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Myelin oligodendrocyte glycoprotein (MOG) antibody-mediated disease: The difficulty of predicting relapses

Samantha E. Epstein[a,*], **Seth Levin**[a], **Kaho Onomichi**[a], **Christopher Langston**[b], **Anusha Yeshokumar**[b], **Michelle Fabian**[b], **Ilana Katz Sand**[b], **Sylvia Klineova**[b], **Fred Lublin**[b], **Kiersten Dykstra**[c], **Zongqi Xia**[c], **Philip De Jager**[a], **Libby Levine**[a], **Rebecca Farber**[a], **Claire Riley**[a], **Wendy S. Vargas**[a]

[a]Columbia Multiple Sclerosis Center & Center for Translational and Computational Neuroimmunology, Department of Neurology, Columbia University Irving Medical Center, 710 West 168th Street, New York, NY, USA 10032

[b]Corinne Goldsmith Dickinson Center for Multiple Sclerosis, Department of Neurology, Icahn School of Medicine at Mount Sinai, 5 East 98th Street, New York, NY, USA 10029

[c]University of Pittsburgh, Department of Neurology, 811 Kaufmann Medical Building, 3471 Fifth Avenue, Pittsburgh, PA, USA 15213

Abstract

Background: While many patients with myelin oligodendrocyte glycoprotein antibody-mediated disease (MOG-AD) will have a monophasic course, 30-80% of patients will relapse after the initial attack. It is not known which factors predict relapse. Here we describe our clinical experience with MOG-AD and evaluate for factors that correlate with relapsing disease.

[*]Corresponding author at: 710 West 168th Street; Floor 2, New York, NY 10032. see2132@cumc.columbia.edu (S.E. Epstein).

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- Patients with MOG-AD may have a monophasic or relapsing disease course.
- 57% of our cohort had a relapsing course.
- The most common relapse phenotype was optic neuritis.
- Neither age, gender, race, initial attack, or antibody titer predicted relapse risk.
- 50% of patients on disease modifying therapy continued to relapse.

Methods: This was a retrospective, multi-institutional study of 54 patients with MOG-AD, including 17 children and 37 adults. Mann-Whitney U and Fischer's Exact tests were used for comparisons and logistic regression for correlations.

Results: Incident attack phenotype included acute disseminated encephalomyelitis (15%), unilateral optic neuritis (ON; 39%), bilateral ON (24%), transverse myelitis (TM; 11%) and ON with TM (11%). Pediatric patients were more likely than adults to present with ADEM (p = .009) and less likely to present with unilateral ON (p = .04). 31 patients (57%) had a relapsing disease course, with time to first relapse of 8.2 months and median annualized relapse rate of 0.97 months. In 40% of patients (n = 22) the first relapse occurred following the withdrawal of treatment for the incident attack. 5 patients converted to seronegative at follow up, 2 of whom later relapsed. Logistic regression revealed no significant relationship between age, gender, race, presentation phenotype, antibody titer, or cerebrospinal fluid results with risk of relapse. For patients who started disease modifying therapy (DMT) prior to the first relapse (n = 11), 64% remained monophasic. 50% (n = 15) of patients on DMT continued to have disease activity, requiring treatment adjustment.

Conclusions: It is difficult to predict which patients with MOG-AD will relapse. Research is needed to determine the optimal timing and choice of treatment.

Keywords

Myelin Oligodendrocyte Glycoprotein (MOG); Demyelinating diseases; Autoimmune diseases; Optic Neuritis; Acute disseminated encephalomyelitis

1. Introduction

Serum antibodies to myelin oligodendrocyte glycoprotein (MOG) cause a unique inflammatory disease of the central nervous system. Recent improvements in detection techniques using cell-based assays and secondary testing for full-length human IgG-1 antibodies against MOG have enabled a clearer clinical distinction between MOG antibody-mediated disease (MOG-AD) and other demyelinating diseases. (Reindl and Waters, 2019, Waters et al., 2020, Zhou et al., 2017)

MOG-AD occurs across all age groups and has a slight female predominance. (Jurynczyk et al., 2017) The most common phenotypes at initial presentation include acute disseminated encephalomyelitis (ADEM), unilateral optic neuritis (ON), bilateral ON, transverse myelitis (TM), or a combination of these. (Jurynczyk et al., 2017, Ramanathan et al., 2016, Wynford-Thomas et al., 2019) There have also been several reports of MOG-AD presenting with seizure disorder. (Reindl and Waters, 2019, Armangue et al., 2020, Hamid et al., 2018)

While many patients with MOG-AD will have a monophasic disease course, 30 - 80% of patients experience relapse after the initial attack. (Reindl and Waters, 2019, Waters et al., 2020, Jurynczyk et al., 2017, Cobo-Calvo et al., 2019, López-Chiriboga et al., 2018) Currently, there is limited understanding of the predictors of relapse in MOG-AD. Prior studies suggest that the dosing and duration of steroid treatment after the initial attack correlates with early relapse risk, (Reindl and Waters, 2019, Jurynczyk et al., 2017, Ramanathan et al., 2018) though no prospective study has examined this association.

Radiologic disease activity alone has demonstrated a low positive predictive value for clinically relapsing disease. (Fadda et al., 2021) The exact relationship between antibody titers and relapse risk is also unclear. Though the finding of MOG-IgG at incident demyelination is useful for diagnosis, how best to use subsequent antibody status in MOG-AD remains an area of active debate. (Duignan et al., 2018, Cobo-Calvo et al., 2019, Hennes et al., 2017) While studies have shown that persistently elevated MOG antibodies correlates with relapse risk (Waters et al., 2020, Jurynczyk et al., 2017, Cobo-Calvo et al., 2019, López-Chiriboga et al., 2018, Jarius et al., 2016) others have shown that many patients with persistently positive titers, especially children, experience a monophasic course. (Waters et al., 2020, Hennes et al., 2017, Hennes et al., 2018) Although the risk of relapse is lower at the time of antibody seronegativity, some patients will have a fluctuating antibody course, alternating between positive to negative and back to positive. (Waters et al., 2020, Hennes et al., 2017, Oliveira et al., 2019) Given these knowledge gaps and complexities, clinicians face challenges in determining which patients should start disease modifying therapy (DMT) and when to start. While DMT decreases annualized relapse rate (ARR) and potentially reduces disability, (Ramanathan et al., 2016, Cobo-Calvo et al., 2019, Ramanathan et al., 2018, Chen et al., 2020) the costs and risks of DMTs present trade-offs.

In this retrospective study of a diverse group of 54 pediatric and adult patients with antibody-confirmed MOG-AD, we describe our clinical experiences and evaluate which factors correlate with relapse risk.

2. Methods

We identified 54 patients with antibody-confirmed MOG disease from three major academic centers, including Columbia University Irving Medical Center, Mount Sinai Health System, and University of Pittsburgh Medical Center based on clinician report. This study received the institutional review board approval at each of the participating centers. All centers used cell-based assays for MOG antibody identification. We obtained clinical and paraclinical data through retrospective chart review at each center for all patients identified based on antibody status. Data reviewed included: clinical notes (from neurologists, ophthalmologists, or primary inpatient teams/consultants) and documented physical examinations throughout the patient's disease course; CSF studies, MOG-Ab results, and MRI of the brain, orbit, and/or spinal cord at initial presentation; and MOG antibody results at follow up. Reported location of lesions and enhancement patterns were based on review of the official neuroradiology report. Oligoclonal bands in the CSF were tested using qualitative isoelectric focusing/electrophoresis to evaluate for unique IgG oligoclonal bands in the CSF. Results were considered positive if two or more bands were present in the CSF and not found in a matched serum specimen.

Clinical phenotypes were classified as either ADEM, unilateral or bilateral ON, TM, or a combination of these based on review of available clinical and paraclinical information. Classification of ADEM was based on International Pediatric MS Study Group recommendations for patients under 18 years of age and Brighton Collaboration criteria (confidence level 1 or 2) for adults. (Tenembaum et al., 2007, Sejvar et al., 2007) Classification as ON was based on typical clinical symptoms as described in the optic

neuritis treatment trial (e.g. acute onset of pain with eye movement, decreased visual acuity, and/or visual field loss) and objective proof of optic nerve involvement by physical exam (i.e. afferent pupillary defect, papillitis, loss of color vision) and/or paraclinical testing. (Beck et al., 1992) A diagnosis of transverse myelitis was based on proposed criteria for acute transverse myelitis by the Transverse Myelitis Consortium Working Group. (Transverse Myelitis Consortium Working Group, 2002)

We used Mann-Whitney U and Fischer's exact tests for comparing two groups and Kruskal-Wallis test for comparing more than two groups. We performed Spearman's rank correlation to assess the relationships among variables. Significance threshold was set at a P value less than .05 for these calculations. We performed logistic regression using R-studio, and set significance threshold at P value of less than .01 using Bonferroni adjustment for multiple test comparisons.

3. Results

3.1. Demographics

Among the 54 patients with laboratory confirmed anti-MOG disease, 17 were children (less than 18 years of age) and 37 were adults. There was a female predominance in both the pediatric (n = 10, 59%) and adult (n = 21, 58%) subgroups. Self-reported race/ethnicities included 50% Caucasian, 19% Black, 19% Hispanic, 9% Asian, and 4% unknown (Table 1).

3.2. Disease onset

Initial presentation included ADEM (15%), unilateral ON (39%), bilateral ON (24%), TM (11%) and ON with TM (11%). Pediatric patients were more likely than adults to present with ADEM (p = .009; RR 6.5, 95%CI [1.5 -29]) and less likely to present with unilateral ON (p = .04; RR 0.36, 95%CI 0.12 – 1.1). Otherwise, both groups had similar clinical outcomes [Table 2].

For patients with an ON phenotype at incident attack with an ophthalmology evaluation available prior to any treatment (n = 14, 41%), 71% demonstrated a relative afferent pupillary defect, 64% color desaturation, 86% decreased visual acuity, 63% visual field deficit, and 57% optic disc edema.

Antibody titers were available in 24 out of the 31 patients tested during initial attack (65%). There was no difference in initial titers between pediatric and adult cases (p = .37) nor between attack phenotypes (p = .98). Out of the 42 patients (78%) with cerebrospinal fluid results at initial presentation, 19 (45%) had an elevated CSF white blood cell count of >10 per mm^3 (median 17, range 0 – 549) and 12 (29%) had a CSF protein level > 50 mg/dL (median 37, range 16 – 105). CSF oligoclonal bands (OCB) were negative in 38 of the 41 (95%) patients tested.

51 patients underwent an MRI of the brain and/or orbits at disease onset. 46% (n = 25) had abnormal T2/FLAIR-hyperintense brain lesions, including 48% with signs of contrast-enhancing active inflammation. Lesion locations included: diffuse (>3 locations; n = 10), subcortical white matter (n = 9), thalamic (n = 5), infratentorial (n = 5), cortical/juxtacortical

(*n* = 4), and periventricular/callosal (*n* = 3). 34 patients (67%) had optic nerve abnormalities. When location of optic nerve pathology was specified in neuroradiology report (*n* = 7, 20%), all were pre-chiasmal. 3 patients with a diagnosis of pediatric ADEM had radiologic evidence of optic nerve pathology without documented clinical evidence of ON during examination; this may have been confounded by encephalopathy, ability to communicate, and/or cooperation with clinical exam. Among the 45 patients (83%) with MRI of the spine at initial presentation, 19 (58%) had at least one spinal lesion; of which 58% (*n* = 11) were short-segment 42% (*n* = 8) were longitudinally extensive. Two patients had conus involvement and one demonstrated cauda equina nerve root thickening/enhancement.

For the onset attack, 72% received treatment with steroids alone, 20% received plasma exchange (PLEX) and/or intravenous immunoglobulin (IVIg), and 7% (UON, *n* = 1; BON, *n* = 2; TM, *n* = 1) received no treatment. There was no significant difference in treatment type based on age or attack phenotype. There was no correlation between initial treatment type and EDSS at last follow up (p=.09).

3.3. Relapsing disease

Thirty-one patients (57%) had a relapsing disease course. Median annualized relapse rate was 0.97 (IQR: 0.33 - 1.44) with 8.2 months (IQR: 2 - 22) as the median time to first relapse. In 22 patients (40% of total, 70% of relapsing patients), the first relapse occurred following the withdrawal of steroids or IVIg treatment after the onset attack. Common relapse phenotypes included optic neuritis (61%), ADEM and ON (16%), TM and ON (16%), TM (3%), and ADEM (3%). [Table 1]

When comparing patients with monophasic and relapsing disease course, there was no difference between the proportion of pediatric and adult patients, race, presence of elevated CSF WBC, nor evidence of enhancing lesions on MRI [Table 2]. Similarly, logistic regression analysis showed no significant association between age, gender, race, presentation phenotype, MOG antibody titer or CSF WBC with relapse. Time to first DMT initiation correlated with a longer time to first relapse ($p = .0002$; $r_s=0.8$) but did not correlate with ARR.

By last follow up, 31 patients (57%) had repeat testing of antibodies, 81% of which remained positive (median 28 months, IQR: 14 – 54). Among patients with persistently positive antibodies, 33% remained monophasic and 67% relapsed (median follow up time 23 months; IQR: 15 – 60). Five patients converted to seronegative within two years, though one later tested positive. Two of the five patients who became seronegative relapsed by the last follow-up (at 12 and 49 months), while the other three remained monophasic (at 9, 13, and 28 months). Patients with relapsing disease had longer follow-up than those with monophasic disease (median 30 and 10 months, respectively; p=.001).

3.4. Treatment

30 patients started steroid-sparing DMTs, including rituximab (*n* = 21, 70%), mycophenolate mofetil (MMF; *n* = 4, 13%), intravenous immunoglobulin (IVIg; *n* = 2, 7%), azathioprine (*n* = 2, 7%), and methotrexate (*n* = 1, 3%) [Table 1]. Nineteen (63%) patients started DMT after the relapse following incident attack. For the patients who started

DMT after the incident attack but prior to additional relapse (n = 11; 5 BON, 3 UON, 2 LETM, 1 short-segmented TM), 64% (n = 7; rituximab n = 6, MMF n = 1) remained monophasic at the time of chart review, with a median follow up time of 13 months (range 11 - 259 months). Due to continued disease activity, five patients switched from their initial DMT (tocilizumab n = 3, rituximab n = 1, MMF n = 1) and ten required add-on therapy that included steroids (n = 7), maintenance IVIg (n = 2) or a second DMT (azathioprine, n = 1). Four patients experienced relapse on rituximab. Only one of these patients had available lymphocyte values at the time of relapse, which revealed a B cell count of 0. In both cases where IVIg was added as adjunct therapy due to refractory disease, remission was achieved shortly thereafter. Two patients discontinued DMT, and one was relapse free nine months from last rituximab infusion.

4. Discussion

We report our real-world, multi-institutional experience managing a diverse population of pediatric and adult patients with MOG-AD. Consistent with prior studies, our patients had a female predominance and initial presentation with ADEM, unilateral or bilateral ON, TM, or the combination thereof. Pediatric patients were more likely to present with ADEM and less likely to present with unilateral optic neuritis than adult patients, but otherwise had similar clinical features. Of note, we did not encounter any patients with predominantly gray matter cortical involvement without a diagnosis of ADEM nor any patients with a primary seizure disorder, both of which have been described in recent studies of MOG-AD. (Reindl and Waters, 2019, Armangue et al., 2020, Hamid et al., 2018) This may be due to the retrospective nature of our chart review and the recent recognition of these phenotypes.

MOG-Abs were previously detected, often transiently, in various demyelinating diseases, including multiple sclerosis (MS) and Neuromyelitis Optica Spectrum Disorder (NMOSD). Recent studies using improved detection techniques have shown that MOG-AD is a unique disease entity based on clinical phenotype, paraclinical data, and immunohistopathology. (Jarius et al., 2016, Jarius et al., 2016, Weber et al., 2018) Similarly in our cohort, most patients had paraclinical findings that differentiated them from MS, including CSF pleocytosis, negative CSF OCBs, MRI findings of LETM, and lesions in the deep gray matter. These findings have several implications, not only for diagnosis, but also for appropriate treatment, as MOG-AD patients often experience relapse on MS DMTs. (Hacohen et al., 2018)

One major challenge in caring for patients with MOG-AD is predicting relapse. In our study, 57% of patients suffered from relapsing disease. The sociodemographic and clinical factors evaluated here were not associated with relapse. Further, we did not observe a correlation between initial MOG-Ab titer and relapse risk. Interestingly, of the five patients who converted from seropositive to seronegative status, two relapsed and one tested positive again within two years. Consequently, titers may not completely predict disease activity. We note that our study was skewed towards adult patients, which may explain a higher proportion of patients with relapsing disease than shown to occur in the pediatric literature.

There is limited understanding of the optimal initial therapy for MOG-AD and the patients who would benefit from early DMT initiation to prevent relapse. In our cohort, 40% of patients relapsed following the withdrawal of steroids or IVIg for the initial attack consistent with prior studies. (Jurynczyk et al., 2017) Interestingly, of the 11 patients who started DMT after incident attack, the majority remained monophasic. Though the clinical rationale for starting DMT prior to first relapse could not be definitively extrapolated from chart review, we note that all 11 patients were started in the year 2018 or earlier. In addition, 10 out of the 11 presented with core clinical features of NMOSD and 7 with BON or LETM, both of which have been considered especially concerning for NMOSD by The International Panel for NMO Diagnosis. (Wingerchuk et al., 2015) The choice for initiation of DMT after incident attack may therefore reflect prior biases of neurologists to consider MOG-AD as part of seronegative NMOSD, including the associated risk of relapse and disability. Given the modest follow-up duration of this cohort, longer prospective studies will be more informative.

Consistent with prior case series, half of the patients continued to experience disease activity during initial DMT, underscoring the urgent need for optimal therapy (Cobo-Calvo et al., 2019, Jarius et al., 2016, Chen et al., 2020). Emerging evidence suggests a potential role of IVIg in treatment. (Chen et al., 2020) In our study, we saw a positive response to IVIg as both maintenance and as adjunct therapy in patients who were refractory to initial DMT, though we caution the interpretation due to the small sample size. Retrospective case series reported relapse in 30 - 60% of the patients while on Rituximab (Chen et al., 2020, Whittam et al., 2020), a notable finding when compared to other demyelinating diseases. (Whittam et al., 2020) In our cohort, 19% of the patients on rituximab had relapse, and at least one patient suffered a relapse despite documented B cell depletion.

Our study had several limitations. This was a retrospective case series with a modest number of patients and a non-standardized approach to patient care. Given the smaller number of pediatric patients, our findings may not be generalizable to a pediatric cohort. Patients were also identified through clinician report by subspecialized providers at large academic centers, all of which may lead to selection bias towards patients with higher disease activity. MOG antibody titers, though all performed via cell-based assay, were collected at different clinical laboratories with variable sensitivity and specificity. In addition, antibody results and titers were not obtained or available for all patients at incident attack. Considering the retrospective nature of the study, detailed neuroimaging information regarding frequency, lesion appearance, and pattern of enhancement was not available for analysis. Finally, as follow-up duration was shorter in patients with a monophasic disease course, we could not exclude the possibility that some of these patients would subsequently relapse.

5. Conclusion

To date, there have been few studies of MOG-AD in pediatric and adult patients. Our study highlights the challenge in predicting relapse and guide clinical management in this patient population. In the absence of rigorous data to distinguish monophasic and relapsing patients, clinicians should exercise caution when considering long-term immunotherapy. Future research should address factors that predict relapse, best practice to incorporate

antibody titers into clinical decision, and the optimal timing of DMT in initiation and discontinuation in patients with MOG-AD.

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Table 1

Patient Demographics and Clinical Presentation.

Patient Demographics and Clinical Presentation	
Clinical Factor median [IQR]	**N (%)**
Age: median (range), y	
Pediatric: 7 (4-16)	17 (31)
Adult: 38 (18-47)	37 (70)
Gender	
Female [a]	33 (59)
Male	22 (41)
Race/ Ethnicity	
Caucasian	27 (50)
Black	10 (19)
Hispanic	10 (19)
Asian	5 (9)
Declined	2 (4)
Onset Attack	
ADEM	8 (15)
Unilateral ON	21 (39)
Bilateral ON	13 (24)
TM	6 (11)
ON + TM	6 (11)
Initial Treatment	
Steroids alone	39 (72)
Steroids + PLEX / IVIg	11 (20)
None / Unknown	4 (7)
Relapse after initial treatment withdrawal	
	22 (40)
Disease Course	
Monophasic	23 (42)
Relapsing	31 (57)
Time to first relapse (months): 8.2 [2- 22]	25 (81)
Annualized Relapse Rate: 0.97 [0.33 - 1.44]	29 (94%)
Relapse Phenotype	
Recurrent ON	19 (61)
ADEM + ON	5 (16)
TM + ON	5 (16)
TM	1 (3)
ADEM	1 (3)
DMT Type	
Rituximab	21 (70)
Mycophenolate Mofetil [b]	4 (13)

Patient Demographics and Clinical Presentation	
Clinical Factor median [IQR]	**N (%)**
IVIg	2 (7)
Azathioprine	2 (7)
Methotrexate	1 (3)
Time to last follow up (months): 15 [9 – 45] (range 2 – 262)	

Abbreviations: y = year; ADEM= acute disseminated encephalomyelitis; ON= optic neuritis; TM= transverse myelitis; PLEX= plasma exchange; IVIg= intravenous immunoglobulin; IQR= interquartile range; DMT = disease modifying therapy.

[a] Female skew was not statistically significant.

[b] One patient was transiently on mycophenolate mofetil and glatiramer acetate.

Table 2

Comparison based on age at disease onset and relapsing disease course. Pediatric patients were more likely than adults to present with ADEM and less likely to present with unilateral ON. When comparing patients with monophasic and relapsing disease, there was no difference between the proportion of pediatric and adult patients, race, presence of elevated CSF WBC, nor presence of enhancing lesions on MRI.

Pediatric vs Adult			
	Pediatric	**Adult**	***P***
Onset Attack: n(%)			
ADEM	6 (35)[a]	2 (5)	**.009**
Unilateral ON	3 (18)	18 (49)	**.04**
Bilateral ON	4 (24)	9 (24)	1.0
TM	0 (0)	6 (16)	.26
ON + TM	4 (24)	2 (5)	.07
Disease Course: n(%)			
Relapsing	10 (58)	22 (59)	1.0
Monophasic	7 (42)	15 (41)	
Annualized Relapse Rate: Median, [IQR]	1.11 [0.33 - 1.36]	0.71 [0.34 - 1.46]	.91
Time to First Relapse: Median [IQR]	8.9 [2.0 - 36]	8.0 [1.8 - 19.1]	.59
DMT initiation: n(%)	6 (35%)	22 (60%)	.14
Disability at last follow up: Median [IQR]	1 [0 - 1.5]	1 [0 - 2]	.39
Disease course			
	Monophasic n (%)	**Relapsing n (%)**	***P***
Age			
Pediatric	10 (59)	7 (41)	.25
Adult	15 (41)	22 (59)	
Ethnicity			
Caucasian	11 (48)	16 (55)	.78
Non-Caucasian	12 (52)	13 (45)	
Antibody titer			
<1:100	13 (59)	18 (75)	.25
>1:100	9 (41)	6 (25)	
CSF WBC			
<10 /mm^3	8 (44)	15 (65)	.21
≥10 /mm^3	10 (56)	8 (35)	
MRI			
Inflammatory	5 (56)	7 (44)	.68
Non-inflammatory	4 (44)	9 (56)	
Disability at last follow up			
EDSS < 2			
EDSS ≥ 2	13 (57)	21 (70)	.57
	10 (43)	10 (30)	

Abbreviations: ADEM= acute disseminated encephalomyelitis; ON= optic neuritis; TM= transverse myelitis; IQR= interquartile range; DMT = disease modifying therapy; CSF= cerebrospinal fluid; WBC= white blood cell; EDSS= Expanded Disability Status Scale.