Section: Neurology

Original Research Article

CLINICAL EXPERIENCE OF NEUROMYELITIS OPTICA SPECTRUM DISORDER WITH AQUAPORIN4-IGG STATUS AND MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY ASSOCIATED DEMYELINATING DISEASES FROM CENTRAL INDIA

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ABSTRACT

Background: Neuromyelitis Optica with Aquaporin4-IgG status (NMOAP4) and Myelin Oligodendrocyte Glycoprotein antibody associated Demyelinating Diseases (MOGAD) are autoimmune CNS disorders affected optic nerve, brain, spinal cord and cause disability when untreated. There is paucity of data on these disorders from central India. Hence this study was conducted.
Objectives: Our study aims to describe demographic profile, clinico-radiological features, recurrences, treatment and outcomes in these two groups.
Materials and Methods: This is an ambispective observational cohort study of NMOAP4 and MOGAD cases fulfilling diagnostic criterias. This is a single center study carried out in Superspeciality hospital, Government medical college, Nagpur.
Results: Total 21 cases of NMOAP4 and 6 cases of MOGAD included. NMOAP4 is common in females (F: M=20:1) and MOGAD equal in both (F: M=1:1). Mean age at onset in NMOAP4 and MOGAD was 30.94± 9.55 and 40.0 ± 11.81 year respectively. Optic neuritis was most common clinical feature in 8/21 cases of NMOAP4 and 5/6 cases of MOGAD. Recurrence and polyphasic illness was seen in NMOAP4. Acute attack responds to steroids/IVIG/PLEX in both disorders. Chronic immunosuppression was tolerated in two groups.
Conclusions: NMOAP4-MOGAD cause recurrent CNS demyelination, disability and needs acute therapy (steroids/IVIG/PLEX) and chronic immunosuppression with azathioprine, mycophenolate mofetil. Injection Rituximab should be considered for refractory cases of both groups but needs monitoring.
Keywords: Demyelinating Diseases, MOGAD, Neuromyelitis Optica.

INTRODUCTION

Neuromyelitis Optica Spectrum Disorders (NMOSDs) are a group of rare, heterogeneous autoimmune demyelinating disorders that primarily affect the optic nerves, spinal cord, and other parts of the central nervous system (CNS).1 These disorders are characterized by recurrent attacks of inflammation leading to significant disability if not promptly diagnosed and treated. Unlike multiple sclerosis (MS), which predominantly affects the myelin sheath, NMOSDs are associated with immune-mediated astrocyte damage.[1]

The hallmark antibody associated with NMOSD is Aquaporin-4 Immunoglobulin G (AQP4-IgG), which targets the aquaporin-4 protein—a water channel protein highly expressed on astrocytes, particularly in the optic nerves, spinal cord, and certain brain regions.2 When the immune system produces AQP4-IgG, it triggers complement activation and astrocyte destruction, compromising

the blood-brain barrier and resulting in demyelination and neuronal damage.2 The detection of AQP4-IgG is a critical diagnostic marker for NMOSD, and cases positive for this antibody are referred to as NMOSD with AQP4-IgG status (NMO-AQP4).[2]

However, not all patients presenting with NMOSD-like symptoms test positive for AQP4-IgG. Studies have shown that approximately one-third of AQP4-IgG-negative NMOSD cases exhibit positivity for Myelin Oligodendrocyte Glycoprotein (MOG) IgG antibody. This condition is classified separately as MOG Antibody-Associated Disease (MOGAD).[3] Unlike NMO-AQP4, which predominantly affects women, MOGAD shows a more balanced gender distribution and often presents with features such as optic neuritis, transverse myelitis, and acute disseminated encephalomyelitis (ADEM).[4]

The clinical, radiological, and immunological profiles of NMO-AQP4 and MOGAD differ significantly, necessitating different diagnostic and therapeutic approaches. Early differentiation between these disorders is essential to initiate appropriate treatment and improve patient outcomes.[5] Despite advancements in diagnostic techniques, there remains a paucity of data regarding the epidemiology, clinical presentation, treatment response, and prognosis of NMO-AQP4 and MOGAD in certain populations, particularly from central India.[6]

The present study aims to address this gap by examining the demographic characteristics, clinical features, radiological findings, recurrence rates, and treatment outcomes of NMO-AQP4 and MOGAD patients presenting to a tertiary care hospital in central India. Understanding the distinct features of these disorders in this regional population will contribute to developing tailored diagnostic and therapeutic strategies, ultimately enhancing patient care and management.

MATERIALS AND METHODS

The primary aim of this study was to evaluate the demographic characteristics, clinical presentations, radiological findings, recurrence rates, treatment strategies, and outcomes in patients diagnosed with Neuromyelitis Optica Spectrum Disorder with Aquaporin-4 Immunoglobulin G (NMO-AQP4) and Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD). The study intended to compare these aspects between the two groups to identify significant differences and commonalities that could aid in optimizing diagnostic and therapeutic approaches.

This research was conducted as an ambispective, single-center, observational comparative cohort study at a tertiary care hospital in Central India. Institutional Ethics Committee approval was obtained before enrolling patients in the study. The study population included patients from both outpatient and inpatient departments of the hospital. The research protocol followed ethical guidelines and ensured patient confidentiality and data protection.

The study included patients diagnosed with NMO-AQP4 based on the International Consensus Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorders.4 It also included MOGAD patients fulfilling the International MOGAD Panel's proposed criteria.4 Only patients with confirmed diagnoses based on clinical presentation, serological testing, and radiological findings were included.

Patients with Multiple Sclerosis, non-autoimmune demyelinating disorders, incomplete diagnostic data, inadequate follow-up, systemic autoimmune diseases unrelated to NMO-AQP4 or MOGAD, and those below 18 years of age were excluded to ensure accurate assessment and comparison.

Data were collected retrospectively and prospectively over a ten-year period, completed within six months. After obtaining informed consent, detailed clinical information was recorded using a structured case record form. The collected data included demographic details (age, gender), clinical symptoms at presentation, radiological findings, recurrence episodes, acute treatment modalities, chronic immunosuppressive therapy, and patient outcomes. Follow-up data were also recorded to assess treatment efficacy and recurrence rates.

The demographic, clinical, radiological, recurrences, treatment aspects are compared in the two groups. Categorical variables were expressed in frequency and percentages. Continuous variables were presented as mean + SD. For non-normally distributed data, median and interquartile range was used. Categorical variables were compared using chi- square test. For small samples, Fischer's exact test was used where applicable. Average follow-up (days) was compared by performing Mann- Whitney test. $P < 0.05$ was considered as statistically significant. Statistical software STATA version 14.0 was used for data analysis.

RESULTS

i) Age at onset of symptoms and gender distribution of cases

A cohort of 21NMOAQP4 and 6MOGAD cases was included in this study. The mean age at onset of symptoms in NMOAQP4 was 30.90 $\pm$ 9.55 years (range 14-48) and in MOGAD it was 40.0 $\pm$11.81 years (range 32-48). Female: male ratio was 20:1 in NMOAQP4 and 1:1 in MOGAD. The occurrence of onset of illness in NMOAQP4 was commonly seen in fourth-fifth decades (10/21 cases), while in MOGAD it was seen in fifth-sixth decades (2/6 cases).

ii) Clinical presentations of cases

Most common clinical manifestation in NMOAQP4 and MOGAD was optic neuritis followed by isolated transverse myelitis, simultaneous optic neuritis and

transverse myelitis, brainstem syndrome, area postrema syndrome, acute disseminated encephalomyelitis (ADEM) as shown in table 2.

iii) Radiological signs in NMOAQ4 and MOGAD groups- Among the clinical cases of optic neuritis in both groups, MRI orbit were normal in most cases. Bilateral optic nerve involvement was common radiological abnormality followed by unilateral optic nerve involvement in both groups as shown in Table 3.

Periventricular White matter hyperintensities, brainstem involvement are seen in the MRI brain of cases of NMOAP4 and MOGAD. Cervical Cord is commonly involved in both groups (Figure 1, 2, 3).

iv) Treatments in both groups. Acute treatment – All NMOAQP4 and MOGAD cases received injection methylprednisolone (MPS) initially for 5-7 days. Response to MPS was significant (p=0.024) statistically in NMOAQP4 group. IVIG (2gram/kg) or Plasmapharesis/PLEX (five cycles for alternate day) was used depending upon response to methylprednisolone therapy.18/21 NMOAQP4 and 2/6 MOGAD cases had good response to acute treatment respectively as shown in table 4.

Disease modifying therapy (DMT) -Azathioprine was the most commonly used drug in both groups Response to DMT was good in 15/21 NMOAQP4cand 3/6 cases of MOGAD. Two cases of NMOAQP4 did not tolerated Azathioprine and one case had pancytopenia. So, Azathioprine therapy was discontinued and another DMT drug was started. (Table 5).

Course of Illness in two groups- the NMOAP4 group had total 39 recurrences/relapse as against 7 relapses in MOGAD cases. Polyphasic illness was commonly observed in NMOAQP4 (13/21 cases) and monophasic illness was common in MOGAD (5/6) cases. The Median follow-up was 1 year (Interquartile range IQR 1-5) in NMOAQP4 group and 1 year in MOGAD group. One death was observed in NMOAQP4 group. Severe disability at follows up (EDSS ≥6) was observed in 4/21 cases of NMOAQP4, while all MOGAD cases had EDSS < 6.

Table 1: Diagnostic criteria for NMOSD with AQP4-IgG status and MOGAD

Diagnostic criteria for NMOSD with AQP4-IgG status
1. At least 1 core clinical characteristic (1/6) 1) Optic neuritis 2) Acute myelitis 3) Acute brainstem syndrome 4) Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting 5) Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions. 6) Symptomatic cerebral syndrome with NMOSD-typical brain lesions.
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses.
Diagnosis of MOGAD (requires fulfillment of A, B, and C)
A) Core clinical demyelinating event i) Optic neuritis, ii) Myelitis, iii) ADEM, iv) Cerebral monofocal or polyfocal deficits, v) Brainstem or cerebellar deficits, vi) Cerebral cortical encephalitis often with seizures.
(B) Positive MOG-IgG test
Supporting clinical or MRI features **Optic neuritis** • Bilateral simultaneous clinical involvement. • Longitudinal optic nerve involvement (> 50% length of optic nerve). • Perineural optic sheath enhancement • Optic disc edema. **Myelitis** • Longitudinally extensive • Central cord lesion or H-sign • Conus lesion. **Brain, brainstem, or cerebral syndrome** • Multiple ill-defined T2 hyperintense lesions in supratentorial and often infratentorial white matter. • Deep grey matter involvement. • Ill-defined T2-hyperintensity involving pons, middle cerebellar peduncle, or medulla. • Cortical lesion with or without lesional and overlying meningeal enhancement.
(C) Exclusion of better diagnoses including multiple sclerosis

Table 2: Clinical manifestations in NMOAQ4 and MOGAD cases

Clinical presentations	NMOAQP4 (n=21)	MOGAD (n=6)	P value
1. Optic Neuritis(ON)	*8 (38.09 %)*	5 (83.33%)	0.077
a. Unilateral ON	4(19.04%)	1(16.66)	1.00
b. Sequential ON	3 (14.28%)	3 (50%)	0.101
c. Bilateral simultaneous ON	1(4.76%)	1 (16.66%)	0.42
2. Isolated Acute transverse Myelitis (ATM)	4 (19.04%)	1(16.66%)	1.00
3. Simultaneous ON + TM	6 (28.57%)	0	0.284
4. Brainstem syndrome	1(4.76%)	0	1.000
5. Area postrema syndrome	1(4.76%)	0	1.000
6.Acute disseminated encephalomyelitis (ADEM)	1(4.76%)	0	1.000

Table 3: Radiological signs in NMOAP4 and MOGAD groups

	Pattern	NMOAQ4	MOGAD	P value
1.Optic	Total clinical ON cases	12	5	0.363
	Normal MRI orbit	7/12	2/5	0.620
	i. Bilateral ON	3/12(25%)	2/5(40%)	0.600
pathway	ii. Unilateral ON	2/12(16.6%)	1/5(20%)	1.000
	iii. Optic chiasma	3/12(25%)	0	0.51
	iv. Optic tract	1/12(8.33%)	0	1.000
	v. Optic radiation	1/12(8.33%)	0	1.000
	vi. Anterior segment ON	1/12(8.33%)	0	1.000
	vii. Posterior segment ON	3/12(25%)	1(20%)	1.000
	viii. Longitudinally extensive ON	1/12(8.33%)	2(40%)	0.191
2. Brain	Periventricular White matter	6/21(28.57%)	2/6(33.33%)	1.000
	cortex	2/21(9.52%)	1/6(16.66%)	0.545
	Corpus callosum	3/21(14.28%)	0	1.000
	Thalamus	2/21(9.52%)	1/6(16.66%)	0.545
3.Brainstem	Midbrain	3/21(14.28%)	0	1.000
	Pons	3/21(14.28%)	1/6(16.66%)	1.000
	Medulla	4/21(19.04%)	0	0.545
	Cerebellum/peduncle	2/21(9.52%)	1/6(16.66%)	0.545
	hippocampus	1/21(4.76%)	0	1.000
4.Spinal	Cervical cord	11/21(52.38%)	1/6(16.66%)	0.182
	Thoracic cord	6/21(28.57%)	0	0.298
Cord	Conus medullaris	1/21(4.76%)	0	1.000
	LETM	9/21(45.85%)	0	0.071
	Short segments myelitis	3/21(14.28%)	0	1.000

Table 4: Acute treatment in NMOAQP4 and MOGAD cases

	Acute treatment			Response to Acute treatment		
Cases	**MPS**	**IVIG**	**PLEX**	**Good**	**Poor**	**P value**
NMOAQP4 (n=21)	21	4	4	18(85.71%)	3(14.28%)	**0.024**
MOGAD (n=6)	6	1	3	2(33.33%)	4(66.67%)	

Table 5: Disease modifying therapy in NMOAQP4 and MOGAD cases

	Disease modifying therapy(DMT)				Response to DMT		
Cases	**Azathioprine**	**MMF**	**Low dose steroids**	**Rituximab**	**Good**	**Poor**	**p value**
NMOAQP4 (n=21)	13	3	4	5	15(71.43%)	5(23.80%)	0.330
MOGAD (n=6)	3	1	0	1	3(50%)	3(50%)	

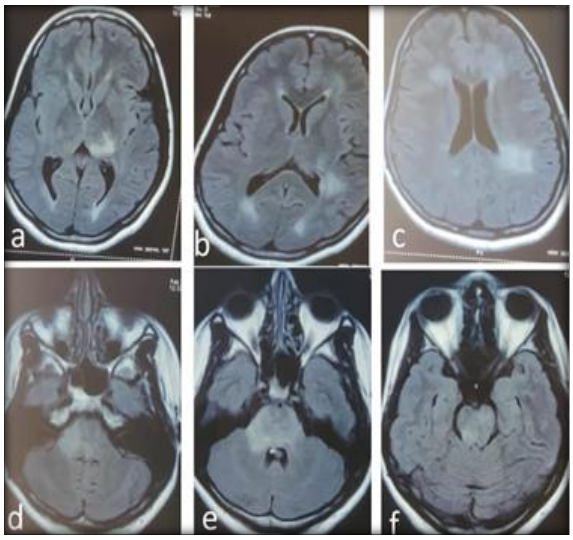

Figure 1. MRI Brain T2FLAIR images showing hyperintense signal in left thalamus (a), bilateral subcortical occipital regions (b), bifrontal region (c), right middle cerebellar peduncle & bilateral pons(d, e) ,midbrain (f) seen in MOGAD cases

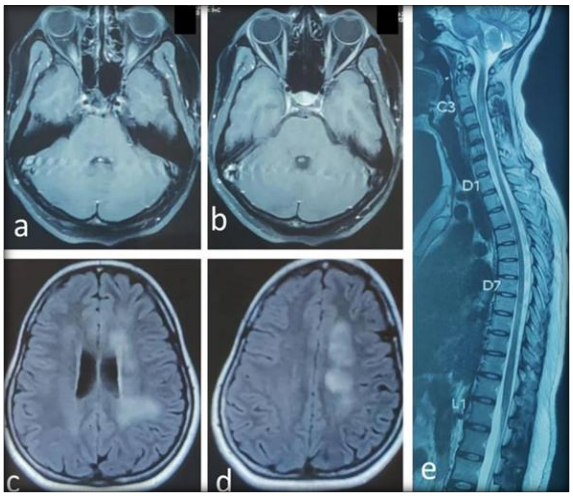

Figure 2. MRI orbit T1 contrast images showing bilateral perineural optic nerve sheath enhancement (a) and (b) increased signal in both optic nerves. (c) and (d) shows large fluffy cortical and subcortical hyperintensities. Cervical cord showing multiple short segment hyperintensities (e) seen in MOGAD cases.

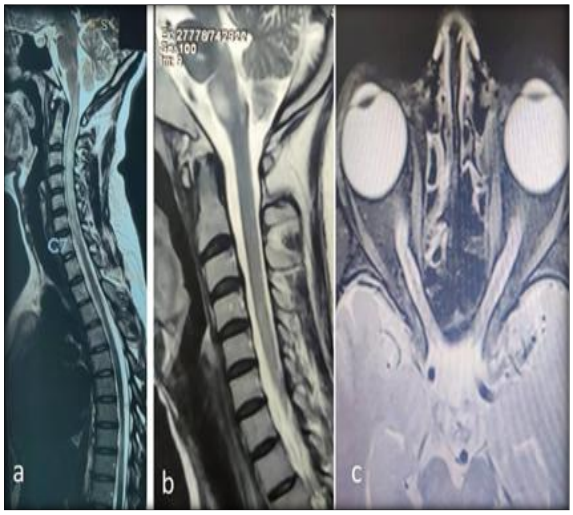

Figure 3: MRI cervical spine showing long segment transverse myelitis (a) up to C7 segments. T2 FLAIR hyperintensities are seen in lower brainstem (b). MRI orbit T2 FLAIR images showing bilateral optic nerve increased signal (c) in the intraconal segments seen in NMOAQP4 cases.

DISCUSSION

Our comparative Study included 21 NMOAQP4 and 6 MOGAD cases similar to the study conducted by Ojha et al5 and less than study by Pujari, et al.6 Our study showed that mean age at onset of symptoms in NMOAQP4 was 30.90 + 9.55 SD years (range 14-48) similar to the findings of study performed by Sachdeva et al,[1] in our study, the mean age of disease onset in MOGAD was 40 + 11.81 SD years, which was higher than Ojha et al5 had average age at onset 32.2 years in MOGAD. Female predominance was seen in this study in NMOAQP4 groups similar to studies by Sachdeva, et al,[1] Jagtap et al,[7] Singh, et al.[8] No gender bias was seen in MOGAD group in this study which is supported by Ojha et al5 in his study. Optic neuritis was the most common clinical feature in NMOAQP4 and MOGAD in our study, which was different from Sachdeva, et al,[1] Jagtap et al,[7] Singh, et al studies1,[7,8] which observed transverse myelitis as most common feature in NMOSD. Optic neuritis was common feature in Ojha et al,[5] and Pujari, et al.6 Unilateral and sequential optic neuritis was common in NMOAQP4 group and sequential optic neuritis was common in MOGAD group in this study. 7/12 cases of optic neuritis cases in NMOAQP4 group and 2/5 optic neuritis cases in MOGAD group had no radiological abnormalities on Neuroimaging studies of orbit, brain. The commonly involved areas in NMOAQP4 were optic nerves, chiasma, tract, radiation, periventricular areas, corpus callosum, thalamus and brain stem. Posterior segment optic neuritis was more common than anterior segment optic neuritis in both groups. These findings were similar to other studies.[1,5-8] Cervical cord was the most common area of involvement on MRI spine imaging in both the groups in our cohort, though cervicodorsal and thoracic cord was commonly involved in other studies.5,8 Longitudinally extensive transverse myelitis (LETM) was seen in 9/21(45.85%) than short segment myelitis 3/21 (14.28%) in NMOAQP4 group in this study consistent with the study conducted by C. Sharma et al.[9]

All cases of both groups were treated with parental steroids during acute attack. 8/21 (38%) NMOAQP4 cases were nonresponsive to parental steroids comparable with other studies.[5,7] The overall response rate to DMT in our study in NMOAQP4 was good (71.43%), while it was equivocal (50%) in MOGAD cases. Polyphasic nature of illness was more observed in NMOAQP4 group of our study 13/21 cases similar to study by Jagtap et al.[7] The median recurrence rate in polyphasic groups was 3/patient in NMOAQP4 and 2/patient in MOGAD group. Jagtap et al,[7] reported median recurrence rate of 4/patient in NMOSD cases, while Ojha, et al,[5] observed a median episode of 2.5/patient in MOGAD cases.

The mean follow-up duration of NMOSD cases was 15.3+ 6 months in study by Sachdeva J et al,[1] comparable of 2.97 year follow-up in our study. While Ojha et al5 had follow-up of 40 months in MOGAD cases, our study had follow-up of 12 months (1 year) in MOGAD. Severe disability (EDSS > 6) on follow-up was observed in 4/21 (19.04 %) cases of NMOAQP4 in this study, while Sachdeva et al,[1] observed 9.3% cases of severe disability in similar groups.

Azathioprine was the most commonly used chronic immunosuppressant in both groups in our study similar to other studies.[6-9] Pancytopenia was observed in one NMOAQP4 patient on azathioprine therapy necessitating change of DMT as seen with Sachdeva et al study.[1] Out of 21 NMOAQP4 cases, in 5 cases (23.80%) Rituximab was used as DMT. In 1/6 (16.67 %) case MOGAD of our study, rituximab was used. In both groups, rituximab was safe well tolerated in our study. Jade et al,[10] reported that rituximab was safe and tolerated in NMO spectrum disorder cases in India. Treatment with rituximab in MOGAD cases needs close monitoring for severe infections and hypogammaglobulinemia.[11]

CONCLUSION

Both NMOAQP4 and MOGAD are multiphasic/recurrent disabling autoimmune demyelinating illness which can be diagnosed with standard diagnostic criteria. In order to avoid relapse or recurrence with Azathioprine and mycophenolate mofetil, chronic disease-modifying therapy is required in addition to acute treatment with steroids, IVIG, and PLEX. Additionally, Rituximab, a DMT, was well tolerated, helpful, and required observation in both groups.

The short one-year follow-up period and limited sample size of this single-center trial make it

impossible to evaluate long-term effects. Understanding illness pathways is hampered by the lack of genetic and biomarker studies, and retrospective data collecting may induce bias. Other limitations include uneven imaging studies and treatment variability.

To improve knowledge of illness etiology and treatment responses, future research should incorporate genetic/biomarker analysis, multicenter trials, and extended follow-up. Clinical management will be improved by establishing standardized treatment regimens, evaluating patient-reported outcomes, and using sophisticated imaging to improve diagnosis accuracy.

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