

## Clinico-epidemiologic characteristics of optic neuritis in a tertiary eye centre in Eastern India based on the status of serum aquaporin-4 antibody

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**Purpose:** To elucidate the clinico-epidemiologic characteristics of optic neuritis based on the status of serum aquaporin-4 antibody (AQP4-Ab) in patients with optic neuritis (ON). **Methods:** Medical records of 106 patients with ON and a follow-up of 3 years were reviewed. For each patient, the following data were extracted: medical history, findings of the ocular examination, brain, orbital or spinal MRI, and serological tests for AQP4. The ON was classified as typical or atypical based on disc examination and improvement in vision after intravenous methylprednisolone (IVMP). The clinical findings (typical or atypical), disease course, and outcomes were analyzed according to the serostatus of the ON. **Results:** 10 patients (9.4%) were seropositive for AQP4-Ab; all had atypical ON. 96 patients (91%) were seronegative for AQP4-Ab: 36 atypical ON and 60 typical ON. Profound visual impairment at presentation was seen in all patients. However, at the end of the study period, seropositive and seronegative atypical ON had poor visual outcomes as compared to seronegative typical ON ( $P = 0.002$ ). Five seropositive and four seronegative patients with atypical ON developed transverse myelitis. Bilateral disease with relapse was more in seropositive patients (80%); however, seronegative with atypical ON also had bilateral presentation and relapse in 42% and 41%, respectively. **Conclusion:** AQP4-Ab seropositive patients mostly present with atypical features such as bilateral recurrent ON, poor visual outcome, and increased incidence of transverse myelitis. However, atypical clinical features can also be seen in seronegative ON with a poor visual outcome and a recalcitrant course.

**Key words:** Aquaporin 4 antibody, NMO-IgG antibody, seronegative, seropositive, transverse myelitis, typical and atypical optic neuritis

Optic neuritis (ON) is an inflammatory disorder of the optic nerve which can be idiopathic or due to demyelinating diseases. Other etiologies include infectious and para-infectious causes and inflammatory and para vaccination immunological responses.<sup>[1]</sup> Multiple sclerosis (MS) and neuromyelitis optica (NMO) are important demyelinating diseases that can have ON as the presenting feature.<sup>[2]</sup> The optic neuritis treatment trial (ONTT) has shown good visual outcomes and a risk of conversion to MS in patients presenting with it.<sup>[3]</sup> However, the visual outcome in the Asian context has been reported to be worse than the ONTT study and this has been attributed to the higher incidence of atypical optic neuritis and their conversion to NMO.<sup>[4-6]</sup> It is important to differentiate between the latter and MS as the treatment strategies of both entities are different and a timely diagnosis will have bearing on long-term visual and neurological outcomes.<sup>[8]</sup> AQP4-Ab is a sensitive and highly specific serum marker for NMO spectrum disorder (consensus diagnostic criteria) and can help in differentiating between the two.<sup>[9]</sup> However, the status

of serum AQP4-Ab in ON and its clinico-epidemiological characteristics and course based on typical or atypical clinical features have not yet been studied in India, though literature from the rest of Asia shows a higher prevalence of this antibody than Caucasian studies.<sup>[10,11]</sup> This study analyzed the status of serum AQP4-Ab in patients presenting with ON as the first symptom (isolated ON) and determined its clinical course and outcome based on this.

### Methods

The study was approved by the institutional ethics committee (1043/IEC/IGIMS/2019), the institute's review board, and adhered to the tenets of the Helsinki Declaration. This retrospective cohort study reviewed the medical records of 106 patients with ON after excluding patients who presented with optic neuropathies such as ischemic, compressive, toxic, metabolic, vascular, and infective ( $n = 72$ ), patients with ON already associated with brain and/or spinal cord MRI

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lesions (n = 34), patients who were lost to follow-up (n = 87), or those refused to test for AQP4 Ab (n = 37). Only patients who had the first episode of ON and were followed up for at least 3 years were included, with the study period being between June 2015 and April 2020. Patients with unilateral ON or bilateral ON (both eyes involved simultaneously or sequentially within 3 weeks) or recurrent ON (a new unilateral attack occurring after an interval of  $\geq 4$  weeks in either eye) were included in the study.<sup>[12]</sup> Demographic and clinical data were recorded. All patients underwent anterior segment and pupil evaluation, color vision test, best-corrected visual acuity for distance (BCVA), and disc examination. Visual evoked potential (VEP), Humphrey visual field analysis (VF, central 30-2 field), and RNFL analysis (OCT-1 Maestro, Topcon Medical System, Oakland, NJ, USA) were done in all cases whenever possible. AQP4-Ab (NMO-IgG or anti-NMO) was detected using immunofluorescence or cell-based assay, both having high sensitivity and specificity.<sup>[13]</sup> Other laboratory tests included a complete hemogram, blood glucose, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA), and Mantoux test. To exclude an associated autoimmune disorder, the patients with raised ANA underwent additional tests, such as angiotensin-converting enzyme (ACE), p-ANCA, c-ANCA, anti-SSA, anti-SSB, anti-Ds DNA, and chest X-ray. All patients had MRI of the brain and orbit using 1.5 or 3 Tesla scanners. Apart from routine MRI brain sequences (T1-weighted, T2-weighted, FLAIR, and diffusion-weighted scans), all patients underwent additional orbital imaging, including the following thin-section (3 mm) sequences: T1-weighted, fat-suppressed scans with and without gadolinium contrast, and T2-weighted scans in multiple planes (axial, coronal, and sagittal). Spinal MRI was performed when clinical findings suggested spinal cord involvement. Acute phase treatment with high-dose IVMP (1 g/day, 3–5 days) and a taper with oral steroids (1 mg/kg/day) for 11 days as per ONTT recommendations were given.<sup>[9]</sup> CSF was examined in selected patients with poor vision (less than 20/200) or in patients suspected of having MS. Follow-up data included final BCVA and recurrence of ON or occurrence of neurological symptoms. Neurological evaluation and repeat MRI were performed when patients developed symptoms suggestive of brain or spinal cord involvement. Typical ON was diagnosed when the disc was normal or mildly edematous without hemorrhage and exudates, and the vision improved (partial or complete) within one month.<sup>[14]</sup> Atypical ON was diagnosed when the disc was normal or severely edematous with or without hemorrhages and exudates, and the vision remained unchanged or partially recovered or decreased at a follow-up of 1 month.<sup>[14]</sup> Based on serum AQP4-Ab serostatus and typical or atypical clinical features of ON, patients were divided into three groups: seropositive atypical ON [AQP4(+)<sup>AT</sup>ON], seronegative atypical ON [AQP4(-)<sup>AT</sup>ON], and seronegative typical ON [AQP4(-)<sup>T</sup>] (idiopathic optic neuritis).<sup>[4]</sup> [AQP4(+)<sup>AT</sup>ON] were diagnosed with NMO spectrum disorder (NMOSD) according to the consensus criteria (but not meeting the 2006 NMO criteria).<sup>[9]</sup> NMO was defined by Wingerchuk criteria (2006)<sup>[15]</sup>; multiple sclerosis (MS) was diagnosed by McDonalds criteria.<sup>[16]</sup> A complete visual recovery was defined as attaining a BCVA of 20/20. A partial visual recovery was considered to be better than presenting BCVA but less than 20/20. No improvement was considered to be BCVA at the end of the 3-year follow-up that was equal to or less than presenting BCVA. In bilateral cases, BCVA of the worse eye was used for data analysis. BCVA with

the logarithm of the minimum angle of resolution (logMAR) notations was used for statistical analysis.

### Statistical analysis

Statistical analysis was performed using SPSS version 23 (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed with Fisher's exact test and continuous variables with independent sample *t* test. One-way ANOVA was used to determine significance between the means of three groups. Kaplan–Meier survival analysis and log-rank test were performed to determine significance.  $P < 0.05$  was considered significant.

## Results

A total of 106 patients who had completed follow-up of 3 years were evaluated. There were 28 male and 78 female patients (M:F ratio: 1:2.8). The mean follow-up period was  $38.4 \pm 4.8$  months (range: 36.0–48.2 months). The median age at onset was 28 years (range: 9–56 years). AQP4(+)<sup>AT</sup>ON was seen in 10 (9.4%) patients. AQP4(-)<sup>AT</sup>ON was seen in 36 (34%) patients. Most patients (60, 57%) had presented with AQP4(-)<sup>T</sup>ON.

### Clinical features of ON based on AQP4 Ab serostatus

Table 1 shows the demography, clinical presentation, presence of autoantibodies, and inflammatory markers along with the visual and neurological outcomes according to AQP4-Ab serostatus and typical or atypical clinical features. Baseline evaluation showed females outnumbering males in all groups with the highest median age at presentation in AQP4(-)<sup>AT</sup>ON. Bilateral involvement was mostly seen in AQP4(+)<sup>AT</sup>ON and AQP4(-)<sup>AT</sup>ON, more than what was seen in [AQP4(-)<sup>T</sup>ON] ( $P < .05$ ). In addition, recurrence was also frequently seen in AQP4(+)<sup>AT</sup> with a significantly earlier time to first recurrence ( $6.0 \pm 0.6$  months) followed by AQP4(-)<sup>AT</sup>ON ( $10 \pm 6.24$  months). It was seen the least in AQP4(-)<sup>T</sup>ON with time to recurrence being  $26.13 \pm 9.2$  months ( $P < 0.05$ , log-rank test).

There was no significant difference in presenting visual acuity among the three groups ( $P > 0.05$ ). However, AQP4(-)<sup>T</sup>ON had better visual outcomes ( $P < 0.05$ ) than the other two groups [Tables 1 and 2], and most patients demonstrated complete visual recovery. Patients with atypical ON irrespective of serostatus had similar visual outcomes at the end of the study period ( $P > 0.05$ ), and none from either group showed a complete visual recovery. Most patients had witnessed an improvement in BCVA after initial high-dose IVMP therapy. However, survival analysis showed that this was followed by a progressive diminution of vision to below 20/200 in 6 AQP4(+)<sup>AT</sup>ON and 23 AQP4(-)<sup>AT</sup>ON patients, with the former showing an early diminution.

RNFL analysis showed decreased RNFL thickness in all quadrants in patients with atypical ON ( $P < 0.05$ ). RNFL analysis was performed after the acute phase was over and stabilization was observed (mean:  $3.7 \pm 1.5$  months). Visual field analysis was performed at baseline and the predominant VF defect was a central scotoma followed by diffuse contraction of fields. VF could not be done in a few cases due to poor vision or young age of the patients.

MRI demonstrated optic neuritis as the thickened optic nerve showing hyper-intense signal on T2-weighted imaging

**Table 1: Clinical parameters of optic neuritis (ON) based on serum AQP4-Ab status and typical/atypical clinical features**

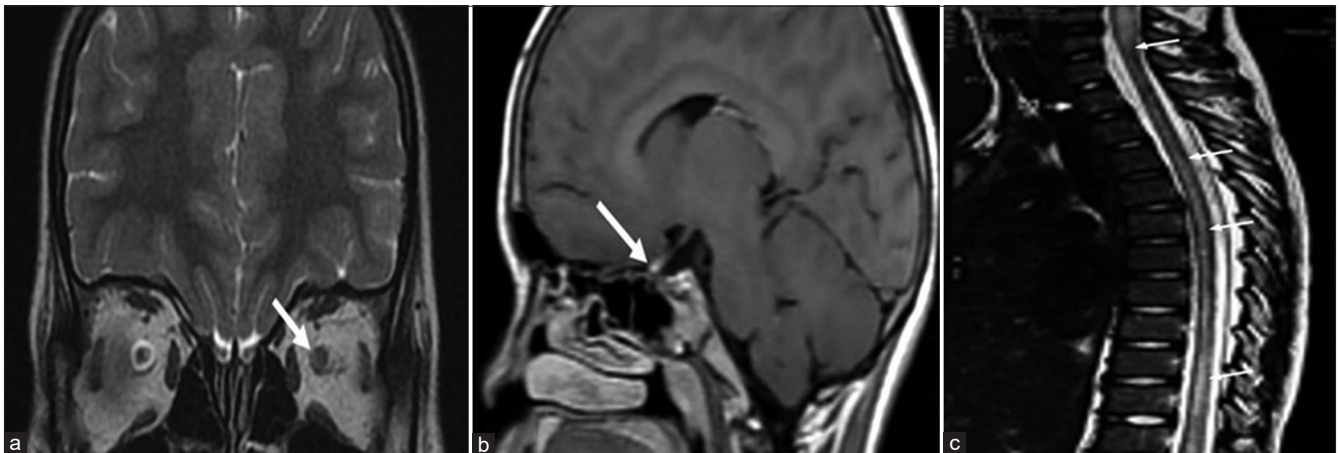
Variables	Seropositive atypical ON AQP4(+) <sup>AT</sup> ON (n=10)	Seronegative atypical ON AQP4(-) <sup>AT</sup> ON (n=36)	Seronegative typical ON AQP4(-) <sup>T</sup> ON (n=60)	P
Number of patients with ON	10	36	60	<0.05 <sup>†</sup>
Median age (years)	28	48	26	
Male:Female	3:7	14:22	11:49	0.71 <sup>†</sup>
Clinical features of ON				
Bilateral Optic Neuritis	8	15	17	0.14 <sup>†</sup>
Disc Edema	7	21	33	
Painful ocular movement	1	13	24	
Predominant visual field defect	Central scotoma	Central scotoma	Central scotoma	
Presenting BCVA	1.66±0.16	1.43±0.26	1.31±0.37	>0.05*
Final BCVA	1.40±0.96	1.12±0.486	0.038±0.073	<0.05*
Blood analysis				
High ESR <sup>§</sup>	3	9	12	0.86 <sup>†</sup>
Raised CRP <sup>¶</sup>	2	10	9	
ANA	2	5	7	
Anti-dsDNA	Nil	2	Nil	
Anti SSA	Nil	1	Nil	
CSF analysis				
Oligoclonal band	None	Nil	2	<0.05 <sup>†</sup>
Pleocytosis	3	6	11	0.63 <sup>†</sup>
Mild Elevation <sup>**</sup>	-	3	Nil	
Mod -High Elevation <sup>**†</sup>				
Recurrence of ON				
Time to first recurrence (months)	6.0±0.6	10±6.24	26.13±9.20	0.04 <sup>†</sup>
At least one recurrence	8	14	12	

BCVA=best-corrected visual acuity, ESR=erythrocyte sedimentation rate, CRP=C-reactive protein, ANA=anti-nuclear antibody. <sup>†</sup>Fisher exact test, \*One-way ANOVA, <sup>§</sup>ESR >20 mm/H, <sup>¶</sup>CRP >10 mg/L, <sup>\*\*</sup>Mild elevation: greater than reference value but <25 cells/ $\mu$ L, <sup>\*\*†</sup>Mod-High elevation: moderate (26-100 cells/ $\mu$ L)

**Table 2: Visual outcome according to serum AQP4-Ab status and clinical features**

Visual Outcome	Seropositive atypical ON AQP4(+) <sup>AT</sup> ON (n=10)	Seronegative atypical ON AQP4(-) <sup>AT</sup> ON (n=36)	Seronegative typical ON AQP4(-) <sup>T</sup> ON (n=60)	P
Complete recovery of BCVA	None	None	56 (93%)	<0.05*
Partial/incomplete recovery <sup>†</sup>	7 (70%)	13 (36%)	04 (7%)	0.01*
No recovery <sup>‡</sup>	3 (30%)	23 (64%)	None	<0.05*

\*Fisher exact test. <sup>†</sup>More than presenting visual acuity but <20/20. <sup>‡</sup>Unchanged or less than presenting BCVA



**Figure 1: MRI demonstrating optic nerve changes in seropositive optic neuritis: (a) T2W coronal image showing thickened left optic nerve with obliteration of peri-optic CSF space (white arrow); (b) T1W sagittal post-contrast image showing marked enhancement of the optic nerve near optic chiasm (white arrow); (c) Sagittal T2-weighted MRI showing high signal (arrows) in almost the entire spinal cord indicating transverse myelitis**

**Table 3: MRI findings according to serostatus and clinical features**

MRI findings	Seropositive Atypical ON [AQP4(+) <sup>AT</sup> ON] (n=10)	Seronegative Atypical ON [AQP4(-) <sup>AT</sup> ON] (n=36)	Seronegative Typical ON [AQP4(-) <sup>T</sup> ON] (n=60)	P
Post-contrast T1-weighted optic nerve enhancement	10 (100%)	34 (94%)	56 (93%)	<0.05*
T2 signal abnormality with hyperintensity	10 (100%)	36 (100%)	58 (97%)	<0.05*
Optic nerve with sheath enhancement	Nil	2 (6%)	Nil	0.4*
Site of lesion				
Anterior	4 (40%)	32 (89%)	60 (100%)	<0.05*
Posterior	6 (60%)	4 (11%)	Nil	
Whole length	Nil	2 (5.5%)	Nil	
Optic chiasma (overlap with posterior lesion)	2 (30%)	2 (5.5%)	Nil	
Length of optic nerve lesion				
Long (> half of orbital length)	6 (60%)	9 (25%)	5 (8%)	<.05*
Short (< half of orbital length)	4 (40%)	27 (75%)	55 (91%)	
Site of extra optic lesion				
Spinal cord				
SSM	Nil	Nil	1 (1.7%)	0.01*
LETM	5 (50%)	4	Nil	
Cerebral cortex	4 (40%)	1	13 (22%)	
Brainstem	1 (10%)	3	2	
Cerebellum	Nil	1	Nil	

SSM=short-segment myelitis (defined as spinal cord lesions extending fewer than three vertebral segments, less than two vertebral segments in length),

LETM=long extensive transverse myelitis (defined as a lesion that spans over three or more contiguous vertebral segments and predominantly involves central gray matter on the spinal cord MRI). \*Fisher exact test

and enhancement on post-contrast fat-suppressed T1-weighted imaging [Fig. 1a]. As shown in Table 3, AQP4(+)<sup>AT</sup>ON patients had a higher incidence of long-segment optic-nerve involvement that frequently extended to its posterior segment than the other two groups. The optic chiasma was involved in two patients in AQP4(+)<sup>AT</sup>ON [Fig. 1b]. In addition, extra-optic lesions in the spinal cord were found more frequently in this group. Spinal MRI, including the entire spinal cord from cervical to lumbar, was performed for all patients in the AQP4(+)<sup>AT</sup>ON group at presentation, whereas only four patients in AQP4(-)<sup>AT</sup>ON and one patient in AQP4(-)<sup>T</sup>ON groups underwent spinal MRI when they developed spinal symptoms at follow-up [Fig. 1c].

The CSF study was done in 18 patients overall, with the maximum being in AQP4(-)<sup>AT</sup>ON patients for diagnostic purposes and in a few AQP4(-)<sup>T</sup>ON patients who were MS suspects. Oligoclonal IgG bands were seen in two cases in the latter; however, there was no significant difference in other CSF parameters. Laboratory investigations showed high ESR and CRP in few patients from all groups ( $P \geq 0.05$ ). ANA was the most common autoantibody overall ( $P \geq 0.05$ ) and was seen in 14 patients. These patients had a presenting VA of < 20/200 along with raised ESR in nine patients. Two AQP4(+)<sup>AT</sup>ON cases with raised ANA later developed TM. Raised anti-dsDNA and anti-SSA antibodies were found in two AQP4(-)<sup>AT</sup>ON patients with raised ANA. None had overt clinical signs of having a collagen-vascular disease.

By the end of the study period, five AQP4(+)<sup>AT</sup>ON and four AQP4(-)<sup>AT</sup>ON patients had developed longitudinally extensive transverse myelitis (LETM). Seven AQP4(-)<sup>T</sup>ON patients were diagnosed with MS while one AQP4(-)<sup>T</sup>ON patient with short-cord lesion and myelitis was diagnosed with opticospinal MS [Fig. 2]. Although myelin oligodendrocyte glycoprotein (MOG) antibody testing was not part of this study

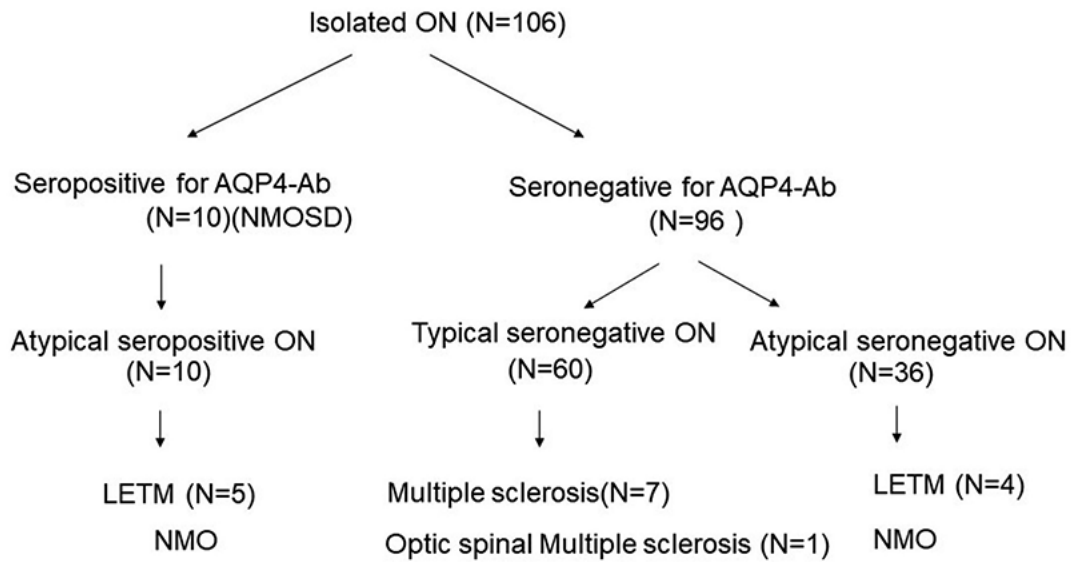
protocol due to the nonavailability of the test during most of the study duration, two AQP4(-)<sup>AT</sup>ON patients with recurrent ON later tested positive for MOG antibody (MOG ON).

All patients with atypical ON were treated with high-dose IVMP followed by oral azathioprine 2.5–3 mg/kg per day for immunosuppression. Two seropositive patients with no improvement in vision and transverse myelitis underwent plasma exchange at different hospitals. Patients in the AQP4(-)<sup>T</sup>ON group were given only pulse steroids. Patients diagnosed with MS were treated further with disease-modifying drugs, such as weekly intramuscular Interferon beta-1a.

## Discussion

The establishment of AQP4 and MOG-Ab as a new diagnostic serological marker for ON has contributed significantly to the understanding of the clinical features and prognosis of ON. There seems to be a higher prevalence of these markers in Asian studies as compared to Caucasians, which show more MS-related ON and may account for the higher incidence of atypical ON in Asia.<sup>[8]</sup> However, the epidemiological and clinical characteristics of ON in Indian patients are not as clear as those from the rest of Asia in terms of presentation with typical or atypical ON and presence of serological markers. Though it would have been desirable to test for both AQP4 and MOG-Ab, we were unable to include patients who were tested for MOG-Ab as it was unavailable to us for most part of the study duration.

On analyzing serostatus for AQP4-Ab in all cases presenting with ON in our study, we found an overall seropositivity of 9.4%. This prevalence of AQP4-Ab in ON in our study was higher than observed for Caucasians (3.1%–7%) but lower than the Japanese and Chinese studies (9.8%– 52.3%). HLA



Abbreviation: ON, Optic neuritis; LETM, Longitudinal extensive transverse myelitis; NMOSD, Neuromyelitis optica spectrum disorder [according to consensus criteria (but not meeting 2006 NMO criteria)]; NMO, Neuromyelitis optica [Wingerchuk criteria,2006]

**Figure 2:** Follow-up of isolated optic neuritis according to serostatus (AQP4-Ab) and clinical feature of typical/atypical ON.

may play a crucial role in the genetic risk of NMO.<sup>[10,17-20]</sup> Cell-based assays are the most sensitive and specific methods for detecting AQP4-Ab in serum and might have given us more seropositivity in our study if all assays were cell-based.<sup>[21]</sup> To the best of our knowledge, there is no published literature regarding the presence of this antibody in patients presenting with clinically isolated optic neuritis in the Indian population.

Forty-three percent of all patients in our study showed atypical clinical features. Of all atypical ON cases, 22% were seropositive for AQP4-Ab. In cases of atypical ON, L. Piccolo *et al.*<sup>[22]</sup> have shown nearly 50% seropositivity. A study in South India showed seropositivity of 20% in patients with severe ON.<sup>[23]</sup> However, no study has analyzed the serostatus in terms of typical and atypical ON in the Indian subcontinent, though an increased incidence of atypical ON in the eastern hemisphere as compared to the western hemisphere has been mentioned in many studies and implicated in the worse visual outcome of optic neuritis.<sup>[4,24]</sup>

Patients with AQP4(+)<sup>AT</sup>ON in our study had a lower median age at onset (28 years) than that in another Asian study.<sup>[25]</sup> Though pediatric onset is rare, with <5% of cases presenting prior to age 18, two of our patients were below 18 years.<sup>[26]</sup> This could be due to differences in race and ethnicity. As seen with many autoimmune diseases, we saw a female preponderance here as well.<sup>[25,27]</sup> All seropositive ON cases in this study had atypical features and these patients were more likely to have bilateral disease with recurrence, poor visual outcome, posterior optic nerve involvement on MRI, and a greater likelihood of developing transverse myelitis.<sup>[25]</sup> Few cases of asymptomatic myelitis in AQP4-Ab positive ON have also been reported and hence an MRI spine in all seropositive ON patients may be advisable.<sup>[28]</sup> Lai *et al.*,<sup>[29]</sup> at the end of a 32-month follow-up,

found 18.2% of seropositive patients developing transverse myelitis and none in their seronegative patients.

Patients with AQP4(-)<sup>AT</sup>ON had a higher age at onset among all groups.<sup>[30]</sup> However, an Indian study showed lower mean age than this study, perhaps due to regional variation.<sup>[23]</sup> Additionally, many patients had bilateral involvement, relapses, and poor visual outcome. Few patients also developed transverse myelitis later and were diagnosed with seronegative NMO.<sup>[15]</sup> A south Indian study found 70% of NMO patients to be AQP4 negative.<sup>[27]</sup> Two of our seronegative atypical ON patients tested positive for myelin oligodendrocyte glycoprotein (MOG) antibody after the study period. They showed perineural optic nerve and optic sheath enhancement on MRI.<sup>[21]</sup> In a study by Piccolo *et al.*,<sup>[22]</sup> 35% of seronegative patients with bilateral relapsing disease developed NMO and 25% were found to be MOG-Ab positive. The etiology of AQP4(-)<sup>AT</sup>ON varies widely and may need different treatment modalities and a long follow-up. With the presence of new biomarkers such as MOG, glial fibrillary acidic protein (GFAP), and a host of others, we are better placed now to evaluate atypical ON and provide better outcomes.<sup>[31]</sup>

Patients with AQP4(-)<sup>T</sup>ON cases had good visual outcomes with few recurrences. This was similar to the ONTT study.<sup>[3]</sup> However, unlike the ONTT, we found that fewer patients developed MS. Pandit *et al.*<sup>[32]</sup> reported that ON in India appeared similar to that in the west, with nearly 50% developing MS in the long term within 5 years of disease onset. However, this was contrary to our findings. One of the reasons could be that our study design was different with a shorter follow-up.

Profound visual impairment on presentation was seen in all patients irrespective of serostatus, but on final follow-up, all

atypical ON [(AQP4(+)<sup>AT</sup> and AQP4(-)<sup>AT</sup>] cases had a poorer visual recovery as compared to the typical ON [AQP4(-)<sup>T</sup>] cases. This has been seen in other studies as well.<sup>[10,20,30]</sup> In a study by Kitley *et al.*,<sup>[33]</sup> 42% Afro-Caribbean, 16% Caucasians, and 12% of Asians had final uncorrected BCVA of <20/180 in seropositive cases. In our study, 60% of seropositive patients had a final BCVA of <20/200. This may be attributed to a combination of factors such as a smaller cohort of seropositive cases and differences in management.

Similar to another Indian report, all the three groups mostly presented to us with disc edema and lack of painful ocular movements.<sup>[34]</sup> This is unlike the ONTT study that was done on a Caucasian population.<sup>[3]</sup> As optic disc swelling has been identified with a lower risk of conversion to MS, the higher rate of papillitis in Asian patients is compatible with the lower rate of developing MS and corroborates our findings.<sup>[35]</sup> In the ONTT, 66.2% of VF defects were diffuse and 33.6% were localized.<sup>[3]</sup> However, central scotoma was the most common VF defect in all groups in this trial. Ishikawa *et al.*<sup>[25]</sup> had central scotoma predominantly in 46% seropositive and 61% seronegative cases. We could not assign a reason for this difference between studies.

The literature on the mean number of relapses of ON and time to its first relapse according to serostatus in patients presenting with ON is scant. However, recurrent ON was noted the most in seropositive cases.<sup>[23,25]</sup> Serum AQP4-Ab testing played a role in the early diagnosis of NMO/NMOSD even before multiple recurrences and the first episode of myelitis. AQP4(-)<sup>AT</sup>ON group also had many relapses, which were significantly more than AQP4(-)<sup>T</sup>ON in our study. Recurrent ON in AQP4(-)<sup>AT</sup>ON can be a predictor for developing NMO or MOG ON; thus, these patients need long follow-up.<sup>[23,30,36]</sup>

Laboratory blood tests may lead to the correct differential diagnosis and assessment of inflammation. Studies indicate that CRP and ESR can assess the level of inflammation, correlate with disease activity, and indicate the onset of neurological symptoms. Many studies have found significantly raised CRP and ESR in seropositive cases unlike in our study. This may be because patients with neurological symptoms as first presenting symptom were also included in the former.<sup>[37,38]</sup> Raised serum ANA was seen in few cases in all the three groups, though more in AQP4(+)<sup>AT</sup>ON cases (n = 2, 20%) [Table 1]. This often indicates immune dysregulation and has been found significantly raised in severe seropositive ON cases in few reports.<sup>[23]</sup> We found raised titers of ANA in a few AQP4(-)<sup>AT</sup>ON along with raised anti-dsDNA and anti-SSA. Patients with higher ANA titers are known to be more susceptible to autoimmune diseases.<sup>[39]</sup> Systemic autoimmune diseases such as SLE and SS have also been found to coexist with NMO.<sup>[21]</sup> This co-association could be due to common genetic factors, such as HLA and non-HLA genes.

The discovery of AQP4-Ab has changed the way demyelinating diseases are treated. Identifying this antibody in ON patients helps us to distinguish it from other conditions such as MS, particularly optico-spinal, which can also present with ON as the first symptom.<sup>[11,22]</sup> The differentiation is important because the treatment strategies, recovery, and prognosis of both are variable. ONTT protocols may not be appropriate for non-MS cases, which may require a different treatment strategy and aggressive management. To summarize,

our study extends our knowledge of optic neuritis and its natural course according to AQP4 serostatus and clinical findings in India. We found the frequency of AQP4 to be less than that reported in many Asian studies. There was a large percentage of atypical ON patients but unlike many other Asian studies, most were seronegative for AQP4.

Limitations: Nonuniform testing with immunofluorescence or cell-based assay for AQP4 Ab and lack of testing for MOG antibody due to unavailability during the major part of the study period was a major limitation. The number of cases found to be seropositive atypical ON was small, which can make it difficult to extrapolate the findings. AQP4 Ab titers at the time of recurrence of ON or occurrence of neurological symptoms could have provided more insight.

## Conclusion

AQP4 seropositive patients are more likely to have atypical features such as bilateral recurrent ON, marked swelling of the optic nerve, poor visual outcome, and an increased risk of transverse myelitis. Atypical clinical features were also seen in many AQP4 seronegative ON in our scenario, showing poor visual outcomes and a recalcitrant course.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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