Anti-MOG Antibody Associated Disorders in Pakistan

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ABSTRACT

Objective: To present clinicopathological features and treatment outcomes of patients who tested positive for anti-myelin oligodendrocyte glycoprotein (MOG) antibodies in the catchment Pakistani population.

Study Design: Observational study.

Place and Duration of the Study: Department of Immunology and Neurology, Shifa International Hospital / Shifa Tameer-e-Millat University, Islamabad, Pakistan, from January 2018 to December 2022.

Methodology: A review of patients referred for anti-MOG antibody testing was conducted. Indirect immunofluorescence was used to analyse all samples on EU 90 cells transfected with MOG genes. Patients who tested positive for anti-MOG antibodies were included in the study. Patients' medical records and interviews were used to gather clinical data, as per the objective.

Results: One hundred and fourteen patients out of 740 were tested positive for anti-MOG antibodies. A total of 59 patients were included for final analysis, and 78 (68.4%) of the seropositive population were male, with a mean age of 24 years ± 15.8 years (range 4-59 years). The most frequent clinical presentation was visual impairment in 39/59 (66%) patients, followed by muscle weakness in 36/59 (61%) and headache in 30/59 (50%) patients. Treatment included intravenous methylprednisolone, oral prednisolone, plasma exchange, rituximab, intravenous immunoglobulins, azathioprine, mycophenolate mofetil, cyclophosphamide, and methotrexate.

Conclusion: The present study showed a higher percentage of males tested positive for anti-MOG antibodies. MOG-associated disorders can affect both children and adults. The most frequent clinical presentations of MOGAD in this study were visual impairment, followed by muscle weakness. The primary clinical phenotype identified was isolated transverse myelitis.

Key Words: *Myelin oligodendrocyte glycoprotein, Optic neuritis, Myelitis, Acute disseminated encephalomyelitis, Demyelinating disease, Autoimmune disorder*.

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INTRODUCTION

Myelin oligodendrocyte glycoprotein (MOG) is an immunogenic component of myelin expressed on the surface of oligodendrocytes in the central nervous system (CNS).[1] Auto-antibodies targeting MOG are associated with MOG antibody-associated disorders (MOGAD), an inflammatory demyelinating disorder characterised clinically by acute attacks of unilateral or bilateral visual loss, limb weakness, sensory loss, headache, seizures, altered mental status, focal neurological features, and bowel or bladder dysfunction. These features can be grouped into the characteristic phenotypes of optic neuritis, transverse myelitis, acute disseminated encephalo-myelitis (ADEM), and aquaporin-4-IgG seronegative neuro-myelitis optica spectrum disorder (AQP4-IgG NMOSD).

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Less common manifestations include cerebral cortical encephalitis, brainstem or cerebellar presentations, and other CNS deficits related to demyelinating lesions.[2,3] The pathological demyelination may involve complement activation by anti-MOG antibodies.[4]

According to a European study, the incidence of MOGAD is between 1.6 and 3.4 per 1,000,000 person per year.[5] In Asia, according to a Japanese study, the incidence was 0.39/100,000.[6] In contrast to multiple sclerosis (MS), which has high prevalence levels in North America and Europe (>100/100,000 inhabitants) and predominantly affects females, MOGAD shows no marked gender or ethnic predominance.[7] Furthermore, unlike the chronic relapsing disease course seen in multiple sclerosis, the neurological dysfunction in MOGAD exists as either a monophasic or relapsing disease.

MOGAD shows clinical and radiological features that distinguish it from MS and AQP4-IgG NMOSD. Reliable serum markers differentiate MOGAD from AQP4-IgG NMOSD; however, the lack of biomarkers for MS complicates the distinction. Consequently, the presence of anti-MOG antibodies, absence of CSF oligoclonal bands, and resolution of T2 lesions on brain and/or spinal cord on MRI in patients with MOGAD helps to differentiate from patients with MS. Unique MRI features include

perineural optic sheath enhancement, optic disc oedema, longitudinally extensive myelitis, central cord lesion or H-sign, and conus lesion.[8]

Testing for autoantibodies should be undertaken in suspected cases using a validated cell-based assay. Serum is a better sampling source than CSF, which has a lower concentration of antibodies.[9] Treatment includes intravenous methylprednisolone, oral prednisolone, plasma exchange, intravenous immunoglobulins, rituximab, mycophenolate mofetil, methotrexate, cyclophosphamide or azathioprine.

Recently proposed diagnostic criteria for MOGAD require a core clinical demyelinating event (optic neuritis, myelitis, ADEM, cerebral monofocal or poly focal deficits, brainstem or cerebellar deficits, and cerebral cortical encephalitis (often with seizures)), a clear positive anti-MOG IgG antibody test, and the exclusion of a better diagnosis.[8]

Data on the prevalence, clinical manifestations, and treatment outcomes of MOGAD in Pakistan are limited, despite its increasing recognition globally. This study will improve understanding, diagnostic accuracy, and treatment strategies within this specific population. The objective of this study was to present the clinicopathological features and treatment outcomes of patients who tested positive for anti-MOG antibodies.

METHODOLOGY

This study was conducted within the Department of Immunology and Neurology at Shifa International Hospital / Shifa Tameer-e-Millat University, Islamabad, Pakistan, after approval from the IRB (Institutional Review Board and Ethics Committee # 0299-23). A review of the data of suspected MOGAD cases was undertaken from January 2018 to December 2022. Testing used indirect immunofluorescence on EU 90 cells (Euroimmun, Luebeck, Germany) transfected with MOG genes (Figure 1). Briefly, diluted patients' samples were incubated on MOG gene-transfected test fields, where autoantibodies in the serum, if present, were bound to the antigen. The bound antibodies were then stained with fluorescein isothiocyanate-labelled anti-human antibodies and viewed under a fluorescence microscope. Patients who were seropositive for anti-MOG antibodies (characteristic fluorescent pattern on microscopy) with fluorescence intensity of +1, +2, and +3, and whose clinical details were available were included in the study, comprising both admitted and outpatients, while seronegative patients and those lacking clinical details were excluded. After obtaining informed verbal consent, clinical information was collected *via* a structured questionnaire by interviewing patients, their relatives and physicians, and by reviewing medical records. Age, gender, and prominent presenting features were noted. The treatment course and clinical outcomes were determined after a follow-up period of one to five years.

Patients with optic neuritis or transverse myelitis were diagnosed by examining clinical features, visual evoked potentials, MRI findings, and laboratory criteria. Patient samples that were referred from another institute were diagnosed by the referring physicians and their clinical information was collected similarly through interviews and chart reviews. Visual-evoked potentials were conducted and an increase in P100 latency equal to or greater than 118 ms was used to label as an abnormal response.[10] Along with the clinical features and radiological findings, the detection of anti-MOG antibodies in the serum confirmed the diagnosis of MOGAD and ruled out MS and neuromyelitis optica.

Descriptive analysis was done. Categorical variables were expressed as counts and percentages and continuous variables were expressed as mean and SD.

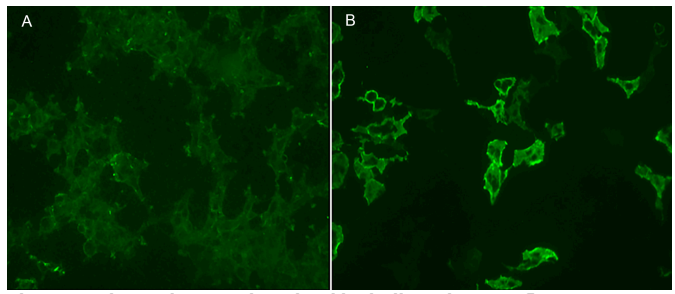

Figure 1: Photomicrograph stained by indirect immunofluorescence on EU 90 cells (Euroimmun, Luebeck, Germany) transfected with MOG genes (objective 20x) showing: (A) Negative control serum for anti-MOG antibodies tested on EU90 cell line transfected with MOG gene showing no staining. (B) Patients' serum positive for anti-MOG antibodies tested diluted (1:10) on EU90 cell line transfected with MOG genes clearly showing granular cytoplasmic bright green fluorescent reaction with accentuation of the cell membrane.

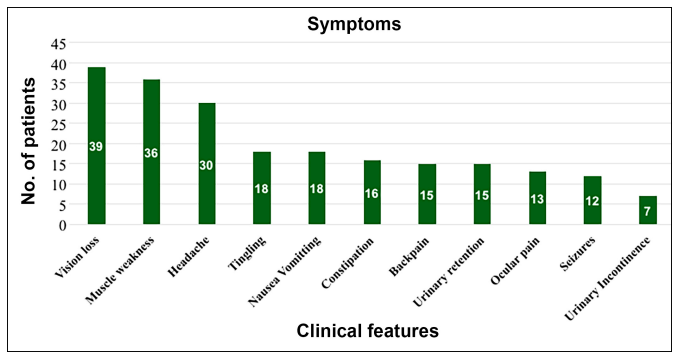

Figure 2: Clinical features of patients with MOGAD.

RESULTS

A total of 740 patients were tested. Anti-MOG antibodies were positive in 114 patients, out of which 81 tested negative for anti-AQP4-IgG antibodies. Males accounted for 78 (68%) with a mean age of 24 ± 15.8 years (range 4-59 years). Fifty-five patients were excluded, among whom 2 expired, and clinical details were unavailable for 53 patients. As a result, a total of 59 patients were included for final analysis.

The most common symptom was visual impairment in (66%) 39/59 patients (28 with bilateral and 11 with unilateral), followed by muscular weakness, which was subdivided into five categories including bilateral paraparesis (n = 21), bilateral quadriparesis (n = 10), lower limb monoparesis (n = 3), right haemiparesis (n = 1), and left haemiparesis (n = 1) was found. Other symptoms included headache, tingling, nausea, back pain, and bladder and bowel dysfunction (Figure 2).

Clinical phenotypes included isolated optic neuritis, isolated transverse myelitis, combined optic neuritis with transverse myelitis and ADEM in 15 (25%), 18 (31%), 24 (41%), and 2 (3%) cases, respectively.

Investigations included testing for oligoclonal bands for 11 (19%) patients. Oligoclonal bands were present only in the CSF in 2 (18%) cases, while bands were absent in both serum and CSF in 4 (36%) cases. Matching bands in both CSF and serum were found in 5 (45%) cases for whom further testing for systemic infection, autoimmune disease, and sarcoidosis was unremarkable. Visual-evoked potentials were tested in 13 (22%) patients, out of which 8 (62%) showed bilateral optic pathway dysfunction, 3 (23%) showed unilateral, and 2 (15%) patients' tests were normal.

MRI showed radiological features of TM in the cervical spine in 1 patient and in the thoracic spine in 4 patients. MRI brain showed T2/FLAIR hyperintensities in supra and infratentorial locations (severe diffuse meningoencephalitis) in 2 patients with ADEM.

Treatment included combinations of first-line therapy consisting of intravenous methylprednisolone, oral prednisolone, intravenous immunoglobulins, and plasma exchange, and second-line medicines, including rituximab, methotrexate, cyclophosphamide, mycophenolate mofetil, and azathioprine. These were given alone or in combination based on patients' affordability and compliance, severity of symptoms, response to treatment, and physician's preference. Intravenous methyl prednisolone 1g daily for 3 days was given to 5 patients, I/V methyl prednisolone 1g daily for 5 days was given to 13 patients, oral prednisolone taper was given to 36 patients, five sessions of PLEX was done in 4 patients, rituximab 1g was given to 4 patients, IVIG was given to 1 patient, azathioprine was given to 19 patients, cyclophosphamide was given to 1 patient, myco-phenolate mofetil was given to 6 patients, and methotrexate was given to three patients. After reviewing the doctors' progress reports, patients' responses to the questionnaire and follow-up investigations, the recovery outcomes were such that 16 (27%) patients experienced full recovery, 29 (49%) patients showed partial improvement, 3 (5%) patients did not improve, and 11 (19%) patients were lost to follow-up.

DISCUSSION

In this cohort, the clinical presentation, laboratory findings, and management and treatment outcomes of 59 patients who presented to this healthcare facility with MOGAD have been reported. The mean age of the patients in the present study was in the second decade. This is consistent with published reports from China[11], Sri Lanka[12], and US[13] but contrasts with a report from India[14] showing a mean age of 12.5 years, which is likely due to the younger age group of their cohort. The current research showed that 68% of the patients were males which compares well with a previous study conducted locally[15] and regionally.[16] However, published literature from China, Sri Lanka, and USA[11-13] showed a female predominance of 55%, 56%, and 58%, respectively. This may be due to a referral bias in Pakistan.

The most common clinical phenotype in the present report was isolated transverse myelitis (31%) while ADEM is more common in younger population studies.[14] Patients presenting with a suspected demyelinating disorder undergo extensive work-up including the test for oligoclonal bands which helps to differentiate between MOGAD and MS. Accordingly, 11 patients were tested for oligoclonal bands, out of which only 2 (18%) showed intrathecal synthesis of immunoglobulins. Similarly, recent publications reported that intrathecal IgG synthesis is rare in MOGAD, occurring in 6-17% of patients.[17]

In this study, a combination of 1st and 2nd line therapy was used, consisting of I/V and oral steroids, IVIG, PLEX, azathioprine, cyclophosphamide, mycophenolate mofetil, rituximab, and methotrexate. Full recovery was reported in 16 (27%) cases, while 29 (49%) cases reported partial recovery. The present figures are consistent with Jarius *et al*., where 44% exhibited partial recovery.[18]

This study has some limitations. Firstly, the data collected may have been influenced by the participants' disease status at the time of sampling. Additionally, the lack of data for many patients limited the sample size. Finally, as MOGAD has been recognised recently as an autoimmune disorder, larger multicentre studies are needed for a better understanding of the epidemiology, clinical presentation, and outcomes associated with MOGAD.

CONCLUSION

In Pakistan, MOGAD showed a higher male prevalence, affecting both children and adults. The most frequent clinical presentations were visual impairment, followed by muscle weakness, with the primary clinical phenotype being isolated transverse myelitis.

DISCLOSURE:

These data were presented in the XXVI World Congress of Neurology (WCN 2023) as a poster presentation and the abstract was published in The Journal of Neurological Sciences.

ETHICAL APPROVAL:

Ethical approval of this study was obtained from the Ethics Committee of Shifa International Hospital / Shifa Tameer-e-Millat University, Islamabad, Pakistan (IRC# 0299-23).

PATIENTS' CONSENT:

Consent of the patient / guardian was taken prior to the writing of the manuscript.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

TM: Acquisition of data and drafting of the manuscript.
AA: Conception and review of the clinical data.
TAA: Critical review and final approval.
All authors approved the final version of the manuscript to be published.

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