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Clinical spectrum of demyelinating disease of central nervous system and frequency of anti AQP4 and anti MOG among them: one-year single-center retrospective study

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Abstract

Background: Inflammatory demyelinating diseases of the central nervous system (CNS) are autoimmune conditions leading to significant neurological disability in adults. Recent classifications include myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) and neuromyelitis optica spectrum disorder (NMOSD) which pose diagnostic challenges due to overlapping clinical and radiological features. This study aimed to assess the clinical spectrum among adults and children diagnosed with CNS demyelinating diseases and to find the proportion of MOG and/or aquaporin-4 (AQP4) autoantibodies amongst them.

Methods: This single-center, retrospective study examined 20 patients diagnosed with CNS demyelinating disorders between March, 2023 and February, 2024. Data pertaining to demographics, disease types, CSF analysis, MRI findings, treatment modalities, and serological profiles for anti-AQP4 and anti-MOG antibodies were collected from hospital records and evaluated.

Results: Among 20 patients [median age, 34 years (IQR, 18.75); males (n=10) and females (n=10)], acute transverse myelitis (TM) was the most common demyelinating disorder at onset (60%) followed by optic neuritis (ON) (20%). CSF analysis found elevated protein levels in 53% and pleocytosis in 33% of patients. MRI findings revealed longitudinal extensive involvement in 52% of patients, predominantly affecting the cervical and dorsal spine. Serological testing identified 15% positive for anti-AQP4 and 10% for anti-MOG antibodies. MOG+ patients were significantly younger than AQP4+ patients (mean age 16.5 vs. 36.66 years, p=0.016). Both MOG+ patients were male, with 50% presenting with acute TM and 50% with acute disseminated encephalomyelitis. Among AQP4+ patients, the male-to-female ratio was 1:2, with 66.66% presenting with acute TM and 33.33% with ON.

Conclusion: CNS demyelinating disorders primarily affect younger individuals, with TM as the most common initial disorder and extensive spinal involvement in cervical and dorsal regions. Serological testing identified three patients with anti-AQP4 and two with anti-MOG antibodies, providing valuable insights into the clinical spectrum of these disorders through cell-based assays.

Keywords: Autoantibodies, Aquaporin-4, CNS Demyelinating Disorders, Myelin Oligodendrocyte Glycoprotein, Neuromyelitis Optica Spectrum Disorder, India

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Background

Inflammatory demyelinating diseases (IDD) of the central nervous system (CNS) encompass a diverse autoimmune inflammatory group of diseases including multiple sclerosis (MS), neuromyelitis Optica spectrum disorder (NMOSD), acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), and acute transverse myelitis (ATM). These diseases represent a significant cause of non-traumatic neurological disability in adults [1,2]. Recently, these CNS demyelinating diseases are categorized into 4 types: a) MS, b) NMOSD, c) myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD), d) seronegative demyelinating syndromes [3]. Among these diseases, NMOSD and anti-MOG syndromes are immune-mediated conditions that primarily affects the optic nerves and spinal cord [4-6]. NMOSD is linked to antibodies targeting aquaporin-4 (AQP4) at the blood-brain barrier astrocytes [4,7], whereas anti-MOG syndromes involve MOG damage on oligodendrocyte surfaces and myelin sheaths [8,9]. Given the overlapping clinical and radiological characteristics and need of reliable diagnosis among these disorders [3,10], this study aims to assess the clinical spectrum of CNS demyelinating diseases and to determine the prevalence of MOG and/or AQP4 autoantibodies among adults.

Methods

Study design and participants

A retrospective analysis of CNS demyelinating disease patients admitted over one year period from March, 2023 to February, 2024 at Kiran Multi Super Speciality Hospital and Research Center, Surat Gujarat located in Western India was done.

Inclusion and exclusion criteria

Patients with a final diagnosis of CNS demyelinating disease by a neurophysician were included in the study. Patients with demyelination secondary to vascular, infection, and/or immunological causes, as well as patients who had left against medical advice were excluded. The study was approved by Institutional Review Board of Kiran hospital, Surat.

Data collection process

Baseline demographic information, comprehensive clinical history including neurological abnormalities, ophthalmic examinations, laboratory findings including cerebrospinal fluid (CSF) analysis (including oligoclonal bands), vasculitis profiles [Antineutrophilic cytoplasmic antibody (ANCA), cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA), perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA)], and treatment modalities were extracted from hospital records. Radiological findings from magnetic resonance imaging (MRI) scans of the brain, spine, and/or orbit, when available, were also recorded. Serum assays for MOG and AQP4 antibodies were performed for all patients using cell-based assays at a referral laboratory. Diagnoses of MS, MOGAD, and NMOSD were established based on the 2015 International consensus diagnostic criteria for neuromyelitis optica spectrum disorders [11]. Treatment for all patients included intravenous methylprednisolone (1g/day for 5 days) followed by oral prednisolone upon discharge. Details of additional immunosuppressive therapies, if administered, were also documented.

Statistical analysis

Descriptive statistics were used to analyze clinical, laboratory, and radiological parameters, with categorical data presented as numbers and percentages, and continuous data as means [standard deviations (SD)] or median [interquartile ranges (IQR)]. A p-value<0.05 was statistically significant.

Results

Description of respondents

During the study period, a total of 22 patients were initially diagnosed with CNS demyelination disorders. Two patients were excluded from further analysis: one due to leaving against medical advice and the other due to demyelination secondary to a non-inflammatory cause. Therefore, the final cohort for analysis consisted of 20 patients. Among these 20 patients [median age, 34 years (IQR, 18.75)], majority of patients (35%) were between the age group of 30 to 40 years. There was an equal distribution of males and females in the study population (Table 1). Vasculitis profiles (ANA, c-ANCA, p-ANCA) were negative for all patients. The types of demyelinating disorders based on type of onset are summarized in Table 2. ATM was the most prevalent type of demyelinating disorder (60%), followed by ON (20%) and MS (15%). Only one patient was presented with ADEM. Fifteen out of the 20 patients underwent CSF examination. CSF pleocytosis (white blood cells >5 cells/cm2) were detected in 33% of patients and elevated CSF protein (> 45 mg/dL) in 53% of patients. Two patients (13.33%) detected with CSF OCB and one patient had an increased immunoglobulin gamma index (Table 3). Radiological (MRI imaging) findings in 19 patients are presented in Table 4. Longitudinal extensive involvement (≥ three contiguous vertebrae) on MRI spine was observed in 52% of patients. MRI spine and brain findings revealed cervical spine involvement in 26% and dorsal spine involvement in 52% of patients.

Table 1: Demographic characteristic of study patients (N=20)

Variables	**n (%)**
Age(years) (Median, IQR*)	34 (18.75)
< 20 years	03 (15)
20-30 years	05 (25)
30-40 years	07 (35)
40-50 years	04 (20)
> 50 years	01 (05)
Gender	
Male	10 (50)
Female	10 (50)

*IQR: interquartile range

Table 2: Types of demyelinating disorders based on type of onset in study patients (N=20)

Type of demyelinating disorders,	**n (%)**
Isolated transverse myelitis	12 (60)
Isolated optic neuritis	04 (20)
Acute disseminated encephalomyelitis	01 (5)
Multiple sclerosis	03 (15)

Table 3: CSF findings of study patients (N=15)

***CSF findings**	**n (%)**
CSF pleocytosis	05 (33)
Elevated CSF protein	08 (53)
CSF oligoclonal bands	02 (13.33)

*CSF: cerebrospinal fluid

Table 4: Radiological (MRI imaging) characteristics of study patients (N=19)

***MRI Spine**	
Type of involvement, n (%)	**n (%)**
Multiple short segment	03 (16)
Longitudinal extensive segment	10 (52)
MRI Spine and Brain	
Site of involvement, n (%)	
Cervical	05 (26)
Dorsal	10 (52)
Lumbar	01 (5)
Cortical and subcortical	02 (10)
Cerebellum peduncle	01 (5)
Periventricular	02 (10)
Corpus callosum	01 (5)

*MRI: magnetic resonance imaging

All patients received intravenous methylprednisolone (1g/day for 5 days) as initial treatment, with two patients (10%) also

undergoing plasmapheresis. Upon discharge, all patients were prescribed a tapering regimen of oral prednisolone. Additionally, 5 patients (25%) received immunosuppressive agents alongside oral prednisolone (Table 5).

Table 5: Treatment modality in study patients (N=20)

Treatment modality	n (%)
Steroid alone	12 (60)
Plasmapheresis	02 (10)
Intravenous immunoglobulin	01 (5)
Immunosuppressive agents + oral prednisolone	05 (25)

Table 6 demonstrates clinical characteristic of anti AQP4 and anti MOG patients. Among 20 patients, 3 patients (15%) were positive for anti AQP4 and 2 patients (10%) for anti MOG in the serum. There was a significant difference in age distribution between MOG+ and AQP4+ cases (mean age (SD), 16.5 (0.7) years vs. 36.66 (4.5) years, p=0.016), (Table 6). Among the MOG+ cases, both patients were male, with one presenting with ATM (50%) and the other with ADEM (50%). Among the AQP4+ cases, there was a male-to-female ratio of 1:2, with two patients (66.66%) presenting with ATM and one patient (33.33%) with ON. Description of clinical characteristic of each patient positive for AQP4/MOG are detailed in supplementary appendix.

Table 6: Clinical characteristic of anti AQP4 and anti MOG cases (N=5)

Case no.	AQP4 positive cases (n=3)				Case no.	MOG positive cases (n=2)			
	Age	Gender	Type of demyelinating disorders	Antibody titer		Age	Gender	Type of demyelinating disorders	Antibody titer
1	32	Female	Optic neuritis	1:32	1	17	Male	Acute transverse myelitis	1:100
2	41	Male	Acute transverse myelitis	1:100	2	16	Male	Acute disseminated encephalomyelitis	1:32
3	37		Acute transverse						
Mean Age (S.D): 36.66 (4.5)		Female	Myelitis	1:100		Mean Age (S.D): 16.5(0.7)			

*P value for age between two group = 0.016; AQP4: aquaporin-4; MOG: myelin oligodendrocyte glycoprotein

Discussion

This single-center, retrospective study in Western India assessed the clinical spectrum of CNS demyelinating diseases and the frequency of MOG and/or AQP4 autoantibodies in 20 patients. In the current study, 75% of the patients were under 30 years old, with an equal distribution between males and females. Likewise, previous studies have also reported a predisposition of young people to CNS demyelinating disease [2, 12-14]. However, these studies reported female preponderance [2,12-14]; this discrepancy may be attributable to small sample size in our study. Isolated TM was the most common initial presentation at onset, followed by isolated ON and MS. TM predominated in both anti-MOG and anti-AQP4 positive patients. This finding aligns with findings of other Indian studies [10,15,16], which also identified TM as the most frequent IDD presentation. The CSF analysis in our study revealed elevated protein levels as the most common finding, followed by pleocytosis. Oligoclonal band measurement in CSF is used to determine intrathecal IgG production [17]. We found approximately 14% of patients with oligoclonal bands. These results are consistent with other studies [2,18-22], which also documented increased CSF protein, pleocytosis, and oligoclonal bands as key diagnostic features of CNS demyelinating disorders. In the current study, MRI findings revealed dorsal spine involvement in 52% and cervical spine involvement in 26% of patients. These results are in confirmation with previous studies by T. Murali Venkateswara Rao and U. Ganga Prasad [2], Gass A. et al. [22], and Pohl D [23], which have demonstrated the high utility of MRI in diagnosing these disorders, despite minor variations in the most common sites of involvement across the studies. The vasculitis profile in the current study indicated that no patients tested seropositive for ANCA, c-ANCA, or p-ANCA autoantibodies. However, this finding is in contrast with previous study [16], which have reported a co-existence of these autoantibodies in 38% to 75% of patients, particularly among AQP4 NMOSD patients than MOGAD patients. In the current study, serum antibody frequencies were 10% for MOG and 15% for AQP4. These results are in line with those reported by Kim et al. [1], who found MOG and AQP4 antibodies in 6.3% and 18.1% of cases, respectively, and Dhar et al. [10], who reported 13% and 16%, respectively. A statistically significant age difference was identified between the AQP4+ and MOG+ groups, with MOG+ patients being younger. This finding is corroborated by several Indian studies that report lower median ages of onset for both AQP4+ and MOGAD patients [4,10,15,16]. Phenotypically, isolated TM with dorsal spine involvement was seen in two AQP4+ patients (titer 1:100), while one AQP4+ patient presented with ON (titer 1:32). Among MOG+ patients, one had isolated TM (titer 1:100) and another had ADEM (titer 1:32). Both MOG+ patients were male, presenting with TM and ADEM, which is consistent with prior research [10,21,22]. Conversely, AQP4+ cases showed a female predominance, with a male-to-female ratio of 1:2 and presented with ATM and ON. These findings align with Dhar's observations of a female predominance, frequent dorsal TM, and less frequent ON in AQP4+ than MOG+ patients [10,24,25]. Similar findings were reported by Dauby S et al. [26], indicating a higher prevalence of females among AQP4+ than MOG+ patients. Additionally, the clinical presentation of MOGAD varies with age: children typically present with ADEM-like lesions, while adults more

frequently exhibit TM or ON. Studies report a positive predictive value of 85.9% for a MOG IgG titer ≥ 1:20 [4]. The current study has some limitations that needs to be acknowledged, including its small sample size and retrospective design. Nevertheless, our findings offer valuable insights into the incidence and clinical characteristics of patients with anti-MOG and anti-AQP4 positive IDD. Future studies with larger cohorts and long-term outcome evaluations are warranted.

Conclusion

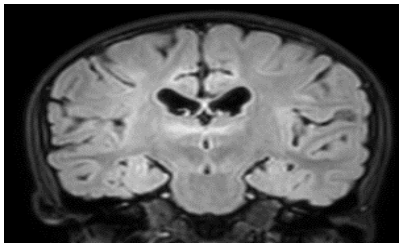
CNS demyelinating disorders predominantly affect younger individuals, with TM being the most common demyelinating disorder at onset, longitudinal extensive involvement primarily in the cervical and dorsal spine. Serological testing revealed three patients with anti-AQP4 and two patients with anti-MOG antibodies. Identifying anti-MOG and anti-AQP4 through cell-based assay provide valuable insights into the clinical spectrum of these disorders.

Supplementary Appendix:

MOG positive cases:

1.Case 1: A 17-year-old male presented with a five-day history of back pain, backache, bilateral lower limb asymmetrical weakness, and urinary retention. His anti-MOG titer was 1:100, and CSF protein was 52 mg/dl. MRI of the spine revealed long segment involvement from C4 to D1. He was treated with intravenous methylprednisolone (IV MPSS) and intravenous immunoglobulin (IVIG) for five days, along with a single dose of Rituximab. He was discharged on the fifth day of admission with a tapering dose of oral prednisolone.

2. Case 2: A 16-year-old male presented with fever, headache, difficulty walking, and mild neck rigidity. His anti-MOG titer was 1:32, and the CSF showed 15 cells. MRI T2-weighted images revealed hyperintensities in the subcortical areas of the bilateral frontal and parietal regions and the bilateral thalamic area, indicative of ADEM. He was treated with IV MPSS and discharged on oral prednisolone and azathioprine.



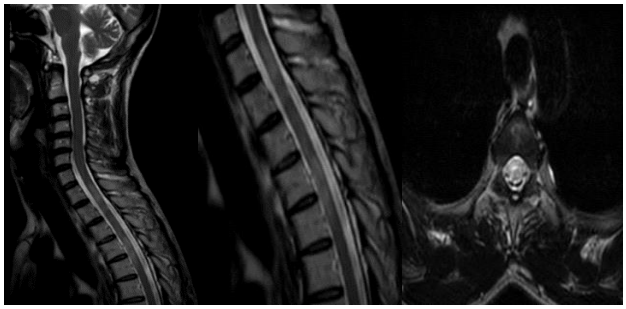
(MOG positive case 2): A 16-year-old male, a follow-up case of ADEM, showed bilateral symmetrical T2W-FLAIR hyperintensities in the thalamus.

AQP4 positive cases:

1.Case 1: A 32-year-old female presented with blurred vision in the left eye and a headache for five days. Her vitals and fundus examination were normal. MRI of the brain and optic nerve showed a slightly thickened optic nerve. Her AQP4 titer was 1:32. She was treated with IV MPSS for five days and discharged on oral prednisolone and azathioprine.

2.Case 2: A 41-year-old male presented with spasmodic back pain radiating to the lower limbs since for two days, tingling, and numbness. He also had a history of diabetes mellitus for one year. His AQP4 titer was 1:100. MRI of the spine showed long segment intra-medullary patchy T2W hyperintensity extending from D1 to D5, involving the dorsal cord. He was treated with IV MPSS and one cycle of plasmapheresis and discharged on oral prednisolone and azathioprine.

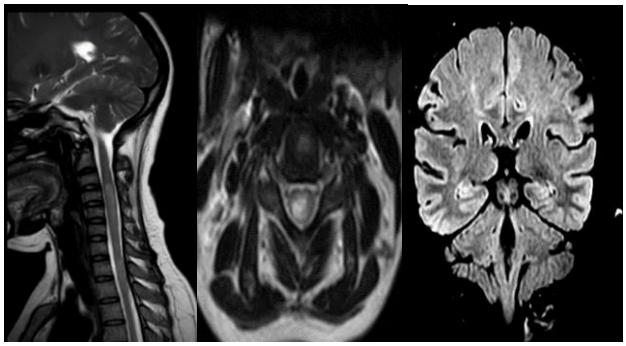
3.Case 3: A 37-year-old female presented with difficulty walking for four days. Her AQP4 titer was 1:100. MRI of the spine revealed involvement from C3-C5 to the lower end of T4, and MRI of the brain showed bilateral periventricular and right parietal deep white matter involvement. She was treated with IV MPSS and discharged on oral prednisolone and azathioprine.



(**AQP4 positive cases 2):**

A 41-year-old male presented with bilateral lower limb tingling for 10-15 days. MRI in acute transverse myelitis revealed:

1. An ill-defined, long segment T2W hyperintense signal in the dorsal spinal cord from the lower endplate of C7 vertebra to the lower endplate of D5 vertebra (approximately length of 9.5 cm).
2. A magnified image of the same.
3. T2W hyperintense signal intensity at the C7-D1 intervertebral disc.



(AQP4 positive case 3):

A 37-year-old female had difficulty walking for 15 days. MRI in acute transverse myelitis showed:

1. Long segment patchy ill-defined T2W hyperintense signal intensity in cervical and upper dorsal spinal cord from level of C3-C4 intervertebral disc to lower end of T4 vertebral body.
2. T2W hyperintense signal intensity at C3-C4 intervertebral disc.
3. T2W-FLAIR hyperintense foci in bilateral periventricular region and right parietal deep white matter.

Abbreviation

IDD: Inflammatory Demyelinating Diseases; CNS: Central Nervous System; MS: Multiple Sclerosis; NMOSD: Neuromyelitis Optica Spectrum Disorder; ADEM: Acute Disseminated Encephalomyelitis; ON: Optic Neuritis; ATM: Acute Transverse Myelitis; MOGAD: Myelin Oligodendrocyte Glycoprotein Antibody Associated Disease; AQP4: Aquaporin-4; CSF: Cerebrospinal Fluid; ANCA:Antineutrophilic

Cytoplasmic Antibody; c-ANCA: Cytoplasmic Antineutrophil Cytoplasmic Antibodies; p-ANCA: Perinuclear Anti-Neutrophil Cytoplasmic Antibodies; MRI: Magnetic Resonance Imaging; SD: Standard Deviations; IQR: Interquartile Ranges.

Declaration

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Availability of data and materials

Data will be available by emailing suranadeval17@gmail.com

Authors' contributions

Heena Faldu (HF) participated in conceptualization, preparation of manuscript. Chahat Patel (CP) participated in data collection, analysis, drafting manuscript. Chahat Patel (CP) participated in data analysis, drafting manuscript. All authors approved the final draft of manuscript.

Ethics approval and consent to participate

We conducted the research following the declaration of Helsinki. Permission to conduct this study was granted by the Kiran Hospital Institutional Ethical Committee, issue date 04/03/2024.

Consent for publication

Not applicable

Competing interest

The authors declare that they have no competing interests.

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