's degree [12 (29.3%)], high school [7 (17.1%)], associate's degree [5 (12.2%)], and master's degree [3 (7.3%)]. The mean BMI of participants was 26.19 ± 5.43 kg/m^2.

Rituximab was the most prescribed treatment [21 (51.2%)] and the second drug was Azaram [18 (43.9%)]. Only 2 (4.9%) participants received mycophenolate mofetil .The mean ± SD of EDSS and duration of disease was 2.65 ± 1.82 and 3.98 ± 3.62, respectively. Patients with NMOSD experienced an average of 3.08 ± 1.63 times relapses during the year before study attendance. 23 (56.1%) participants had seropositive status of NMO-IgG.

Table 2 presents the differences of each subtest of MACFIMS or NAART score between normal BMI category and other BMI groups. In the most subtests of MACFIMS, the mean scores were higher in the normal BMI category compared with the other BMI groups, but this differences were not significant (P > 0.05). The mean ± SD score of NAART test in the normal BMI group was 40.47 ± 3.51 which was significantly higher than overweight patients with 36.00 ± 5.74 score (P = 0.02). The NAART test score in patients with normal BMI was also more than obese category, but the difference was not significant (P > 0.05).

As it is shown in table 3, the result of D-KEFS-Descriptive was inversely correlated by age (P = 0.05, r = -0.30). Duration of disease was not correlated with any subtests of MACFIMS or NAART (P > 0.05), while higher EDSS was significantly correlated with lower scores of SDMT (P < 0.01, r = -0.50), CVLT-II-Delayed Recall (P = 0.02, r = -0.35), BVMT-R (P = 0.03, r = -0.33), and BVMT-R-Delayed Recall (P = 0.01, r = -0.39). On the other hand, relapse rate had a significant correlation with CVLT-II (P = 0.03, r = -0.34) and CVLT-II-Delayed Recall (P = 0.01, r = -0.38).

Table 4 reports the cognition difference between gender and NMO-IgG categories. The score of PASAT subtest was significantly higher in male patients compared to female ones (53.33 ± 4.50 vs. 45.06 ± 10.08, P = 0.05). NMO-IgG seronegative participants showed better cognitive function, so that they had significantly higher scores in terms of CVLT-II-Delayed Recall (12.44 ± 1.97 vs. 10.69 ± 2.75, P = 0.02), COWAT (27.77 ± 6.76 vs. 22.47 ± 9.78, P = 0.05), and D-KEFS-Descriptive (32.83 ± 9.55 vs. 22.21 ± 11.44, P < 0.01) compared with seropositive patients.

The cognitive function among levels of education was different in terms of SDMT (P = 0.01) and NAART (P = 0.01). More analysis revealed that SDMT score was 22.38 ± 6.53 scores higher in patients with bachelor's degree compared to those with high school degree (P = 0.01). NAART test results were 8.13 ± 2.56 (P = 0.02) and 10.71 ± 3.72 (P = 0.05) scores higher in bachelor and master groups compared to high school category, respectively (Table 5).

Discussion

The remarkable result to emerge from the data is the association between cognitive function and BMI, age, gender, EDSS, relapse rate, educational level, and NMO-IgG status among patients with NMOSD, so that overweight patients with NMOSD showed poorer result in terms of NAART test in comparison with normal weight patients with NMOSD. The higher scores were also found in the most MACFIMS' subtests in normal BMI group compared to overweight or obese patients, but the difference was not significant. Non-significant results could be attributed to the small sample size of the present study and it is possible that in the future studies with larger sample size, more correlation will be obtained. Better cognitive performance was associated with lower age, male gender, lower EDSS and relapse rate, NMO-IgG seronegativity, and higher level of education.

Few studies investigated the association between disease duration and cognitive function.[19,20] Aligned with the other reports, we found no significant association in terms of NMOSD duration and cognitive function, which suggests occurrence of early cognitive deficit in some patients but for the other ones, it is not avoidable and progressive concomitant of NMOSD.[20]

It is a fact that increasing age may have negative effects on neuropsychological function.[10] Some studies mentioned this effects in patients with NMOSD. Saji et al. in 2012 reported the negative impact of age on the most cognitive tests measured including SDMT, PASAT3, PASAT2, 10/36 Spatial Recall (SPART), and SPART Delayed Recall (SPART-D) among participants with NMOSD.[13] Consistent with previous investigation, our data suggest the possible negative correlation of age and cognition in terms of D-KEFS-Sorting subtest of MACFIMS.

Table 2. The cognition difference between body mass index (BMI) categories among patients with neuromyelitis optica spectrum disorder (NMOSD)

Variables	18.5 ≤ BMI < 25 (n = 17)	25 ≤ BMI < 30 (n = 13)	30 ≤ BMI < 35 (n = 7)	BMI ≥ 35 (n = 3)	P[1]	P[2]	P[3]
CVLT-II	49.35 ± 9.55	53.53 ± 7.51	51.85 ± 13.50	47.33 ± 9.71	0.20	0.61	0.74
PASAT	46.41 ± 9.93	47.00 ± 9.66	45.83 ± 12.73	51.00 ± 0.00	0.87	0.91	0.65
SDMT	48.41 ± 12.12	43.92 ± 19.41	43.42 ± 7.50	33.66 ± 24.50	0.44	0.32	0.11
CVLT-II-Delayed Recall	11.41 ± 2.62	11.53 ± 1.89	11.42 ± 2.63	10.66 ± 5.50	0.88	0.98	0.70
BVMT-R	26.35 ± 4.15	22.15 ± 10.36	20.42 ± 9.69	22.00 ± 11.13	0.13	0.16	0.21
COWAT	26.05 ± 8.39	22.69 ± 5.26	24.00 ± 7.85	20.66 ± 17.47	0.21	0.58	0.39
D-KEFS-Descriptive	28.17 ± 12.20	25.76 ± 9.35	28.85 ± 14.87	16.00 ± 10.39	0.56	0.90	0.12
D-KEFS-Sorting	7.52 ± 3.12	6.84 ± 2.70	11.58 ± 9.45	4.66 ± 2.88	0.53	0.10	0.15
BVMT-R-Delayed Recall	10.41 ± 2.06	9.00 ± 4.22	9.57 ± 3.25	7.00 ± 4.58	0.23	0.45	0.13
JLO	21.40 ± 5.15	20.27 ± 4.81	17.57 ± 3.69	18.50 ± 7.77	0.57	0.06	0.48
NAART	40.47 ± 3.51	36.00 ± 5.74	37.85 ± 4.45	31.66 ± 4.01	0.02	0.14	0.39

Data are presented as mean ± standard deviation (SD); P-values are calculated using independent samples t-test

[1]The difference between normal and overweight category; [2]The difference between normal and category I obesity; [3]The difference between normal and category II obesity

BMI: Body mass index; CVLT-II: California Verbal Learning Test-second edition; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modalities Test; BVMT-R: Brief Visuospatial Memory Test-Revised; D-KEFS: Delis-Kaplan Executive Function System; JLO: Judgment of Line Orientation Test; COWAT: Controlled Oral Word Association Test; NAART: North American Adult Reading Test

Table 3. The correlation between age, disease duration, Expanded Disability Status Scale (EDSS), relapse rate, and cognition in patients with neuromyelitis optica spectrum disorder (NMOSD)

Variables	CVLT-II	PASAT	SDMT	CVLT-II-Delayed Recall	BVMT-R	COWAT	D-KEFS-Descriptive	D-KEFS-Sorting	BVMT-R-Delayed Recall	JLO	NAART
Age	0.75 (0.05)	0.54 (0.10)	0.16 (-0.22)	0.63 (-0.07)	0.35 (-0.14)	0.41 (-0.13)	0.07 (-0.27)	0.05 (-0.30)	0.31 (-0.16)	0.32 (-0.17)	0.80 (0.03)
Duration of disease	0.82 (0.03)	0.49 (-0.12)	0.95 (< -0.01)	0.78 (0.04)	0.52 (0.10)	0.32 (0.15)	0.47 (0.11)	0.79 (-0.04)	0.70 (0.06)	0.90 (-0.02)	0.35 (0.15)
EDSS	0.18 (-0.21)	0.37 (-0.15)	< 0.01 (-0.50)	0.02 (-0.35)	0.03 (-0.33)	0.50 (-0.18)	0.77 (-0.04)	0.76 (0.04)	0.01 (-0.39)	0.44 (-0.13)	0.21 (-0.01)
Rate of relapse	0.03 (-0.34)	0.29 (0.18)	0.42 (-0.13)	0.01 (-0.38)	0.37 (-0.14)	0.10 (-0.26)	0.55 (-0.09)	0.98 (< -0.01)	0.40 (-0.13)	0.30 (0.18)	0.42 (-0.13)

Data are presented as P-value (r)

EDSS: Expanded Disability Status Scale; CVLT-II: California Verbal Learning Test-second edition; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modalities Test; BVMT-R: Brief Visuospatial Memory Test-Revised; D-KEFS: Delis-Kaplan Executive Function System; JLO: Judgment of Line Orientation Test; COWAT: Controlled Oral Word Association Test; NAART: North American Adult Reading Test

Table 4. The cognition difference between gender and neuromyelitis optica immunoglobulin G (NMO-IgG) categories among patients with neuromyelitis optica spectrum disorder (NMOSD)

Variables	Gender			NMO-IgG		
	Women (n = 34, 82.9%)	Men (n = 7, 17.1%)	P	Positive (n = 18, 43.9%)	Negative (n = 23, 56.1%)	P
CVLT-II	52.41 ± 7.86	45.28 ± 14.85	0.25	49.39 ± 9.60	53.50 ± 9.25	0.17
PASAT	45.06 ± 10.08	53.33 ± 4.50	0.05	46.94 ± 8.94	45.94 ± 10.90	0.76
SDMT	45.91 ± 16.57	43.85 ± 9.20	0.75	43.43 ± 16.70	48.27 ± 13.76	0.32
CVLT-II-Delayed Recall	11.58 ± 2.51	10.85 ± 2.96	0.50	10.69 ± 2.75	12.44 ± 1.97	0.02
BVMT-R	24.55 ± 6.69	19.42 ± 12.80	0.33	22.04 ± 8.66	25.77 ± 6.95	0.14
COWAT	25.08 ± 9.29	23.42 ± 7.06	0.65	22.47 ± 9.78	27.77 ± 6.76	0.05
D-KEFS-Descriptive	26.23 ± 11.15	30.00 ± 15.17	0.44	22.21 ± 11.44	32.83 ± 9.55	< 0.01
D-KEFS-Sorting	7.14 ± 2.95	11.85 ± 9.61	0.24	7.21 ± 6.17	8.88 ± 2.47	0.28
BVMT-R-Delayed Recall	9.88 ± 3.03	8.42 ± 3.99	0.28	9.26 ± 3.38	10.11 ± 2.98	0.40
JLO	20.55 ± 4.83	19.00 ± 5.41	0.46	20.30 ± 5.42	20.18 ± 4.36	0.94
NAART	38.41 ± 6.39	36.57 ± 3.55	0.46	37.69 ± 6.64	38.61 ± 5.22	0.63

Data are presented as mean ± standard deviation (SD); P-values are calculated using independent samples t-test

CVLT-II: California Verbal Learning Test-second edition; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modalities Test; BVMT-R: Brief Visuospatial Memory Test-Revised; D-KEFS: Delis-Kaplan Executive Function System; JLO: Judgment of Line Orientation Test; COWAT: Controlled Oral Word Association Test; NAART: North American Adult Reading Test; NMO-IgG: Neuromyelitis optica immunoglobulin G

Table 5. The cognition difference between educational level categories among patients with neuromyelitis optica spectrum disorder (NMOSD)

Variables	Educational level categories					
	High school (n = 7, 17.1%)	Diploma (n = 14, 34.1%)	Associate's degree (n = 5, 12.2%)	Bachelor's degree (n = 12, 29.3%)	Master's degree or higher (n = 3, 7.3%)	P
CVLT-II	47.86 ± 8.67	49.07 ± 11.65	50.60 ± 5.94	55.42 ± 8.91	53.00 ± 5.57	0.41
PASAT	42.20 ± 15.97	45.15 ± 8.30	48.50 ± 3.11	49.82 ± 9.89	44.00 ± 11.53	0.61
SDMT	32.29 ± 12.37	44.29 ± 10.66	39.40 ± 28.25	54.67 ± 9.08	56.33 ± 12.50	0.01*
CVLT-II-Delayed Recall	9.86 ± 3.24	11.57 ± 2.50	11.60 ± 2.30	11.92 ± 2.54	12.67 ± 1.15	0.44
BVMT-R	19.71 ± 9.11	24.50 ± 7.02	18.00 ± 11.11	26.33 ± 7.00	28.00 ± 3.46	0.16
COWAT	19.29 ± 7.30	24.93 ± 9.36	22.60 ± 7.16	27.58 ± 6.96	29.67 ± 16.86	0.28
D-KEFS-Descriptive	20.86 ± 10.65	27.29 ± 12.83	25.00 ± 11.22	29.00 ± 12.61	33.67 ± 3.79	0.52
D-KEFS-Sorting	5.86 ± 2.85	9.36 ± 7.16	6.40 ± 3.29	7.67 ± 3.31	10.00 ± 2.00	0.50
BVMT-R-Delayed Recall	7.14 ± 4.38	10.43 ± 2.62	8.40 ± 4.51	10.42 ± 2.19	10.67 ± 1.15	0.13
JLO	17.00 ± 4.15	20.58 ± 4.83	19.75 ± 6.65	21.18 ± 4.77	22.67 ± 4.93	0.44
NAART	32.29 ± 8.96	38.64 ± 4.86	36.20 ± 5.12	40.42 ± 3.55	43.00 ± 3.00	0.01&

Data are presented as mean ± standard deviation (SD); P-values are calculated using one-way analysis of variance (ANOVA)

*SDMT subtest result was significantly 22.38 ± 6.53 scores higher in patients with bachelor's degree vs. high school degree (P = 0.01); &NAART subtest results were significantly 8.13 ± 2.56 (P = 0.02) and 10.71 ± 3.72 (P = 0.05) scores higher in bachelor and master group vs. high school category, respectively.

CVLT-II: California Verbal Learning Test-second edition; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modalities Test; BVMT-R: Brief Visuospatial Memory Test-Revised; D-KEFS: Delis-Kaplan Executive Function System; JLO: Judgment of Line Orientation Test; COWAT: Controlled Oral Word Association Test; NAART: North American Adult Reading Test

As the present data underlined, the protective effect of higher level of education on cognitive deficit is pointed in many studies.[10] The possible underlying mechanism of this correlation could be attributed to education forming brain reserve capacity or cognitive reserve (CR).[21] CR is described as brain networks with higher efficiency and more neuronal capacity which result in lower vulnerability of brain against disturbance.[21]

Until now, the correlation between physical disability based on EDSS and cognitive function is not proved definitely.[10] Available data show that cognitive impairment could occur in patients with NMOSD with low level of disability and reciprocally, patients with high grade of physical disability may do not suffer from any cognitive dysfunction. These data propose that cognitive performance is independent from physical disability. But on the other hand, there is growing evidence on the connection between high EDSS and poor cognitive function.[10] Our results supported this evidence and showed that EDSS had negative correlation with the score of SDMT, CVLT-II-Delayed Recall, BVMT-R, and BVMT-R-Delayed Recall. It seems that a meta-analysis on this important topic is necessary to give a more convincing answer in this regard. But at the moment, it could be concluded that more attention should be paid to the assessment of cognitive changes along with the other examinations of disease progression.

Our data revealed a higher score of PASAT in men compared to women. The present study had small sample size and according to lower prevalence of NMOSD in men, only seven participants with male gender were included. Thus, future studies with larger sample sizes and multi-center studies are needed to approve our result. Estrogen use in women, depression, and occupation are factors which could affect the difference of cognition in gender groups,[22-24] which are unfortunately not available in the present study.

It seems that seropositive NMOSD patients manifest different clinical and paraclinical features compared with seronegative patients. For example, seropositive patients experience more intense attack and motor dysfunction is more prevalent among them.[9] But based on our knowledge, until now, no study mentioned poor psychological manifestations of patients with NMOSD in association with AQP4-Ab status. Few studies investigated the interaction of AQP4-Ab and cognitive function in mice. Fan et al. outlined the possible inhibition of neuronal plasticity by NMO-IgG which resulted in deteriorating in consolidation of memory and spatial memory in mice.[11,12] Skucas et al. confirmed this link by reporting spatial memory deficiency in aquaporin-4 (AQP4) knockout mice.[25] Saji et al. attempted to clarify the full extent of cognitive deficit in patients with NMOSD. They claimed that the underlying mechanism for cognitive impairment in patients with NMOSD referred to a unique dynamic between astrocytes and NMO-IgG, which resulted in considerable diffuse cortical neuronal loss all over the brain and finally, neurodegeneration independent of clinical attack.[13]

As far as we know, our data for the first time proposed indirect correlation of annual rate of relapse and cognitive impairment, so that participants with higher relapse rate obtained lower scores of CVLT-II and CVLT-II-Delayed Recall. Until the future reports confirm this correlation, it is necessary to pay more attention to the assessment of cognitive performance in patients with NMOSD with higher annual relapse rate.

Higher BMI is an adiposity indicator which in the most people, is associated with higher body fat.[16,26] The prevalence of obesity and overweight is growing worldwide.[27] Obesity is correlated with elevated risk of chronic diseases such as stroke, diabetes, hypertension (HTN), cardiovascular diseases (CVDs), cancer, osteoarthritis (OA), respiratory disorders, liver and gallbladder diseases, infertility, and etc.[26]

Pieces of evidence indicate that obesity and/or feeding with high-fat diet are associated with impairment in memory, learning, and executive functioning in experimental studies.[27-30] There is inconsistency in the relation between obesity and cognitive impairment, but some recent reviews and meta-analyses mentioned the association between obesity and cognitive dysfunction, acceleration in cognitive decline, and neurodegeneration.[14,31] It seems that this relationship refers to obesity-induced systemic inflammation which leads to neuro-inflammation.[27]

To our knowledge, no prior study mentioned the association between obesity/BMI and cognitive function in patients with NMOSD. Owji et al. in a recently published paper investigated this association among patients with RRMS.[15] Consistent with our result, they reported an indirect correlation between BMI and cognitive performance. The significant results were found in terms of PASAT and SDMT subtests of MACFIMS

battery.[15] They proposed some pathways in explanation of what they found; for instance, the role of higher physical activity in better cognitive function and its indirect association with obesity or the lower level of serum vitamin D in overweight and obese people as well as patients with multiple sclerosis (MS) and the effect of sufficient vitamin D level on cognitive performance.[15] The lower levels of serum vitamin D[32] and physical activity[33] are found in patients with NMOSD compared with healthy population too. Therefore, the relation between overweight and poor cognitive performance could be referred to mediation of these factors.

It is confirmed that obesity is in association with low-grade chronic systematic inflammation.[34,35] This systematic inflammation has long been known as the underlying mechanism in the association between obesity and cognitive dysfunction.[27] The hypothalamus is responsible for a group of psychological functions in the body which many of them are inter-related with cognition aspects such as memory, learning, and attention.[36] Recently, some evidence proposed the role of peripheral inflammation in the initiation of local inflammation in hypothalamus which could affect synaptic plasticity, lead to neurodegeneration, and even begin atrophy of brain.[27]

Our work clearly has some limitations. We did not investigate inflammatory factors as intermediate mechanism as well as magnetic resonance imaging (MRI) data. This study was the first one on the association between BMI, NMO-IgG status, and cognitive function in patients with NMOSD and more investigations by larger sample size are needed to approve our results.

Based on the rare characteristic of NMOSD, the sample size of the present study is small which could be mentioned as the limitation of the study.

Conclusion

Based on our knowledge, the present study is the first one which investigated the possible association between cognitive function and BMI or NMO-IgG status. One of the most important ways for weight loss is lifestyle modification including adherence to healthy diet and being physically active. There is no definite treatment for NMOSD or cognitive dysfunction in patients with NMOSD. Thus, modification in lifestyle could be an achievable and helpful way for these patients. On the other hand, understanding the clinical and demographic factors affecting cognitive impairment can increase the awareness of health care providers to identify patients at risk of cognitive impairment, leading to early diagnosis of cognitive impairment in patients with NMOSD and increasing the quality of health services.

Conflict of Interests

The authors declare no conflict of interest in this study.

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