

Clinical outcomes of transverse myelitis with myelin oligodendrocyte glycoprotein antibody versus negative cases among adults in Isfahan, Iran: A comparative study

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Keywords

Transverse Myelitis; Magnetic Resonance Imaging; Multiple Sclerosis; Neuromyelitis Optica; Myelin Oligodendrocyte Glycoprotein

Abstract

Background: The aim of this study was to evaluate the status of anti-myelin oligodendrocyte glycoprotein (MOG) antibodies in patients with transverse myelitis (TM) and compare the clinical and imaging characteristics of MOG immunoglobulin G (IgG)-positive with negative cases.

Methods: This cohort study enrolled 71 patients diagnosed with new-onset of TM who were being

followed at a referral university clinic in Isfahan, Iran, from November 2016 to January 2019. Magnetic resonance imaging (MRI) images and blood samples for anti-MOG, anti-aquaporin 4 (anti-AQP4) (using the cell-based technique), and vasculitis-related antibodies were collected from patients. Outcomes were assessed by the evolution of the Expanded Disability Status Scale

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(EDSS) score and brain and spinal cord imaging findings within three months. All patients underwent imaging and clinical assessment during a mean period of one year as a follow-up. We compared the characteristics of clinical and radiological outcomes in MOG-IgG-positive and negative cases.

Results: Of the total population studied, there were 26.8% men and 73.2% women, with a mean age of 33 ± 10 years. 12 (16.9%) patients were seropositive for MOG antibody and 17 (89.5%) were positive for anti-AQP4 antibodies. There was no significant association between anti-MOG antibody seropositivity and age, gender distribution, the presence of other autoimmune diseases, and number and interval of relapses. However, the involvement site of the spine at first imaging was significantly different between seronegative and seropositive patients.

Conclusion: In patients with MOG antibody disease (MOG-AD) TM, the MRI findings suggest a preferential involvement of the cervical-thoracic section in seropositive cases which may help differentiate from non-MOG demyelination TM.

Introduction

Transverse myelitis (TM) is a heterogeneous inflammatory disorder presenting with the motor, sensory, and/or autonomic dysfunctions that occur due to spinal cord transverse plane interruptions in descending and ascending neural pathways.¹

Epidemiologic studies have presented a prevalence of 1 to 4 cases per million people with a bimodal distribution of TM in the second and fourth decades of life.² Underlying etiologies may be acquired inflammatory conditions such as multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMO-SD), infectious ones, viral or bacterial infections like syphilis, Epstein-Barr virus (EBV), herpes simplex virus (HSV), Lyme disease, systemic autoimmune diseases such as systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), sarcoidosis, antiphospholipid syndrome (APS), and also spinal cord infarction.³⁻⁶ Last but not least underlying causes of TM particularly in elder population are tumoral lesions and paraneoplastic etiologies.⁷⁻¹⁰

Acquired autoimmune etiologies, including MS and neuromyelitis optica (NMO) are the most common underlying reasons for TM incidence. Early accurate differentiation of MS and NMO-SD is crucial because certain drugs for NMO-SD do work in MS (rituximab) but not the other way around. Evidence shows that some drugs of MS may worsen NMO-SD. The anti-aquaporin 4

(anti-AQP4) antibody is one of the best available tests for diagnosing NMO-SD and its differentiation from MS. Negative antibody will not rule out the diagnosis of NMO-SD.^{11,12}

Myelin oligodendrocyte glycoprotein (MOG) is a member of immunoglobulins (Igs) lying on the most outer layer of myelin. This protein makes up only 0.05% of total myelin protein proportion and plays a significant role in integrity, intercellular interactions, and also myelin adherence. The situation of MOG and also its late expression during a person's development has raised the hypothesis that autoantibodies against MOG, as a surface protein, may play a significant role in inflammatory demyelinating disorders.^{13,14}

Studies considering anti-MOG antibody are getting more attention now, but so far, limited publication focusing on its role have rendered controversial results. Thus, this study aims to assess anti-MOG antibody status (seronegative vs. seropositive) among the patients with TM presentation referred to Al-Zahra University Hospital in Isfahan. We further compare demographic, clinical, and neuroimaging findings in the seropositive group with the seronegative group.

Materials and Methods

This is a prospective cohort study conducted on 71 patients with new-onset presentations of TM referred to clinics affiliated to Isfahan University of Medical Sciences, Isfahan, Iran, from November 2016 to January 2019. Patients over 18 years old with presentations of TM were diagnosed by a neurologist based on symptom onset between 4 hours to 21 days, presentation of bilateral sensory or/and motor or/and sphincteric dysfunctions, and accessible brain and spine magnetic resonance imaging (MRI). Patients unwilling to participate in the study or further laboratory tests and patients whose serum levels of anti-MOG antibody was borderline were excluded from the study. After approval of the study protocol by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1397.353), all information about the study process was presented to patients and they were all requested to sign a written consent form of participation.

The diagnosis of TM was made considering Transverse Myelitis Consortium Working Group held in 2002 as follows:

1. Presentation of spinal-related sensory, motor, or autonomic dysfunction
2. Presence of bilateral symptoms, but not

necessarily symmetric

3. Presence of clearly diagnostic sensory level
4. Ruling out neural compressive etiologies through spinal imaging
5. Confirmation of inflammation present in the spine through the findings of cerebrospinal fluid (CSF) extraction including CSF pleocytosis and increased IgG index or findings of spinal gadolinium (Gd) enhancement imaging
6. The most severe progression of symptoms from 4 hours to 21 days within their onset¹⁵

The diagnosis of TM was made by a target neurologist to minimize bias. From 96 cases included in the study, later on, 22 patients refused to do anti-MOG lab work-up or return for follow-up. 2 patients were found to have tumoral etiologies and one patient showed vascular anomaly. Thus, the study continued with 71 patients through census assessment.

Patients were requested to take blood samples for anti-MOG antibody, anti-AQP4 antibody, and vasculitis-related autoantibodies, including antinuclear antibody (ANA), double-stranded deoxyribonucleic acid (dsDNA), antineutrophil cytoplasmic antibodies (ANCA: cANCA and pANCA), lupus anticoagulant (LA), and antiphospholipid assessing. Also, acute phase reactants including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were checked. The assessments were done using enzyme-linked immunosorbent assay (ELISA). Laboratory tests were all performed in a target laboratory to prevent testing bias.

Anti-MOG antibody and anti-AQP4 were assessed using a cell-based technique with a Euroimmun kit made in Germany. Samples for antibodies were extracted before treatment.

Spinal and brain MRI was performed for all patients at symptom onset and another one within three months after diagnosis for the follow-up. To minimize bias, imaging was performed by a target device (1.5 T, Siemens, Germany) and was analyzed by a target radiologist expert in neuroimaging.

Based on laboratory findings and images, diagnosis of MS and NMO-SD was made using McDonald criteria 2010¹⁶ and NMO-SD diagnostic criteria for adult patients,¹⁷ respectively.

As all patients presented a new onset of TM symptoms, they received methylprednisolone pulse therapy (1000 mg daily) for three to five days. In the cases that they did not respond well to pulse-therapy, plasmapheresis was performed (1.5 plasma volumes every other day for 10 days).

Patients with a diagnosis of NMO-SD and MOG antibody disease (MOG-AD) were then orally treated with prednisolone and azathioprine (150 mg per day). If symptoms were controlled, glucocorticoid therapy was tapered within three months of their disease onset. Patients with MS received further treatment, after initial pulse therapy, based on present guidelines for MS treatment.

Data from patients, including age, gender, family history status of MS/NMO-SD, presence of other autoimmune diseases, the first presentation of patients (sensory or motor), patients' acute treatment prescribed at disease onset, and an association of visual disturbances and sphincter dysfunction were collected. Additionally, first episode duration, number of relapses, intervals between relapses, neuroimaging of admission and three-month follow-up, and Expanded Disability Status Scale (EDSS) calculated at admission and at three-month follow-up were gathered. Clinical relapse was presumed as a second clinical inflammatory episode that affects the level of spinal cord after one month from the first attack. Patients' anti-MOG antibody serum status was also recorded in the study checklist.

Data were analyzed using the SPSS software (version 21, IBM Corporation, Armonk, NY, USA). Quantitative and qualitative data were presented as mean $\pm$ standard deviation (SD), median [interquartile range (IQR)], and frequency and percentage. The Normality of continuous data was evaluated using the Kolmogorov-Smirnov test. Mann-Whitney U test was used for comparing non-normally-distributed data between groups. Qualitative data were compared between groups using the chi-square test and Fisher's exact test. The statistical significance level was set at $P < 0.05$.

Results

In the current study, 71 (26.8% men and 73.2% women) patients with a documented diagnosis of TM were assessed with the mean age of 33.94 ± 10.33 years. Among assessed patients, 5 individuals (7.0%) had a positive family history of demyelinating diseases, and 6 patients (8.5%) presented other autoimmune disorders. Two cases had positive vasculitis test in favor of lupus. Spinal fluid tests were negative for viral or bacterial infections. Nineteen of total patients fulfilled the revised 2015 NMO-SD diagnostic criteria [AQP4-IgG-positive: 17 (89.5%), AQP4-IgG-negative: 2 (10.5%)]. Only one patient with AQP4

autoantibody-negative NMO-SD had positive test for MOG antibody. 23 patients met McDonald criteria for relapsing-remitting MS (RRMS). Studied population onset EDSS was 2 but improved to 1.5 within three months following treatment initiation. Eventually, 15 cases (21.0%) had episodes of relapses with a mean interval of 12 months after the first attack. The most common first presentation of patients was motor dysfunction with paraparesis being more prevalent than quadriparesis. Additionally, 12 cases (16.9%) presented sensory dysfunction, 18 cases (25.4%) claimed visual disturbances, and 8 cases (11.3%) reported urinary incontinence. In general, the studied population was followed for a median of 12 months (Table 1). Anti-MOG antibody seropositivity and patient's characteristics and follow-up have been recorded (Table 1). Among the studied population regarding anti-MOG antibody seroprevalence, 12 patients (16.9%) were positive.

The MRIs were conducted at disease onset which were repeated within three months after treatment as a follow-up. After the first episode of myelitis, all patients were further evaluated with clinical and radiological examinations at least for a mean follow-up of one year. Number of relapses and their intervals were followed-up over a period ranging from 3 months to 2 years and the data were recorded in table 1.

Considering the fact that patients entered the

study at different points of time within these two years and some illness relapses occurred months after the scheduled follow-up period, we designed the study to be limited to compare the outcome between subgroups results over a period of three months.

Findings did not show any significant difference between seronegative and seropositive patients except for the fact that MRI findings in seronegative patients were significantly different in site of spinal involvement (contiguous lesions in cervical, thoracic-lumbar, and cervical-thoracic) in comparison with seropositive patients. The most common site of involvement in both seropositive and seronegative MOG antibody patients remained to be cervical-thoracic and cervical spine, respectively (Table 2). Even though statistically significant due to the limited number of seropositive patients, the difference in site of spinal involvement was inconclusive. Long extending lesions (i.e., lesions with more than three segments involved) with central location have been seen among all patients with NMO-SD and 9 of 12 patients with MOG antibody. Among MOG antibody-negative group, 16 individuals had no certain underlying cause and were considered as idiopathic subgroup.

The etiology of TM among patients based on their anti-MOG antibody seroprevalence has been demonstrated in figure 1.

Table 1. Clinical and demographic characteristic

Variable	Group			
	Positive MOG (n = 12)	Negative MOG (n = 59)	All patients (n = 71)	P
Age (year)	30.5 [23.5-33.7]	33.0 [29.0-40.0]	33.0 [28.0-39.0]	0.208
Gender				
Men	2 (16.7)	17 (28.8)	19 (26.8)	0.494
Women	10 (83.3)	42 (71.2)	52 (73.2)	
Family history	2 (16.7)	3 (5.1)	5 (7.0)	0.196
EDSS score at onset	2.0 [1.5-2.5]	2.0 [2.0-2.5]	2.0 [2.0-2.5]	0.537
Other autoimmune disease	1 (8.3)	4 (6.8)	6 (8.5)	0.999
Relapse	2 (16.7)	13 (22.0)	15 (21.1)	0.731
Time of relapse (month)	16.0 [12]	12.0 [7.0-24.0]	12.0 [8.0-24.0]	0.946
Last EDSS score	1.5 [1.0-2.0]	1.5 [1.0-2.0]	1.5 [1.0-2.0]	0.743
First symptoms				
Sensory	1 (8.3)	11 (18.6)	12 (16.9)	0.460
Motor	11 (91.7)	48 (81.4)	59 (83.1)	
Motor presentations				
Paraparesis	10 (90.9)	33 (68.8)	43 (72.9)	0.259
Quadriparesis	1 (9.1)	15 (31.3)	16 (27.1)	
Urinary incontinence	2 (16.7)	6 (10.2)	8 (11.3)	0.615
Visual	3 (25.0)	15 (25.4)	18 (25.4)	0.999
Abnormal MRI	5 (41.7)	36 (61.0)	41 (57.7)	0.216
Follow duration (month)	9.0 [3.0-12.0]	12.0 [3.0-24.0]	12.0 [3.0-24.0]	0.452

Data are presented as number (percent) and median [interquartile range (IQR)]

MOG: Myelin oligodendrocyte glycoprotein; EDSS: Expanded Disability Status Scale; MRI: Magnetic resonance imaging

Table 2. Neuroimaging findings of study population regarding anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibody seroprevalence

Radiological findings	Group			P
	Positive MOG (n = 12)	Negative MOG (n = 59)	All patients (n = 72)	
	Brain MRI at onset			
Normal	7 (58.3)	23 (39.0)	30 (42.3)	0.216
Abnormal	5 (41.7)	36 (61.0)	41 (57.7)	
	Spine MRI at onset			
Cervical	3 (25.0)	43 (72.9)	46 (64.8)	0.005*
Thoracic-lumbar	4 (33.3)	9 (15.3)	13 (18.3)	
Cervical-thoracic	5 (41.7)	7 (11.9)	12 (16.9)	
	MRI at follow-up			
Increase	0 (0)	10 (16.9)	10 (14.1)	0.204
No change	2 (16.7)	7 (11.9)	9 (12.7)	
Decrease	10 (83.3)	35 (59.3)	45 (63.4)	
Normal	0 (0)	7 (11.9)	7 (9.9)	

Data are presented as number (percent)

*Regardless of spinal cord involvement region, a significant difference was observed in comparison between seropositive and seronegative subgroups

MOG: Myelin oligodendrocyte glycoprotein; MRI: Magnetic resonance imaging

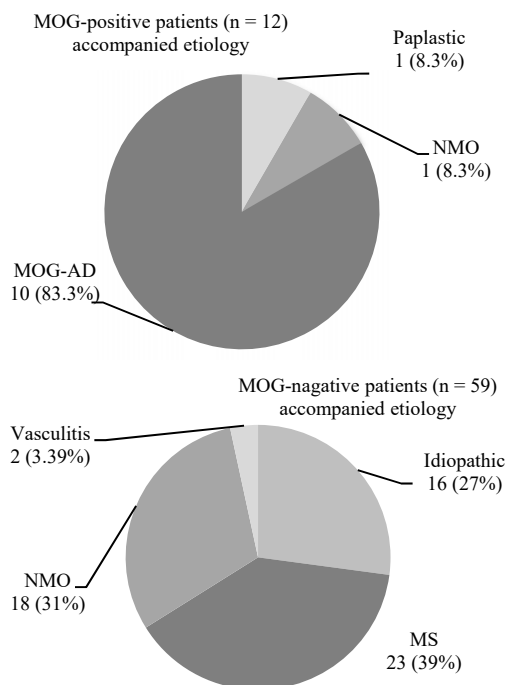


Figure 1. Etiologic findings of transverse myelitis (TM) among myelin oligodendrocyte glycoprotein (MOG)-seropositive and seronegative patients
MS: Multiple sclerosis; NMO: Neuromyelitis optica; MOG-AD: Myelin oligodendrocyte glycoprotein antibody disease

The most common underlying etiology among seropositive cases was MOG-AD diagnosis. However, as it was observed in this study, the anti-MOG antibody can be positive for a patient with NMO-SD criteria that was eventually diagnosed with NMO-SD. Also, anti-MOG antibody was

positive in a patient with breast cancer who was diagnosed with paraneoplastic cancer after she was found to have a positive paraneoplastic panel. Seronegative ones were mostly diagnosed as MS followed by NMO. Additionally, two patients had ANA and dsDNA vasculitis in favor of SLE.

Additional analysis was carried out to compare mentioned variables between MOG antibody-positive and other subgroups separately. There were statistically significant differences in age ($P = 0.009$) and spinal MRI ($P = 0.050$) between MOG-AD cases and idiopathic subgroup. In addition, the same analysis was performed between MOG antibody-positive subgroup and patients with NMO-SD and a significant difference was found among these groups for age ($P = 0.030$) and spinal MRI ($P = 0.003$). Moreover, in patients with MOG-AD and MS, only brain MRIs showed to be statistically significant ($P = 0.020$).

Discussion

In our study, 16.9% of patients were anti-MOG antibody seropositive that is almost comparable with previous studies' declared rate of 6%-14% of seropositivity among patients presenting longitudinally extensive TM (LETM).¹⁸⁻²⁰ No similar study to date has been designed to evaluate outcome of all inflammatory LETM.

The only study that reported a considerable high seropositive rate of 23% was performed by Cobo-Calvo et al.¹¹ This is while our findings were obtained among patients referring to us with symptoms of TM. These various rates may have been resulted due to different definitions

utilized for TM; furthermore, ethnicity variations, diversity of races, genetic factors, and perhaps unintentional biases in selecting a population to study can be inevitable.

Most of the previous studies tried to emphasize the role of anti-MOG antibody in pediatric demyelinating disorders such as acute disseminated encephalomyelitis (ADEM) and early-onset MS.^{14,21,22}

Although most studies conducted on adults presented no significant difference between seropositive and seronegative patients regarding their age,^{14,23} Cobo-Calvo et al. reported significantly younger patients, referring with LETM who were seropositive for anti-MOG antibody,¹¹ while our study has not confirmed this hypothesis.

Another important point is the higher rate of women in comparison to men regarding patients' anti-MOG antibody seroprevalence. Although no significant difference was detected in the current study, this female dominance may have merely occurred due to a higher rate of autoimmune demyelinating disorders incidence in women and not due to the female gender being a probable risk factor for anti-MOG antibody autoimmunity. The dominance of women regarding seropositive anti-MOG antibody status has been previously explained by other authors as well.^{20,24} It should be mentioned that some studies have presented a higher frequency of seropositivity among men.²⁵ Due to controversial reports, further studies are recommended.

In the current study, the number of relapses, relapse interval, EDSS at disease onset, and final EDSS were not different between anti-MOG seropositive and seronegative groups, though relapse interval was higher among the seropositive group which is in contrast with studies conducted previously. In general, previous studies have presented better outcomes of patients with MOG-AD considering their long-term benign outcomes and better EDSS status detected in follow-up visits, while they have declared more severe first episode of TM among seropositive cases.^{20,25,26} Spinal MRI findings at disease onset showed significant site of spine involvement among seronegative cases which is presented in this study for the first time. This lesion distribution difference between MOG antibody-positive and negative cases might be due to our limited number of cases or ethnic genetic predisposition. Although no statistical difference was detected in follow-up spine MRI considering anti-MOG seroprevalence of patients, all of the seropositive ones showed

either unchanged or better status, while no one had deteriorated status compared with onset. This finding confirms what was previously presented by other authors.^{20,22,26} Mentioned findings may be attributed to the better response of seropositive patients to steroids as we induced remission in the entire MOG antibody-positive patients under pulse corticosteroid therapy, while 8.5% of seronegative ones required plasmapheresis. The other hypothesis is contributed to the nature of the anti-MOG antibody that has been found in animal studies as injection of this antibody in mice was accompanied by transient demyelinating symptoms rehabilitated within two weeks.^{27,28}

Among all the seropositive patients, only one person (8.33%) met the NMO-SD diagnostic criteria who experienced optic neuritis (ON), long segments of spinal cord involvement, and positive NMO antibody. It is while most of the previous studies tried to evaluate the association of MOG-AD with NMO-SD and even add anti-MOG seropositivity among NMO-SD criteria.^{19,25,29} Recently, some studies have presented that TM may merely occur due to the presence of anti-MOG without meeting NMO-SD criteria, but all are limited to case reports.³⁰⁻³² In the current study for the first time worldwide, there are plenty of MOG-AD cases not meeting NMO-SD criteria. Therefore, further studies regarding a new diagnosis or making new criteria as a differentiated diagnosis for the incidence of TM are strongly recommended.

The sample size has been determined based on the prevalence of the disease and a short follow-up period is a limitation of the study. The results are also explanatory due to this small sample size. It should be considered that in further observation, patients may lead to the diagnosis of NMO-SD. So, further studies are needed.

Conclusion

Based on this study, in patients with TM, variables of age, gender, relapse rate and interval, and EDSS did not differ between MOG antibody-positive and MOG antibody-negative patients, whereas spinal MRI and lesion distribution differences between MOG-positive and negative cases may help in the differentiation of demyelinating TM types. As most of seropositive patients in the current study did not meet NMO-SD criteria, the occurrence of TM may merely be associated with the presence of anti-MOG antibody without fulfilling NMO-SD criteria. Due to the limited number of studies in this regard, further ones are strongly recommended.

Conflict of Interests

The authors declare no conflict of interest in this study.

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