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The Clinical and Radiologic Features of Patients with Myelin Oligodendrocyte Glycoprotein (MOG) Antibody-Associated Disease (MOGAD) in the City of Sakarya, Türkiye

Türkiye, Sakarya İlinde Myelin Oligodendrosit Glikoprotein (MOG) Antikor İlişkili Hastalığı (MOGAD) Olan Hastaların Klinik ve Radyolojik Özellikleri

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ABSTRACT

Objective: The study aims to share our knowledge on myelin oligodendrocyte glycoprotein antibody (anti-MOG) seropositivity in patients with demyelinating diseases, focusing on their clinical, serologic, and radiologic characteristics, as well as treatment options for MOG associated disease (MOGAD) cases.

Methods: This retrospective study included 332 of 450 demyelinating disease cases, aged 18 to 65 years, who were referred to our clinic from 2017 to 2023 with clinical and/or radiological signs of demyelination, followed by testing for the anti-MOG antibody. We applied the revised 2017 McDonald criteria and the 2023 MOGAD diagnostic criteria to those who tested positive for anti-MOG. Cases of anti-MOG seronegative multiple sclerosis (MS) and non-MOGAD were excluded. We detailed the clinical, serologic, and radiologic characteristics and treatment protocols of anti-MOG-positive/low-positive cases.

Results: Among the cases, 16 were clear/low anti-MOG seropositive; of these, 10 were diagnosed with MOGAD, three were MS associated with anti-MOG seropositivity, and three were considered possible MOGAD and followed up. Four MOGAD cases (40%) were double positive for anti-MOG and oligoclonal bands. Three MOGAD cases also had autoimmune diseases. Rare clinical presentations included sixth cranial nerve palsy, tetraparesis secondary to acute disseminated

ÖZ

Amaç: Çalışmamız demyelinizan hastalığa sahip olgularımızda miyelin oligodendrosit glikoprotein antikoru (anti-MOG) seropozitifliğini ve MOG ilişkili hastalıklar (MOGAD) tanısı alan olgularımızda klinik, serolojik, radyolojik özellikleri, tedavi seçenekleri hakkındaki deneyimlerimizi paylaşmayı amaçlamaktadır.

Yöntemler: Bu retrospektif çalışmaya, 2017-2023 yılları arasında kliniğimize klinik ve/veya radyolojik demiyelinizasyon bulgularıyla sevk edilen, 18-65 yaş aralığındaki 450 demiyelinizan hastalık olgusundan, anti-MOG antikor testi yapılan 332'si dahil edildi. Anti-MOG pozitif olgulara revize edilmiş 2017 McDonald kriterlerini ve 2023 MOGAD tanı kriterlerini uyguladık. Anti-MOG pozitif/düşük pozitif vakaların klinik, serolojik ve radyolojik özelliklerini ve tedavi protokollerini ayrıntılı olarak açıkladık. Anti-MOG seronegatif multipl skleroz (MS) ve non-MOGAD olguları çalışma dışı bırakıldı. Anti-MOG pozitif/düşük pozitif olguların klinik, radyolojik özellikleri ve tedavi protokolleri incelendi.

Bulgular: Üç yüz otuz iki olgudan anti-MOG pozitif 16 olgu tespit edildi. Üçü anti-MOG sero-pozitifliğinin eşlik ettiği MS, 10'u MOGAD tanısı aldı. Üç olgu ise olası MOGAD olarak değerlendirildi ve yakın takibe alındı. MOGAD'da eşlikçi oto-immun hastalıklar 3 olgumuzda mevcuttu. Dört olgumuz anti-MOG ve oligoklonal bant dual pozitifliğine sahipti (%40). MOGAD olgularımızdaki ender klinik prezentasyonları sırasıyla;

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ABSTRACT

encephalomyelitis, wall-eyed bilateral internuclear ophthalmoplegia and progressive transverse myelitis in adulthood. A total of 300 cases were diagnosed with MS, and 1% of these cases were anti-MOG with low levels of seropositivity.

Conclusion: The pathogenesis, treatment, and prognosis of MOGAD differ from those of other demyelinating diseases. We aim to highlight the importance of recognizing MOGAD due to its potential association with autoimmune diseases, progressive nature, and dual seropositivity. Thus, it should be considered for its unique clinical and radiologic features.

Keywords: Myelin oligodendrocyte glycoprotein, MOG, myelin oligodendrocyte glycoprotein antibody associated disease, atypical demyelinating diseasesi MOGAD.

ÖZ

altıncı kraniyal sinir tutulumu, erişkinlik döneminde akut dissemine ensefelomiyelit, Wall-eyed bilateral internükleer oftalmopleji kliniği ve progresif seyirli transvers myelit kliniğine sekonder tetraparezi idi. Üç yüz otuz olgu MS tanısı aldı. MS olgularında anti-MOG düşük-seropozitifliği %1 idi.

Sonuç: MOGAD'ın patogenezi, tedavisi ve prognozu diğer demiyelinizan hastalıklardan farklıdır. Çalışmamızda nadiren otoimmün hastalıklarin eşlikçi olduğu, progresif seyrin ender olduğu, dual sero-pozitiflik gösterebilen MOGAD'a dikkat çekmek, klinik ve radyolojik özellikleriyle akılda tutulması gereken bir hastalık olduğunu vurgulamak istedik.

Anahtar Sözcükler: Miyelin oligodendrosit glikoprotein, MOG, miyelin oligodendrosit glikoprotein ilişkili hastalıklar, atipik demiyelinizan hastalıklar, MOGAD

INTRODUCTION

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) has been identified as a distinct immune-mediated demyelinating disease of the central nervous system, and recently published diagnostic criteria for MOGAD have facilitated its identification (1,2). Although the global prevalence of the disease is still uncertain, studies suggest an incidence of 1.6-3.4 cases per million people per year in Europe, with a prevalence of 20 per million (3,4). The median age of onset is between 20 and 30 years, with similar frequencies observed in both genders (2,5).

Clinically, MOGAD is characterized by either monophasic or relapsing attacks that may include unilateral or bilateral optic neuritis (ON), acute disseminated encephalomyelitis (ADEM), cerebral monofocal or polyfocal deficits, brainstem or cerebellar deficits, and cerebral cortical encephalitis, often associated with epilepsy (2). The phenotype varies with age of onset, typically presenting as ON in adults and ADEM in children (6). The histopathologic mechanisms of MOGAD are distinct from other demyelinating diseases, such as multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD), and this distinction extends to imaging features, treatment options, and responses. Standard immunomodulatory treatments for demyelinating diseases are often ineffective in MOGAD and may even worsen the disease (7,8).

In this study, we investigated the presence and frequency of MOG antibodies in a cohort of patients with demyelinating diseases, along with the clinical, radiologic, and serologic features and treatment options for these cases based on the 2023 MOGAD diagnostic criteria in Sakarya, Türkiye.

MATERIALS AND METHODS

Patient Selection

This study has a single-center, retrospective, observational research design. Following our inclusion criteria, we included patients aged 18 to 65 years with one or more demyelinating diseases, such as ON, myelitis; cerebral monofocal or polyfocal deficits; brainstem or cerebellar deficits; or cerebral cortical encephalitis often associated with epilepsy, along with typical or atypical demyelinating lesions on cranial and spinal magnetic resonance imaging (MRI). A total of 450 cases were referred to our outpatient demyelinating disease clinic between 2017 and 2023. Patients who were not tested for MOG antibodies were excluded (n=96). We collected demographic, clinical, radiologic, and serologic data for the included cases. We systematically applied the revised 2017 McDonald criteria to 332 cases evaluated for anti-MOG antibodies, and the 2023 MOGAD diagnostic criteria to those that were anti-MOG seropositive (2,9). Cases that were anti-MOG seronegative and diagnosed with MS according to the 2017 revised McDonald criteria, as well as those with anti-MOG seronegative demyelinating features that did not meet MS diagnostic criteria, were excluded from the study. Anti-MOG seropositive cases were evaluated in subgroups as part of our research (Figure 1 and Figure 2).

Radiologic Methods

MRI scans were performed using a 1.5 Tesla scanner (Voyager, GE Medical Systems, USA). Routine imaging included axial pre- and post-contrast T1-weighted, axial and sagittal T2-weighted, and axial fluid-attenuated inversion recovery images of the brain. In addition, cervical spine imaging included sagittal T1-weighted, sagittal T2-weighted, and post-contrast sagittal T1-weighted fat-saturated images. A radiologist with a decade of experience retrospectively reviewed these images.

Laboratory Methods

Serologic tests related to demyelinating diseases, including anti-MOG, anti-neuromyelitis optica aquaporin-4 (AQP4), and oligoclonal band (OCB), were performed before intravenous steroid administration (10). Isoelectric focusing followed by immunoblotting was used to detect OCBs in serum and cerebrospinal fluid (CSF) in the neuroimmunology laboratory. A cell-based indirect immunofluorescence assay was used to detect AQP4 antibodies in serum (11). Detection of MOG antibodies in serum was performed using a live cell-based assay method at Koç University Research Center for Translational Medicine (12).

Statistical Analysis

Data analysis was performed using SPSS 23.0 (IBM) software. Normality and homogeneity of the data were assessed by the Kolmogorov-Smirnov test and the Levene's test, respectively. Data

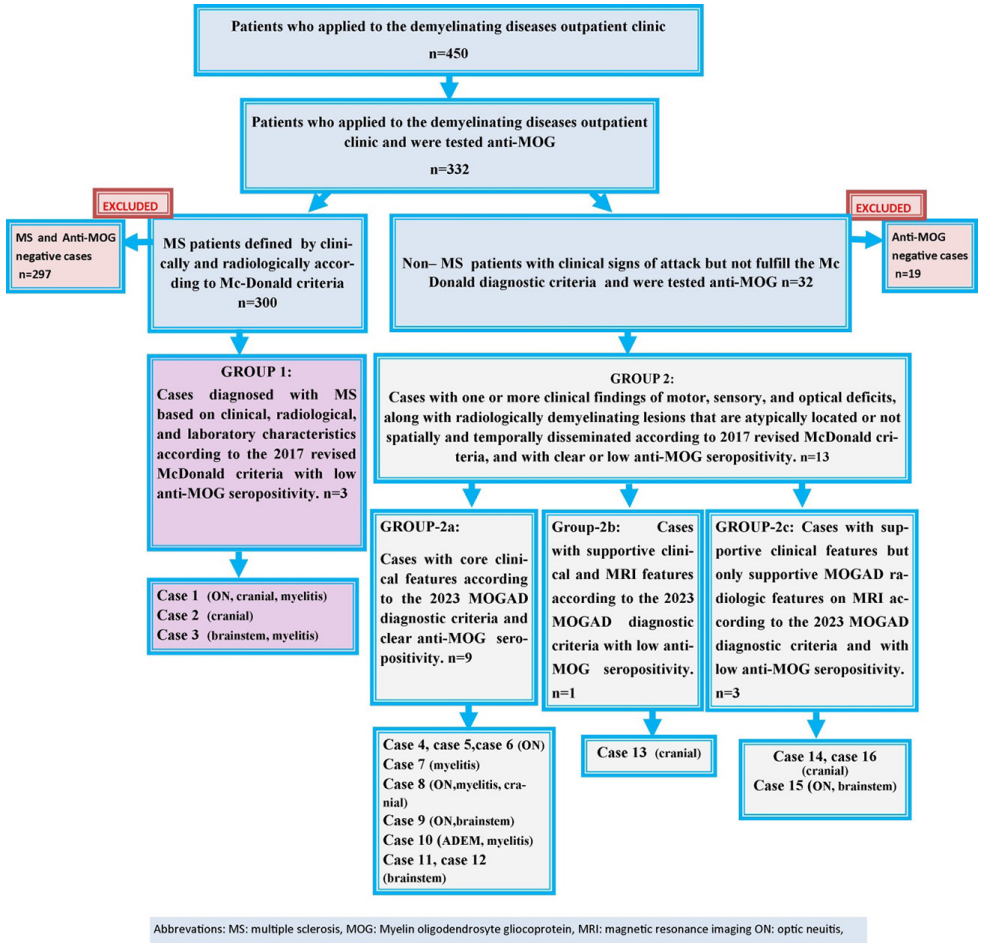


Figure 1. The schema of patient selection and grouping of the cases within the scope of the study.

distributions were presented as mean ± standard deviation or median (minimum-maximum) based on normality and homogeneity. All tests were two-tailed, and $p<0.05$ was considered statistically significant.

Ethical approval was obtained from the Ethics Committee of Sakarya University Faculty of Medicine on June 30, 2022 (approval number: 146336, date: 30.06.2022).

RESULTS

We evaluated 332 cases with one or more clinical core demyelinating events according to the MOGAD diagnostic criteria 2023, and known serologic status for anti-AQP4, anti-MOG, and OCB. Among these, 16 cases with clear or low-positive anti-MOG serology were investigated for MOGAD (Figure 2) and categorized based on clinical, radiologic, and serologic features. Detailed data are shown in Tables 1-5.

Group 1: Cases diagnosed with MS based on clinical, radiological, and laboratory characteristics according to the 2017 revised McDonald criteria with low anti-MOG seropositivity.

There were three cases in this group: one male and two females. The median disease duration was 3 years (range 3-33), and the median age at onset was 52 years (range 42-54). Detailed clinical, radiologic, and serologic features, as well as treatment options, are summarized in Table 1 and Table 2.

These cases exhibited core clinical features (Figure 2) but lacked additional supportive clinical or MRI features according to the 2023 MOGAD criteria. Despite being diagnosed with MS according to the 2017 McDonald criteria, they also had anti-MOG seropositivity. In our study, the rate of low anti-MOG seropositivity in MS cases was 1%.

Group 2: Cases with one or more clinical findings of motor, sensory, and optical deficits, along with radiologically demyelinating lesions that are atypically located or not spatially and temporally disseminated according to 2017 revised McDonald criteria, and with clear or low anti-MOG seropositivity.

This group included 13 cases evaluated according to the 2023 MOGAD diagnostic criteria (Figure 1). All cases met the core clinical features of MOGAD and were further divided into three subgroups according to their clinical, radiologic, and serologic characteristics.

Group 2a: Cases with core clinical features according to the 2023 MOGAD diagnostic criteria and clear anti-MOG seropositivity.

This group included nine cases, three males, and six females. The median disease duration was 3.5 years (1-22 years) and the median age at onset was 39.5 years (21-58 years). One case (case 4) had a late onset (≥50 years), while the others developed the disease in adulthood (18-49 years). Detailed clinical, radiologic, and serologic features, as well as treatment options, are presented in Tables 1-5. Three cases had accompanying autoimmune diseases.

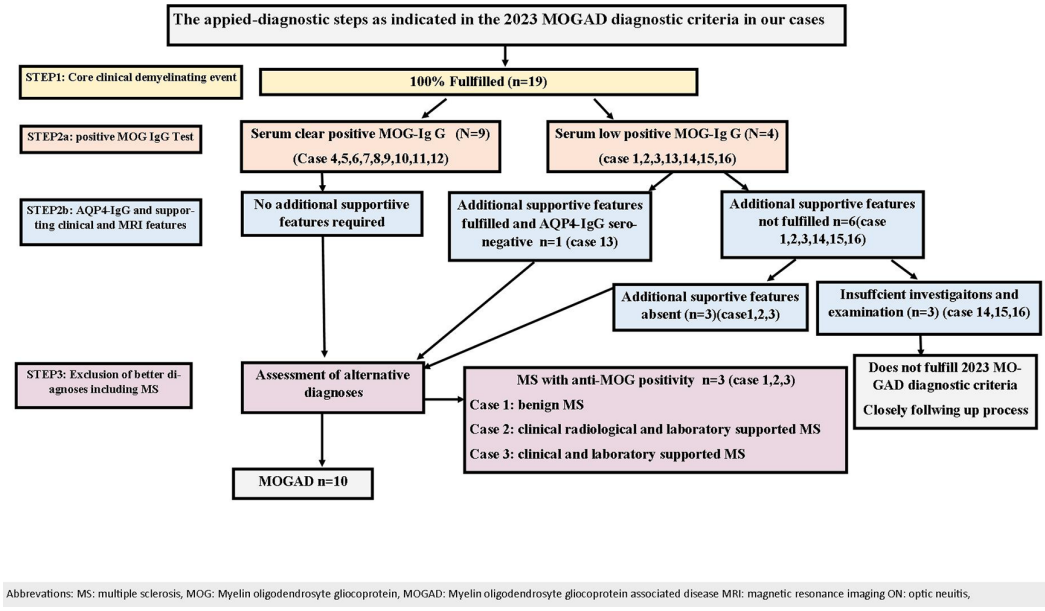


Figure 2. The schema of patient selection and grouping of the cases according to the 2023 MOGAD diagnostic criteria.

MOGAD: Myelin oligodendrocyte glycoprotein antibody-associated disease

Rare clinical presentations included sixth cranial nerve involvement in case 9; adult-onset ADEM and recurrent myelitis in case 10; wall-eyed bilateral internuclear ophthalmoplegia (WEBINO), in case 12; and tetraparesis secondary to transverse myelitis (TM) with a relapsing-progressive course in case 7. Indeed, case 7 was refractory to intravenous methylprednisolone (IVMP) and plasmapheresis, requiring ongoing treatment with rituximab and intravenous immunoglobulin (IVIG). The clinical courses of the cases were as follows: five were relapsing, three were monophasic, and one had a relapsing-progressive course. OCB seropositivity was detected in four cases. The dual positivity rate, defined as the OCB seropositivity alongside clear anti-MOG seropositivity, was 40% among the MOGAD cases in our study. Treatment options varied, with four cases receiving azathioprine, three receiving rituximab, and one receiving a combination of IVIG and rituximab. Demographic, clinical, radiologic, and serologic characteristics and treatment options are summarized in Tables 1-5.

Group 2b: Cases with supportive clinical and MRI features according to the 2023 MOGAD diagnostic criteria with low anti-MOG seropositivity.

Case 13, a female, had a disease duration of 3 years. Her clinical, radiologic, and serologic features and treatment options are detailed in Table 1 and Table 5.

Group 2c: Cases with supportive clinical features but only supportive MOGAD radiologic features on MRI according to the 2023 MOGAD diagnostic criteria and with low anti-MOG seropositivity.

There were three cases in this group: one male and two females. The median disease duration was 3 years (2-9 years) and the median age was 22 years (21-29 years). Clinical presentations included isolated ON and brainstem attacks in case 15 and cerebral cortical deficit findings in cases 14 and 16. OCB was negative in all cases (Table 1). Despite low anti-MOG seropositivity, these cases were considered suspicious for MOGAD, and were followed closely, as their clinical and radiologic features did not meet the revised 2017 McDonald criteria or the additional supporting clinical and MRI criteria for 2023 MOGAD. Detailed demographic, clinical, radiologic, and serologic data are presented in Tables 1-5.

DISCUSSION

MOGAD differs from other central neuroinflammatory diseases because of its unique clinical, radiologic, and immunologic features (13) and specific diagnostic criteria (2). In our study, 10 cases were diagnosed with MOGAD. It is noteworthy that MOG serology in the same patient can fluctuate from seropositivity to low seropositivity or even seronegativity within six months of symptom onset (14). In our study, three cases with low anti-MOG seropositivity were closely followed clinically, radiologically, and serologically because they did not fully meet the diagnostic criteria. We believe that the monophasic nature of the disease and the timing of anti-MOG serologic testing (>6 months after symptom onset) may contribute to the diagnostic challenges.

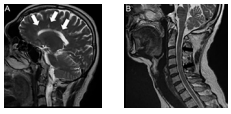
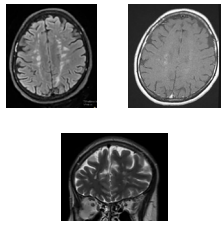
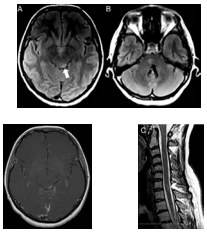
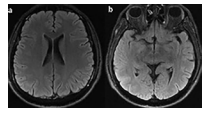
Anti-MOG seropositivity is found in 0-2.5% of MS cases (15). The coexistence of anti-MOG and OCB seropositivity may complicate the diagnosis of demyelinating diseases. In our study, three out of 300 MS cases had low anti-MOG seropositivity, but none had additional data supporting a core clinical event of MOGAD. Our results indicate a 1% rate of anti-MOG seropositivity in MS, which is consistent with the existing literature. Dual seropositivity for anti-MOG and OCB occurs in 15-50% of MOGAD cases (16,17). Although the clinical significance of this dual serology is not fully understood, it is associated with a higher incidence of polyfocal clinical presentations, greater lesion burden on MRI, more brain lesions, lesser optic nerve enhancement, and a higher relapse rate compared with anti-MOG monoseropositivity (17,18). In our study, 40% of the 10 MOGAD cases were dual seropositive. These cases, in line with the literature, showed a greater lesion burden on MRI, multifocal clinical presentation, and minimal contrast enhancement of the optic nerve.

Table 1. The clinical and laboratory features of the cases

Patients	Clinics	Finally diagnosis	Anti-MOG	OCB	CSF cells (/ µL)	CSF protein (mg/dL)	Ig G Index	Anti-AQP4
Case-1 (group 1)	Cranial, spinal attacks, ON	MS with anti MOG positivity	Low positive	Unknown	Unknown	Unknown	Unknown	Unknown
Case-2 (group 1)	Trunkal ataxia, hypoesthesia, ms	Clinical, radiological and laboratory supported MS- MS with anti MOG positivity	Low positive	Patern 2 positive (CSF)	21	33.9	1.25	Negative (serum)
Case 3 group 1)	Paraparesis, transvers myelitis Ms	Clinical and laboratory supported MS- MS with anti MOG positivity	Low positive	Patern 2 positive (8 bant)	20 eritrocyte	80.3	0.843	Negative (serum)
Case-4 (group 2a)	ON	MOGAD	Positive	Tip 4 positive (CSF)	Non	31.1	0.51	Negative (serum)
Case-5 (group 2a)	Recurrent ON	MOGAD	Positive	Negative (CSF)	Unknown	Unknown		Negative (serum)
Case-6 (group 2a)	ON	MOGAD	Positive	Negative (CSF)	10 eritrocyte	31.4	0.826	Negative (serum)
Case-7 (group 2a)	Paraparesis, transvers myelitis	MOGAD	Positive	Negative (CSF)	Non	30.2	0.5	Negative (serum)
Case-8 (group 2a)	ON, Thoracal spinal attack	MOGAD	Positive	Tip-2 positive (11 bant)	10 eritrocyte	8.54	0.85	Negative (serum)
Case 9 (group 2a)	6.cn palcy.	MOGAD	Positive	Patern 3 positive	Neither erytrocye or leucocyte	30.40	0,51	Negative (serum)
Case-10 (group 2a)	ADEM, myelitis	MOGAD	Positive	Negative (CSF)	20 leucocyte	31	0.40	Negative (serum)
Case-11 (group 2a)	Ataxia, brainstem attack	MOGAD	Positive	Negative (CSF)	No cell	35.4	0.36	Negative (serum)
Case-12 (group 2a)	Bilateral INO, cranial attack	MOGAD	Positive	Tip 3 positive	No cell	17.4	0.72	Negative (serum)
Case-13 (group 2b)	Hemiparesis, cranial attack	MOGAD	Low positive	Not tested	Not tested	Not tested		
Case-14 (group 2c)	Vertigo, ON. cranial lesion	Following up	Low positive	Patern 1	No cell	43.7	0.34	Negative (serum)
Case-15 (group 2c)	ON	Following up	Low positive	negative (CSF)	No cell -	30.1	0.71	Negative (serum)
Case-16 (group 2c)	Vertigo, dizziness, cranial attack	Following up	Low positive	negative (CSF)	No cell -	32.3	0.62	Negative (serum)

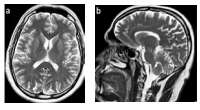
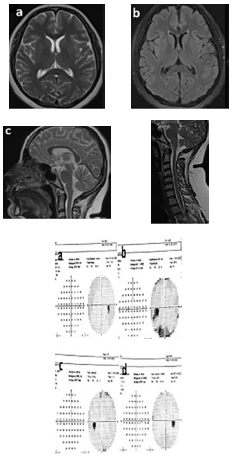
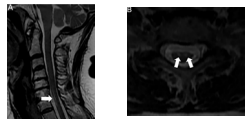
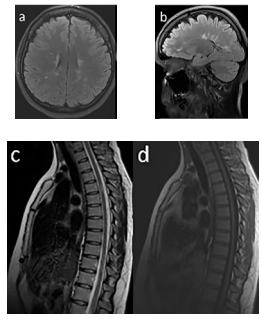
ADEM: Acute disseminated encephalomyelitis, MS: Multiple sclerosis, MOG: Myelin oligodendrocyte glicopretein, MOGAD: Myelin ologodendrocyte glicoprotein associated disease MRI: Magnetic resonance imaging, ON: Optic neuritis, OCB: Oligoclonal band, Anti-AQP4: Anti-aquoporin 4, CSF: Cerebrospinal fluid

Table 2. The clinical and radiological features of anti-MOG positive cases/1

Patients	Case 1	Case 2	Case 3	Case 4
Current age	52 years	41 years	50 years	49 years
Age of onset /gender	21 years/male	39 years female	49 years female	47 years male
Clinical presentation	Optic attacks, cranial, myelitis	Numbness and hypoesthesia on arm and legs, and truncal ataxia	paraplegia	Optic attack
Clinical course	Three (the last attack was ten years ago)	Two	Two	Relapsing
Attack count	Relapsing	Relapsing	Relapsing	Two
Radiologic Imaging / electrophysiologic findings	Periventricular hyperintense lesions perpendicular to the corpus, cervical sagittal T2-weighted hyperintense lesions not exceeding one vertebra length are observed in the spinal cord at the C2-3 and C5 levels	Cerebral white matter hyperintense lesions some of which extend perpendicular to the callosal septal interface in the periventricular area on FLAIR and T2 series on MRI, contrast enhancement on the left centrum semiovale.	Hyperintense lesions in mesencephalon medulla oblongata and a hyperintense lesion not exceeding one vertebra length in the spinal cord C7-T1, contrast enhancement on the left lateral tectum	No lesion
				
Acute treatment option	Methyl prednisolone IV	Pulse methyl prednisolone 1000 mg/day IV for 5 days	Pulse methyl prednisolone 1000mg/day IV for 5 days	First: 7 days IV 1000mg/ day pulse steroid second: no response to 3 days IV 1000mg/day pulse steroid therapy then plasmaphereses.
Finally diagnosis	MS with anti MOG positivity	Clinical, radiological and laboratory supported MS MS with anti MOG positivity	Clinical, radiological and laboratory supported MS MS with anti MOG positivity	MOGAD
Maintanence Treatment option	No treatment	Ocrelizumab	Ocrelizumab	Rituximab
Disease duration	30 years	3 years	1 years	2 years
Recovery clinical	Partial	Partial	Partial	
Resolution of lesion radiologic	Chronic lesions	Chronic lesions	Chronic lesions	No lesion
Additional disease	Non	Non	N	Ankylosing spondylitis, left eye was blind as a sequele.

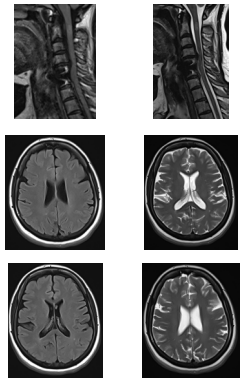
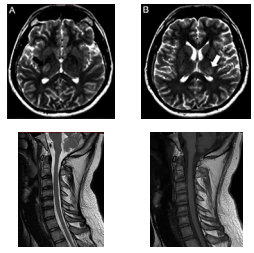
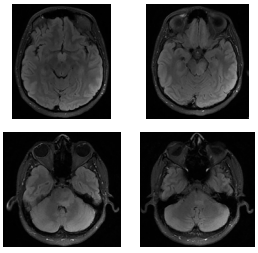
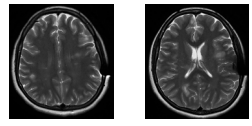
MS: Multiple sclerosis, MOG: Myelin oligodendrocyte glicopretein, MOGAD: Myelin ologodendrocyte glicoprotein associated disease MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery

Table 3. The Clinical and radiological features of anti-MOG positive cases/2

Patients	**Case 5**	**Case 6**	**Case 7**	**Case 8**
Current age	42 years	19 years	55 years	27 years
Age of onset /gender	23 years male	18 years female	54 years female	26 years/female
Clinical presentation	Optic attacks with different sides	Left Optic attack	Two Spinal attack-paraplegia	Optic attack, myelitis, and cranial hemi-hypoesthesia on the right
Clinical course	Relapsing	Monophasic	Relapsing-progressive	Two
Attack count	Four	One	Two	Relapsing
Radiologic Imaging / electrophysiologic findings	No lesion	No lesion visual field tests at pre/post treatment of third case at below.	A lesion in the size of two vertebrae, involving the anterior segment of the cord, is observed at the level of the C6-7 intervertebral disc.	Multiple demyelinating lesions in the periventricular area one of them was contrast enhanced and a two-segment-long lesion in the thoracal
				
Acute treatment option	IV 1000 mg/day pulse steroid	Methyl prednisolone IV 1000mg/day for 7 days and followed by oral 1mg/kg/day with a gradually reduced dose was performed during follow-up	Methyl prednisolone IV 1000mg/day for 5 days and followed by 0.75mg/kg/day oral long-term steroid therapy which was gradually reduced monthly	First: no therapy. second: methyl prednisolone IV 1000mg/day for 5 days and long-term steroid therapy
Finally diagnosis	MOGAD	MOGAD	MOGAD	MOGAD
Maintanence Treatment option	Azathioprine	Azathioprine	Rituximab/IVIG (because of progression)	Rituximab
Disease duration	20 years	1 year	1 year	1 year
Recovery clinical	Partial	Complete	Progressively	Complete
Resolution of lesion radiologic	No lesion	No lesion	Partial	Persistant
Additional disease	Non	Non	Non	Non

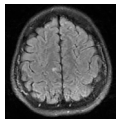
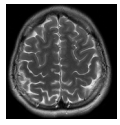
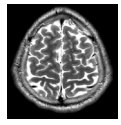
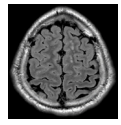
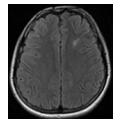
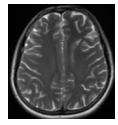
MS: Multiple sclerosis, MOG: Myelin oligodendrocyte glicopretein, MOGAD: Myelin ologodendrocyte glicoprotein associated disease MRI: Magnetic resonance imaging, ON: Optic neuritis

Table 4. The clinical and radiological features of anti-MOG positive cases/3

patients	**Case 9**	**Case 10**	**Case 11**	**Case 12**
Current age	46 years	31years	23 years	29 years
Age of onset /gender	42 years/female	27 years/male	23 years/female	29 years/female
Clinical presentation	ON, 6. CN palcy	ADEM, myelitis	Brainstem	Bilateral INO, dizziness
Attacks count	Two	Two	One	One
Clinical course	Relapsing	Relapsing	Monophasic	Monophasic
Radiologic Imaging / electrophysiologic findings	T2 hyperintense lesion at the level of C2 vertebra, Millimetric hyperintense lesion on T2 and Flair sequences located in deep white matter in both parietal lobes and right temporal lobe	Hyperintense lesions right globus pallidus to the posterior leg of the internal capsule posterior to the left thalamus	Hyperintensity in flair and T2 at the level of the mesencephalon, in the left half of the pons, in the left middle cerebellar peduncle and adjacent to the 3rd ventricle, without significant enhancement appearance on cranial MRI	The subcortical white matter lesions in fronto-temporal lobe on left side, and in the occipital lobe on right side that had signal changes of hypointense in T1A series, hyperintense in T2A series and had contrast enhancement appearance
				
Acute treatment option	Pulse methyl prednisolone 1000mg/day IV for 7 days	Methyl prednisolone 1000mg/day IV for 5 days	Methyl prednisolone 1000mg/day intravenously for 5 days	Methyl prednisolone IV 1000mg/day for 5 days and Plasmapheresis
Finally diagnosis	MOGAD	MOGAD	MOGAD	MOGAD
Maintanence Treatment option	Azathioprine 150 mg/day	Azatioprine	Rituximab	Rituximab
Disease duration	4 years	4 years	1 year	1 year
Recovery clinical	Complete	Complete	Complete	Complete
Resolution of lesion radiologic	Chronic lesions	No lesion	Complete	No
Additional disease	Diabetes mellitus, hashimato, asthma	Non	Non	Familial mediterranean fever

ADEM: Acute disseminated encephalomyelitis, MOG: Myelin oligodendrocyte glicopretein, MOGAD: Myelin ologodendrocyte glicoprotein associated disease MRI: Magnetic resonance imaging, ON: Optic neuritis, INO: Internuclear ophalmoplegia, FLAIR: Fluid-attenuated inversion recovery

Table 5. The clinical and radiological features of anti-MOG positive cases/4

Patients	**Case 13**	**Case 14**	**Case 15**	**Case 16**
Current age	27 years	21 years	42 years	29 years
Age of onset /gender	24 years Female	19 years Male	39 years Female	26 years Female
Clinical presentation	Numbness, hypoesthesia, hemiparesis, allodinia	Intermittent dizziness, unsteady gait, blurred vision and numbness on face	Left optic attack and sixth nerve palsy.	Vertigo, dizziness
Attacks count	Two		One	One
Clinical course	Relapsing	Recurrent attack	Monophasic	Monophasic
Radiologic Imaging / electrophysiologic findings	Millimetric flair t2 hyperintense lesion in the subcortical white matter in the right parietal at the vertex level	Periventricular a few and subcortical 3-4 hyperintense in T2A series on cranial MRI	The hyperintense lesion in T2A and Flair series had irregular borders extending towards the mesencephalon at the level of the pons	Nonspecific hyperintense lesion in the t2a series with a diameter of about 5 mm adjacent to the frontal horn of the left lateral ventricle on ventricular cross-sections.
	   		Not available	 
Acute Treatment option	Pulse methyl prednisolone 1000mg/ day IV for 5 days	No treatment	Oral prenisolone	No treatment
Finally diagnosis	MOGAD	Following up	Following up	Following up
Maintanence Treatment option	Rituximab	No treatment	No treatment	No treatment
Disease duration	3 years	3 years	3 years	3 year
Recovery clinical	Partial	Complete	Complete	
Resolution of lesion radiologic	Chronic lesions	Chronic lesions	No lesion	Chronic lesions
Additional disease	Non	Non	Non	Non

MS: Multiple sclerosis, MOG: Myelin oligodendrocyte glicopretein, MOGAD: Myelin ologodendrocyte glicoprotein associated disease MRI: Magnetic resonance imaging, ON: Optic neuritis

The incidence of MOGAD is approximately 1.6-2.39 per million people per year, with a similar gender distribution (2,19). However, our study found a female predominance (70%), which differs from the literature. We attribute this discrepancy to the small size of our disease cohort.

In adults, ON is the most common clinical manifestation of MOGAD (20). Consistent with the literature, ON was the most common phenotype in our study (n=5), while there was only one case that presented with ADEM, which is rare in adults. MOGAD-ON typically presents bilaterally, either synchronously or sequentially (20), and often follows a relapsing course (6). In our study, the clinical courses of the three MOGAD-ON cases were different: one had bilateral ON occurring sequentially, one had monophasic ON, and one had relapsing unilateral ON. We believe that the sequela of optic atrophy in the contralateral eye prevented bilateral ON presentation, in case 4. According to the literature, the radiologic phenotype of MOGAD-ON includes an edematous, swollen, and tortuous optic nerve with T2 hyperintensity along the prechiasmatic pathwayff and typical peripheral enhancement of the optic nerve and orbital fat on orbital MRI (21). In our study, radiologic imaging appeared normal for MOGAD-ON. We believe that the delay between clinical onset and imaging, along with the subsequent resolution of symptoms, may have influenced our radiologic findings. Although MOGAD-ON may improve without treatment, corticosteroids are highly effective in the acute phase (21,22). All of our ON cases showed clinical recovery, supporting these findings.

TM is the second most common clinical manifestation of MOGAD, occurring in 26% of cases (20). TM may occur as an isolated disease, in association with ON, or as part of ADEM (23). Longitudinal involvement of three or more vertebral segments is a common radiologic feature, although shorter, fragmented, or multifocal spinal cord lesions are also seen. The clinical course of our three MOGAD-TM cases varied: one presented with isolated monophasic myelitis, another with myelitis associated with a history of ON, and the third with ADEM and relapsing myelitis. Radiologic features included a two-segment long T2 hyperintense lesion in the anterior segment

of the spinal cord at the C6-7 level in case 7, a two-segment long contrast-enhanced lesion on thoracic MRI in case 8, and a vertebra-long focal T2 hyperintense lesion in the left anterior horn of the spinal cord in case 10. Although MOGAD-TM generally has a good prognosis (2), case 7 had a progressive course and was refractory to treatment, contrary to typical expectations.

MOGAD brain lesions are predominantly located in the supratentorial region and typically present as a few (≤3) bilateral, hyperenhancing, ill-defined T2 hyperintense lesions (24). These lesions often appear in the deep gray matter (5) and middle cerebellar peduncles (25), with diffuse involvement of the pons and areas adjacent to the fourth ventricle more common than in seropositive NMOSD (25). Most MOGAD brain lesions resolve on follow-up MRI (60-79%), although some persist (2,8). In our study, radiological findings were resolved completely in three cases, partially in one case, and persisted in two cases.

Two cases presented with rare neuro-ophthalmologic manifestations: one with WEBINO and the other with sixth nerve palsy. Only one case of WEBINO and two cases of sixth nerve palsy have been reported in MOGAD (26,27). Our understanding of MOGAD-related optic nerve involvement beyond ON is expanding, with new phenotypic findings such as WEBINO and sixth nerve palsy being documented.

Recent studies suggest that the late onset of inflammatory demyelinating disease may be associated with more severe clinical findings and higher levels of disability (28). Our seventh MOGAD case is consistent with this hypothesis, as it involved an age of onset over 50 years, a progressive course of paraplegia, and an inadequate response to treatment. In the literature, MOGAD has been associated with comorbid rheumatologic diseases such as SLE and Sjögren's syndrome (29,30). In our study, three cases had concomitant autoimmune diseases: ankylosing spondylitis (AS), Familial Mediterranean Fever (FMF), and Hashimoto's thyroiditis. Only one AS+MOGAD case has been documented, suggesting that TNF-alpha inhibitors may exacerbate MOGAD symptoms (31). Our AS + MOGAD case did not receive any immunosuppressive or TNF-alpha inhibitor treatment at diagnosis. Therefore, we believe that our case may be the first in the literature. While MS is often associated with FMF, the association between FMF and MOGAD is poorly documented in the literature (32). Thus, our case of FMF + MOGAD is considered rare. Hashimoto's thyroiditis is known to coexist with both MS and MOGAD (33,34). Our case of MOGAD + Hashimoto's thyroiditis supports these findings.

The acute treatment regimen for MOGAD typically involves high-dose IV corticosteroids for 3-5 days, similar to other demyelinating diseases, although there is no consensus on tapering steroids after acute treatment (35,36). IVIG or plasma exchange is often used when standard treatment fails to produce adequate improvement (38,39). In our study, two cases underwent plasma exchange after 5 days of IVMP, one case received IVIG after IVMP, and another was treated with IVMP for 5 days followed by gradual tapering of long-term oral steroids, which were reduced gradually over the following months. Long-term treatment includes various immunosuppressive agents based on the experience of individual centers, mycophenolate mofetil, azathioprine, rituximab, and IVIG, administered either intravenously or subcutaneously (37). In our study, azathioprine, rituximab, and repeated IVIG were used for maintenance therapy.

Study Limitations

The limitations of our study can be divided into three main categories. First, the small number of cases diagnosed with MOGAD. Secondly, a lack of access to CSF and complete radiological data for all cases. Finally, a delay in performing serologic tests was observed in three cases. Our study emphasizes the need for more extensive research to better understand the diagnosis, clinical presentation, effective treatment, and course of MOGAD.

CONCLUSION

We aimed to highlight the importance of recognizing MOGAD due to its potential association with autoimmune diseases, progressive nature, and dual seropositivity. Thus, it should be considered for its unique clinical and radiologic features. Despite the limited size of our series, our findings contribute to the literature supporting the generally mild clinical course of MOGAD.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Sakarya University Faculty of Medicine on June 30, 2022 (approval number: 146336, date: 30.06.2022).

Informed Consent: Retrospective study.

Acknowledgment

The authors declare no competing interests. The anti-MOG assays in this study were performed at Koç University Research Center for Translational Medicine (KUTTAM). This project was supported by TUBITAK (project number: 118S397). We thank Dr. Atay Vural for supervising the MOG-IgG assays.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.S., O.T., M.Y., T.D., D.K., Concept: S.S., E.Ç., O.T., D.K., Design: S.S., D.K., Data Collection or Processing: S.S., D.K., Analysis or Interpretation: S.S., D.K., Literature Search: S.S., D.K., Writing: S.S., E.Ç., O.T., M.Y., D.K.

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