Cognitive Impairment in Neuromyelitis Optica

Ahmet YABALAK[1] , **Burcu ALTUNRENDE**[2] , **Gülşen AKMAN DEMİR**[2]

[1]Department of Neurology, VM Medical Park Pendik Hospital, İstanbul, Turkey
[2]Department of Neurology, Demiroğlu Bilim University Faculty of Medicine, İstanbul, Turkey

ABSTRACT

Introduction: There are few studies on cognitive impairment in neuromyelitis optica (NMO). The purpose of this study is to assess the factors that may be related with the frequency and level of cognitive impairment in Turkish NMO patients.

Methods: 22 patients with the diagnosis of NMO are evaluated retrospectively. Cognitive function was evaluated with Brief Repeatable Battery of Neuropsychological tests (BRB-N), Beck Depression Inventory (BDI) and Addenbrooke Cognitive Evaluation (ACE-R). The groups with and without cognitive impairment were compared according to age, sex, level of education, pathologic findings on cranial MRI, NMO Ig existence and EDSS score. The relation of the clinical, radiological and demographic values and patients' depression level was evaluated. The specificity and sensitivity of ACE-R test on detecting cognitive impairment were assessed through ACE-R test results.

Results: The mean age of the patients was 42.8±10.9.45.5% (n=10) of the patients had cognitive impairment and 50% (n=11) had depression.

The group with cognitive impairment had significantly older age, lower educational status, higher EDSS and BDI scores (p<0.05). The mostly affected cognitive domains were memory impairment, attention and processing dysfunction. When the specificity and sensitivity of ACE-R test on NMO patients were evaluated, diagnostic level of the test was found to be statistically good since it could detect cognitive impairment with a sensitivity of 88% and specificity of 75% on a cut off level of 82.5.

Conclusion: In our study, cognitive impairment and depression were detected in approximately half of the patients with BRB-N and BDI tests. It can be concluded that ACE-R test can be used to detect cognitive impairment in NMO patients. Since cognitive impairment and depression are frequent in NMO patients, it is important to assess the patients' cognitive functions and arrange the treatments to improve their quality of life, .

Keywords: Neuromyelitis optica, cognitive impairment, depression, BRB-N, ACE-R

INTRODUCTION

Neuromyelitis optica (NMO) is an inflammatory disease of the central nervous system, characterized by optic neuritis and longitudinal extensively transverse myelitis (LETM), which is usually relapsing but may also be monophasic, with a prevalence ranging from 0.53 to 4.4 per 100.000 population (1). The disease described by Eugene Devic in the 19th century, was thought to be a subtype of Multiple Sclerosis (MS) until recently. However, after the demonstration of autoantibodies against aquaporin 4 (Aqp4), the water channel protein of the central nervous system, it was determined that NMO is a different pathophysiological condition from multiple sclerosis (2). It has been reported in many studies over the last 20 years that cognitive impairment has been observed in MS patients and the cognitive functions such as working memory, attention, word fluency and information processing speed especialy are affected in MS patients (3, 4). Although cognitive complaints such as forgetfulness and attention deficit are observed in NMO patients similar to MS patients in clinical practice, there are very few studies about the cognitive impairment in NMO in the literature. The purpose of this study is to assess the factors that may be related with the frequency and level of cognitive impairment in Turkish NMO patients.

METHODS

22 patients with the diagnosis of neuromyelitis optica spectrum disorders (NMOSD) according to Wingerchuck 2015 diagnostic criteria (5) followed by Neurology outpatient clinic of Demiroglu Bilim University Faculty of Medicine were included in the study. The patiens' demographic data were obtained from their files which were reviewed retrospectively after obtaining the approval of the ethics committee. The inclusion criteria were; the diagnosis of NMO between 18–65 years of age, expanded disability status scale (EDSS) <7, not having severe visual impairment, severe hearing impairment and disability of hand movements, and not receiving steroid treatment in the last two months as it may affect cognitive functions. Exclusion criteria were; other neurological or psychiatric diseases and alcohol or substance addiction.

Brief Repeatable Battery of Neuropsychological tests (BRB-N), Beck Depression Invantery (BDI) and Addenbrooke Cognitive Evaluation (ACE-R) tests were used for evaluation. ACE-R test can be performed in approximately 16 minutes and includes a short mini mental test (6). BRB-N was developed to evaluate cognitive functions in MS; it consists

of a combination of tests 10/36 Spatial Recall Test (SPART), Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition Test (PASAT), Word-List Generation Test (WLG) and Selective Reminding Test (SRT) (7, 8). BDI, published by Beck et al. in 1961, is a test for simple and quick diagnosis of depression (9). In our study, normative data of Turkish population were used for BRB-N test. It was accepted that cognitive dysfunction was present in patients performing less than 5th percentile in at least two tests (10). In the Turkish validity and reliability study for the BDI test, it was accepted that patients with a cut-off score of 17 or higher had depression, while other patients had no depression (9, 11).

Data were analyzed with IBM SPSS Statistics 20.0 program. Descriptive statistical methods (mean, standard deviation) were used for the evaluation of the study data. Student's t-test was used for comparison of the normally distributed data and Mann-Whitney U test was used for the comparison of the non-normal distributed data between the two groups. In the comparison of two independent groups, Fisher's exact test was used if all expected values were less than two and Chi-Square test was used if all expected values were two or more.

When comparing two independent groups, Spearman correlation test was used to evaluate ordinal data and to test the linear relationship between two variables that do not show normal distribution. ROC curve analysis was used to measure the value of diagnostic tests. Significance level was accepted as $p \leq 0.05$ for all statistics.

RESULTS

In this study, 22 patients' data were retrospectively evaluated. Twenty women (90.9%) were included in the study. The mean age was 42.86±10.98 (range, 23–65) years, mean education time was 9.95±4.28 years, and the mean disease duration was 8.54±6.19 (range, 2–25) years. The mean number of attacks was 4.77±4.37 (range, 1–21) and the mean EDSS score was 3.45±1.70 (range, 1–6.5).

Other autoimmune diseases were seen in 7 patients (% 31.8); five patients had autoimmune thyroiditis, one had myasthenia gravis, and one had autoimmune thyroiditis, antiphospholipid antibody syndrome and Sjogren's syndrome.

There were 18 patients (81.8%) seropositive for anti-Aqp4 antibody and 4 patients (18.2%) were seronegative. None of the patients had anti-myelin oligodendrocyte glycoprotein (MOG) antibodies. Cranial magnetic resonance imaging (MRI) was normal in 13 cases (59.1%), while non-specific white matter lesions were observed in eight cases (36.4%) and periaquaductal brainstem lesion in one case (4.5%). Monophasic form was observed in 4 cases (18.2%) and relapsing form in 18 cases (81.8%). Demographic, clinical, serological and radiological characteristics of the patients are presented in Table 1.

According to the normative data of Turkish society, patients considered to have abnormal cognitive performance if their results were below the 5th percentile in at least two subtests of BRB-N test (10). Cognitive impairment was found in 45.5% of the patients (n=10).

There was a statistically significant relationship between cognitive impairment and advanced age (p=0.03) and lower education time (p=0.03), but no significant relationship was found between gender and marital status. While there was a significant relationship between cognitive impairment and high EDSS (p=0.01), no significant relationship was found between the number of episodes and duration of disease. There was no significant correlation between NMO Ig G antibody seropositivity, presence of other autoimmune disease and cranial MRI findings. The comparison of demographic, clinical and laboratory/radiological data of the groups with and without cognitive impairment is presented in Table 2.

Table 1. Demographic, clinical, serological and radiological characteristics of patients

Age (year), Mean ± SD (min., max)	42.86±10.98 (23–65)
Gender, n (%)	
Female	20 (90.9)
Male	2 (9.1)
Marital Status, n (%)	
Married	17 (77.3)
Single	3 (13.6)
Divorced	2 (9.1)
Education time (year), Mean ± SD (min., max)	9.95±4.28 (5–15)
Disease duration (year), Mean ± SD (min., max)	8.54±6.19 (2–25)
Number of attacks, Mean ± SD (min., max)	4.77±4.37 (1–21)
EDSS, Mean ± SS (min., max)	3.45±1.70 (1–6.5)
Additional autoimmune disease, n (%)	7 (31.8)
Pathological cranial MRI finding, n (%)	9 (40.9)
NMO IgG (+), n (%)	18 (81.8)
Disease form, n (%)	
Recurrent	18 (81.8)
Monophasic	4 (18.2)

EDSS, expanded disability status scale; MRI, magnetic resonance imaging; NMO, neuromyelitis optica; SD, standard deviation.

Table 2. Comparison of demographic, clinical and laboratory/radiological data of groups with and without cognitive impairment

	CI yes n=10 (% 45.5)	CI no n=12 (% 54.5)	P
Age, Mean ± SD (year)	48.40±10.90	38.25±9.05	0.03*
Education time, Mean ± SD (year)	7.90±3.79	11.75±3.93	0.03*
Gender, n (%)			
Female	10 (100)	10 (83.3)	0.48**
Male	0 (0)	2 (16.7)	
Martial status, n (%)			
Married	8 (80)	9 (75)	
Single	0 (0)	3 (25)	0.08***
Divorced	2 (20)	0 (0)	
Disease time, Mean ± SD (year)	9.20±6.03	8.00±6.53	0.58*
Number of attacks, Mean ± SD (year)	5.70±5.86	4.00±2.62	0.67*
EDSS, Mean ± SD (year)	4.55±1.78	2.54±0.96	0.01#
NMO, n (%)			
IgG (+)	10 (100)	8 (66)	0.09**
IgG (-)	0 (0)	4 (33)	
Pathological cranial MRI finding, n (%)			
Yes	6 (60)	3 (25)	0.09***
No	4 (40)	9 (75)	
Additional autoimmune disease, n (%)			
Yes	2 (20)	5 (42)	0.27***
No	8 (80)	7 (58)	

*Mann-Whitney U test; ** Fisher's exact test; *** Chi square test; #, Spearman correlation test; EDSS, expanded disability status scale; CI, cognitive impairment; NMO, neuromyelitis optica; SD, standard deviation.
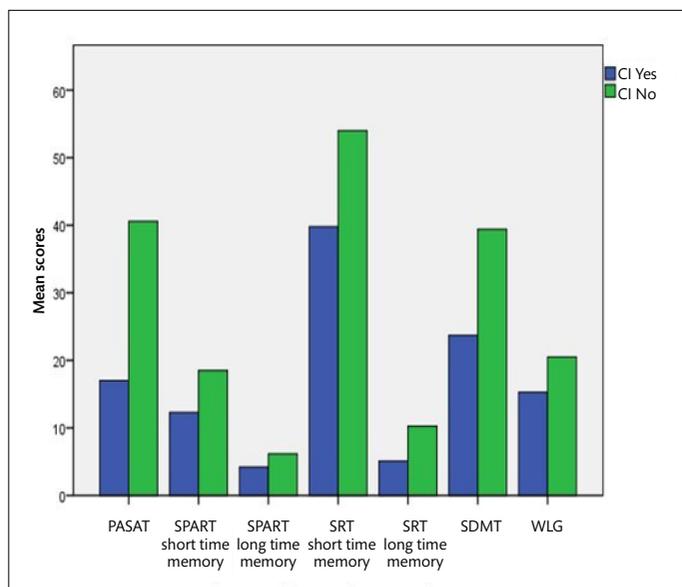
Figure 1. Mean BRB-N subgroup test scores of patients with and without cognitive impairment.

Table 3. Comparison of BRB-N subgroup test scores with and without cognitive impairment

	CI yes, n=10 (% 45.5)	CI no, n=12 (% 54.5)	P
Neuropsychological tests	**Mean ± SD**	**Mean ± SD**	
PASAT	17±7.70	40.58±12.43	0.00*
SPART Short time memory	12.3±4.24	18.5±5.97	0.01*
SPART Long time memory	4.2±2.74	6.16±2.44	0.10*
SRT Short time memory	39.8±6.46	54±5.47	0.00*
SRT Long time memory	5.1±1.37	10.25±1.48	0.00*
SDMT	23.7±10.33	39.41±10.67	0.003*
WLG	15.3±3.77	20.5±4.01	0.009*

* Mann-Whitney U test; CI: cognitive impairment; PASAT, paced audio serial addition test; SDMT, symbol digit modalities test, SPART, spatial recall test; SRT, selective reminding test; SD, standard deviation; WLG, word list generation test.

Table 4. Correlation of depression, age, education, duration of disease and number of attacks with neuropsychological tests

Neuropsychological test	BDI	Age	Education Time	Disease Time	Number of attacks
PASAT	-0.569**	-0.384	0.435*	-0.208	-0.152
SDMT	-0.318	-0.300	0.377	0.224	0.123
SRT Short time memory	-0.579**	-0.491*	0.533*	-0.164	-0.123
SRT Long time memory	-0.467*	-0.275	0.550**	0.029	-0.129
SPART Short time memory	-0.083	-0.201	0.375	0.007	-0.011
SPART Long time memory	-0.082	-0.410	0.223	0.208	0.143
WLG	-0.632**	-0.324	0.246	-0.116	0.079

Spearman correlation test, *p<0.01, **p<0.05; BDI, Beck depression inventory; PASAT, paced auditory serial addition test; SDMT, symbol digit modalities test; SPART, spatial recall test; SRT, selective reminding test; SD, standard deviation; WLG, word list generation test.

When the BRB-N subgroup test scores of patients with and without cognitive impairment were compared; a significant correlation was found between cognitive impairment and low PASAT score, low SPART short term memory score, SRT short (SRT-STM) and long term memory (SRT-LTM) scores, SDMT and WLG test score. There was no statistically significant difference between SPART long-term memory scores of patients with cognitive impairment (Figure 1/Table 3). Correlation analysis was performed between the mean scores of BRB-N subtests and BDI score, age, education time, disease duration and total number of attacks. Correlation analysis showed that PASAT test was positively correlated with education time, negatively with BDI score, SRT-STM test was negatively correlated with BDI score and age, education time was positively correlated, SRT-LTM test was negatively with BDI score, positively with education time and WLG test was negatively correlated with BDI score (Table 4).

Since ACE-R test was applied to 17 of 22 cases in our study, the results of these cases were evaluated. The mean ACE-R test scores were 81.64±12.68 (range, 42–96). Of the 17 patients who underwent ACE-R test, 8 (47%) had cognitive impairment with BRB-N test, while 9 (53%) had normal cognition. The mean ACE-R scores of patients with cognitive impairment detected by BRB-N test were 74.62±15.21 (range, 42–91). The mean ACE-R scores of the patients who were cognitively good
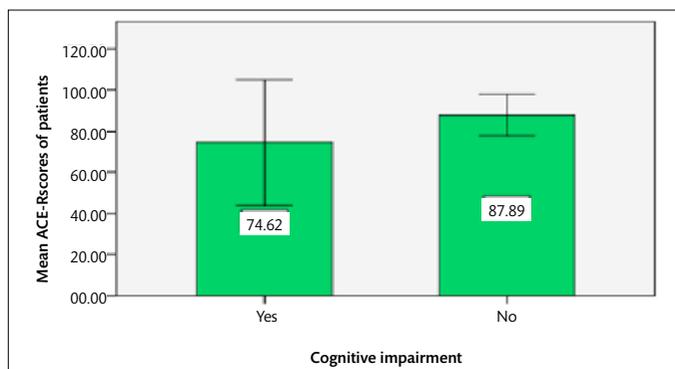

Figure 2. Mean ACE-R scores of patients with and without cognitive impairment. ACE-R scores of patients with cognitive impairment were significantly lower than patients without cognitive impairment (p=0.02).

were 87.89±5.11 (range, 81–96). ACE-R scores of patients with cognitive impairment were significantly lower than those without cognitive dysfunction (p=0.02) (Figure 2).

The ROC curve analysis performed to evaluate the sensitivity and specificity of ACE-R test in the detection of cognitive impairment in NMO
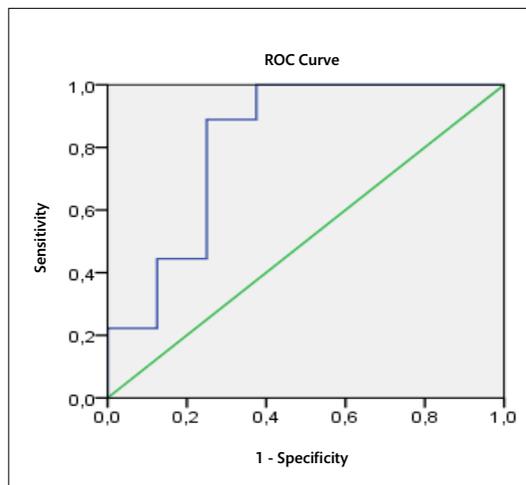
Figure 3. Roc curve for ACE-R test in diagnosis of cognitive impairment.

Figure 4. Mean BDI score of patients with and without cognitive impairment. BDI scores were found to be significantly higher in patients with cognitive impairment than in patients without cognitive impairment (p<0.01).

patients revealed that the area under the curve was 0.819. This means that the ACE-R test has a good diagnostic value in the detection of cognitive impairment (Figure 3). When the Roc curve coordinate values on the table is examined, the optimum cut-off value is found to be 82.5 which is closest to the upper left corner. The sensitivity of ACE-R test was 88% and specificity was 75% at 82.5 cut-off point in the detection of cognitive impairment in NMO patients.

The mean BDI scores of the patients included in the study were 16.95±9.67 (2–35). Depression was found in 50% (n=11) of patients who underwent BDI. No statistically significant difference was found between the two groups in terms of age, education level, number of attacks, disease duration, EDSS and gender (Table 5). BDI scores were significantly higher in patients with cognitive impairment than those without (p<0.01) (Figure 4). 8 (36%) patients out of 22 had both depression and cognitive impairment. When Chi-square test was used to evaluate the relationship between depression and cognitive impairment, a statistically significant correlation was found (p=0.01).
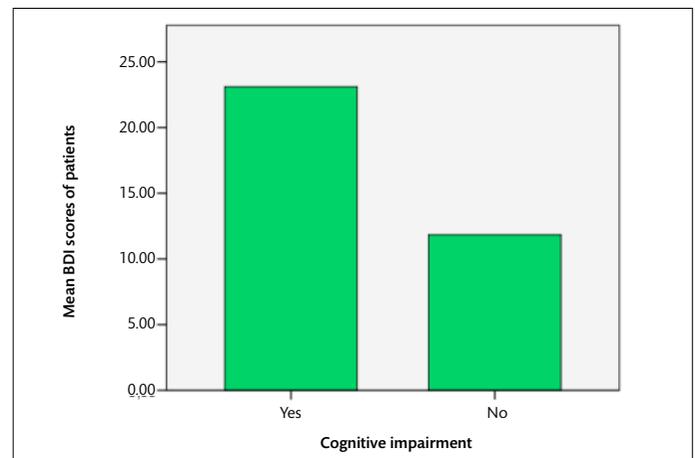
Table 5. Demographic and clinical data of patients with and without depression

	Depression Yes, n=11 (% 50)	Depression No, n=11 (% 50)	P
	Mean ± SD	Mean ± SD	
Age, Mean ± SD (year)	47.27±11.13	38.45±9.30	0.07*
Education time, Mean ± SD (year)	9.27±3.90	10.63±4.71	0.47*
Number of attacks, Mean ± SD (year)	6.18±5.74	3.36±1.68	0.27*
Duration of disease, Mean ± SD (year)	10.45±7.65	6.63±3.72	0.30*
EDSS, Mean ± SD (year)	4.04±1.69	2.86±1.56	0.09**
Gender, n (%)			
Female Male	11 (100) 0 (0)	9 (81.9) 2 (18.1)	0.23***

*Mann-Whitney U test; ** Spearman correlation test; *** Fisher's exact test; EDSS, expanded disability status scale; SD, standard deviation.

DISCUSSION

In NMO, cognitive impairment was reported in the range of 54–57% (12–14). In our study, cognitive impairment was found in 45.5% of the cases; which is slightly lower than the literature. The cases included in our study were relatively highly educated; there were no uneducated patients, and 31.8% of the patients were university graduates (15 years of education). Cognitive impairment may be affected by many factors such as age, and education level.

Although there have been conflicting reports in the literature that NMO patients may or may not have a significant relationship between age and cognitive impairment (13, 15), we found a significant relationship between advanced age and cognitive impairment in our study. In our study, there was no significant relationship between gender and marital status and cognitive impairment. It was observed that the frequency of cognitive impairment increased as the education level decreases and the EDSS score increases. Although there was no statistically significant relationship between cognitive impairment and EDSS in the studies (13, 15), it was reported that there was a significant relationship between disturbances in BRB-N battery subtests and EDSS (13, 15). There was no significant relationship between the disease duration, the number of attacks and anti-Aqp4 seropositivity and cognitive impairment in accordance with the literature (12, 13, 15).

In the study conducted by Blanc et al., NMO patients had a distinct "subcortical" type of cognitive dysfunction similar to the cognitive involvement observed in MS; information processing speed, attention, executive functions and memory deterioration (12). In the study performed by Dian et al., attention, information processing speed and short-term memory were impaired in NMO patients (16). Vanotti et al., reported that NMO patients had prominent word fluency, attention and memory impairment (14). In the study conducted by Saji et al., attention, verbal memory, information processing speed and visuospatial functions were observed in the foreground (13). In our study, selective recall test and 10/36 spatial recall tests were performed in 8 cases; in the symbol digit modalities test, verbal fluency test and PASAT tests, it was observed that 4 cases performed below the 5th percentile according to normative data. According to this data, the most commonly affected cognitive profile in patients were memory deficits, attention and executive functions. Although the cognitive profile was similar to MS patients, memory deficits were more prominent in our patients.

Imaging and pathology studies on the cause of cognitive impairment in MS patients have shown that brain atrophy and cortical demyelination

cause cognitive impairment (17, 18). Demyelination has been shown to be frequent in MS patients, especially in the cingulate, insular, frontal and temporal cortex (17). It has been shown that as MS becomes chronic, diffuse cortical demyelination develops and with transition to secondary progressive phase, demyelination affects 70% of the cerebral cortex and 90% of the cerebellar cortex (19, 20). In NMO patients, cognitive impairment develops even though no significant pathology was detected in conventional MRI examinations. Vanotti S. et al., reported that there was no significant difference in cognitive impairment in patients with and without cranial MRI abnormality (14).

In our study, no statistically significant difference was found between the cases with and without pathology in the brain MRI examination in terms of cognitive impairment. In the study performed by He et al., the presence of microscopic brain lesions in patients with normal brain MRI examination by diffusion tensor imaging (DTI) suggested that these lesions may be responsible for cognitive impairment. Neuropsychological tests showed a significant correlation between low scores and fractional anisotropy (FA), mean diffusivity (MD) values of the local areas of the corpus callosum, and it was shown that microscopic involvement may occur with cognitive impairment even if routine brain MRI examination was normal. In NMO patients, especially corpus callosum genu, splenium, trunk sections, medial frontal cortex and anterior cingulate cortex were found to be associated with microscopic involvement and cognitive impairment (16).

In the study conducted by Blanc et al., it was found that global and focal white matter volume decreased in NMO patients compared to healthy controls; NMO patients with cognitive impairment; global white matter volume was found to be statistically significantly lower than those without cognitive impairment. A significant correlation between neuropsychological test performance and white matter volume has been reported (15). Popescu et al., found that myelin was preserved in all cortical layers and increased astrogliosis. Although cortical demyelination was not observed despite the development of more severe neuronal damage in NMO patients, the pathology was thought to be different in MS and NMO, although the affected cognitive profile was similar (21).

When ACE-R scores of patients with and without cognitive impairment were compared, scores of patients with cognitive impairment were significantly lower. When the diagnostic power of ACE-R test was evaluated, it was found that the diagnostic value of cognitive impairment was found to be at a good level according to ROC curve analysis. The cut-off value in the detection of cognitive impairment was calculated as 82.5 with 88% sensitivity and 75% specificity. According to the study data, ACE-R test is a potential test for the diagnosis of cognitive impairment in NMO patients; It was considered that the studies to be performed in larger case groups would be more beneficial in order to evaluate the cut-off value and effectiveness of ACE-R test.

Depression may develop secondary to cognitive dysfunction and may be the first symptom of depression. There are contradictory results in studies on the coexistence of depression and cognitive impairment (22). Neu P. et al., reported that verbal memory and verbal fluency were impaired in severe depression attacks (23). When the studies conducted in MS patients are examined, there are different conclusions that there is a significant association between depression and cognitive impairment. Rao et al, observed that the lack of correlation between measurements of cognitive impairment and depression in MS patients suggests that depression will not be a causal factor in the development of cognitive impairment (24). It has been suggested that the relationship between depression and cognitive impairment is best correlated with working memory and information processing speed, and when depression is moderate, working memory, information processing speed and executive functions may be affected (25–27). The general view is that depression

affects cognitive and non-cognitive functions, but does not cause global cognitive deterioration, but also affects attention, ability to maintain attention and concentration, causing secondary memory impairment (25). Depression in MS patients has been shown to have a direct biological association with plaque and lesions in the CNS (28). There are studies suggesting that cognitive functions may improve with the treatment of depression in MS patients (29).

In a study conducted by Kawahara et al., depression was observed more frequently in patients with NMO than MS patients (30). The frequency of depression was 50% in our cases.

There was no significant correlation between depression and age, education, sex, total number of attacks, disease duration, EDSS score and cranial MRI.

The BDI score was found to be significantly higher in patients with cognitive impairment and a significant association was found between depression and cognitive impairment, in line with the literature (12, 16).

The limitations of our study were the low number of cases, the lack of a control group, the lack of evaluation in terms of symptoms such as fatigue and pain that may affect cognitive functions that may be associated with depression, and the lack of long-term follow-up data. However, in a rare disease as NMO, 22 cases from a single center is a significant number. It may be possible to evaluate cognitive functions by using volumetric and DTI imaging examinations on non-conventional MRI with further prospective, controlled studies.

In conclusion, although different pathogenic mechanisms occur in NMO patients, cognitive impairment is observed in a profile similar to MS patients (impaired attention, memory and executive functions) and to a considerable extent (45–57%).

Cognitive impairment in NMO, which may affect patients' daily life activities, work life and social life, is neglected due to limited time in outpatient clinic conditions, difficulty in accessing neuropsychological tests and financial reasons. Instead of BRB-N, the inexperienced ACE-R test can be used as a potential screening test in outpatient clinics in order to detect cognitive impairment in NMO patients.

In addition, it should be remembered that depression is common in NMO patients; it should be known that treatment of depression and cognitive impairment can significantly improve the quality of life of patients.

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