A Comparative Analysis of Clinical and Imaging Features of Aquaporin 4 (AQP4) Antibody Positive, Myelin Oligodendrocyte Glycoprotein (MOG) Antibody Positive and Double Seronegative Subtypes of Neuro Myelitis Optica Spectrum Disorder (NMOSD)

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Abstract

Objectives: Study was conducted with aim of comparing subtypes types of NMOSD based on serology. **Methods:** In this retrospective study, patients ≥18 years were included satisfying IPND 2015 criteria. Three groups were created based on seropositivity for AQP4 antibody, MOG antibody or double seronegative. Demographic, clinical and imaging were compared using regression analysis. **Results:** Forty-six patients, 28 (60.9%) AQP4+, 11 (23.9%) MOG + and remaining 7 (15.2%) double seronegative were included. Thirty-seven patients (80.4%) had presenting symptoms localized to optic nerve and/or cord [AQP4 + 22 (78.5%), MOG + 9 (81.8%) and double seronegative 6 (85.7%)]. Presentation with bilateral optic neuritis was more common in AQP4- patients. Twenty (86.8%) out of the 23 patients who had relapsing disease localized to optic nerve and/or spinal cord [AQP4 + 13/14 (92.8%), MOG + 3/5 (60%) and double seronegative 4/4 (100%)]. Relapses were more common in AQP4+ (77% vs 12% vs10%). In AQP4 negative group disability (EDSS 4.2 vs 3.3) and progression index was relatively less (1.6 vs 1.1). CSF pleocytosis (38.8% vs 17.9%) and raised proteins (66.6% vs 32.1%) were also more common. Optic nerve MRI (>50% optic nerve and chiasma involvement) was more commonly abnormal in AQP4 negative (52.9% vs 31.2%). Regression analysis revealed females to be significantly higher in AQP4 positive NMOSD (89.3%) when compared to MOG positive (36.4%) and double seronegative (42.9%). **Conclusion:** Gender was the only significant difference between the three groups. There was trend towards greater disability and more relapses in AQP4 + groups.

Keywords: AQP4 antibody, comparison, MOG antibody, NMOSD, seronegative

INTRODUCTION

Neuromyelitis optica spectrum disorders (NMOSD) are rare inflammatory disorders of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage. The area most affected are optic nerves and spinal cord. NMOSD is distinct from classic relapsing-remitting multiple sclerosis with respect to pathogenesis, imaging features, biomarkers, neuropathology, and treatment. In India, they form a sizeable 13.9% of all demyelinating disorders.[1]

The discovery of a disease-specific serum immunoglobulin G (IgG) antibody that selectively binds aquaporin 4 (AQP4) has led to increased understanding of this diverse spectrum of disorders. The International Panel for Neuromyelitis optica Diagnosis (IPND) was convened in 2015 to develop revised diagnostic criteria. They proposed a set of diagnostic criteria based on the presence or absence AQP4 IgG antibody.[2] If AQP4 antibody is positive then one core clinical characteristic is adequate, however if it is negative, then at least two core clinical characteristic are needed of which one of them should be optic neuritis, longitudinally extensive myelitis or area postrema syndrome. The core clinical characteristics are stringently defined and need to be satisfied prior to making a diagnosis of NMOSD using the IPND criteria. As per a recent comparative evaluation, the IPND 2015 criteria were most sensitive (97%) when compared to criteria of 1999 and 2006.[3]

Using the most sensitive serology tests, studies (including one from India) have found that around 15% of patients with NMOSD may be negative for this antibody.[4,5] However, more commonly this seronegative status may be as high as 30--50% based on the type of assay, the timing of test and the criteria used.[6] About 20--30% of patients who are negative for AQP4 antibody may be positive for antibodies against myelin oligodendrocyte protein (MOG).[6,7] A study from India found around 30% of patients suspected to have NMOSD were

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positive for AQP4 antibody and another 20% for anti MOG.[5] The remaining subset of patients with a phenotype of NMOSD remain seronegative for both auto antibodies.

MOG antibody disease may represent a distinct disease with varied presentation, one of them being NMOSD. Previous studies, including those from India, have compared AQP4 positive disease with MOG antibody disease and double seronegative NMOSD.[5,6] However, the findings of these studies are very heterogenous and merit more research in this field. Do adult patients with demyelinating disease, who satisfy the IPND 2015 criteria for NMOSD, have some phenotypical differences based on their serological status? Our study attempted to answer this question.

METHODS

This study was a retrospective chart review analysis of data extracted from the larger database of a multicentric project on primary demyelination (AFMRC 4511/2014) funded by Indian Armed Forces Medical Research Committee. Part of the data of this project has already been published.[8] However, the data analysed as a part of the current study has neither been presented nor been published earlier.

Patients were included in the study if they were 18 years or older, were diagnosed to have NMOSD and should have had the disease for at least one month after diagnosis. The diagnosis of NMOSD was established by IPND 2015 criteria.[2] Patients were excluded if they had any other demyelinating disease like multiple sclerosis, secondary cause of demyelination like infection, inflammatory disorders, granulomatous disorders, toxic, metabolic, vascular, or hereditary conditions. Patients with primary demyelination and clinically isolated syndrome (e.g., transverse myelitis or isolated optic neuritis) who could not clearly be classified as NMOSD as per the above criteria were also excluded.

A data extraction proforma was designed which included demographic data like age, sex, education, economic status, addictions, presence of other comorbidities, both autoimmune and non-autoimmune diseases and family history. The clinical variables included duration of disease, neurological localization at presentation, course of illness, number of relapses, annualized relapse rate (ARR defined as number of relapses per patient divided by duration of disease in years) and disability status at the time of being included into the study. Expanded Disability Status Scale (EDSS) was used to assess disability at least one month after last relapse. Progression index (EDSS/duration of disease in years) was calculated. Variables related to investigations included in the study were total leukocyte count in CSF, CSF sugar, CSF proteins, abnormal visual evoked potentials (VEP) defined as prolonged *P* 100 latencies and abnormal brain stem auditory evoked potential/response (BAER). Imaging data included were presence of at least one gadolinium enhancing lesion in brain during course of illness, presence of at least one T2 lesion in the last available MRI brain, >50% optic nerve or

chiasma involvement, ≥3 spinal segments involved, dorsal medulla involvement and peri-ependymal involvement in for of T2W and FLAIR hyperintensities.

Earlier, as a part of multicentric project on primary demyelination (AFMRC 4511/2014) funded by Indian Armed Forces Medical Research Committee, neurologists from eight Indian Armed Forces Medical Services Neurosciences Centres located across the country had been invited to participate in the study. A study protocol, data extraction proforma in Excel sheet, patient consent form and patient information sheet in Hindi and English was mailed to the centres. Institutional ethics clearance was taken at all participating centres. Informed written consent was taken from all participants. All participating centres were asked to read out the contents of consent form and patient information sheet in case the patient was illiterate or understood a language other than Hindi or English. The completed proformas from all centres were mailed back to the principal investigator for coalition and analysis. The study was conducted over three years with new cases included till December 2019. Data extracted for the current study was divided into three groups as per the seropositivity for AQP4 antibody, MOG antibody or being double seronegative.

Sample size for this study was calculated using an online calculator available at www.datavis.ca. A sample size of at least six for each pair-wise comparison using analysis of variance (ANOVA) was calculated using the primary outcome of mean difference in EDSS of at least 0.5 with mean anticipated EDSS in one group being 3.0 (±0.5) and mean EDSS in another group being 4 (±0.5), alpha error of 0.05 and power of study being 80%. Data analysis was done using IBM SPSS Statistics Data Editor version 20. Non-parametric tests like Kruskal--Wallis test and Chi-square test were used where indicated for univariate analysis. A regression analysis was done for significant differences between the three groups among those variables which were significant on univariate analysis. A *P* value of less than 0.05 was taken as significant.

RESULTS

Out of the 46 patients with NMOSD who were included in the study 28 (60.9%) were positive for AQP4 antibody, 11 (23.9%) were anti-MOG antibody positive and the remaining 7 (15.2%) were double seronegative. The centres at different cities contributing to the cases were New Delhi (35), Pune (7) and Kolkata (4). The tests for the antibody were done at individual centres through commercial laboratories. The details of the technique of the tests (cell-based vs ELISA or any other) were not available.

Table 1 shows the demographic characteristics, disability, duration of disease and ARR. Univariate analysis revealed females to be significantly more in AQP4 positive group. Although they were not significant there was a trend towards greater disability and higher progression index in AQP4 positive group.

Table 2 shows the clinical syndrome at presentation. Thirty-seven patients (80.4%) had their presenting symptoms localized to the optic nerve or cord or both, the break-up being as follows: AQP4+ 22/28 (78.5%), MOG+ 9/11 (81.8%) and double seronegative 6/7 (85.7%). Seven out of thirty five patients, for whom the data was available, presented with bilateral optic neuritis; 1 was AQP4 positive 6 were negative (3 MOG positive and 3 double seronegative). There was no significant difference among the groups.

Twenty three patients had relapsing disease, 20 out of 23 (86.8%) patients had relapses localized to optic nerve and/or spinal cord. A total of 70 relapses were recorded with distribution as shown in Table 3. Although there was no significant difference among the groups, AQP4 positive group had a higher proportion of relapsing patients.

Table 4 shows the comparison of CSF parameters, evoked potentials and MRI. A higher proportion of patients with AQP4 negative had trend towards inflammatory CSF (WBCs >5,

proteins >40 mg/dl), however this was not significant. None of the CSF sample tested for oligoclonal band were positive. AQP4 negative group also had higher number of patients with bilaterally prolonged VEPs. Proportion of patients with >50% optic nerve involvement or optic chiasma involvement, T2 brain lesions and dorsal medullary lesions were higher in AQP4 negative group.

When regression analysis was done on the variables significant on univariate analysis, only gender remained significantly different [Table 5]. Figures 1-5 are MRI images with of some of our cases.

Discussion

Regression analysis of our data has shown that gender was the only significant difference in the three groups of adult patients satisfying the IPND 2015 criteria for NMOSD and who were segregated into three groups based on their serological status. Females were more common in AQP4 antibody group. We

Table 1: Comparison of Demographics, disability, duration and ARR

| Variable	Aquaporin 4 Antibody Positive (n=28)	MOG antibody Positive (n=11)	Seronegative (n=7)	P
Female Gender (%)	25 (89.3)	4 (36.4)	3 (42.9)	<0.01
Age in years	37.2 (17.7)	33.9 (12.6)	35.4 (12.1)	0.99
Education Status up to Class 12 (%)	19 (67.8)	8 (63.6)	4 (57.1)	0.86
Family Income <6 lakhs/year (%)	24 (85.7)	6 (54.5)	5 (71.4)	0.12
Presence of other autoimmune disease(s) (%)	4 (14.3)	0	2 (28.6)	0.21
Mean duration of disease in months (SD)	69.1 (70.1)	20.1 (18.3)	40.4 (30)	0.05
Mean ARR (SD)	0.54 (0.59)	0.56 (0.31)	0.48 (0.37)	0.57
Mean EDSS (SD)	4.2 (2.6)	3.5 (2.1)	3.1 (2.1)	0.43
Mean Progression Index (SD)	1.6 (3.7)	1.1 (0.6)	1.1 (0.9)	0.39

Table 2: Clinical syndrome at presentation & course

Syndrome at presentation	Aquaporin 4 antibody positive (n=28)	MOG antibody positive (n=11)	Seronegative (n=7)	P
Optic Neuritis (ON) (%)	10 (35.7)	4 (36.4)	2 (28.6)	0.62
Myelitis (%)	10 (35.7)	5 (45.5)	2 (28.6)	
Area Postrema syndrome (%)	1 (3.6)	0	0	
Brainstem syndrome (%)	2 (7.1)	0	1 (14.3)	
Diencephalic Syndrome (%)	0	1 (9.1)	0	
Cerebral Syndrome (%)	3 (10.7)	1 (9.1)	0	
ON + myelitis (%)	1 (3.6)	0	1 (14.3)	
ON + Brainstem syndrome (%)	1 (3.6)	0	0	
ON + Cerebral Syndrome (%)	0	0	1 (14.3)	

Table 3: Comparison of clinical syndromes in relapses (n=23)

Relapse localization	Aquaporin 4 antibody positive (n=14)	MOG antibody positive (n=5)	Seronegative (n=4)	P
Total number of relapses (%)	54 (77.1)	9 (12.9)	7 (10)	0.28
Optic Neuritis	17 (32.1)	2 (22.2)	3 (42.8)	
Myelitis	22 (40.7)	4 (44.4)	3 (42.8)	
Optic Neuritis + Myelitis	4 (7.5)	2 (22.2)	0	
Brainstem	7 (12.9)	1 (11.1)	1 (14.4)	
Cerebrum	4 (7.5)	0	0	

did not find any significant difference in other demographic features, disability profile, ARR, number of relapses, presenting clinical syndrome, clinical syndrome during relapse, CSF profile, evoked potentials and MRI features.

Table 6 summarizes recent studies which have compared the subtypes of NMOSD. The universal thread which exists
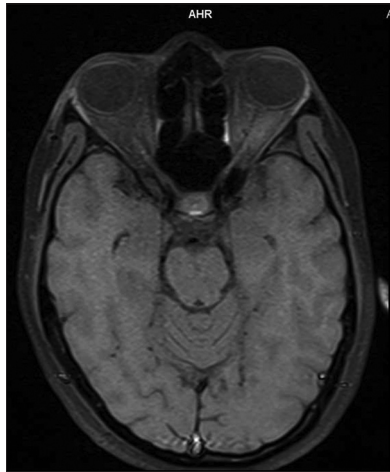
Figure 1: 20 year old girl with recurrent vision loss with AQP-4 antibody positive. FLAIR axial imaging showed bilateral atrophy with hyperintensity involving posterior left optic nerve and optic chiasma

in almost all the studies is that there is male dominance in AQP4 negative patients. The same has been replicated in our study. However, certain other differences, found not to be statistically significant in our study, have been noted in some, but not all previous studies. It has been documented that, patients with NMO or NMOSD, who were AQP4 negative, but anti-MOG positive had more optic nerve involvement than spinal cord involvement, more lumbar cord involvement, had bilateral optic neuritis, they presented more frequently with simultaneous optic neuritis & spinal cord involvement, had monophasic more than relapsing course, their outcomes were better, they were less disabled and had better therapeutic outcomes than AQP4 positive patients.[5,6,9-15] Other studies have also found that patients who are AQP4 antibody negative are likely to have more brain lesions, CSF pleocytosis and low CSF-serum sugar ratio.[10,12] Our study did not find any of these differences to be significant, similar to a study by Sepúlveda *et al.*[16]

The variability of results across studies suggests that there is more to it than meets the eye. Some of the differences among the studies may be related to variation in inclusion criteria, diagnostic criteria used, testing and other methodology across studies. It is important to note that MOG antibody disease has been reported to have a varied presentation including localized optic nerve and spinal cord involvement (NMOSD),
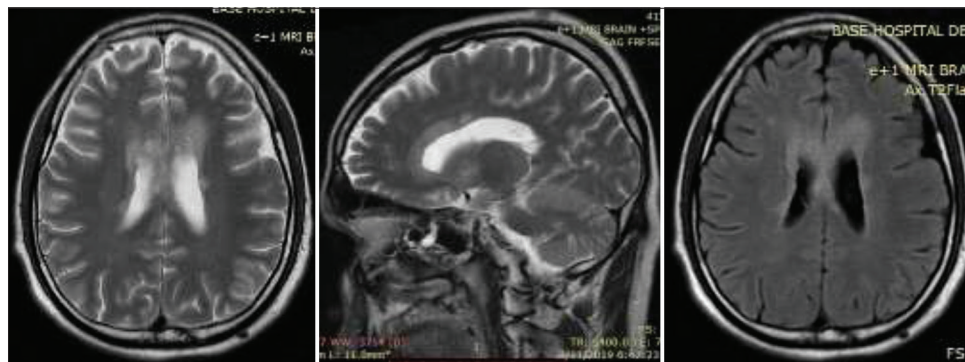
Figure 2: 27 year old soldier with recent onset memory loss and behavior change with AQP-4 antibody positive. T2 axial and sagittal images and FLAIR axial images showing hyperintensity along the periventricular and frontal subcortical white matter and anterior half of corpus callosum

Table 4: Comparison of CSF, Evoked Potentials and MRI

Investigation at presentation	Aquaporin 4 Antibody Positive (*n*=28)	MOG antibody Positive (*n*=11)	Seronegative (*n*=7)	*P*
CSF WBCs >5 (%)	5 (17.9)	5 (45.5)	2 (28.6)	0.21
Mean CSF Sugar in mg/dL (SD)	67 (16)	65 (21)	73 (16)	0.29
CSF Protein >40 (%)	9 (32.1)	8 (72.7)	4 (57.1)	0.06
Bilateral abnormal VEP (%)	8 (28.6)	5 (45.5)	4 (57.1)	0.15
Abnormal BAER (%)	4/20 (20)	1/10 (10)	1/7 (14.3)	0.77
Gad enhancing lesion in brain (%)	2 (7.1)	1 (9.1)	1 (14.3)	0.83
At least 1 T2 lesion in Brain (%)	11 (39.3)	3 (27.3)	4 (57.1)	0.34
MRI ON >50% or chiasma involved (%)	5/16 (31.2)	4/10 (40)	5/7 (71.4)	0.2
MRI Cord with ≥3 segment involvement (%)	17 (60.7)	7 (63.6)	4 (57.8)	0.90
MRI dorsal medulla involvement (%)	2 (7.1)	0	3 (42.9)	0.01
MRI peri-ependymal (%)	2 (7.1)	1 (9.1)	2 (28.6)	0.26

ADEM (especially paediatric), acute brainstem syndrome, cortical encephalitis.[17] Inclusion of some of these patients who do not strictly comply with IPND 2015 for AQP4 negative NMOSD may account for some of the variations seen. Many of the series had included paediatric patients. However, some of the differences documented in AQP4 negative NMOSD (both MOG positive and double seronegative) when compared to AQP4 positive patients may be related to actual variations linked to different pathophysiology. Further, it is also possible that patients who are double seronegative may have some yet to be discovered antibodies which may account for some of the phenotypical differences noted in these studies.

The most obvious reasons for not finding any significant difference among the groups in our study is because of the small sample size and its retrospective nature. However, there were certain notable trends in our study (seen in previous studies), which, although not significant, do deserve to be mentioned. Bilateral optic neuritis as a presenting feature was more common in AQP4 negative patients. There was a trend towards lesser disability in AQP4 negative (MOG antibody positive and double seronegative)

patients (EDSS 4.2 vs 3.3). Progression Index (a measure of progression of disability over time in those with relapses or progression) was relatively less in AQP4 negative disease. CSF pleocytosis (38.8% vs 17.9%) and raised proteins (66.6% vs 32.1%) was seen more commonly in AQP4 negative group. Visual evoked potentials were more commonly prolonged bilaterally in the AQP4 negative group (50% vs 28.6%). Optic nerve MRI (>50% optic nerve and chiasma involvement) was more commonly abnormal in patients who were AQP4 negative (52.9% vs 31.2%). Dorsal medullary involvement in form of T2 and FLAIR hyperintensities on MRI was more commonly noted
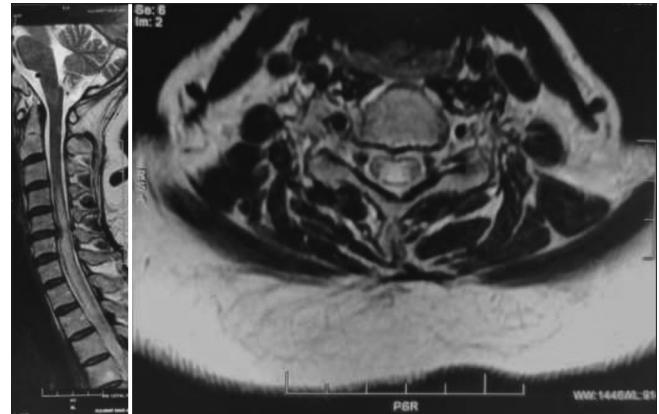
Figure 3: 42 year old female presented with complete progressive quadriparesis with AQP 4 positive antibody. T2 sagittal and axial STIR imaging showed a hyperintense signal with expanded cord involving C4- T4 and patchy hyperintensity over C1 extending to rostral medulla with predominant central cord involvement

Table 5: Regression analysis

Variable	Unstandardized Coefficients		Standardized Coefficients	$t^{\ddagger}$	P
	B^*	$SE^{\dagger}$	Beta		
Gender	-0.681	0.217	-0.422	-3.142	0.003
MRI dorsal medulla	0.511	0.321	0.214	1.593	0.119

Regression output: B^*=coefficient; $SE^{\dagger}$=Standard error; $t^{\ddagger}$=t-statistic

Table 6: Summary of previous studies (in the order of the year they were published)

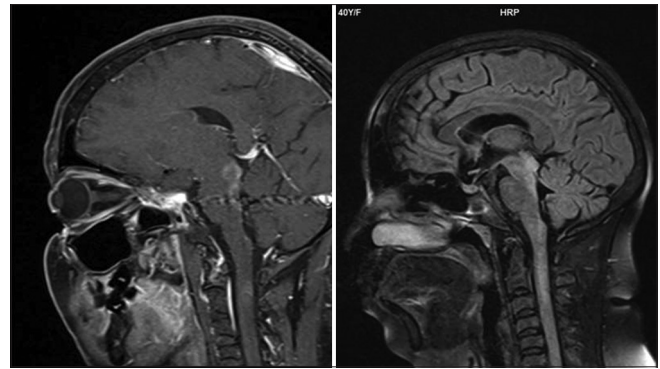| Author	Total patients & breakup	Difference in method	Comparison & Chief findings
Sato, 2014, Japan[6]	215; AQP4 + 139; Anti MOG + 16; seroneg 60	Paediatric pts included, both NMO & NMOSD included	Anti MOG +: more male, ON>SC involved, bilateral simultaneous ON, more single attack, lesions in lower portion of SC, better recovery after attack.
Pandit, 2016, India[5]	125; AQP4 + 38; anti MOG 25; seroneg 62	NMO + NMOSD (2006); paediatric pts included	51 satisfied 2006 criteria (AQP4 + 32/38; 2/25 MOG + & 17/62 seroneg); AQP4 + female dominant, relapsing course, higher EDSS, 63.1% presenting with LETM; dorsal and lumbar lesions in MOG + and cervical in AQP4 +
Sepúlveda, 2016, Spain[16]	127; AQP4 + 95: Anti MOG + 9; seroneg 22	Paediatric pts included; 2006 criteria used	Anti MOG +: more male, better outcomes. No difference among 3 groups in presenting clinical syndrome at onset, EDSS, ARR
van Pelt ED, Netherland 2016[9]	102; AQP4 + 41; Anti MOG + 20; seroneg 41		Anti MOG vs AQP4 +: more males; frequent presentation with ON + TM simultaneous; monophasic; less disabled on last follow up
Fan, 2017, China[10]	55; AQP4 + 30; AQP4-25	Pts with NMO	AQP4- vs AQP4 +: more brain lesions, infra tentorial lesions; similar spinal cord lesion length
Antonio-Luna, 2017, Mexico[11]	100; AQP4 + 70; AQP4-30	NMO + NMOSD included	AQP4 + vs AQP4-: more disabled & visual involvement, more relapses & more spinal segments involved
Kunadison, 2018, Thailand[12]	42 AQP4 + 30; AQP4-12	NMO & NMOSD using 2006 criteria	AQP4 + vs AQP4-: more female patients, immunosuppressant treatment, serum albumin less than 4 g/dL, CSF pleocytosis, low CSF-serum glucose ratio and extensive transverse myelitis
Wang, 2018, China[13]	67; AQP4 + 49; AQP4-18	IPND 2015 criteria	AQP4 + vs AQP4-: Difference in sex, course of disease & EDSS
Ojha PT, India, 2020[14]	48; AQP4 + 27; Anti MOG + 21	Paediatric pts, pts with demyelination and positive AQP4 and MOG included	Anti MOG + vs AQP4 +: no female predilection, preferential optic nerve involvement, characteristic neuroimaging abnormalities, and favourable therapeutic response and outcome.
Du Q, China, 2021[15]	594; AQP4 + 517; Anti MOG + 26; seroneg 51		Anti MOG + & double-seronegative patients had less severe clinical attacks, better prognoses, lower EDSS scores

*ON optic nerve, SC spinal cord

Figure 4: 45 year old male presented with subacute bilateral vision loss followed by complete paraplegia, MOG +. MRI Brain T1 post contrast axial section showing expanded B/L optic nerve with anterior half contrast enhancement sparing chiasma and left preoptic enhancement seen. MRI Sagittal T2 spine imaging showed T9-L1 hyperintensity with expanded cord

Figure 5: 40 year old female presented with neck pain recurrent hiccups, vomiting and diplopia in a double seronegative patient. T1 post contrast sagittal and FLAIR sagittal imaging showed hyperintensity involving periaqueductal gray matter over dorsal midbrain and pons. Cervical hyperintensity also seen from C1-C3 with rostral medulla extension on FLAIR section

in AQP4 negative patients. Relapses were noted in only half of our patients possibly due to early institution of immunosuppressive drugs. Among those who had relapses, the localization remained commonly in optic nerve and/or cord.

In addition to small sample size, our study had other limitations, the chief among them being the collection of data through chart review. The data was contributed primarily from Delhi with smaller contributions from Pune and Kolkata and cannot be considered multicentric. Contrary to previous studies our study had the least number of patients in the double seronegative group. This is possibly due to negative selection bias. While collecting data retrospectively patients at various centres may have been excluded as they did not meet the IPND 2015 criteria for AQP4 negative NMOSD which is more stringent than criteria for AQP4 positive patients. This would have negatively affected the seronegative group the most, making it smaller. Further, the serology testing for AQP4 and MOG may have been done after starting therapy or on follow up reducing positivity rate. Being a retrospective study, some of the data collected depended on patient recall, especially related to presenting symptoms, and may be prone to recall bias. The other significant limitation was that the methodology of tests done to determine the AQP4 antibody status was not known. Cell-based studies would have been ideal.

In conclusion, our study, despite its short comings, contributes to the limited literature available, especially from India, on the comparison of the serological-based subgroups of NMOSD diagnosed using the IPND 2015 criteria. It is important to continue to look for differences in the subgroups of this heterogenous condition. These subgroups may have a yet undiscovered different pathophysiology but common phenotypical presentation. It is obvious that much work

needs to be done as this condition forms a significant chunk of primary demyelination disorders in Asia. These differences will help us further understand the pathophysiology and have implications on therapeutics.

Conflicts of interest
There are no conflicts of interest.

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