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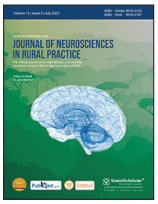

Original Article

A comparative analysis of demographic, clinical and imaging features of myelin oligodendrocyte glycoprotein antibody positive, aquaporin 4 antibody positive, and double seronegative demyelinating disorders – An Indian tertiary care center prospective study

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ABSTRACT

Objectives: The aim of the study was to study the demographical, clinical, radiological features, and outcome of anti-myelin oligodendrocyte glycoprotein (MOG) antibody spectrum disorder and compare these features with patients negative for anti-MOG antibody. MOG antibody-associated disease (MOGAD) and aquaporin-4 (AQP4) antibody-related diseases are immunologically distinct pathologies. Our aim was to compare the clinical and radiological features of MOG antibody-related diseases with AQP4 antibody-related diseases and seronegative demyelinating diseases (Non-multiple sclerosis).

Materials and Methods: This was a prospective and cohort study conducted at an apex tertiary care institute in the northern part of India from Jan 2019 to May 2021. We compared clinical, laboratory, and radiological findings of patients with MOGAD, AQP4 antibody-related diseases, and seronegative demyelinating disease.

Results: There were a total of 103 patients – 41 patients of MOGAD, 37 patients of AQP4 antibody-related diseases and 25 seronegative demyelinating disease. Bilateral optic neuritis was the most frequent phenotype in patients with MOGAD (18/41) whereas myelitis was the most common phenotype in the AQP4 (30/37) and seronegative groups (13/25). Cortical, juxtacortical lesions, anterior segment optic neuritis, optic sheath enhancement, and conus involvement in myelitis were radiological findings that separated MOGAD from AQP4 related diseases. Nadir Expanded Disability Status Scale (EDSS) and visual acuity were similar across the groups. Last follow-up EDSS was significantly better in the MOG antibody group as compared to AQP4 antibody group (1 [0–8] vs. 3.5 [0–8]; $P = 0.03$). Encephalitis, myelitis, and seizures were more common in the younger population (<18 vs. >18 years) in MOGAD (9 vs. 2, $P = 0.001$; 9 vs. 7, $P = 0.03$; 6 vs. 0, $P = 0.001$).

Conclusion: We identified several clinical and radiological features that can help physicians to distinguish MOGAD from AQP4-immunoglobulin G+neuromyelitis optica spectrum disorder. Differentiation is vital as treatment response might vary among both groups.

Keywords: Myelin oligodendrocyte glycoprotein antibody, Aquaporin 4 antibody, Neuromyelitis optica spectrum disorders, Transverse myelitis, Optic neuritis

INTRODUCTION

Myelin oligodendrocyte glycoprotein (MOG) is surface glycoprotein protein located on most outer layer of oligodendrocyte. Different clinical and radiological findings separate MOG antibody-associated disease (MOGAD) from the Aquaporin-4 -immunoglobulin G-positive neuromyelitis optica spectrum disorder (AQP4-IgG+NMOSD).[1] Most data on clinical and radiological differences of these disorders come from Western countries and Caucasian populations.

This observation demands a study comparing clinical, radiological findings, and treatment outcomes between MOGAD and AQP4-IgG+NMOSD.

MATERIAL AND METHODS

This was an prospective and cohort study conducted at an apex tertiary care institute (All India Institute of Medical Sciences, Delhi) in the northern part of India. The study was approved by the Institute Ethics Committee. (Ref No-IECPG-577/26.09.2019, RT-18/24.10.2019).

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All patients attending either the outpatient clinic or getting admitted in the Department of Neurology between the period of January 2019 and May 2021 who fulfilled the following inclusion criteria were included in the study.

Inclusion criteria

Patients presenting with a clinical syndrome compatible with demyelination such as optic neuritis, transverse myelitis, encephalitis, and brainstem encephalitis that were either positive for anti-MOG antibody or anti aquaporin 4 antibodies or were negative for both antibodies, that is, seronegative were included in the study.

Exclusion criteria

Patients who had alternative causes such as sarcoidosis, neoplastic, paraneoplastic, infectious etiology, and those with a diagnosis of multiple sclerosis were excluded from the study.

Acute disseminated encephalomyelitis (ADEM) was diagnosed by International Paediatric Multiple Sclerosis Study Group criteria: Revisions to the 2013 definitions.[2] Encephalitis was defined according to international criteria for inflammatory or infectious encephalitis.[3] ADEM-like lesions were defined as diffuse, poorly demarcated, and large (>1–2 cm) lesions involving predominantly the cerebral white matter and deep grey matter (e.g., thalamus or basal ganglia). Tumefactive demyelinating lesion (TDL) was defined as a T2-weighted magnetic resonance imaging (MRI) "margin to margin" size of 2 cm or more.[4] We defined chronic relapsing inflammatory optic neuritis (CRION) as per the criteria given by Petzold and Plant.[5]

Data collection

All patients were evaluated for demographic and clinical data. Disability was evaluated by Expanded Disability Status Scale (EDSS) and visual acuity in case of ON. Cerebrospinal fluid examination was done to look for infectious causes. Neuroimaging data were collected by doing MRI of the brain, optic nerve, and spinal cord using the Phillips Enginia and GE machine. All serum samples were analyzed to detect AQP4 and MOG antibodies. Cell based immunoassay using transfected cell lines for *in vitro* determination in serum/plasma for quantitative determination of human IgG antibodies to aquaporin 4 receptors and antibody to MOG protein were used.

Eventually all the patients were divided in three groups

1. MOG antibody positive
2. AQP4 antibody positive
3. MOG/AQP4 antibody negative i.e. Seronegative.

Finally, we performed only pairwise comparisons (MOG vs. AQP4 or MOG vs. seronegative).

Statistical analysis

Central tendencies were expressed as mean or median. The demographic, clinical, laboratory, and outcome parameters between the three groups, MOGAD, AQP4-IgG+NMOSD, and AQP4/MOG antibody negative, that is, seronegative were compared using Fisher's exact test for categorical variables and independent *t*-test or Mann–Whitney U test (whichever appropriate) for continuous variables. The variable with *P* value below 0.05 was considered significant. The statistical analysis was done using SPSS version 20 software.

RESULTS

Demographic data

A total of 103 patients were included in our study – 41 anti-MOG antibody positive, 37 AQP4 antibody-positive, and 25 patients were negative for both antibodies. Pediatric age group (<18 years) patients were more common in the MOGAD (36.5%). The predilection for female sex was higher in the AQP4 antibody group as compared to MOGAD (81% vs. 41%; $P = 0.0004$). Median follow-up duration was similar across three groups. Relapsing course of the disease was most commonly seen in the AQP4-IgG+NMOSD (86.5%) followed by MOG antibody cohort (56%) [Table 1].

Clinical presentation

At presentation, myelitis was seen more frequently in AQP4-IgG+NMOSD as compared to MOGAD (81% vs. 39%; $P = 0.0002$, Table 1). Bilateral ON (38 events in 18 patients) was the most frequent phenotype in the MOGAD, whereas myelitis was the most frequent phenotype in the AQP4-IgG+NMOSD (54 events in 30 patients) and in the seronegative group (15 events in 13 patients). Encephalitis was seen significantly more in the MOGAD as compared to the AQP4-IgG+NMOSD (11 vs. 0; $P = 0.001$) [Table 1]. None of the patients had area postrema syndrome in the MOGAD as well as in seronegative group while it was present in 24% patients of AQP4-IgG+NMOSD. Seven patients had recurrent isolated ON in patients with MOGAD. These patients had normal imaging apart from optic nerve involvement. We diagnosed these patients as chronic relapsing inflammatory optic neuritis (CRION). We could report one patient in seronegative group as CRION.

The proportion of patients with seizures was higher in MOGAD (15%) as compared to AQP4-IgG+NMOSD although it was not statistically significant (6 vs. 1; $P = 0.1$) [Table 1]. The median age of patients who had seizures was 12 years. Paroxysmal tonic spasms were seen only in the AQP4-IgG+NMOSD.

Table 1: Demographics and clinicoradiological phenotypes comparison between MOG antibody, AQP4 antibody, and seronegative group.

	MOG antibody group	AQP4 antibody group	*P*-value MOG versus AQP4	Seronegative	*P*-value MOG versus seronegative
Total number of patients	41	37		25	
Median age (Range)	23 (10–66)	26 (11–55)	0.47	28 (13–57)	0.23
Pediatric age group (<18 years) (%)	15 (36.5)	8 (21.6)	0.14	5 (20)	0.15
Female (%)	17 (41.5)	30 (81)	0.0004	10 (40)	0.90
Median disease duration *n* months (Range)	28 (3–156)	32 (3–174)	0.63	22 (3–96)	0.15
Median follow-up in months (Range)	20 (3–30)	19 (3–30)	0.56	19 (3–30)	0.63
Disease course monophasic (%)	18 (43.9)	5 (13.5)	0.003	18 (72)	0.02
Disease course relapsing (%)	23 (56.1)	32 (86.5)	0.003	7 (28)	0.02
Median total demyelination events/patient (Range)	2 (1–7)	2 (1–6)	0.11	1 (1–4)	0.01
Unilateral ON (%)	10 (24.4)	8 (21.6)	0.77	5 (20)	0.68
Bilateral ON (%)	18 (43.9)	19 (51.3)	0.51	5 (20)	0.04
Myelitis (%)	16 (39)	30 (81)	0.0002	13 (52)	0.30
Brainstem syndrome (%)	3 (7.3)	6 (16.2)	0.36	2 (8)	0.91
Cerebral syndrome (%)	4 (9.8)	0	0.11	2 (8)	0.8
Cerebellum syndrome (%)	2 (4.9)	0	0.49	1 (4)	1
Encephalitis (%)	11 (26.8)	0	0.001	3 (12)	0.15
Area postrema (%)	0	9 (24.3)	0.001	0	–
Seizures (%)	6 (14.6)	1 (2.7)	0.11	0	0.07
Paroxysmal tonic spasm (%)	0	4 (10.8)	0.04	0	-
FLAMES (%)	6 (14.6)	0	0.02	0	0.07

MOG: Myelin oligodendrocyte glycoprotein, AQP4: Aquaporin-4, ON: Optic neuritis; FLAMES**:** FLAIR-hyperintense lesions in anti-MOG-associated encephalitis with seizures

Neuroimaging

ADEM like lesions (7 vs. 1; $P = 0.059$), cortical (9 vs. 0; $P = 0.003$) and juxta-cortical (9 vs. 2; $P = 0.03$) brain lesions were more often seen in the MOGAD [Table 2, Figures 1 and 2]. Periventricular lesions were more common in the AQP4-IgG+NMOSD (11 vs. 20; $P = 0.014$) [Table 2]. Anterior segment ON was more common in the MOGAD (24 vs. 10; $P = 0.005$) while posterior segment ON (9 vs. 19; $P = 0.01$) and chiasmal involvement (4 vs. 13; $P = 0.007$) was more frequent with AQP4-IgG+NMOSD. Optic sheath enhancement was observed more often in the MOGAD (7 vs. 1; $P = 0.059$). All myelitis in the AQP4-IgG+NMOSD were longitudinally extensive myelitis (LETM). Cervical and dorsal segment involvement was seen in equal proportion in the MOGAD and AQP4-IgG+NMOSD. Conus involvement was more prevalent in patients with MOGAD myelitis (29%) as compared to AQP4-IgG+NMOSD (3%) ($P = 0.02$) [Figure 2]. A total of five patients (MOGAD – four and seronegative cohort – one) had TDL. None of the patients in the AQP4-IgG+NMOSD had TDL. All patients with tumefactive demyelination had a relapsing illness. All the six patients with seizures in the MOGAD had FLAIR cortical hyperintensity along with fever at the time of onset with or without altered sensorium. Cortical lesions and FLAIR hyperintense lesions in anti-MOG associated encephalitis with seizures (FLAMES) were seen exclusively in younger patients. Mean age of patients with FLAMES was 11 years.

Treatment and outcome

All patients across the three groups received intravenous methylprednisolone at the time of an acute attack. Plasma exchange or intravenous immunoglobulin (IVIg) were used as rescue therapy if the treatment response to steroid was not satisfactory. Both plasma exchange therapy and IVIg were administered in significantly higher proportions in the AQP4-IgG+NMOSD. Azathioprine was the most common initial steroid sparing immunosuppressive agent used in all the three groups. Use of Rituximab as a steroid-sparing agent was highest in the AQP4-IgG+NMOSD. Escalation therapy with rituximab was required most commonly in the AQP4-IgG+NMOSD (12/31, 38.7%) as compared to the MOGAD (4/38, 10.5%). Ten patients in the AQP4-IgG+NMOSD had changed to injection rituximab because of relapse on the previous therapy (nine patients on azathioprine and one patient on mycophenolate mofetil). All four patients in the MOGAD were changed to injection rituximab therapy because of relapse on azathioprine therapy. About 40% patients in the seronegative group were not given any long-term immunosuppression following a short course steroid therapy and rescue therapy if required. There was no

Table 2: Radiological characteristics and outcome of the study cohort.

	MOG antibody group *n* (%) *n*=41	AQP4 antibody group *n* (%) *n*=37	*P*-value MOG vesus AQP4	Seronegative *n* (%) *n*=25	*P*-value MOG versus seronegative
Brain MRI					
Focal lesion	21 (51.2)	24 (64.8)	0.22	13 (52)	0.95
ADEM like lesions	7 (17)	1 (3)	0.059	3 (12)	0.73
Cortical lesions	9 (22)	0	0.003	0	0.01
Juxtacortical	9 (22)	2 (5.4)	0.03	0	0.01
Periventricular lesions	11 (26.8)	20 (54)	0.014	10 (40)	0.26
Brainstem lesions	11 (26.8)	15 (40.5)	0.19	8 (32)	0.65
Tumefactive demyelinating lesions	4 (10)	0	0.11	1 (4)	0.64
Optic nerve MRI					
Anterior segment ON	24 (58.5)	10 (27)	0.005	4 (16)	0.001
Posterior segment ON	9 (22)	19 (51.3)	0.01	6 (24)	0.84
Chiasmal Involvement	4 (9.8)	13 (35.1)	0.007	5 (20)	0.07
Optic sheath Involvement	7 (17)	1 (2.7)	0.059	3 (12)	0.73
Spinal cord MRI	*n*=39	*n*=37		*n*=25	
Myelitis	17 (43.6)	29 (78.4)	0.0017	15 (60)	0.1
LETM	14 (35.9)	29 (78.4)	0.0001	13 (52)	0.2
SSTM	3 (7.7)	0	0.2	2 (8)	1
Conus Segment involvement	5 (29.4)	1 (3.4)	0.02	2 (13.3)	0.4
EDSS and visual outcome across three groups					
Outcome (visual acuity)	**MOG antibody *n* (%)**	**AQP4 antibody *n* (%)**	***P*-value MOG versus AQP4**	**Seronegative *n* (%)**	***P*-value MOG versus seronegative**
Nadir vision	*n*=25	*n*=20		*n*=7	
>3/60	4 (16)	3 (15)	1	3 (42.9)	0.15
≤3/60	21 (84)	17 (85)		4 (57.1)	
Vision at 3 months	*n*=15	*n*=9		*n*=5	
>3/60	12 (80)	8 (88.9)	1	4 (80)	1
≤3/60	3 (20)	1 (11.1)		1 (20)	
Outcome (EDSS)					
Median EDSS at nadir (Range) [*n*]	7.25 (3–8) [22]	7.75 (1–8.5) [30]	0.15	7 (3–8) [18]	0.73
Median EDSS last follow-up (Range) [*n*]	1 (0–8) [17]	3.5 (0–8) [25]	0.03	1 (0–8) [15]	0.66

MRI: Magnetic resonance imaging, MOG: Myelin oligodendrocyte glycoprotein, AQP4: Aquaporin-4, LETM: Longitudinally extensive transverse myelitis, SSTM: Short segment transverse myelitis, ADEM: Acute disseminated encephalomyelitis EDSS: Expanded disability status scale, MOG: Myelin oligodendrocyte glycoprotein

difference in the nadir EDSS across the groups. Improvement following discharge (5 vs. 6; $P = 0.4$) and at 3 month follow-up was also similar (1 vs. 3.75; $P = 0.15$). Median EDSS at the last follow-up was better in the MOGAD than AQP4-IgG+NMOSD (1 vs. 3.5; $P = 0.03$) [Table 2]. About 81% percent patients had vision <3/60 at nadir in our study (85% in NMO group and 84% in MOG group) [Table 2]. There was no difference in visual acuity between the groups at discharge, 3-month follow-up, and at last follow-up.

DISCUSSION

In our study, we compared MOGAD with AQP4-IgG+NMOSD and seronegative demyelinating disorders. A study from the southern part of India found similar results as that of our study.[6] A higher proportion of MOGAD had a monophasic course compared to AQP4-IgG+NMOSD. Various types of phenotypes of MOGAD were observed across the cohort. Bilateral optic neuritis was the most common phenotype followed by myelitis. Eight patients (seven in MOGAD and one patient in seronegative group) had CRION. Encephalitis-like presentation separates the MOGAD from the AQP4-IgG+NMOSD. Incidence of encephalitis is typically higher in the younger population. Although, ADEM is the most common phenotype in the pediatric age group, it can be seen in adults also.[7] We had a patient in the MOGAD who presented with ADEM-ON at 50 years of age. All the patients who presented with seizures had peculiar clinicoradiological findings. All these patients presented with fever and had FLAIR cortical hyperintensity. Budhram *et al.* explained this novel phenotype for the first time and labeled it as FLAMES.[8] It also adds to the list of differential diagnosis of patients presenting with fever and

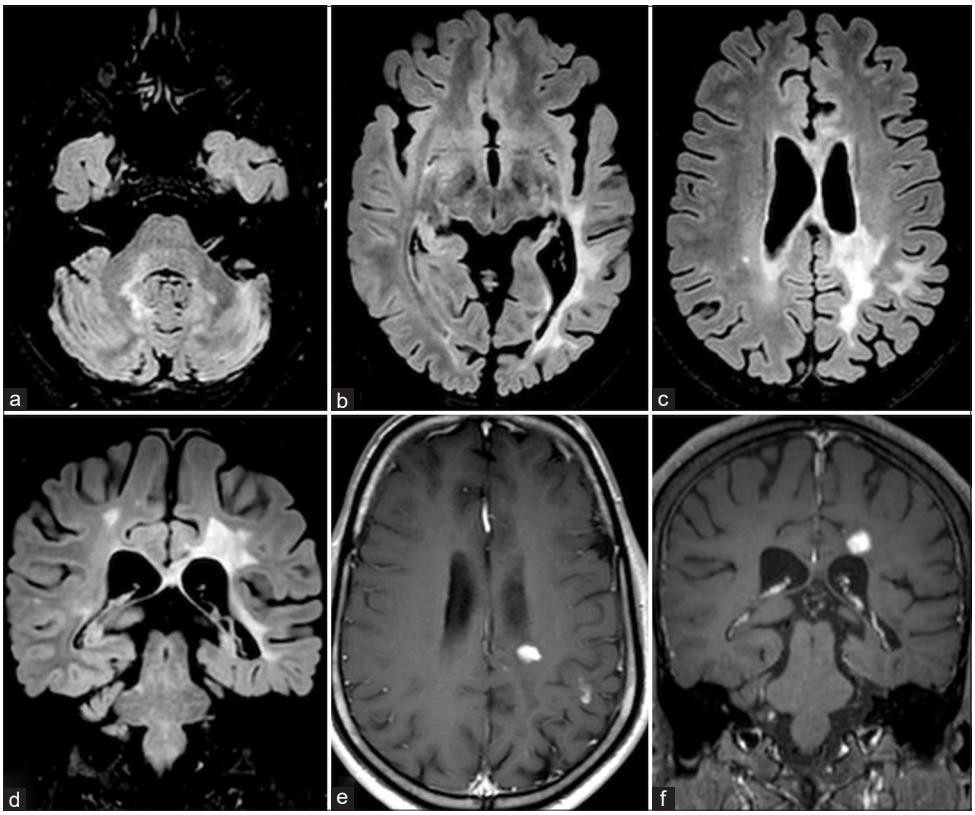

Figure 1: Magnetic resonance imaging images showing leukodystrophy like picture in a case of positive anti-myelin oligodendrocyte glycoprotein antibody – Axial (a-c) and coronal (d) FLAIR sections show multifocal confluent white matter hyperintensity in bilateral middle cerebellar peduncle (a), left cerebellar hemisphere (a), left peritrigonal white matter (b), and along periventricular and subcortical white matter of left posterior parietal lobe (c and d). Post-contrast axial (e) and coronal (f) sections show foci of nodular enhancement in the left parietal lobe.

seizures. Myelitis was the most common manifestation in the AQP4-IgG+NMOSD. ADEM like lesions, FLAIR cortical hyperintensity and juxtacortical lesions were more common in the MOGAD in comparison to AQP4-IgG+NMOSD. Pathological features such as widespread diffuse inflammation, the coexistence of perivenous, intracortical, and confluent demyelination in contrast to focal chronic active plaques and leukocortical demyelination in MS can explain large fluffy lesions such as ADEM, TDL, and cortical hyperintensities in MOGAD.[9] In our study, area postrema lesion was exclusively seen in AQP4-IgG+NMOSD. In the study by Salama *et al*., 57% of the MOGAD had cortical lesions as compared to none in the AQP4-IgG+NMOSD. About 50% of patients in the AQP4-IgG+NMOSD had lesions in area postrema in contrast to 7% in the MOGAD.[10] Involvement of anterior segment along with optic nerve sheath enhancement on MRI was more common with the MOGAD optic neuritis. Preferential involvement of posterior segment of optic nerve and optic chiasma was seen in the AQP4-IgG+NMOSD optic neuritis. In the study by Ramanathan *et al*., 62% of patients in the MOGAD had anterior segment optic neuritis, 64% patients in AQP4-IgG+NMOSD had posterior segment optic neuritis.[11] Interestingly, 15% of the MOGAD optic neuritis had chiasmal involvement in our cohort which is traditionally involved in AQP4-IgG+NMOSD. Optic nerve sheath enhancement was seen in 17% of the MOGAD optic neuritis in contrast to the study done by Chen *et al*., in which 50% of patients had optic nerve sheath enhancement.[12] The distinction between ON and optic perineuritis is important as the latter has a better response to steroids.

Although both MOGAD and AQP4-IgG+NMOSD commonly presented with myelitis, there were differences among the two groups. MOGAD myelitis had lesser events of LETM as compared to the AQP4-IgG+NMOSD myelitis. Fourteen out of 17 (82.3%) MOGAD myelitis were LETM, in contrast, all AQP4-IgG+NMOSD myelitis were LETM in our study. In the study, done by Dubey *et al*. 79% of the MOGAD myelitis was LETM opposed to 82% LETM in the AQP4-IgG+NMOSD myelitis.[13]

Conus involvement in the MOG antibody myelitis has been shown to be more frequently involved as compared to AQP4-

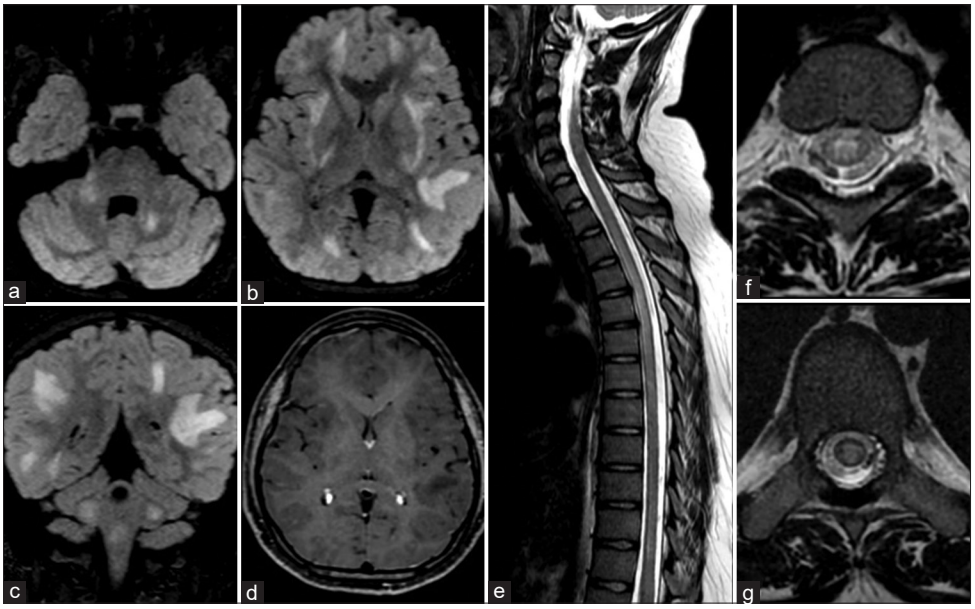

Figure 2: MRI Brain of anti- MOG antibody positive patient (a-d) and spine (e-g) images shows multifocal variable sized FLAIR hyperintense white matter lesions (a-c) in supra and infratentorial compartments with no obvious enhancement on post contrast section (d). Long segment central (H-shaped) intramedullary hyperintensity is seen in cervical-dorsal spinal cord (e-g) extending up to the conus (longitudinally extensive transverse myelitis).

IgG+NMOSD.[14] We observed similar results (29% vs. 3%) in our cohort as well. Frequent conus involvement can explain more severe neurogenic bladder, prolonged catheterization, and erectile dysfunction in MOGAD myelitis.[14] Frequent conus involvement, ADEM-like lesions, and deep grey matter involvement in the spinal cord (known as "H sign") are radiological characteristics that differentiate MOGAD myelitis from AQP4-IgG+NMOSD myelitis. Involvement of the oilgodendrocytes which are present in the grey matter of spinal cord and brain can explain the radiological findings such as the "H-sign" and ADEM like lesions observed in MOGAD.[13]

The published MOGAD cohorts showed a relapsing course in 42–44% of patients.[15] Disability in MOGAD is accrued predominantly due to recurrent relapses. Hence, many clinicians in our center maintain patients on long-term immunosuppressive therapy. The severity of deficits at first presentation, treatment response after the first clinical event, amount of recovery and residual deficits, risk of cumulative disability, and presence of other medical conditions can be considered before starting a long-term immunosuppressive agent.[16]

Limitations

Our study has a few limitations. First, it carries the inherent limitations of all the observational studies. Second, some of the data regarding initial presentation was analyzed retrospectively and may have led to recall bias. Third, we could not assess the long-term outcome of all patients because of the ongoing COVID-19 pandemic.

CONCLUSION

Our study provides various clinical and radiological features of MOGAD which are distinct from AQP4-IgG+NMOSD and seronegative demyelinating disorders which will aid clinician in better understanding and management of these patients. In the ever growing spectrum of diseases associated with MOG antibody, chronic relapsing inflammatory optic neuritis (CRION), FLAMES, and TDL were some of the novel clinicoradiological presentations identified in our study.

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Declaration of patient consent

The study was approved by the Institute Ethics Committee.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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