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Clinical, Demographic, and Radiological Characteristics of Patients Demonstrating Antibodies Against Myelin Oligodendrocyte Glycoprotein

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Background: Optic neuritis, myelitis, and neuromyelitis optica spectrum disorder (NMOSD) have been associated with antibodies against myelin oligodendrocyte glycoprotein-immunoglobulin G (anti-MOG-IgG). Furthermore, patients with radiological and demographic features atypical for multiple sclerosis (MS) with optic neuritis and myelitis also demonstrate antibodies against aquaporin-4 and anti-MOG-IgG. However, data on the diagnosis, treatment, follow-up, and prognosis in patients with anti-MOG-IgG are limited.

Aims: To evaluate the clinical, radiological, and demographic characteristics of patients with anti-MOG-IgG.

Study Design: Multicenter, retrospective, observational study.

Methods: Patients with blood samples demonstrating anti-MOG-IgG that had been evaluated at the Neuroimmunology laboratory at Ondokuz Mayıs University's Faculty of Medicine were included in the study.

Results: Of the 104 patients with anti-MOG-IgG, 56.7% were women and 43.3% were men. Approximately 2.4% of the patients were diagnosed with MS, 15.8% with acute disseminated encephalomyelitis (ADEM), 39.4% with NMOSD, 31.3% with isolated optic neuritis, and 11.1% with isolated myelitis. Approximately 53.1% of patients with spinal involvement at clinical onset demonstrated a clinical course of NMOSD. Thereafter, 8.8% of these patients demonstrated a clinical course similar to MS and ADEM, and 28.1% demonstrated a clinical course of isolated myelitis. The response to acute attack treatment was lower and the disability was higher in patients aged > 40 years than patients aged < 40 years at clinical onset. Oligoclonal band was detected in 15.5% of the patients.

Conclusion: For patients with NMOSD and without anti-NMO antibodies, the diagnosis is supported by the presence of anti-MOG-IgG. Furthermore, advanced age at clinical onset, Expanded Disability Status Scale (EDSS) score at clinical onset, spinal cord involvement, and number of attacks may be negative prognostic factors in patients with anti-MOG-IgG.

INTRODUCTION

Conditions such as neuromyelitis optica (NMO) neuromyelitis optica spectrum disorder (NMOSD), optic neuritis, and myelitis may be found in association with the presence of antibodies against myelin oligodendrocyte glycoprotein-immunoglobulin G (anti-MOG-IgG). Although rare, presence of anti-MOG-IgG may also be demonstrated in patients diagnosed with multiple sclerosis (MS).[1] Patients with an isolated/recurrent optic neuritis and myelitis who also demonstrate atypical radiological and demographic features of MS can be evaluated for anti-myelin oligodendrocyte glycoprotein-associated disorders (MOGAD). The relationship of anti-MOG-IgG positivity with such clinical profiles and its prognostic importance are becoming increasingly crucial. The clinical position of anti-MOG-IgG positivity in terms of diagnosis, treatment, patient follow-up, and prognosis remain unknown.

Neuromyelitis optica spectrum disorder is an autoimmune chronic inflammatory disease that causes demyelination and axonal degeneration in the central nervous system. Currently, anti-NMO antibodies and anti-MOG-IgG can be detected using a cell-based immunoassay.[2] In patients with NMOSD and without anti-NMO antibodies, the presence of anti-MOG-IgG may vary between 10-40%.[3,4] This rate may vary according to the clinical subtype of the patients, and further studies are needed on the subject. Rarely, anti-NMO antibodies and anti-MOG-IgG can be positive together in NMOSD.[5] Anti-MOG-IgG positivity may be seen in patients of all age groups. Positivity in patients with pediatric NMOSD is more prevalent among those with acute disseminated encephalomyelitis (ADEM).[6,7] Anti-MOG-IgG should be preferably identified before initiating the acute attack treatment (high-dose steroids and/or plasmapheresis). These treatments may affect the serum antibody titer. Thus, if anti-MOG-IgG is not detected despite clinicoradiological features

suggesting anti-MOG-IgG positivity, the test can be repeated during this period. Anti-MOG-IgG may be detected by tests later during the clinical course.[8]

Treatment of patients with anti-MOG-IgG should be planned after considering the clinicoradiological features and other laboratory parameters. Although high-dose intravenous (IV) steroid is the first choice during acute attacks, plasmapheresis can be performed if there is no response to IV steroids.[9] Because patients with ADEM only have a single clinical episode, no additional treatments other than acute attack treatment is recommended.[9-11] In patients with NMOSD and anti-MOG-IgG, immune treatments are administered according to the number of clinical attacks, affected systems, and radiological features. Furthermore, azathioprine and rituximab are commonly used as immunomodulatory treatment (IMT).[9,12,13]

In this study, we aimed to evaluate the clinical, radiological, and demographic characteristics of patients with anti-MOG-IgG.

MATERIALS AND METHODS

Study population

Patients in whom serum samples were found to be positive for anti-MOG-IgG at the Neuroimmunology laboratory of Ondokuz Mayıs University's Faculty of Medicine between January 2018 and September 2020 were included in the study. The patients included in the study were from 38 different centers. All the samples were collected after the first attack and before the initiation of acute attack treatment. Patients with anti-MOG-IgG after the initial attack were included in the study. The clinical, radiological, and demographic characteristics of the patients were retrospectively obtained from the data records of neurology specialists at the centers where patients were being treated. The parameters assessed were sex, age, initial complaint, diagnosis, magnetic resonance imaging (MRI) findings, oligoclonal band (OCB) positivity, response to the acute attack treatment, total number of acute attacks, IMT responses, and Expanded Disability Status Scale (EDSS) score. Anti-MOG-IgG was analyzed using a cell-based immunoassay and an Euroimmune kit. The OCB in the serum and cerebrospinal fluid (CSF) of all the included patients were measured using the isoelectric focusing method. Brain MRI that demonstrated involvement of areas such as the periventricular, juxtacortical, and cerebellar peduncles regions were considered typical for MS, and involvement of areas other than these regions were considered atypical for MS. The study was approved by Ondokuz Mayıs University's Clinical Research Ethics Committee (approval number: OMÜ KAEK 2020/582, date: 09.10.2020).

Statistical analysis

The data was analyzed using IBM SPSS 20.00 program. For normally distributed data, two independent groups were compared using the t-test, and more than two independent groups were compared using the ANOVA test. For data that were not normally distributed, two independent groups were compared using the Mann-Whitney U test, and more than two groups were compared using the Kruskal-Wallis test. Data with more than two replicates were analyzed using the Friedman test, and the correlations were analyzed using the Spearman's rank correlation. The relationship between qualitative variables was evaluated with the Pearson's and Fisher's chi-square tests. The prognostic factors affecting the final EDSS score were determined using multiple linear regression analysis. Statistical significance was set at $p < 0.05$.

RESULTS

Analysis of clinical and demographic data

The study included 104 patients in whom the serum tested positive for anti-MOG-IgG. Of the 104 patients, 56.7% were women and 43.3% were men. The female/male ratio was 1.3/1.

The study included a range of patients, the youngest being age 5, and the eldest at 76 years of age. The mean age was 33.46 while the median age was 33. Although the initial EDSS score evaluated at the time of diagnosis varied between 0 and 8, the mean EDSS score was found to be 2.85 and the median EDSS score was 3. The final EDSS evaluation of the patients during the study inclusion period varied between 0 to 7.5, with a mean EDSS score of 1.59 and a median EDSS score of 1. The lowest attack count was 1 and the highest was 15. The mean number of attacks was 2.55 while the median number of attacks was 1.

The patients initially presented with spinal cord involvement (33.7%), optic neuritis (45.5%), and other complaints (20.8%). In 10 patients, the brain stem was involved first. Six of these patients presented with symptoms indicative of area postrema involvement such as nausea, vomiting, and hiccups. Approximately 2.4% of the patients were diagnosed with MS, 15.8% with ADEM, 39.4% with NMOSD, 31.3% with isolated optic neuritis, and 11.1% with isolated myelitis (Table 1).

The involvement findings of brain and spinal MRI of the patients are shown in Table 2. Approximately 52.5% of the brain MRIs were normal, whereas 18.1% and 29.2% demonstrated typical and atypical involvement for MS, respectively. Cervical MRIs revealed the involvement of < 2 segments and > 2 segments in 16.5% and 23.1% of the patients, respectively. However, 60.4% of the cervical MRIs were normal. Thoracic MRI revealed the involvement of < 2 segments and > 2 segments in 16.9% and 19.3% of the patients, respectively. However, 63.9% of the thoracic MRIs were normal. Lumbar MRIs demonstrated the involvement of < 2 segments in 12.7% of the patients. However, 87.3% of the lumbar MRIs were normal. The number of patients with lumbar involvement was less than those with cervical involvement, and conus medullaris involvement was observed.

Oligoclonal band analysis revealed that 15.5% of the patients had OCB type 2 positivity (presence of IgG bands in the CSF but not in the serum). An OCB was not detected in 84.5% of the patients.

Examination of the relationship between variables

The patients' age and sex distribution, response to first acute attack treatment, and clinical follow-up diagnosis were compared. There

was no difference in age distribution based on sex. Additionally, there was no correlation between the clinical follow-up diagnosis and age. The patients who completely responded to the first attack treatment were younger than those who partially responded. The mean age of the patients demonstrating partial treatment response was higher than those demonstrating complete treatment response ($p = 0.001$) (Table 3).

There was a statistically significant correlation between the first and final EDSS scores ($p < 0.001$). The most recent EDSS score was significantly lower than the initial score. Although there was no significant difference in the first EDSS score between the age groups (> 40 years and < 40 years, $p = 0.931$), there was a significant difference in the final EDSS score between the age groups ($p < 0.001$). Patients aged > 40 years had a higher final EDSS score than patients aged < 40 years. Furthermore, the first EDSS score was significantly different according to the initial symptom of the first acute attack ($p = 0.020$). However, there was no significant difference between the first and final EDSS scores according to sex ($p = 0.321$ and $p = 0.138$, respectively). Although the first EDSS score of patients with initial spinal cord involvement was higher than the EDSS score of patients with other initial symptoms, there was no significant difference in the final EDSS score ($p = 0.521$) (Table 4).

TABLE 1. Demographic Characteristics of the Patients Demonstrating anti-MOG-IgG.

Variables		n	%
Sex	Female	59	56.7
	Male	45	43.3
Initial complaint	Spinal complaints	34	33.7
	Optic neuritis	46	45.5
	Others	21	20.8
Diagnosis	MS	3	2.4
	ADEM	15	15.8
	NMOSD	39	39.4
	Isolated optic neuritis	31	31.3
	Isolated myelitis	11	11.1

anti-MOG-IgG, antibodies against myelin oligodendrocyte glycoprotein-immunoglobulin G; MS, multiple sclerosis; ADEM, acute disseminated encephalomyelitis; NMOSD, neuromyelitis optica spectrum disorder.

TABLE 2. Clinical, Radiological, and CSF Findings of the Study Patients.

Variables		n	%
Brain MRI	Normal	52	52.5
	Typical for MS	18	18.1
	Atypical for MS	29	29.2
Cervical MRI	Involvement of < 2 segments	15	16.5
	Involvement of > 2 segments	21	23.1
	Normal	55	60.4
Thoracic MRI	Involvement of < 2 segments	14	16.9
	Involvement of < 2 segments	16	19.3
	Normal	53	63.9
Lumbar MRI	Involvement of < 2 segments	8	12.7
	Normal	55	87.3
	Non-user	24	23.1
	Azathioprine use	58	55.8
	Rituximab use	22	21.2
Oligoclonal band	Positive	13	15.5
	Negative	71	84.5

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

Brain MRIs revealed a lesion in 94.1% of the patients diagnosed with MS and ADEM, 51.4% of the patients with NMOSD, 20% of the patients with isolated optic neuritis, and 36.4% of the patients with isolated myelitis.

The factors affecting the patients' final EDSS score as well as the relationship between the disease course and final EDSS score that is necessary for identifying the prognostic indicators such as age, sex, first acute attack treatment response, diagnosis groups, total number of acute attacks, and IMT responses were investigated. Multiple linear regression analysis revealed that the final EDSS score was low in young patients with a good response to the first acute attack treatment, a low total number of attacks, and good response to IMT. This model explained 42% of the variation in the final EDSS score. Sex and clinical diagnoses were not significantly correlated with the final EDSS score (Table 5).

DISCUSSION

Neuromyelitis optica spectrum disorder is a rare inflammatory disease of the central nervous system that is less prevalent than MS. Patients may present with clinical features related to the involvement of the optic nerve, spinal cord, and area postrema. In patients with NMOSD but without anti-NMO antibodies, anti-MOG-IgG may be present. Although patients with anti-MOG-IgG usually present with clinical features similar to those of MS and anti-NMO-positive NMOSD, they can also present with a spectrum of neurological findings related to the involvement of cerebral gray matter, white matter, and meninges.

In our study, 33.7% of the patients first presented with spinal cord involvement, 45.5% presented with optic neuritis, and 20.8% presented with other complaints. This indicates that optic neuritis and myelitis are the primary complaints at the beginning of the

TABLE 3. Relationship Between Age and the Patient's Sex, Response to Acute Attack Treatment, and Clinical Follow-up Diagnosis.

		n	Mean age	S	t/F	*p*
Sex	Female	59	32.95	15,056	-0.433	0.666
	Male	45	34.13	12,009		
Response to acute attack treatment	Complete	55	29.15	11,696	-3.421	**0.001***
	Partial	43	38.26	14,674		
Clinical follow-up diagnosis	MS	3	29.31	18,402	1.02	0.387
	ADEM	15	22.42	17,301		
	NMOSD	39	35.56	15,136		
	Isolated optic neuritis	31	34.42	9,743		
	Isolated myelitis	11	33.82	9,250		

MS, multiple sclerosis; ADEM, acute disseminated encephalomyelitis; NMOSD, neuromyelitis optica spectrum disorder.

TABLE 4. Relationship Between Clinical and Demographic Characteristics and the First and Last EDSS Scores.

		Minimum	Maximum	Range	Median	IQR	*p*
First EDSS		0.00	8.00	8.00	3.00	2	**<0.001***
Last EDSS		0.00	7.50	7.50	1.00	1	
First EDSS	Age ≤ 40	0.00	8.00	8.00	3.00	2	0.931
	Age > 40	0.00	8.00	8.00	3.00	2	
Last EDSS	Age ≤ 40	0.00	5.00	5.00	1.00	2	**<0.001***
	Age > 40	0.00	7.50	7.50	2.50	2	
First EDSS	Female	0.00	5.00	5.00	3.00	2	0.321
	Male	1.00	8.00	7.00	3.00	2	
Last EDSS	Female	0.00	7.50	7.50	1.00	2	0.138
	Male	0.00	6.00	6.00	1.50	1	
First EDSS	Spinal involvement	0.00	8.00	8.00	3.00[a]	2.13	**0.020***
	Optic neuritis	1.00	4.50	3.50	2.50[a,b]	2.00	
	Others	0.00	4.50	4.50	2.00[b]	2.00	
Last EDSS	Spinal involvement	0.00	6.00	6.00	1.50	1.63	0.521
	Optic neuritis	0.00	5.00	5.00	1.00	2.00	
	Others	0.00	7.50	7.50	1.00	0.63	

EDSS, Expanded Disability Status Scale; IQR, interquartile range.

TABLE 5. Multiple Linear Regression Analysis to Identify the Factors Affecting the Final EDSS Score.

	B	Std. error	t	*p*	Adjusted R-squared
(Constant)	-1.667	0.623	-2.676	**0.010**	0.420
Age	0.036	0.010	3.725	**<0.001***	
Sex	0.269	0.233	1.154	**0.253**	
Response to attack treatment	0.564	0.250	2.258	**0.028***	
Diagnosis	-0.167	0.099	-1.688	**0.097**	
Total number of attacks	0.096	0.044	2.170	**0.034***	
Response to immune treatment	0.685	0.246	2.789	**0.007***	

EDSS, Expanded Disability Status Scale; Std, standard

clinical course. The clinical onset of myelitis is more frequently seen in NMOSD than in MS, and this frequency distribution is similar to that seen in NMO.[14] The other clinical findings at initial presentation were encephalopathy, nausea and vomiting, hiccups, diplopia, and clinical features related to brain stem involvement. Approximately 2.4% of the patients were diagnosed with MS, 15.8% with ADEM, 39.4% with NMOSD, 31.3% with isolated optic neuritis, and 11.1% with isolated myelitis. This clinical distribution demonstrates the importance of the clinical picture of MOGAD in determining the differential diagnosis of isolated myelitis and isolated optic neuritis if no other etiology is identified. Thus, acute attacks may be the most common clinical form of MOGAD, and the presence of anti-MOG-IgG should be considered to differentiate this condition from similar attacks seen in MS and NMO.

We did not find a significant correlation between the initial complaint of the patients and the age groups. The frequency distribution of the first complaint was similar between patients aged > 40 years and those aged < 40 years. However, there was no significant relationship between the initial symptom and the patient's clinical form. These results indicate that the initial symptom at clinical onset and the clinical course of anti-MOG-IgG positivity were similar in both age groups. Furthermore, patients with an MS- and ADEM-like clinical course had a lower mean age of disease onset than those with other clinical forms; however, this difference was not statistically significant. This may be attributed to the small number of pediatric patients included in our study. Patients with anti-MOG-IgG with disease onset in childhood have a more ADEM-like clinical course than those with disease onset in adulthood.[9,13] Due to the low number of pediatric patients in our study, this difference may not have gained statistical significance. In approximately 50% of the patients with a clinical onset earlier than 40 years of age, the initial presentation was optic neuritis. In patients aged > 40 years, the prevalence of optic neuritis was 32%. Thus, the most common presentation at disease onset in both groups was optic neuritis. This result indicates that the presence of anti-MOG-IgG should be considered when determining the differential diagnosis of optic neuritis, regardless of age.

We found a significant correlation between the initial complaint of the patients with MOGAD and the diagnosis received. Among the patients whose initial complaint was related to spinal involvement, 53.1% demonstrated a clinical course of NMOSD, 18.8% demonstrated a clinical course similar to MS and ADEM, and 28.1% demonstrated a clinical course of isolated myelitis. Among the patients whose first complaint was optic neuritis, the presenting attack was the only episode in 56.8% of the patients. These results indicate that compared to patients with spinal cord involvement at the time of disease onset, those with optic nerve involvement were more likely to have an isolated attack without any recurrences. Approximately 9.1% of the patients with optic neuritis at disease onset demonstrated an MS- and ADEM-like clinical course. This percentage which was considerably lower than that of patients with spinal cord involvement at disease onset. Thus, the probability of an MS- and ADEM-like clinical course is higher in patients with initial spinal cord involvement than in those with initial optic involvement. Similarly, in patients with initial spinal cord involvement, NMOSD was significantly more prevalent than optic neuritis. These study findings indicate that initial spinal cord involvement in patients with anti-MOG-IgG may be a negative prognostic factor. Spinal cord involvement in MS, ADEM and NMOSD are also generally accepted as unfavorable prognostic factors.

Patients with MS and anti-MOG-IgG were patients who were definitively diagnosed with MS according to the 2017 revised McDonald criteria. In our study, 94.1% of the study patients with an ADEM- and MS-like clinical course demonstrated an involvement that was typical or atypical for MS on brain MRI. The rates were 51.4%, 36.4%, and 20% in patients with NMOSD, isolated myelitis, and isolated optic neuritis, respectively. There was no similar relationship between spinal cord MRI findings and clinical course. The rate of involvement of > 2 segments in cervical MRIs was 23.1% in patients with anti-MOG-IgG. This rate was higher than that in patients with MS and lower than that in patients with NMOSD,[15,16] and in between that of these two groups in patients with MOGAD. In thoracic MRIs, the rates of involvement of < 2 and > 2 segments were 16.9% and 19.3%, respectively, which was similar to the frequency of involvement in the cervical region. Cervical region involvement is higher in patients with MS than in patients with NMOSD.[17] In our study, the rate of cervical spine involvement was similar to the rate of thoracic spine involvement in patients with MOGAD; however, this similarity was not seen in patients with MS or NMOSD. Furthermore, the lumbar spine was rarely affected in patients with MS. Lumbar spine involvement is reportedly slightly higher in patients with NMOSD than in patients with MS.[17] In our

patients with anti-MOG-IgG, the rate of lumbar spine involvement on MRI was 12.7%. This rate was higher than that in patients with MS and NMO. Thus, our study findings indicate that the presence of anti-MOG-IgG should be considered in the differential diagnosis of lumbar spinal cord pathologies, especially in patients with advanced age and subacute paraparesis.

For patients with MOGAD, effective immunotherapies are used on the basis of clinical, radiological, and demographic characteristics. The aim of the treatment is to reduce the clinical and radiological attacks in the patients and prevent possible disease progression. IMTs that are sometimes used in the treatment of MS may also be included after considering the clinical, hematological, CSF, and radiological findings of the patients, especially those with an MS-like course. In our patients with anti-MOG-IgG, the clinical and radiological findings were similar to that of NMOSD, which is similar to the findings of previous studies.[18]

In our study, the mean initial EDSS score demonstrated a wide range (0-8), which was wider that the range in patients with MS. The high rate of spinal involvement and an extended spinal cord involvement in patients with anti-MOG-IgG are important factors that increase patient disability at clinical onset.[19,20] In our study, the EDSS score was higher in patients with spinal cord involvement than in patients with other initial presentations. Furthermore, the rate of disability statistically significantly decreased after acute attack treatments and immunotherapy. Regardless of the disability and affected system at clinical onset, clinical well-being can be achieved via acute attack treatments and prophylaxis with immunotherapy. In our study, the relationship between treatment and age at clinical onset (< 40 years and > 40 years) demonstrated similarities. The treatment for acute attacks in patients aged < 40 years at disease onset produced a better response than immunotherapy shown to be effective for the disease. Thus, advanced age at clinical onset may be a negative prognostic factor. The final EDSS score was statistically significantly higher patients with cervical spine involvement than in patients with thoracic or lumbar spine involvement. Furthermore, there was a positive correlation between the final EDSS score and the total number of attacks. This relationship was weaker than the relationship between EDSS and spinal cord involvement and age at clinical onset. However, the EDSS score was not related to the patient's sex. In our study, clinical onset and course were similar in both sexes. Male sex is a known poor prognostic factor in patients with MS.[21] Thus, our study findings indicate that unlike in patients MS, sex is not a negative prognostic factor in patients with anti-MOG-IgG.

An OCB was detected in 15.5% of the patients with anti-MOG-IgG, which is similar to the positivity rate in patients with NMOSD. OCB positivity is reportedly > 90% in patients with MS.[9,18,22] Thus, similar to patients with NMOSD, patients with anti-MOG-IgG may rarely demonstrate OCB positivity in CSF samples.[18,20,21]

This study has several limitations. One such limitation was that the long-term clinical and radiological data of patients with anti-MOG-IgG were scarce. Additionally, the immunotherapies used varied between patients and data on long-term treatment response were insufficient. Further studies evaluating biomarkers other than OCB in blood or CSF samples in patients with MOGAD are required to better understand the disease's immunopathogenesis and clinical course.

The presence of anti-MOG-IgG may be helpful in the diagnosis of patients with NMOSD who do not demonstrate anti-NMO antibodies. Patients with anti-MOG-IgG can be of any age, with an almost equal sex distribution. In patients with anti-MOG-IgG, advanced age at clinical onset, high initial EDSS score, spinal cord involvement, and high number of attacks may be unfavorable prognostic factors. Clinical studies with a larger sample size are needed to determine the relationship between anti-MOG-IgG presence and the clinical course and treatment responses in patients with anti-MOG-IgG.

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