Open Access

Original Article

Clinicopathological Features of Pakistani Patients with Myelin Oligodendrocyte Glycoprotein Antibody Associated Disease (MOGAD)

Muhammad Zain Arshad, Muhammad Omair Riaz, Dawood Ahmad, Muhammad Hussain, Ayesha Tanveer*, Maryam Bibi

Department of Immunology, Armed Forces Institute of Pathology/National University of Medical Sciences (NUMS), Rawalpindi Pakistan,
*Department of Radiology, Combined Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan

ABSTRACT

Objective: To characterize clinicopathological features of patients with Myelin Oligodendrocyte Glycoprotein Antibody Associated Disease in local population for early diagnosis and treatment.
Study Design: Cross-sectional study.
Place and Duration of Study: Department of Immunology, Armed Forces Institute of Pathology, Rawalpindi Pakistan, from Jun 2021 to Jan 2023.
Methodology: Our study involved consecutive random sampling of 400 individuals presenting at Armed Forces Institute of Pathology for serum Anti Myelin Oligodendrocyte Glycoprotein antibody testing by indirect immunofluorescence. Commercial Anti Myelin Oligodendrocyte Glycoprotein Antibody Indirect Immunofluorescence Test Slides along with controls were used and immunofluorescence was observed using fluorescent microscope BA-310. Detailed data was collected on a predesigned proforma, and qualitative and quantitative variables were analysed using statistical software.
Results: Eleven (2.75%) patients were positive for Anti Myelin Oligodendrocyte Glycoprotein antibodies with a male to female ratio of 1.6:1 (p =0.882). Mean age of diagnosis was 30.3±12 years. At time of diagnosis, all patients had 2 or more core clinical characteristics, of which, most prevalent was transverse myelitis, optic neuritis and headache/fever present in 4(80%) patients. The average diagnostic delay in our study was 20 months.
Conclusions: By having a high index of suspicion for presenting core clinical characteristics of Myelin Oligodendrocyte Glycoprotein Antibody Associated Disease, clinicians may be able to diagnose and treat this rare ailment in a timely manner to decrease diagnostic delay and prevent associated morbidity and mortality.

Keywords: Anti Myelin Oligodendrocyte Glycoprotein Antibody, Myelin Oligodendrocyte Glycoprotein Antibody Associated Disease, Optic Neuritis, Transverse Myelitis.

How to Cite This Article: *Arshad MZ, Riaz MO, Ahmad D, Hussain M, Tanveer A, Bibi M. Clinicopathological Features of Pakistani Patients with Myelin Oligodendrocyte Glycoprotein Antibody Associated Disease (MOGAD). Pak Armed Forces Med J 2024; 74(6): 1564-1568.*
DOI: https://doi.org/10.51253/pafmj.v74i6.9945

INTRODUCTION

Neurological disorders are a diverse group of diseases corresponding to approximately 50% of all rare disorders in which autoimmune demyelinating diseases of the Central Nervous System (CNS) are included in the context of organ-specific autoimmunity due to which their differential diagnosis can be broad, including Multiple Sclerosis (MS), Neuromyelitis Optica Spectrum Disorder (NMOSD) and Myelin Oligodendrocyte Glycoprotein Antibody Associated Disease, Acute Disseminated Encephalomyelitis (ADEM).[1] Myelin Oligodendrocyte Glycoprotein Antibody Associated Disease (MOGAD), also referred to as Myelin Oligodendrocyte Glycoprotein IgG Associated Encephalomyelitis (MOG-EM), is a rare demyelinating antibody mediated disease of the CNS, with several presentations, ranging from optic neuritis, acute demyelinating encephalomyelitis, transverse myelitis and cortical encephalitis. Although, MOGAD has similar presentation to NMOSD, it is a separate entity with a different pathogenic mechanism.[2] As myelin oligodendrocyte glycoprotein, is a protein which is only expressed on the surface of oligodendrocytes and myelin in the CNS, it has been widely accepted as a putative candidate antigen and antibody target in demyelination.[3] The general incidence of MOG-IgG seropositivity is 0.16 per 100,000 individuals[4] with prevalence of MOGAD in Malaysian population noted to be 0.12 per 100,000 individuals, with marked female ratio of 2:1.[5] The presence of a specific IgG antibodies in the serum (and sometimes CSF) against MOG, is diagnostic, and usually detected by cell-based assays (CBA).[6] Although the ideal specimen for testing is serum, however, evaluating CSF could increase diagnostic sensitivity in patients with seronegative

Correspondence: Dr Muhammad Zain Arshad, PAFMJ Office, Army Medical College, Abid Majeed Road, Rawalpindi Pakistan
Received: 16 Feb 2023 revision received: 30 Mar 2023; accepted: 31 Mar 2023

status,[7] however, diagnosis is usually made on the basis of seropositivity with clinical and Magnetic Resonance Imaging (MRI) findings.[8] The disease course of MOGAD can be either monophasic or relapsing[9] with CBA of anti MOG-IgG antibody (fixed or live) and titer (low or high) linked with severity of MOGAD.[10] MOGAD is scarcely described in local literature with very few studies available. Timely diagnosis and prompt immunotherapy can alter the course of this potentially lethal yet curable disease. This study aimed to present clinicopathological features, immunological investigations and clinical outcomes of patients with autoantibody-proven MOGAD in order to facilitate Pakistani clinicians in early diagnosis and timely treatment of this rare illness.

METHODOLOGY

This cross-sectional study was carried out at Department of Immunology, Armed Forces Institute of Pathology (AFIP), Rawalpindi Pakistan, over 20 months duration, from June 2021 to January 2023, after gaining approval from institutional Ethics Review Committee, via letter IRB/21/1592. Written informed consent from all enrolled patients was taken. We used consecutive random sampling to enroll our patients after calculating sample size of 400, using OpenEpi calculator, with prevalence of anti MOG antibody set at 7%, as found in literature, and confidence level of 95% with margin of error of ±2.5 %.[4]

Inclusion Criteria: Patients of belonging to either gender, with age ranging from 6 months to 75 years were included.

Exclusion Criteria: Patient with hemolyzed, lipemic or icteric serum samples were excluded.

We used serum samples (30 µl, diluted 1:10) from patients, applied to wells containing myelin oligodendrocyte glycoprotein (MOG)-transfected cells fixed on slides. The slides were incubated at room temperature for 30 minutes, rinsed with PBS-Tween, and then treated with FITC-labeled secondary antibodies for another 30 minutes. After a second PBS-Tween rinse, a mounting medium was added, and the slides were prepared for analysis under a fluorescence microscope. Samples showing characteristic granular fluorescence on the cell membrane were classified as positive, while non-transfected cells exhibited no staining. Qualitative (gender, positivity of anti MOG antibody, intensity) was expressed as frequency and percentages and quantitative variables (age) was expressed as Mean±SD. Data was analyzed using Statistical Package for Social Sciences (SPSS) version 23.0 and chi-square test was used to compare positivity and negativity in male and female patients, where *p*-value of ≤0.05 was considered statistically significant.

RESULTS

Out of 400 enrolled patients, 246(61.5%) were males and 154(38.5%) were females. Our data revealed 11(2.75%) patients were positive for anti MOG antibodies (Figure-1), of which 7 were males and 4 were females. Mean age of diagnosis was 30.3±12 years and male-female ratio was 1.6:1(p-value =0.882). At the time of diagnosis, patients having MOGAD had Transverse Myelitis, Optic Neuritis, headache or fever present in 4(80%) patients. Common presenting clinical characteristics among patients with MOGAD are enumerated in Table-I. Average diagnostic delay in present study was found to be 20 months. We noted that 4(80%) patients showed monophasic course of disease. Indirect immunofluorescence result in antibody proven MOGAD patients showed + intensity in 6(55%), ++ in 4(36%) and weak positivity in 1(9%) patient as listed in Table-II.

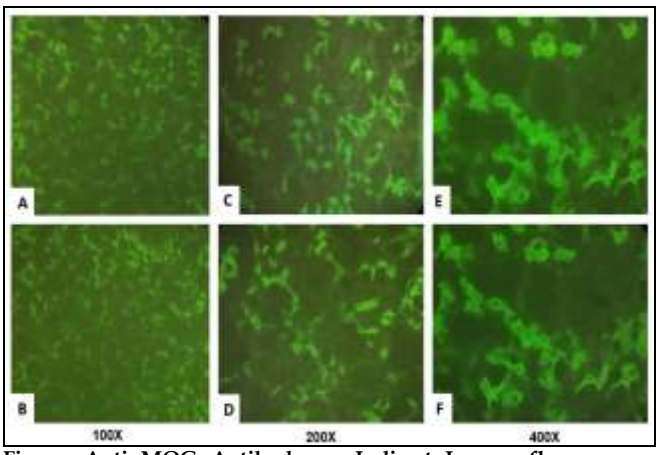

Figure: Anti MOG Antibody on Indirect Immunofluorescence (n=11)

DISCUSSION

The specificity of anti MOG antibody reported in literature is 97.8%, showing its reliability as a diagnostic tool.[11] In our present study, the mean age of presentation among 11 antibody proven MOGAD patients was 30.3 years, which was consistent with that reported in literature, where mean age of presentation was 36 years,[12] however, in terms of male to female ratio, one study revealed a slight female to male predominance of 1.5:1, in contrast to our study

Table-I: Comparison of Clinicopathological Features in MOGAD (n = 11)

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Age	29 years	30 years	30 years	8 years	10 years
Gender	Male	Female	Female	Female	Male
Onset of disease	29 years	29 years and 8 months	29 years and 7 months	7 years and 10 months	18 months
Diagnostic delay	1 week	4 months	5 months	2 months	8 years
Presenting Core Clinical Characteristic	Optic Neuritis	Fever and Headache	Headache	Fever and Headache	Headache
Core Clinical Characteristic					
Optic Neuritis	Present (Unilateral)	Present (Bilateral)	Present (Unilateral)	Absent	Present
ADEM	Absent	Absent	Present	Present	Absent
Transverse Myelitis	Present (On MRI)	Present	Present	Present	Absent
Brain demyelinating syndrome	Absent	Absent	Absent	Absent	Absent
Miscellaneous (Headache, Fever, Seizures)	Absent	Present	Present	Present	Present
Total Core Clinical Characteristic	2	3	4	3	2
MRI Findings	Typical findings	Typical findings	Typical findings	Typical findings	Typical findings
Course of disease	Monophasic	Monophasic	Monophasic	Monophasic	Relapsing
Other autoimmune disease	No	No	No	No	No
Comorbidity	No	No	No	No	No
Vaccination Status					
EPI	Vaccinated	Vaccinated	Vaccinated	Vaccinated	Vaccinated
Covid	Vaccinated	Vaccinated	Vaccinated	Vaccinated	Vaccinated
Flu	Vaccinated	Unvaccinated	Unvaccinated	Unvaccinated	Unvaccinated
Current Status	Asymptomatic	Symptomatic	Symptomatic	Asymptomatic	Symptomatic

Table-II: Results of Immunological Investigations (n = 11)

Parameter	Results
Mean Age±SD	30.3±12 years
Gender (Male / Female ratio)	7/4 (1.6:1)
Result for Anti MOG Ab	
Time of testing (n = 11)	During Attack
Specimen (n = 11)	Serum
Result (n = 11)	Positive
Intensity (n = 11)	Weak positive 1, Positive 6, Strong positive 4
Repeat testing (n = 2)	Positive
Result of Immunological tests	
Anti Aquaporin-4 Antibody (n = 11)	Negative
Oligoclonal Band / CSF IgG index (n = 2)	Raised(n = 1), Negative(n = 1)
Anti Nuclear Antibodies (n = 7)	Negative
Anti Neutrophil Cytoplasmic Antibodies (n = 5)	Negative
RA factor (n=2)	Negative
Anti CCP Antibodies (n = 1)	Negative
Anti dsDNA Antibodies (n = 4)	Negative
Anti TTG Antibodies (n = 1)	Negative
Anti Thyroid Microsomal Antibodies (n = 1)	Negative
Anti ENA Antibodies (n = 5)	Negative
Anti Cardiolipin IgG / IgM Antibodies (n = 1)	Negative
Anti Beta 2 GP I Antibodies (n = 1)	Negative
Serum NMDA Antibodies (n = 2)	Negative
Serum AMPA 1 and 2 Antibodies (n = 2)	Negative
Serum LG1 Antibodies (n = 2)	Negative
Serum GABA B Receptor Antibodies (n = 2)	Negative
Anti CASPR2 Antibodies (n = 2)	Negative
Complement C3 and C4 levels (n = 1)	Raised

which found male to female ratio of 1.6:1, but other studies have reported equal male to female ratio, as well.[10,13] One study showed that severe headache` was a presenting clinical feature in 50 % of MOGAD patients,[14] however, 80 % of patients in our study presented with headache. In our study, optic neuritis

was a presenting clinical characteristic of 1(20%) case, and in literature, optico-spinal phenotype of MOGAD is more common in adolescents and adults[15] as optic neuritis is a major clinical presentation in MOGAD and may occur alone, recurrent or bilateral, in approximately 50% of cases, in contrast with our study, where optic neuritis was present in 80% of cases. One study showed that seropositivity for anti-MOG antibody titers ranged from 1:40 to 1:10000, with similar trends observed in our results.[16] Optic neuritis and transverse myelitis were the most frequent clinical finding in our study, which is consistent with findings of another author, who reported optic neuritis and myelitis with long segmental lesions as the most common symptoms of MOGAD in adults[17] but another showed relapsing course in 40–80% of children and adults but we encountered monophasic course of MOGAD in our study.[18] In literature, average diagnostic delay was 54 months (4.5 years) whereas we found an average diagnostic delay of 20 months, which may have occurred due to improved cell based assays over time.[19]

CONCLUSION

High index of suspicion should be kept for MOGAD in patients presenting with optic neuritis or transverse myelitis associated with headache or fever. By keeping a low threshold for presenting clinical characteristics clinicians may be able to diagnose and treat this rare disease timely and prevent associated morbidity and mortality.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

The following authors have made substantial contributions to the manuscript as under:

MZA & MOR: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

DA & MH: Conception, data analysis, drafting the manuscript, approval of the final version to be published.

AT & MB: Data acquisition, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Boziki M, Sintila SA, Ioannidis P, Grigoriadis N. Biomarkers in rare demyelinating disease of the central nervous system. Int J Mol Sci 2020; 21(21): 8409. https://doi.org/10.3390/ijms21218409
2. Ambrosius W, Michalak S, Kozubski W, Kalinowska A. Myelin oligodendrocyte glycoprotein antibody-associated disease: current insights into the disease pathophysiology, diagnosis and management. Int J Mol Sci 2020; 22(1). https://doi.org/10.3390/ijms22010114
3. Ramanathan S, Dale RC, Brilot F. Anti-MOG antibody: the history, clinical phenotype, and pathogenicity of a serum biomarker for demyelination. Autoimmun Rev 2016; 15(4): 307-324. https://doi.org/10.1016/j.autrev.2016.01.007
4. de Mol CL, Wong YYM, van Pelt ED, Wokke BHA, Siepman TAM, Neuteboom RF, et al. The clinical spectrum and incidence of anti-MOG-associated acquired demyelinating syndromes in children and adults. Mult Scler J 2019; 26(7): 806-814. https://doi.org/10.1177/1352458519864922
5. Ong ZM, Arip M, Ching YM, Kumar L, Terumalay S, Sim SH, et al. The prevalence, demographics, clinical features, neuroimaging, and inter-ethnic differences of MOGAD in Malaysia with global perspectives. Mult Scler Relat Disord 2022; 67: 104168. https://doi.org/10.1016/j.msard.2022.104168
6. Messias K, Marques VD, Messias A. Myelin oligodendrocyte glycoprotein antibody-associated optic neuritis: an update. Arq Bras Oftalmol 2023; 86. https://doi.org/10.1590/0004-2749-2023-0004
7. Mariotto S, Gajofatto A, Batzu L, Delogu R, Sechi G, Leoni S, et al. Relevance of antibodies to myelin oligodendrocyte glycoprotein in CSF of seronegative cases. Neurology 2019; 93(20): e1867-e1872. https://doi.org/10.1212/WNL.0000000000008450
8. Narayan R, Simpson A, Fritsche K, Salama S, Pardo S, Mealy M, et al. MOG antibody disease: a review of MOG antibody seropositive neuromyelitis optica spectrum disorder. Mult Scler Relat Disord 2018; 25: 66-72. https://doi.org/10.1016/j.msard.2018.07.017
9. Banwell B, Bennett JL, Marignier R, Kim HJ, Brilot F, Flanagan EP, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. Lancet Neurol 2023; 22: 122–131. https://doi.org/10.1016/S1474-4422(22)00460-7
10. Sechi E, Cacciaguerra L, Chen JJ, Mariotto S, Fadda G, Dinoto A, et al. Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD): a review of clinical and MRI features, diagnosis, and management. Front Neurol 2022; 13. https://doi.org/10.3389/fneur.2022.886588
11. Sechi E, Buciuc M, Pittock SJ, Chen JJ, Fryer JP, Jenkins SM, et al. Positive predictive value of myelin oligodendrocyte glycoprotein autoantibody testing. JAMA Neurol 2021; 78(6): 741-746. https://doi.org/10.1001/jamaneurol.2021.0966
12. Orlandi R, Mariotto S, Gajofatto A. Prevalence, incidence, and season distribution of MOG antibody-associated disease in the province of Verona, Italy. Mult Scler Relat Disord 2022; 63: 103884. https://doi.org/10.1016/j.msard.2022.103884
13. Sutton P, Lutz MW, Hartsell FL, Kimbrough D, Tagg NT, Skeen M, et al. Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease: presentation and outcomes of adults at a single center. J Neuroimmunol 2022; 373: 577987. https://doi.org/10.1016/j.jneuroim.2022.577987
14. Asseyer S, Hamblin J, Messina S, Mariano R, Siebert N, Everett R, et al. Prodromal headache in MOG-antibody positive optic neuritis. Mult Scler Relat Disord 2020; 40: 101965. https://doi.org/10.1016/j.msard.2020.101965
15. Reindl M, Waters P. Myelin oligodendrocyte glycoprotein antibodies in neurological disease. Nat Rev Neurol 2019; 15(2): 89-102. https://doi.org/10.1038/s41582-018-0112-x

16. Rempe T, Tarhan B, Rodriguez E, Viswanathan VT, Gyang TV, Carlson A, et al. Anti-MOG associated disorder: clinical and radiological characteristics compared to AQP4-IgG+ NMOSD: a single-center experience. Mult Scler Relat Disord 2021; 48: 102718. https://doi.org/10.1016/j.msard.2020.102718
17. Li Y, Liu X, Wang J, Pan C, Tang Z. Clinical features and imaging findings of myelin oligodendrocyte glycoprotein-IgG-associated disorder (MOGAD). Front Aging Neurosci 2022; 14. https://doi.org/10.3389/fnagi.2022.841052
18. Bartels F, Lu A, Oertel FC, Finke C, Paul F, Chien C. Clinical and neuroimaging findings in MOGAD–MRI and OCT. Clin Exp Immunol 2021; 206(3): 266-281. https://doi.org/10.1111/cei.13666
19. Dauby S, Dive D, Lutteri L, Andris C, Hansen I, Maquet P, et al. Comparative study of AQP4-NMOSD, MOGAD, and seronegative NMOSD: a single-center Belgian cohort. Acta Neurol Belg 2022; 122(1): 135-144. https://doi.org/10.1007/s13760-021-01719-x