ORIGINAL ARTICLE

Cognitive function and brain magnetic resonance imaging profiles in neuromyelitis optica spectrum disorder and multiple sclerosis

Fereshteh Ashtari[1], Pouran Najarzadeh[1], Vahid Shaygannejad[1], Iman Adibi[1], Neda Ramezani[1], Fariba Davanian[2], Sahar Akbaripour[1], Majid Barekatain[1]

[1]Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Paramedical School, Isfahan University of Medical science, Isfahan, Iran

Background The objective of this study was to investigate cognitive performance and brain volume profile in patients with neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS). **Materials and Methods:** In a historical cohort study, 29 MS patients, 31 NMOSD patients, and 20 healthy controls (HCs) underwent neuropsychological assessment using the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS). Patients with MS and NMOSD also underwent a 1.5-tesla magnetic resonance imaging scan and high-resolution three-dimensional T1-weighted MPRAGE sequence. **Results:** The Symbol Digit Modalities Test scores were significantly lower in MS (mean [standard deviation (SD)] =44.1 [14]) and NMOSD (mean [SD] =45.5 [14.3]) patients compared to HCs (mean [SD] =57 [9.5], $P < 0.001$). Scores of the Controlled Oral Word Association Test were also lower in MS (mean [SD] =25.9 [9.8]) and NMOSD (mean [SD] =24.6 [10.2]) patients compared to HCs (mean [SD] =36.6 [9.8], $P < 0.001$). Additionally, the MS group performed worse on the Brief Visuospatial Memory Test (BVMT) compared to the NMOSD group (9.4 ± 3.4 vs. 7.1 ± 3.7 $P < 0.001$). In MS patients, there was a significant correlation between all cognition scores and total brain lesions, as well as between every test except BVMT-Revised with thalamic volumes. In NMOSD patients, a correlation was found between gray matter volume and the learning phase of the California Verbal Learning Test-II as well as between total lesion percentage and verbal memory and information processing speed. **Conclusion:** Both NMOSD and MS patients experienced impairment of information processing speed, working memory, and verbal fluency, whereas visuospatial memory impairment was only observed in MS patients. Despite lower total brain lesion and less thalamic atrophy, patients with NMOSD are at risk of cognitive impairment. Microscopic structural abnormalities may be a possible cause.

Key words: Cognition, multiple sclerosis, neuromyelitis optica

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INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease that impairs the functions of the central nervous system.[1,2] Cognitive dysfunction is one of the major contributors to decreased quality of life in MS patients.[3] Up to 65% of MS patients experience cognitive dysfunction during the course of the disease.[4] The most common cognitive deficits in MS are alterations in memory and decreased information processing speed. Reports also indicate less prevalent impairments in executive function and visuospatial capacities.[5,6]

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory disorder with unknown etiology.[7,8] Brain involvement in NMOSD is not as common as MS.[9] Cognitive dysfunction in NMOSD, which is usually a debilitating disease, has been less investigated. However, cognitive dysfunction, primarily

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Address for correspondence: Dr. Pouran Najarzadeh, Isfahan Neuroscience Research Center, Kashani Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: dr.p.najarzadeh@gmail.com
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in the areas of attention, memory, and executive function, has been reported in 29%–67% of patients with NMOSD.[10]

Magnetic resonance imaging (MRI) studies have shown that gray matter volume is significantly reduced in relapsing-remitting MS, not only compared to the general population but also compared to NMOSD.[11] A significant reduction in white matter volume has been observed in patients with NMOSD but less than in MS.[12] Studies of MRI-related cognitive dysfunction in MS and NMOSD patients have yielded conflicting results. Cognitive impairment in MS has been reported to be significantly associated with the volume of lesions in white matter and brain atrophy.[13]

In NMOSD, the relationship between cognitive function and thalamic atrophy has been reported.[14] Another study has shown that atrophy in the right thalamus and the prefrontal cortex contributes to cognitive dysfunction in patients with NMOSD.[15]

This study was conducted due to the lack of sufficient studies on the cognitive function of Iranian NMOSD patients. The aim was to investigate cognitive function in NMOSD and MS patients and its relationship with MRI parameters.

MATERIALS AND METHODS

Study design and participants

This historical cohort study was conducted at Kashani MS Center, Isfahan, Iran, between April 2019 and March 2021.

Thirty-one patients with a definite diagnosis of NMOSD and 29 relapsing-remitting MS patients were enrolled in the study.

All patients with NMOSD fulfilled the 2015 international consensus diagnostic criteria,[8] and MS patients met the 2017 McDonald criteria.[16] The eligibility criteria were steroid free for at least 2 months, age between 20 and 55, and visual acuity of ≥20/40.

Subjects who were unable to perform neuropsychological tests and those with severe psychiatric diseases, alcohol and drug abuse, and family history of cognition impairment were excluded. The Beck Depression Inventory (BDI) was used as a screening tool to exclude individuals exhibiting moderate to severe depression from the study based on established reliability and validity criteria.[17] The BDI is a self-report questionnaire that measures the severity of depression symptoms.[17]

The study enrolled 31 patients with NMOSD, 29 patients with MS, and 20 healthy controls (HCs). Healthy individuals had no history of neurological and mental illness and no family history of MS or NMOSD.

The Regional Bioethics Committee at Isfahan University of Medical Sciences approved the study (IR.MUI.MED.REC.1400.348), and written informed consent was obtained from participants. Basic data, including age, sex, age of onset, disease duration, and educational level were collected from electronic sources and medical records. Each patient was interviewed to complete the structural questionnaire and underwent a neurological examination.

Neuropsychological assessment

All patients and HCs underwent neuropsychological tests using the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) by a trained clinical neuropsychologist. This battery includes several tests that evaluate different cognitive domains, such as processing speed, memory, and executive function. The Controlled Oral Word Association Test (COWAT) assesses verbal fluency. The Judgment of Line Orientation Test evaluates visuospatial perception. The California Verbal Learning Test-II (CVLT-II) assesses verbal learning and memory, and the Brief Visuospatial Memory Test-Revised (BVMT-R) evaluates visuospatial learning and memory. The Symbol Digit Modalities Test (SDMT) assesses information processing speed and working memory, and the Paced Auditory Serial Addition Test evaluates attention and information processing speed. The Delis–Kaplan Executive Function System is for the evaluation of executive function.[18]

Brain magnetic resonance imaging acquisition

Patients with MS and NMOSD underwent a brain MRI using a 1.5 T magnetic resonance scanner at the Kashani Hospital (Siemens Avanto scanner system, Germany, Henkestr Erlangen) within 2 months of cognitive tests. High-resolution three-dimensional (3D) T1-weighted MPRAGE sequence (slice thickness: 1, echo time: 0.00273, repetition time: 2.2, inversion time: 0.9, flip 8°, base resolution: 224) and FLAIR 3D sequence (echo time: 0.331, repetition time: 4.5, inversion time: 1.8, flip angle: 120) were taken to examine the volume of the whole brain and the volume of subcortical structures and lesions.

Magnetic resonance imaging analysis and automated segmentation methods

Among the obtained images, proper-quality images were uploaded to the Volbrain website[19] for initial segmentation. This system performed preprocessing on the image, including denoising[19] and inhomogeneity correction.[20] Then, the segmentation process was done automatically on the images for the initial automated measurement of gray matter, white matter, and total brain volume.

Manual volumetric analysis

In the next step, the MS lesions' masks (periventricular, juxtacortical, deep white matter, and infratentorial lesions) were checked in ITK snap image processing software,[21] and two experienced observers blinded to the patient's clinical information checked all images.[22] Finally, an expert neuroradiologist reviewed and manually edited the revised masks.

Volume normalization was calculated by dividing the volume of each structure by the total intracranial volume (the sum of all voxels classified as gray or white matter or as cerebrospinal fluid).[23]

Statistical analysis

The data were analyzed with IBM SPSS Statistics, version 22 (IBM Corp., Armonk, N.Y., USA). Due to our small sample sizes (<50 samples), we used a Shapiro–Wilk test to determine whether our sample had a normal distribution. Age, level of education, disease duration, age of onset of the disease, and Expanded Disability Status Scale (EDSS) were compared between three groups using Kruskal–Wallis test. Chi-square test was applied to compare three groups' gender difference. Neurocognitive parameters were compared between groups using one-way-ANOVA with Bonferroni *post hoc* test.

To compare two groups of MS and NMOSD, *Student's t-distribution* were used in parametric distributions. Mann–Whitney *U* test and Fisher's exact test were used for nonparametric variables. To assess the correlation of demographic and clinical parameters with neuropsychological aspects and MRI volumes, Pearson's correlations were used for parametric and nonparametric variables. Statistical significance was considered as $P < 0.05$.

RESULTS

Study population characteristics

A total of 29 patients with MS (mean [standard deviation (SD)] age, 35.83 [9.20] years; 25 women [80.6%]), 31 NMOSD patients (mean [SD] age, 35.75 [8.59] years; 23 women [79.3%]), and 20 HC individuals (mean [SD] age, 38.35 [2.03] years; 17 women [58%]) were analyzed in this study. There were no significant differences in mean age and gender ratio between the groups. There were no significant differences in disease duration, EDSS, and education between MS and NMOSD patients [Table 1].

Table 1: Demographic and baseline clinical parameters in patients with neuromyelitis optica spectrum disorder, relapsing-remitting multiple sclerosis, and healthy control

	NMOSD (*n*=31)	MS (*n*=29)	HCs (*n*=20)	*P*
Age (years), mean±SD	35.83±9.20	35.75±8.59	38.35±2.03	0.972
Gender, *n* (%)				
Male	6 (19.4)	6 (20.7)	3 (15)	0.897
Female	25 (80.6)	23 (79.3)	17 (85)	
Education level (years), mean±SD	13.80±2.44	14.27±3.10	14.22±2.55	0.516
Disease duration (years), mean±SD	10.9±4.7	11±5.1	NA	0.648
Age of onset (mean±SD)	25.06±9.25	26.10±9.01	NA	0.662
EDSS (mean±SD)	1.77±1.17	2.01±1.22	NA	0.437

EDSS=Expanded Disability Status Scale; NMOSD=Neuromyelitis optica spectrum disorder; MS=Multiple sclerosis; HCs=Healthy controls; NA=Not available; SD=Standard deviation

Cognitive function and neuropsychological tests

SDMT scores of patients with MS (mead [SD] =45.5 [14.3]) and patients with NMOSD (mean [SD] =44.1 [14]) were lower in comparison to SDMT scores of HCs (mean [SD] =57 [9.5], $P < 0.05$). However, there was no significant difference between SDMT scores of patients with MS and those with NMOSD ($P > 0.05$). A similar difference between COWAT scores of HCs (mead [SD] =36.6 [9.8]) and those with MS (mead [SD] =25.9 [9.8]) or NMOSD (mead [SD] =26.4 [10.2]) was also observed. The difference between COWAT scores of MS and of the NMOSD group was not significant statistically ($P > 0.05$).

The comparison of BVMT-R total learning scores showed lower values in patients with MS (mean [SD] =7.1 [3.7]) than in patients with NMOSD (mean [SD] =9.4 [3.4]) and HCs (mean [SD] =10.4 [2.18], $P < 0.05$). All neuropsychiatric measures in three groups of the study are summarized in Table 2.

Brain magnetic resonance imaging volumetric assessment and correlation with cognitive function

Brain MRI showed that in MS patients, the total lesion percentage was significantly higher, and the volumes of white matter and thalamus were significantly lower than in NMOSD patients [Table 3].

According to the analysis of the linear correlation, there was a significant negative correlation between most cognitive domains and total lesion percentage [Table 4]. Moreover, thalamic volumes were positively correlated with scores on every test, except BVMT-R. In patients with MS, white matter volume was positively correlated with CVLT-II recall scores ($r = 0.51$, $P = 0.003$) and both BVMT-R total learning scores ($r = 0.65$, $P = 0.001$) and BVMT-R delayed recall scores ($r = 0.55$, $P = 0.008$).

In the NMOSD group, a significant correlation was observed between the gray matter volume (GM) and CVLT-II test in the learning phase. In addition, the total lesion percentage was negatively correlated with SDMT and CVLT-R [Table 5].

Table 2: Comparison of neuropsychological measures in patients with neuromyelitis optica spectrum disorder, multiple sclerosis, and healthy controls

Neuropsychological measures	Mean±SD			*P*		
	NMOSD	MS	HCs	NMOSD versus HCs	MS versus HCs	MS versus NMOSD
CVLT-II						
Total learning	52.3±11.2	48.7±12.4	54.6±8.4	>0.05	>0.05	>0.05
Delayed recall	10.7±3.3	10.2±2.8	12±2	>0.05	>0.05	>0.05
PASAT	42.7±13.4	41.5±12.4	48.6±8.1	>0.05	>0.05	>0.05
SDMT	45.5±14.3	44.1±14	57±9.5	<0.001	<0.001	>0.05
BVMT-R						
Total learning	9.4±3.4	7.1±3.7	10.4±2.18	>0.05	<0.001	<0.001
Delayed recall	0.89±0.06	0.81±0.07	0.88±0.06	>0.05	>0.05	>0.05
COWAT	26.4±10.2	25.9±9.8	36.6±9.8	<0.001	<0.001	>0.05
DKEFS						
Description sore	7.1±2.5	6.5±3	8.2±2.4	>0.05	>0.05	>0.05
Correct sort	22.7±8.9	21.6±10	27±8.9	>0.05	>0.05	>0.05
JLO	19.7±6.2	18.7±6.6	20.9±5	>0.05	>0.05	>0.05

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; COWAT=Controlled Oral Word Association Test; DKEFS=Delis–Kaplan Executive Function System; JLO=Judgment of Line Orientation Test; NMOSD=Neuromyelitis optica spectrum disorder; MS=Multiple sclerosis; HCs=Healthy controls; SD=Standard deviation

Table 3: Magnetic resonance imaging parameters in patients with neuromyelitis optica spectrum disorder and multiple sclerosis

Parameter	Mean±SD		*P*
	NMOSD (*n*=31)	MS (*n*=29)	
Brain volume			
TIV	1341.88±132.17	1279.21±315.00	0.360
WM	518.91±66.03	432.41±74.69	0.000
GM	679.39±62.62	649.04±54.44	0.083
Thalamus	10.61±1.28	8.72±1.94	0.000
Right thalamus	5.26±0.69	4.39±0.99	0.001
Left thalamus	5.35±0.61	4.32±0.96	0.000
Lesion			
Total lesion percentage	0.05±0.12	0.73±0.88	0.000

NMOSD=Neuromyelitis optica spectrum disorder; MS=Multiple sclerosis; TIV=Total intracranial volume; WM=White matter volume; GM=Gray matter volume

DISCUSSION

Our data showed that verbal fluency, information processing speed, and working memory were significantly impaired in both groups of NMOSD and MS compared to HCs. In our patients, visuospatial learning and memory function were significantly impaired in MS patients but not in NMOSD patients. MS patients were also significantly impaired in BVMT-R score compared to NMOSD patients and HCs.

While the study revealed that MS patients had higher impairment in most MCFIMS domains than NMOSD patients, the differences were insignificant. The only item significantly impaired in MS compared to NMOSD was visuospatial memory.

In a study by Blanc *et al*., lower scores in SDMT and digit span tests were reported in NMOSD and MS patients compared to HCs. They reported no differences between NMOSD and MS patients regarding cognitive function, which is consistent with our findings.[24] Moreover, impairment in visual processing speed and semantic fluency was reported in NMOSD. Eun Bin Cho reported an increased risk of dementia in MS and NMOSD patients with a higher rate in MS.[25]

Our results were consistent with a previous study reporting that cognitive performance was impaired mainly in perceptual organization, processing speed, and working memory in both MS and NMOSD patients, but with fewer cases of confidence interval (CI) in NMOSD patients.[26] However, contrary to our result, another study reported that visual memory was most affected in NMOSD.[27]

MS patients with a higher total lesion percentage and a smaller volume of the thalamus are more likely to suffer from cognitive impairment, especially in information processing speed, working memory, and verbal fluency. Our study also found that, compared to NMOSD, MS patients had a significantly lower volume of white matter and thalamus and a significantly higher total lesion percentage in the brain. Our results showed that there was a higher correlation between MRI parameters and neuropsychological domains in MS patients compared to NMOSD patients. On the other hand, visuospatial learning and verbal memory begin to occur in patients with reduced white matter volume. However, despite these structural differences, there was no significant difference in verbal fluency, information processing speed, and working memory between the two groups, indicating comparable cognitive performance. These findings suggest that there is a possibility of microscopic structural abnormalities in the brain of NMOSD patients, which cannot be seen in a normal brain MRI but can negatively affect cognitive function. Our

Table 4: Correlation of magnetic resonance imaging parameters and neuropsychological tests in relapsing-remitting multiple sclerosis patients

Parameters	Total lesion percentage	Thalamus	WM	GM	TIV
CVLT-II - total learning					
r	−0.68	0.71	0.49	0.32	0.43
P	0.001	<0.001	0.36	0.40	0.26
CVLT-II delayed recall					
r	−0.53	0.79	0.51	0.50	0.15
P	0.015	<0.001	0.003	0.13	0.13
BVMT-R total learning					
r	−0.59	0.41	0.65	0.55	0.36
P	0.005	0.22	0.001	0.34	0.48
BVMT-R delayed recall					
r	−0.64	0.72	0.55	0.11	0.562
P	0.002	<0.001	0.008	0.52	0.06
COWAT					
r	−0.51	0.58	0.40	0.43	0.31
P	0.02	0.006	0.49	0.10	0.24
SDMT					
r	−0.71	0.88	0.39	0.58	0.32
P	<0.001	<0.001	0.33	0.56	0.42

CVLT-II=California Verbal Learning Test, Second Edition; BVMT-R=Brief Visuospatial Memory Test-Revised; COWAT=Controlled Oral Word Association Test; SDMT=Symbol Digit Modalities Test; TIV=Total intracranial volume; WM=White matter volume; GM=Gray matter volume

Table 5: Correlation of magnetic resonance imaging parameters and neuropsychological tests in patients with neuromyelitis optica spectrum disorder

Parameter	Total lesion percentage	Thalamus	WM	GM	TIV
CVLT-II - total learning					
r	−0.18	0.34	0.50	0.54	0.32
P	0.22	0.53	0.43	0.004	0.42
CVLT-II delayed recall					
r	−0.47	0.20	0.35	−0.19	0.31
P	0.02	0.44	0.39	0.60	0.36
BVMT-R total learning					
r	−0.43	0.23	0.57	0.17	0.35
P	0.24	0.59	0.10	0.47	0.30
BVMT-R delayed recall					
r	−0.23	0.43	0.30	0.19	0.44
P	0.36	0.40	0.14	0.34	0.11
COWAT					
r	−0.59	0.51	0.29	0.49	0.27
P	0.24	0.45	0.45	0.14	0.23
SDMT					
r	−0.49	0.40	0.20	0.40	0.55
P	0.017	0.51	0.25	0.49	0.35

CVLT-II=California Verbal Learning Test, Second Edition; BVMT-R=Brief Visuospatial Memory Test-Revised; COWAT=Controlled Oral Word Association Test; SDMT=Symbol Digit Modalities Test; TIV=Total intracranial volume; WM=White matter; GM=Gray matter

results showed that in NMOSD patients, the reduction of gray matter volume is associated with verbal learning disorder, and the total white matter lesions are associated with information processing speed impairment and verbal learning and memory impairment.

Recent studies reported silent progressive brain atrophy and cortical thinning of the frontal cortex in NMOSD patients that can explain cognitive impairment in these patients.[28,29] We found a correlation between MRI parameters and some neuropsychological tests in each group. In the NMOSD group, there was a significant correlation between gray matter volume (GM) and verbal learning. In addition, the total lesion percentage negatively correlated with information processing speed and verbal memory. In a study by Blanc *et al*., cognitive dysfunction was associated with reduced white matter volume in NMOSD patients. Their results contradicted ours, as they did not find a relationship between gray matter volume and cognitive performance.[30] On the other hand, Kim *et al*. reported a reduction in thalamus volume in NMOSD patients with cognitive impairment.[31]

Another study reported significant atrophy of the thalamus in MS and NMOSD patients, but it was more severe in MS. The results of this study indicated a relationship between the severity of thalamus volume reduction and cognitive function in both diseases.[15]

In our study, the total brain lesion and thalamic volume significantly correlated with numerous components of neuropsychological tests in the MS group. A higher percentage of total brain lesions in MRI and a smaller thalamus volume are associated with multiple cognitive domain impairments including verbal memory, executive function, information processing speed, working memory, spatial memory, and verbal fluency. As can be seen, more cognitive domains were impaired in MS patients compared to NMOSD patients. These findings can be attributed to the idea that the brain structure involvement in MS is greater than in NMOSD.

In our study, MS patients had severe visuospatial memory impairment compared to NMOSD patients. Masuda *et al*. reported worse performance on specific cognitive variables in MS compared to NMOSD patients. They attributed this difference to a reduction in the volume of the left superior temporal gyrus.[11]

In line with our study, Moore *et al*. reported that cognitive function was similar in frequency and patterns in MS and NMOSD patients.[32] Vanotti *et al*. also reported that NMOSD patients experience disturbances in attention, visual memory, verbal memory, and verbal fluency, but their cognitive function is not significantly different from MS patients.[33,34]

Although several studies show a high prevalence of cognitive dysfunction in NMOSD and MS, there are some discrepancies in studies, which could be due to differences in ethnic backgrounds and the presence of confounding variables in statistical analyses. The main limitation of our study was the small sample size. Therefore, conducting more studies with a larger sample size is suggested for better clarification and more definitive conclusions.

CONCLUSIONS

Our study showed despite the lower total brain lesion load and less thalamic atrophy, NMOSD patients are at risk of cognitive impairment similar to MS patients.

Information processing speed, working memory, and verbal fluency were more affected than visuospatial memory in NMOSD patients.

These findings suggest microscopic structural abnormalities in NMOSD patients, not visible on conventional brain MRI. Further studies are needed to investigate the relationship between CI and microscopic structural abnormalities in the brains of NMOSD patients.

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Conflicts of interest

There are no conflicts of interest.

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