

Clinical profile, imaging features and short term visual outcomes of Indian optic neuritis patients with and without seromarkers for myelin oligodendrocyte glycoprotein and neuromyelitis optica

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Purpose: To analyze clinical profile, imaging features, and short-term visual outcomes of optic neuritis patients in Indian population with and without seromarkers for myelin oligodendrocyte glycoprotein (MOG)/neuromyelitis optica (NMO). **Methods:** Electronic medical records of 203 optic neuritis patients who presented between June 2018 and December 2019 to the Neuro-ophthalmology services of a tertiary care center in India were retrospectively analyzed. **Results:** Of 203 patients, 57 patients (28.08%) were positive for MOG-antibody and 20 patients (9.85%) were positive for NMO antibody. 114 patients (56.16%) were double-negative (negative for both antibodies) and 12 patients (5.91%) were diagnosed as multiple sclerosis (MS). None of the patients had both antibodies. Mean age of presentation was 31.29 ± 1.035 years. There was female preponderance in NMO-optic neuritis (NMO-ON) and MS-optic neuritis (MS-ON) groups (1:5). Mean vision on presentation was worse ($\log\text{MAR } 1.570 \pm 0.863$) in NMO-ON group. The mean visual acuity showed statistically significant recovery ($\log\text{MAR } 0.338 \pm 0.639$) in the final follow-up in MOG-optic neuritis (MOG-ON) group. Multivariate logistic regression analysis revealed poor visual outcome in patients presenting with retrobulbar neuritis, optic disc pallor, bilateral sequential optic nerve involvement, and with positive NMO antibody. Optic neuritis patients presenting with disc edema associated with pain and positive for MOG antibody were found to have a better visual outcome. **Conclusion:** In this Indian optic neuritis cohort, the prevalence of MOG-ON was higher than NMO-ON. MOG-ON had a better visual outcome than NMO-ON. The incidence of MS-ON was less compared to the western literature. A significant number of patients (114 patients, 56.16%) were double negative for both seromarkers and yet had presented with optic neuritis with no clinical or imaging features suggestive of MS/MOG associated disease (MOG AD)/NMO spectrum disorder (NMO SD).

Key words: Double-negative optic neuritis, magnetic resonance imaging, multiple sclerosis -optic neuritis, myelin oligodendrocyte glycoprotein-optic neuritis, neuromyelitis optica-optic neuritis, optic neuritis, seromarkers

Optic neuritis (ON) is an inflammatory disorder of the optic nerve, which can be due to demyelinating, inflammatory, infectious, or noninfectious causes, the most common being multiple sclerosis (MS) as per the western literature.^[1] Optic neuritis treatment trial (ONTT) is the gold standard study that is followed globally by clinicians in treating ON. Typical ON can be of demyelinating or idiopathic etiology. ONTT had concluded that there can be 50% incidence of MS in ON patients by 15 years.^[2] ON in Asian population has been reported to be atypical unlike the western population.^[3-5] Discovery of serological biomarkers for ON has revolutionized the treatment protocols for ON. NMO antibody (NMO Ab) and myelin oligodendrocyte glycoprotein antibody (MOG Ab) can be seen in monophasic as well as polyphasic ON. The presence

of these seromarkers along with classical clinical features can help us effectively manage these distinct neuroinflammatory disorders.^[6] Since there is limited Indian literature regarding the association of these seromarkers with ON and their management paradigms, we performed this study.

Methods

Medical records of 203 ON patients who presented to the Neuro-ophthalmology services of a tertiary care eye center in India between June 2018 and December 2019 were retrospectively analyzed. All acute and chronic ON patients, with or without central nervous system (CNS) demyelination,

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with or without previous history of ON, who have undergone magnetic resonance imaging (MRI) brain and orbit and serum NMO and MOG Ab testing were included. Optic neuropathies of infectious, granulomatous, ischemic, hereditary, infiltrative, toxic, and traumatic etiologies were excluded. Cases were considered acute if the duration of presentation was less than 4 weeks from the onset of vision loss and chronic if it was more than 4 weeks.

All patients have undergone Snellen's visual acuity assessment, color vision assessment by Ishihara's pseudo isochromatic chart, detailed anterior and posterior segment evaluation by slit-lamp, and indirect ophthalmoscopy in each visit. All patients also had visual field testing by Humphrey's visual field analyzer-30-2 SITA standard program. Visual acuity recorded was converted to logarithm of minimum angle of resolution (logMAR) for statistical analysis. All patients had undergone serum NMO and MOG Ab testing by fixed cell-based indirect immunofluorescence assay. Commercially available CBIIFA (EUROIMMUN, Germany) kit provides simultaneous detection of both these seromarkers (NMO and MOG Ab). The sample dilution was 1:10 as per the recommended dilution for qualitative or semiquantitative evaluation. Patients with atypical ON features (painless ON, poor recovery ON, bilateral ON, elderly age) had additional blood workup including basic hemogram, rheumatoid arthritis factor (RA factor), antinuclear antibody (ANA), antinuclear cytoplasmic antibody (ANCA), angiotensin-converting enzyme, lysozyme, and Mantoux skin test. Magnetic resonance imaging (MRI) of brain and orbit were performed with 1.5 Tesla HDxt 16 channel GE system and reported at a single referral radiology center. Imaging findings like the presence of T2 hyperintense signals in the optic nerve and brain, location of the signal, and post-contrast enhancement were noted wherever available in the records. MRI whole spine screening was done for patients with myelitis symptoms and signs, recurrent ON, or as advised by the neurologist. All patients have undergone referral neurological evaluation and management. Based on the clinical characteristics, imaging features, associated brain/spine involvement, recurrence, sero positivity, and treatment response, we classified the study cohort into 4 groups.

- MOG positive-optic neuritis (MOG-ON)
- NMO positive-optic neuritis (NMO-ON)
- Double negative-optic neuritis (DN-ON): Optic neuritis with negative NMO and MOG antibody
- Multiple sclerosis-optic neuritis (MS-ON): Optic neuritis with MS features and negative for both antibodies

All patients with acute ON had intravenous methylprednisolone 250 mg every 6th hour for 3 to 5 days followed by oral steroids 1 mg/kg/body weight tapered over 11 days as per ONTT. Patients who had no visual recovery post steroid therapy by 2 to 4 weeks had received second-line treatment. Intravenous immunoglobulin (IVIG) 0.4 mg/kg/day for 5 days, Rituximab 1 g intravenous infusion 2 doses, 2 weeks apart, plasmapheresis in 3 sessions on alternative days were the commonly used second line of management. Subsequently, MOG-ON / NMO-ON / DN-ON groups were on maintenance therapy with one of these immunosuppressants like oral steroids 0.5–1 mg/kg/body weight/day, azathioprine 2.5 mg/kg/body weight/day, and mycophenolate mofetil 500–1000 mg/day. MS-ON

group had received immunomodulators like interferon beta-1a 30 µg/0.5 ml subcutaneous weekly injections or oral teriflunomide 7 mg per day.

Statistical analysis

Statistical analysis were conducted using SPSS V 23.0 software (Chicago, Illinois, United States). Categorical variables were reported as frequency and percentage while continuous variables as mean, standard deviation, median, and inter quartile range (IQR). Kolmogorov-Simonov test was used to validate the normality assumption for continuous variables. Chi-square test for independence or Fisher's exact test was used between two qualitative variables, as appropriate. Continuous variables were compared using Wilcoxon signed-rank test and Mann-Whitney U test. One-way ANOVA was used to compare the mean difference among three or more groups. Univariate binary logistic regression was used to assess the risk factors influencing visual outcome. All tests were two-tailed and a *P* value of less than 0.05 was considered significant.

Results

Of 203 patients, 57 patients (28.08%) were positive for MOG Ab, 20 patients (9.85%) were positive for NMO Ab, 114 patients (56.16%) were double-negative, and 12 patients (5.91%) were double negative and clinically suspected MS (5.91%). Their clinical characteristics were further analyzed in four subgroups. None of these patients were positive for both antibodies. Of 203 patients, 43 patients were less than 18 years of age. 109 patients were acute cases and 94 patients were chronic cases. 113 patients had undergone plain-MRI brain and orbit and 90 patients had Gadolinium-enhanced MRI brain and orbit. Clinical characteristics and neuroimaging features of all these four subgroups are enumerated in Tables 1 and 2.

MOG-ON: This group included 79 eyes of 57 patients. Mean age of presentation was 29.6±15.4 years. 17 patients (29.8%) were less than 18 years of age. Mean follow-up was 5.5 ± 9.9 months (median 2 months, range 0.5–60). Both sexes were equally affected (28 male and 29 female). 58 eyes (73.4%) had painful vision loss. Bilateral simultaneous vision loss was noted in 34 eyes of 17 patients (43%), 6 eyes of 3 patients (7.6%) had bilateral sequential vision loss, and subclinical fellow eye involvement was seen in 5 eyes of 5 patients (6.32%). Mean vision on presentation was logMAR 1.316 ± 0.962. On presentation, 35 eyes had disc edema (44.9%), 6 eyes (7.7%) had retrobulbar neuritis, and 38 eyes (48.1%) had disc pallor. Most common visual field defect noted was generalized constriction in 18 eyes (22.8%), followed by central or ceaco-central defects, inferior altitudinal defects, temporal defects, three quadrant defects, superior defects, and enlarged blind spot. MRI Brain was normal in 44 patients (77.2%); 13 patients (22.8%) had T2 hyperintense signals in supratentorial, infratentorial, brainstem, and thalamic regions. MRI of orbit revealed T2 hyperintense signals in the optic nerves in all 57 patients and contrast enhancement was noted in 27 patients. 53 patients (92.9%) had anterior short segment of the optic nerve involvement and 6 patients (10.52%) had optic nerve sheath thickening and periorbital fat enhancement. 7 patients had MRI whole spine screening of which 1 patient had longitudinally extensive transverse myelitis lesions (LETM) involving cervicothoracic cord. 46 of 57 patients who were suspected to have atypical ON had additional blood workup, of which 3 patients were

Table 1: Comparison of clinical parameters in MOG-ON/NMO-ON/Double negative-ON/MS-ON groups

Characteristics	MOG-ON	NMO-ON	Double negative-ON	MS-ON	P
	n=57 patients	n=20 patients	n=114 patients	n=12 patients	
Age (years)	29.6±15.4	30.06±14.72	32.37±14.82	31.08±9.75	0.17
Gender Male: Female	1:1.03	1:5.66	1:1.11	1:5	0.01
Optic neuritis					
Mean vision at presentation (logMAR)	1.316±0.962	1.570±0.863	0.814±0.926	0.355±0.797	0.01
Pain, no of eyes/total (%)	58/79 (73.4)	4/26 (15.4)	70/178 (39.3)	7/9 (77.8)	<0.05
Bilateral simultaneous presentation, no of eyes/total (%)	34/79 (43.0)	12/26 (46.2)	96/178 (53.9)	0 (0.0)	0.01
Sequential, no of eyes/total (%)	6/79 (7.6)	0 (0.0)	13/178 (7.3)	0 (0.0)	0.01
Subclinical other eye involvement, no of eyes/total (%)	5/79 (6.32)	3/26 (11.53)	17/178 (9.5)	0 (0.0)	0.56
Recurrence, no of patients/total (%)	11/57 (19.3)	8/20 (40)	14/114 (12.2)	2/12 (16.6)	0.06
Vision at last follow-up (logMAR)	0.338±0.639	1.01±0.942	0.511±0.707	-0.013±0.032	<0.05
Disc findings					
Edema, no of eyes/total (%)	35/79 (44.9)	2/26 (7.7)	31/178 (17.4)	1/9 (11.1)	0.02
Retrobulbar Neuritis, no of eyes/total (%)	6/79 (7.7)	8/26 (27.1)	20/178 (11.2)	1/9 (11.1)	0.01
Pallor, no of eyes/total (%)	38/79 (48.1)	16/26 (61.5)	127/178 (71.3)	7/9 (77.7)	0.04
Other than optic nerve involvement					
CNS symptoms, no of patients/total (%)	7/57 (12.7)	1/20 (5)	4/114 (3.4)	2/12 (16.6)	
Myelitis, no of patients/total (no of eyes/total (%)	1/57 (1.8)	1/20 (5)	1/114 (0.09)	2/12 (16.6)	

Table 2: MRI characteristics of optic neuritis patients in MOG-ON/NMO-ON/Double negative-ON/MS-ON groups

	MOG-ON	NMO-ON	Double negative-ON	MS-ON	P
MRI Brain					
Normal, No of patients/total (%)	44/57 (77.2)	12/20 (60)	83/114 (72.8)	1/12 (8.3)	<0.05
Abnormal, no of patients/total, (%)	13/57 (22.8)	8/20 (40)	30/114 (26.5)	11/12 (91.7)	
Site involved	Supratentorial infratentorial brainstem, thalamus	Subcortical, deep white matter non-MS lesion, brainstem	Supratentorial, infratentorial, periventricular region Non-MS lesions	Periventricular, cortical and juxta cortical lesions, Supratentorial, Infratentorial lesions	
MRI Orbit					
T2W hyperintense signal, no of patients/total (%)	57/57 (100)	20/20 (100)	56/114 (49.1)	4/12 (33.3)	
Thinned out optic nerves	-	-	57/114 (50)	-	
Site-Anterior short segment of optic nerve	53/57 (92.9)	3/20 (15)	47/56 (83.9)	4/4 (100)	
Site-Posterior long segment (chiasm, retrochiasm) involvement	4/57 (7.01)	17 (85) Chiasm -8 Retrochiasm and tract -9	9/56 (16.1)	-	
Optic nerve sheath thickening	6/57 (10.52)	-	1/114 (0.87)	-	
MRI spine					
Normal, no of patients/total (%)	6/7 (85.7)	0/1 (0)	10/17 (58.8)	2/8 (25)	
Abnormal	1/7 (14.28)	1/1 (100)	7/17 (41.2)	6/8 (75)	
LETM*	1	1	5	1	
STM†	-	-	2	5	

*LETM - Longitudinally extensive transverse myelitis defined as signals involving three or more spinal segments. †STM - Short segment transverse myelitis defined as signals involving one or less than three spinal segments

positive for ANA and 1 patient was positive for human leukocyte antigen B27 (HLA B27). 28 of 57 patients had cerebrospinal fluid (CSF) analysis and 24 patients had normal CSF, 3 patients had oligoclonal band (OCB), and 1 patient had MOG antibody in CSF. 21 eyes of 16 patients were lost to follow-up post-treatment. 63 eyes of 46 patients (87.5%) were treated with intravenous methylprednisolone followed

by oral steroids taper. 12 eyes of 7 patients (16.6%) with poor response to steroids therapy received second-line treatment like IVIG (3 eyes of 2 patients), rituximab (8 eyes of 5 patients), and plasmapheresis (1 eye of 1 patient). 39 eyes of 29 patients were on immunosuppressants; azathioprine and mycophenolate mofetil were commonly used immunosuppressants. Recurrent ON was noted in 11 patients (19.3%), acute demyelinating

encephalomyelitis was noted in 7 patients (12.73%), and transverse myelitis in one patient (1.8%). Mean visual acuity in the final follow-up was logMAR 0.338 ± 0.639 which was statistically significant ($P < 0.05$).

NMO-ON: 26 eyes of 20 patients with positive NMO antibody were included in this group. Mean age of presentation was 30.06 ± 14.72 years. 5 patients (25%) were less than 18 years of age. Mean follow-up was 9.2 ± 15.3 months (median 6, range 0.5–60). This group of NMO-ON revealed female preponderance (3 males, 17 females). Bilateral simultaneous involvement was noted in 12 eyes of 6 patients (46%) and subclinical fellow eye involvement in 3 eyes of 3 patients (11.53%). 22 eyes (84.6%) had painless attacks. Mean vision on presentation was logMAR 1.570 ± 0.863 . On presentation, the optic disc was pale in 16 eyes (61.5%), edematous in 2 eyes (7.7%), and 8 eyes (27.1%) presented as retrobulbar neuritis. MRI Brain was normal in 12 patients (60%). 8 of 20 (40%) patients had hyperintense brain signals, located in subcortical deep white matter areas in 5 patients and in the pontine region in 2 patients. Incidentally, a superior cerebellar arachnoid cyst and a chronic centrum semiovale infarct each were observed in two patients. MRI orbit showed contrast-enhancing hyperintense T2 optic nerves signals in 10 patients. Chiasmal thickening and enhancement was noted in 8 patients (40%) and 9 patients (45%) had posterior long segment involvement of optic nerve. MRI whole spine screening was done in a patient who had associated myelitis symptoms, which showed LETM lesion involving C2-C7 segment of the spinal cord. 17 of 20 patients had additional blood workup for atypical ON, of which 1 patient was ANA positive. 11 patients had undergone CSF analysis and were found to be normal. 19 eyes of 14 patients (79.2%) had received intravenous methylprednisolone followed by oral steroids. 9 eyes of 6 patients (34.6%) received second-line treatment with IVIG (2 eyes of 1 patient) and rituximab (7 eyes of 5 patients). 17 eyes of 13 patients were on azathioprine. 8 patients (40%) had recurrent ON and 1 patient (5%) had associated CNS symptoms like tingling, numbness, and paraesthesia of limbs, and 1 patient (5%) had myelitis symptoms. The mean visual acuity in the final follow-up of 15 patients was logMAR 1.01 ± 0.942 .

MS-ON: 12 patients with features of Multiple sclerosis as per McDonald's MS diagnostic criteria were included in this group.^[7] 6 of 12 patients had acute ON, 3 patients had recurrent ON attacks, and 3 patients were referred by neurologists for neuroophthalmic evaluation. Mean age of presentation was 31.08 ± 9.75 years. None of the patients were less than 18 years in this group. Mean follow-up was 4.6 ± 4.3 months (median 4, range 1–12). 10 of 12 patients were female. Mean vision on presentation was logMAR 0.355 ± 0.797 . 7 eyes had painful unilateral vision loss. MRI Brain showed classical MS lesions in 11 patients (91.66%). These T2 hyperintense lesions were located in periventricular, cortical, juxtacortical, supratentorial, and infratentorial regions in brain. MRI orbit showed T2 hyperintense signals and contrast enhancement in the optic nerve in 4 patients. All 4 patients had short segment T2 hyperintense signals in the anterior optic nerve. 8 patients had undergone MRI whole spine screening of which 5 patients had short lesions involving less than 3 segments of the cervical cord, 1 patient had longitudinally extensive signal extending from C2-C7, and 2 patients had normal spine. 9 of 12 patients had CSF analysis. 3 patients had OCB in CSF, but 6 patients

were lost to follow-up. 9 patients (9 eyes) with ON had received intravenous methylprednisolone followed by oral steroids. 8 patients (8 eyes) were on immunomodulators like interferon beta-1a or teriflunomide and 1 patient (1 eye) was on mycophenolate mofetil. 2 patients had recurrent ON, 2 patients had associated CNS symptoms like tingling, paraesthesia in lower limbs, ataxia, and paraparesis. Mean visual acuity in the final follow-up was logMAR -0.013 ± 0.032 .

Double negative-ON: DN-ON group included 178 eyes of 114 patients. Mean age of presentation was 32.38 ± 14.82 years. 21 patients (18.4%) were less than 18 years of age. Mean follow-up was 7.6+11 months (median 3, range 0.25–60). Both sexes were equally affected in this group (54 males and 60 females). Mean vision on presentation was logMAR 0.814 ± 0.926 . Bilateral simultaneous ON was noted in 96 eyes of 48 patients (53.9%) and subclinical fellow eye involvement was seen in 17 eyes of 17 patients (9.5%). 70 eyes (39.3%) had painful vision loss. On presentation, optic discs were pale in 127 eyes (71.3%), edematous in 31 eyes (17.4%), and 20 eyes (11.2%) presented as retrobulbar neuritis. MRI Brain was normal in 83 patients (72.8%), 30 patients (26.3%) had T2 hyperintense lesions in supratentorial, infratentorial, and periventricular regions, but were not classical MS lesions as per McDonalds criteria. One patient had incidental acoustic schwannoma and another had ischemic brain changes. MRI Orbit showed T2 hyperintense signal in optic nerves in 56 patients (49.12%), 57 patients (50%) had thinned optic nerves, and imaging details were not available in one patient. Of 56 patients with T2 hyperintense optic nerve signals, 46 patients had contrast enhancement. 47 out of 56 patients (83.9%) with optic nerve signals had short segment optic nerve involvement and 9 patients (16.1%) had long posterior optic nerve segment involving chiasm and one patient had lesions extending up to the optic tract. Periopic nerve sheath thickening was noted in 1 patient (0.8%). 17 patients had MRI whole spine screening, 5 patients had LETM lesion involving cervicothoracic cord, and 2 had short segment signals in thoracic region. Of 105 patients who had additional blood workup, 4 were positive for RA factor, 3 patients were positive for ANA, 3 were positive for P-ANCA, and 1 patient was positive for antiphospholipid antibody. Of 50 patients who had CSF analysis, 45 had normal CSF analysis. CSF proteins were raised in 2 patients, OCB was positive in one patient, and NMO Ab was detected in CSF in 2 patients. However, none of these patients had clinical or imaging features suggestive of MS/NMO SD. 123 eyes of 77 patients (76.4%) were treated with intravenous methylprednisolone followed by oral steroids and 6 patients (8 eyes) had received only oral steroids. 15 eyes of 8 patients (12.39%) had second-line treatment, 6 eyes of 3 patients had IVIG, and 9 eyes of 5 patients had rituximab. 12 eyes of 8 patients were on immunosuppression, either azathioprine or mycophenolate mofetil, 4 eyes of 3 patients had received interferon beta-1a, and 15 eyes of 9 patients were on oral steroids only. In this group, 14 patients (12.1%) had recurrent ON. Associated CNS symptoms like paraesthesia, paraparesis, and sensory disturbances in lower limbs were noted in 4 patients (3.4%) and transverse myelitis in 1 patient (0.09%). Mean vision in the final follow-up of 70 patients was logMAR 0.511 ± 0.707 , which was statistically significant ($P < 0.05$).

Discussion

ON in Indian population^[5] has not been reported extensively in literature. Unlike the Western literature, we have limited data about the natural behavior of ON, its association with CNS neuro inflammatory diseases, and the prevalence of seromarkers in Indian ON.^[8] Novel discoveries of these biomarkers, namely, the NMO Ab and MOG Ab, have tossed our understanding of the spectrum of demyelinating diseases. Literature states that the prevalence of these autoantibodies is higher in the nonwhite population.^[3,9] In this Indian cohort, we found that the prevalence of MOG-ON (28.08%) was higher than NMO-ON (9.85%) and 5.91% ON patients were diagnosed with MS. We had a significant number of DN-ON patients (56%) similar to Mayo clinic report by Jitrapaikulsan *et al.*,^[10] although they had analyzed only recurrent ON patients. The clinical characteristics of these groups MOG-ON, NMO-ON, DN-ON, and MS-ON were compared and analyzed statistically [Table 1]. Our cohort had wider age range of 5–72 years, including both adult and pediatric age groups. Median age was in 2nd–3rd decade in all these groups similar to other studies.^[9,10] Literature shows that the prevalence of MOG-ON is higher in pediatric patients.^[9] In our cohort, MOG-ON group had 29.8% and NMO-ON group had 25% pediatric age group patients. Our pediatric ON groups need further analysis and evaluation in the future as many were lost to follow-up. MOG-ON and DN-ON groups had no sex predilection, unlike the NMO-ON and MS-ON groups which showed strong female preponderance, similar to literature.^[4,11,12] Mean vision on presentation was worse in NMO-ON group compared to MOG-ON and DN-ON groups. Ishikawa *et al.*^[11] reported MOG-ON presented frequently with disc edema and painful ocular movements, similar to our results [Fig. 1]. Optic disc pallor was noted in these patients probably due to chronic presentation, subclinical ON, or recurrent neuritis. As per ONTT (1991),^[2] pain on ocular movements was noted in 92.2%; however, previous Indian studies have reported lesser association of pain (25%).^[5] Interestingly we found a higher rate of painful vision loss in MOG-ON group. The pain on ocular movements could be explained by inflammation of the optic nerve sheath and periorbital fat around the optic nerves, which is pathognomonic of MOG-AD (associated disease).^[12] Jitrapaikulsan *et al.*^[10] reported MOG-ON have more bilateral simultaneous presentation than NMO-ON or DN-ON group. Our study showed more bilateral simultaneous

presentation (53%) in the DN-ON group than NMO-ON and MOG-ON groups (46% and 43%, respectively).

We observed, MOG-ON had more short optic nerve segment involvement and NMO-ON had long optic nerve segment involvement in MRI brain and orbit similar to literature^[13] [Fig. 2]. MRI Brain lesions were noted in higher proportion in MS-ON patients (91.7%) and NMO-ON patients (40%). Ishikawa *et al.*^[12] reported MOG-ON had optic nerve lesions (91%) and few brain (2%) and spine (8%) lesions. However, in our cohort, 22.8% of MOG-ON group and 26.5% of DN-ON group had brain lesions on MRI [Table 2]. Salama^[14] and Kim *et al.*^[15] have reported NMO-ON have higher spinal cord involvement than MOG-ON. Jarius *et al.*^[16] reported MOG-ON to have more relapsing attacks with or without myelitis in long-term follow-up. In our study, one MOG-ON patient had presented with LETM. This suggests that MOG-AD does exhibit overlapping features with MS or NMOSD and thus we need prospective trials to understand the natural course of these diseases. CSF analysis in MOG-AD is classically different from that of MS as reported by Jarius *et al.*^[17] In our cohort, 33.3% of MS-ON group had OCB in CSF analysis; however, 10.7% of MOG-ON group and 2% of DN-ON group had OCB in CSF.

ONTT recommends intravenous methylprednisolone therapy followed by oral steroids as first-line treatment for acute ON. Stiebel Kalish *et al.*^[18] also confirmed that acute treatment in MOG-ON and NMO-ON with intravenous steroids is associated with better visual recovery and delay in initiation of intravenous steroids is detrimental to visual recovery. Patients with poor recovery with initial steroid therapy are recommended for second-line treatment with plasmapheresis, IVIG/rituximab, etc.,. Several studies recommend early plasmapheresis for better visual outcome in NMO-ON, but there is less clarity in MOG-ON.^[19,20] Li *et al.*^[21] have reported high-dose steroids in addition to IVIG was superior to only steroid therapy in patients with poor recovery. In our cohort, second-line treatment was with IVIG and rituximab. Maintenance therapy depends on the underlying cause of optic neuritis—MS/NMO SD/MOG AD. Long-term immunosuppression is recommended for NMO-ON and relapsing MOG-ON^[22,23]. The traditional choice of immunosuppressants are azathioprine, mycophenolate mofetil, and rituximab.^[24] Although rituximab is used widely for NMOSD, it is not officially an FDA approved drug for the disease. Recently, FDA has approved three

Table 3: Logistic regression analysis of factors influencing visual outcome

Visual acuity better than 0.5 logMAR (6/18 IN Snellen chart)		95% Confidence interval		P
Variable	Odds ratio	Lower limit	Upper limit	
Pain	2.24	1.191	4.21	0.01
Positive MOG antibody	2.2173	1.045	4.695	0.04
Disc edema	4.561	1.786	11.648	<0.05
Visual acuity worse than counting finger (CF)				
Vision on presentation <=CF	2.624	1.685	4.085	0
RBN*	4.632	1.202	17.856	0.03
Disc pallor	3.937	1.298	11.942	0.01
Bilateral sequential	3.92	1.084	14.183	0.04
Positive NMO antibody	4.406	1.444	13.447	<0.05

*Retrobulbar neuritis

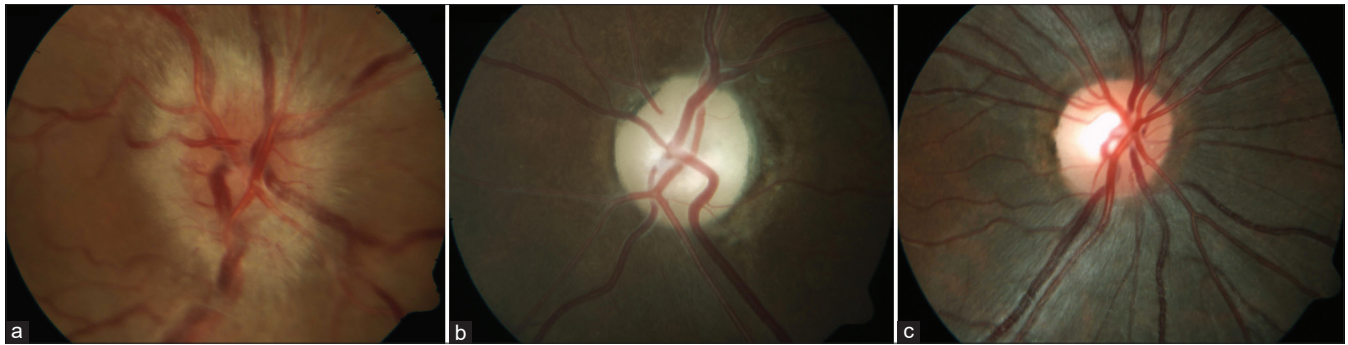


Figure 1: Clinical photographs of disc appearance in optic neuritis. a) Disc edema. b) Disc pallor. c) Retrobulbar neuritis

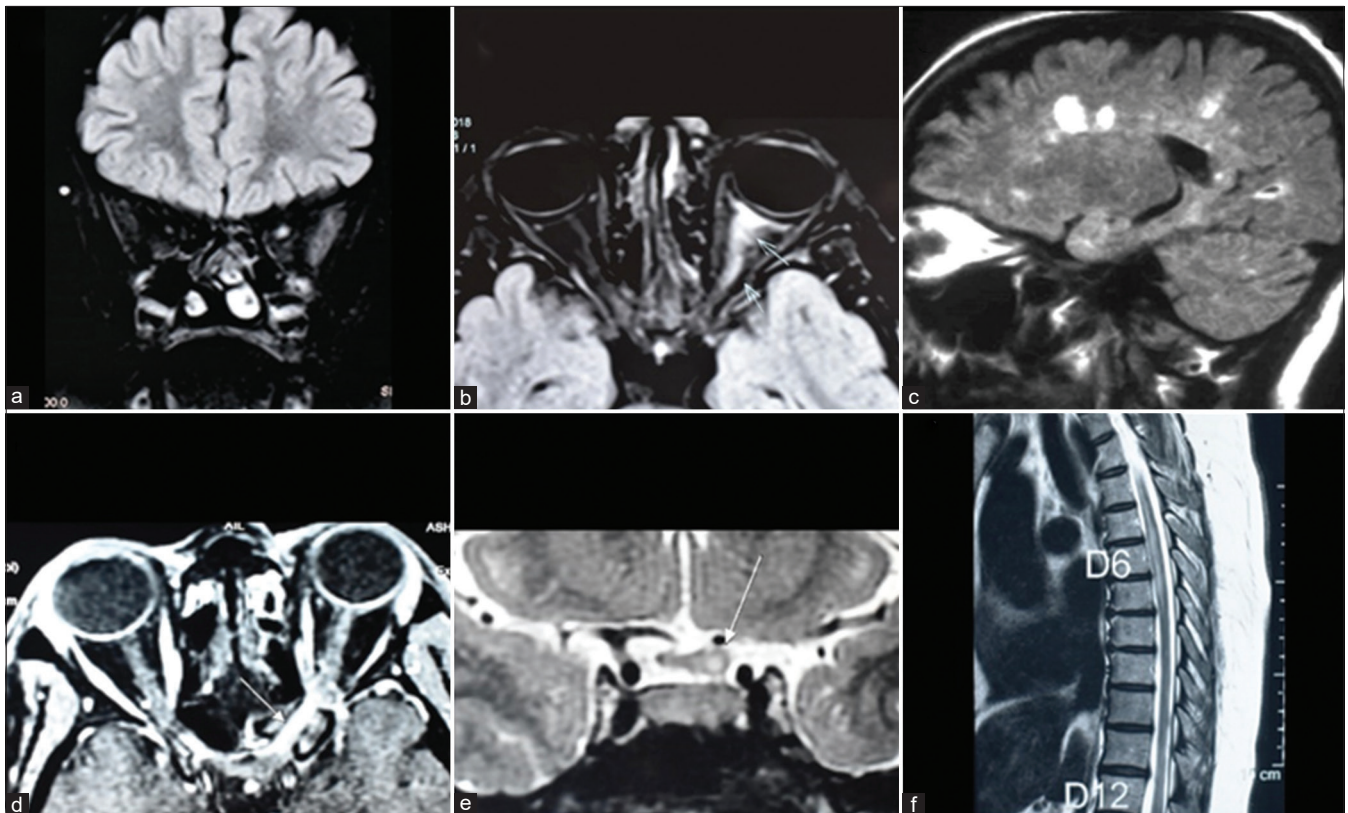


Figure 2: MRI features: a) MRI orbit coronal STIR sequence showing hyperintense signal in the left intraorbital optic nerve. b) Axial post-contrast T1 section showing left perioptic haziness and thickening in retrobulbar segment of the optic nerve. a and b images were noted in MOG-ON. c) Brain sagittal T2 FLAIR sequence showing periventricular ovoid hyperintense signal suggestive of Dawson's finger in a patient with MS. d) Axial post-contrast T1 section of orbit showing enhancement in left intracranial optic nerve in NMO-ON. e) Coronal T2WI showing bulky left half of the chiasm with T2 hyperintense signal in NMO-ON. f) MRI spine sagittal section showing T2 hyperintense signal from D2-D7 suggestive of longitudinally extensive transverse myelitis

drugs for NMO Ab positive NMOSD, namely, eculizumab, inebilizumab, and satralizumab. In our country, these drugs are used restrictedly due to poor availability and higher cost.^[25] Similarly, more targeted therapies for MOG AD are expected to evolve in future. Disease-modifying therapy (DMT) like interferon and glatiramer acetate should be considered for ON with MS features only. It is better to avoid DMT for all poor recovery ON without clear MS features, as it is proven to worsen NMOSD and ineffective in MOG-ON.

Multivariate logistic regression analysis was done to identify the factors affecting the visual outcome [Table 3].

The factors affecting visual outcome better than 6/18, which were statistically significant, were the presence of pain, disc edema, and positive MOG Ab. It is well reported in the literature that MOG-ON patients have good visual recovery and NMO-ON patients have poor visual recovery.^[26-28] Patients presenting with bilateral sequential involvement, counting fingers close to face vision, retrobulbar neuritis, optic disc pallor and with positive NMO Ab were all associated with poor visual outcome. In this cohort, 56.16% patients were in DN-ON group. These patients had more bilateral optic nerve involvement, were negative for NMO and MOG Ab, and had no classical clinical or imaging features of MS/NMOSD/

MOGAD. This DN-ON group needs long-term follow-up to understand their natural disease course.

There are many limitations in our study like it being retrospective in nature, with no control group, lack of standardized treatment protocol for all patients due to varied duration of presentation, lack of long term follow up. However, this study can add a significant value to the literature regarding biomarkers prevalence in Indian ON patients.

Conclusion

In this Indian ON cohort, the prevalence of MOG-ON was higher than NMO-ON. The incidence of MS was less compared to western literature. MOG-ON patients had good post-treatment visual recovery. Patients with profound vision loss, retrobulbar neuritis or pale disc, bilateral sequential involvement on presentation and patients with positive NMO Ab had poor visual outcomes. There was a significantly higher number of double-negative optic neuritis (DN-ON) patients in this study population, which needs more careful follow up to look for their subsequent seroconversion to MOG/NMO antibody or develop MS or await a newer antibody to bloom in this part of the World!!!.

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Conflicts of interest

There are no conflicts of interest.

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