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Clinical characteristics and outcomes of myelin oligodendrocyte glycoprotein antibody-seropositive optic neuritis in varying age groups: A cohort study in China

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ABSTRACT

Purpose: To investigate the clinical characteristics and outcomes of myelin oligodendrocyte glycoprotein antibody-seropositive optic neuritis (MOG-ON) in patients with varying ages of onset in China.

Methods: Patients displaying symptoms of MOG-ON were recruited from the Neuro-ophthalmology Department in the Chinese People's Liberation Army General Hospital from January 2016 to May 2018. They were assigned to one of three subgroups based on age of onset: pediatric (< 18 years), young (18–46 years), and middle-aged (> 46 years) MOG-ON.

Results: 110 patients (188 eyes) were assessed, including 58 pediatric (52.7%), 34 young (30.9%), and 18 middle-aged (16.4%) patients. Of the pediatric patients, 93.9% had good recovery of visual acuity (≥0.5) compared with 79.7% of young patients and 66.7% of middle-aged patients ($p < .001$). The annual relapse rate was lower in the pediatric group than young and middle-aged groups (0.32 ± 0.50 vs 0.73 ± 0.87 vs 0.49 ± 1.08, $p = .036$). Six children (10.3%) were diagnosed with acute disseminated encephalomyelitis, while seven young patients (20.6%) were diagnosed with aquaporin-4 antibody seronegative neuromyelitis optica spectrum disorder upon follow-up. The average peripapillary RNFL and macular GCIPL thicknesses were not statistically different between subgroups ($p = .996$, $p = .608$). Overall, MRIs of the optic nerve showed perineural enhancement in 52.0% of patients and longitudinal extensive involvement in 87.7%. MRIs also revealed a greater proportion of pediatric patients with intracranial optic nerve involvement than in the other two subgroups (45.4% vs. 21.2% vs. 36.7%, $p = .014$).

Conclusion: Pediatric ON was the most common MOG-ON subgroup. Pediatric patients had different clinical features, including better recovery of visual acuity, lower annual relapse rate, and more intracranial optic nerve involvement than young and middle-aged patients. Additionally, age of onset may be a potential predictor for determining visual prognosis with MOG-ON.

1. Introduction

Optic neuritis (ON) is an inflammatory, demyelinating disease of the optic nerve. Much of our understanding of ON stems from the Optic Neuritis Treatment Trial (ONTT), a well-known, multicenter, randomized control trial which focused on young adults between the ages of 18 and 46 years [1]. ON can occur as an idiopathic, isolated event, however it also occurs in conjunction with central nervous system demyelinating diseases, such as neuromyelitis optica spectrum disorder (NMOSD), multiple sclerosis (MS), and acute disseminated encephalomyelitis (ADEM) [2,3]. The aquaporin-4 antibody (AQP4-Ab) is a marker for the diagnosis and prognosis of ON. Additionally, recent findings have suggested the potential value of the myelin oligodendrocyte glycoprotein antibody (MOG-Ab) to differentiate between ON phenotypes, further expanding the possibility of utilizing this technique for the diagnosis of this disease [4].

In Caucasians, detection of AQP4-Ab and MOG-Ab may be less common than previously reported in isolated ON. [5–7] Frequency of MOG-Ab detection was rare (1.7%) in ONTT, and AQP4-Ab was not found at all in ONTT patients. [7] However, some studies have suggested the association of MOG-Ab seropositivity with recurrent ON attacks that can lead to significant visual loss [8]. Chen et al. [9] found that the majority of MOG-Ab-seropositive ON (MOG-ON) patients displayed significant recovery and retained long-term visual function.

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Despite these findings, there are few large-scale studies of MOG-ON, and the clinical phenotypes are poorly defined [8]. [9] To date, the clinical characteristics and prognosis of MOG-ON and their relation to age of onset is still unclear in China. Therefore, this cohort study recruited Chinese patients with MOG-ON onset occurring during one of three age ranges: pediatric, young, and middle-aged. Following patient recruitment, clinical characteristics and prognosis were assessed.

2. Materials and methods

2.1. Patient enrollment

Clinical data were retrospectively collected from hospitalized patients diagnosed with MOG-ON at the Neuro-ophthalmology Department of the Chinese People's Liberation Army General Hospital (PLAGH) between January 2016 and May 2018. This study protocol was approved by the Ethics Committee at the Chinese PLAGH and met the tenets of the Declaration of Helsinki as well as applicable Chinese laws. Informed consent was obtained from patients and their parents. The patients with ON at acute stage were treated with intravenous methylprednisolone (20 mg/kg/day for children, 1 g/day for adults) for 3–5 days, followed by a taper of oral prednisone (starting dose 1 mg/kg/day) with varying durations, based on the ages of and recovery from optic neuritis. Follow-up data was obtained through clinical examinations during return visits, and surveys via telephone with patients and their parents. Twenty of the included patients were reported in an earlier series of 65 demyelinating ON [10]. All patients were followed a minimum of 6 months. The main follow-up data included BCVA, relapse condition. If we cannot get the BCVA or relapse condition, this patient is belonging to incomplete patient clinical follow-up data. Clinical routine visits at 3 months,6 months,12 months and if the patients relapsed.

2.2. Diagnostic criteria

ON was diagnosed in accordance with the ONTT guidelines [1]. Relapse of optic neuritis was defined as any repeat attack at least 30 days after the initial attack. The detailed inclusion criteria were as follows: (1) the patient presented with acute loss of visual acuity or visual field irrespective of eye pain, (2) the serum MOG antibody was positive, and (3) at least one visual abnormality of visual field defect, abnormal visual evoked potential, and/or relative afferent pupillary defect.

Exclusion criteria included (1) the presence of ametropia, glaucoma, anterior segment, retinal, or macular diseases, (2) any other type of optic neuropathy, such as vascular, hereditary, toxic, metabolic, infiltrative, or compressive optic neuropathy, (3) the presence of craniocerebral lesions other than those from demyelinating diseases involving the optic chiasm or optic pathway downstream of the optic chiasm and optic cortex, and (4) incomplete patient clinical follow-up data.

2.3. Laboratory examinations

Serum and cerebrospinal fluid (CSF) samples were obtained from each patient at maximum one month following the ON attack. Serum samples were tested for the presence of MOG and AQP4 antibodies using a fixed cell-based assay (Euroimmun, Lübeck, Germany) [10]. Based on the age of disease onset, MOG-ON patients were categorized as pediatric (< 18 years) and adult (≥ 18 years) groups. Then, we had divided adult group into the younger age group (18–46 years) and the older age group (> 46 years). In order to facilitate the description, the former group is called young (18–46 years) for short, the latter group is called middle-aged (> 46 years) for short, and placed in the according subgroup.

All patient sera were tested for auto-antibodies, including antinuclear antibody (ANA), human leukocyte antigen-B27 (HLA-B27), anti-thyroglobulin antibodies (ATAs), anti-thyroid peroxidase autoantibody (anti-TPOAb), anti-Sjögren's-syndrome-related antigen A (SSA), anti-Sjögren's-syndrome-related antigen B (SSB), anticardiolipin antibodies (ACLs and b2-GPI), anticentromere antibody (ACA), antineutrophil cytoplasmic antibody (ANCA), rheumatoid factor (RF), and antiperinuclear factor (APF) in the Examination Center for Biomedical Research of PLAGH. The CSF was tested for white blood cell count, and protein and IgG levels. Measurements were considered elevated if white cell count was > 10/μl, protein level > 400 mg/L, and IgG level > 3.4 mg/dL.

2.4. Neuro-ophthalmology examinations

Best corrected visual acuity (BCVA) was used as the main outcome, and was determined using the standard vision logarithm table at a distance of 5 m. Those unable to read any letters at 1 m were further examined using finger counts, hand movements, or perceived light. BCVAs were transformed into values representing the logarithm of the minimum angle of resolution (LogMAR). Among these values, counting the number of fingers held before the eye was transformed as a LogMAR value of 1.85, hand movement as a LogMAR value of 2, light perception as a LogMAR value of 2.7, and failure to perceive light as a LogMAR value of 3.0 [11]. A good visual outcome was defined as a final BCVA of 0.5 or better (LogMAR 0.3) and a poor outcome was defined as a BCVA of < 0.1 (LogMAR 1.0).

Peripapillary retinal nerve fiber layers (pRNFLs) and macular ganglion cell-inner plexiform layers (mGCIPLs) were assessed at least 6 months post ON attack using high-definition spectral domain optical coherence tomography (SD-OCT: Carl Zeiss Meditec, Dublin, CA, USA). All enrolled patients underwent orbital magnetic resonance imaging (MRI) with T2 weighted image and gadolinium-enhanced T1 sequences. The anterior visual pathways were divided into five segments: orbital, canalicular, intracranial, and optic chiasm and tract [12]. A longitudinally extensive optic nerve lesion indicates that the lesion involved more than half of the segments of the whole optic nerve. Head or spinal MRIs were performed in patients with myelitis or systemic symptoms.

2.5. Statistical analysis

Demographic parameters were described and compared between the three different age-based cohorts. Statistical analyses were conducted using SPSS 20.0 software (IBM Corporation, New York, USA). A one-way ANOVA test was used for parametric comparisons among the three subgroups, while the Kruskal Wallis Test was used for non-parametric comparisons. Categorical data were analyzed using R × C table Chi-square tests or Fisher's exact tests where appropriate. All probability values were two-tailed and considered to be significant at $p < .05$.

3. Results

3.1. Demographics and clinical characteristics

Table 1 summarizes the demographics and clinical characteristics of the MOG-ON patients enrolled in the present study. A total of 110 patients (154 affected eyes at first ON attack and 188 affected eyes at follow-up time) were assessed in this study cohort, including 58 pediatric (52.7%), 34 young (30.9%), and 18 middle-aged (16.4%), of which 63 were female (57.3%). The mean and median age of onset was 23.3 ± 16.7 years and 15 years (range of 2–67 years) respectively. At the initial attack, 44 patients (40.0%) experienced bilateral involvement, while 66 (60.0%) experienced unilateral involvement. The follow-up duration ranged from 6 to 217 months, with a mean time of 36.59 ± 39.02 months. All patients underwent serum MOG-Ab and AQP4-Ab testing, revealing 110 patients with MOG-ON. No patients

Table 1
Patient demographics and clinical characteristics in this MOG-ON cohort.

	Total	Percentage (%)
Number of patients (eyes)	110 (188)	
Age of onset, year		
Mean	23.3 ± 16.7	
Median (range)	15 (2–67)	
Age groups, year		
< 18	58	52.7
18–46	34	30.9
> 46	18	16.4
Sex		
Female	63	57.3
F/M ratio	1.3:1	
Follow-up, month		
Mean ± SD	36.59 ± 39.02	
Median (range)	24(6–217)	
Experience		
Bilateral attack	44	40.0
Unilateral attack	66	60.0
Optic disc edema*	73	47.4
Ocular pain	83	75.5
Abnormal autoimmune antibodies	21	19.1
Initial BCVA		
≤0.1	119	78.3
0.1–0.5	23	15.1
≥0.5	10	6.6
Median (Log MAR)	0.02 (1.7)	
Presenting BCVA		
≤0.1	14	7.4
0.1–0.5	14	7.4
≥0.5	160	85.1
Median (Log MAR)	1.0 (0.0)	
Treatment at acute stage		
IV methylprednisolone	102	92.7

* Incidence of optic disc edema was calculated by eyes. MOG, myelin oligodendrocyte glycoprotein; IV, intravenous; BCVA, best corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution.

were found to be both MOG-Ab and AQP4-Ab seropositive. In this study cohort, 119 eyes (78.3%) were 0.1 or worse at the initial attack, and 160 eyes (85.1%) were 0.5 or better at the final visit.

102 (92.7%) of the patients were treated with IV methylprednisolone in the initial attack at acute stage in our hospital. However, eight patients with first ON attack were not treated with IV methylprednisolone because they transferred to our center at remission stage.

Table 2 presents the demographics and clinical characteristics of the different ages of onset in the respective subgroups. In the pediatric group, the mean age of onset was 10.1 years (range of 2–17 years) compared to 30.2 years (range of 18–46 years) for the young group, and 53.0 years (range of 47–67 years) for the middle-aged group. There was a similar proportion of female patients in the pediatric and young subgroups (50% vs. 61.8%), and slightly more in the middle-aged group (72.2%, $p = .204$). Overall, pain associated with movement was present in 83 patients (75.5%), optic disc edema was noted in 73 patients (47.4%), and abnormal autoimmune antibodies were found in 21 patients (19.1%). We next observed that the frequencies of ocular pain, bilaterality, and optic disc swelling, and the presence of abnormal autoimmune antibodies were not significantly different between the three subgroups. Among the patients with cerebral spinal fluid (CSF) available for analysis, 12/86 (14.0%) had an elevated white blood cell count of > 10 /μl, 21/86 (24.4%) had an elevated protein concentration of > 400 mg/dL, and 10/86 (11.6%) had an elevated IgG level of > 3.4 mg/dL in CSF. The levels of white blood cells, protein, and IgG in the CSF were also not significantly different between subgroups.

3.2. Visual outcomes and clinical prognosis

Table 3 compares the visual outcomes and clinical prognosis of patients in the various MOG-ON subgroups. The BCVA at nadir at first onset was not statistically different between the three subgroups ($p = .561$). After treatment of the initial attack, 81 eyes (97.6%) in the pediatric group had good visual recovery (≥0.5) compared to eyes in the young (41, 91.1%) and middle-aged groups (19, 79.2%) ($p = .003$). At the final visit, 93 eyes (93.9%) had more pronounced visual recovery (≥0.5) in the pediatric group compared with the young (47, 79.7%) and middle-aged groups (20, 66.7%; $p < .001$). The comparison of LogMAR values after treatment following the initial attack and at the final visit revealed a significant difference in the three MOG-ON subgroups ($p < .001$). During follow-up, 58 patients (52.7%) experienced at least one episode of recurrence of ON. Chronic relapsing inflammatory optic neuropathy (CRION) with relapse after steroid reduction or cessation was diagnosed in 28 patients (25.5%). The pediatric group had a lower annual recurrence rate than the young and middle-aged groups (0.32 ± 0.50 vs 0.73 ± 0.87 vs 0.49 ± 1.08, $p = .036$). The ratio of conversion to NMOSD over the course of the follow-up period is elevated in the young patients compared with pediatric and middle-aged patients (20.6 vs. 3.4 vs. 0.0%, respectively, $p = .010$). Six pediatric patients had an ON attack concurrently with an episode of ADEM and received a final diagnosis of ADEM-ON. None of the MOG-ON patients were assigned the diagnosis of multiple sclerosis.

3.3. OCT measurements

Table 4 presents the pRNFL and mGCIPL thicknesses as measured by spectral domain-OCT. The pRNFL thickness measurements were taken in 57 pediatric, 38 young, and 10 middle-aged patients' eyes. The SD-OCT system automatically analyzed pRNFL thickness in the superior, temporal, inferior, and nasal quadrants. We found no significant difference in average pRNFL thickness between the three subgroups (68.68 ± 12.63 vs 68.68 ± 14.24 vs 68.30 ± 11.10 μm, $p = .996$). The mGCIPL thicknesses measurements were taken in 57 pediatric, 38 young, and 10 middle-aged patients' eyes, and there were no significant differences in this value between the three subgroups (59.74 ± 7.57 vs 59.00 ± 8.62 vs 57.10 ± 6.37 μm, respectively, $p = .608$).

3.4. MRI manifestation

Table 5 gives the optic nerve MRI results, which revealed T2 hyperintensity with or without enhancement. The 106 of 110 patients had optic nerve MRI scans in our hospital. The other four patients had orbit MRI scans with different parameters in other hospital, so we only analyzed the 106 MRI results of optic nerve. Overall, optic nerve MRI scans showed perineural enhancement in 52.0%, longitudinal extensive in 87.7%, orbital portion in 95.5%, canalicular portion in 68.7%, intracranial portion in 36.9%, chiasmal in 11.3%, and optic tract in 1.9% of the patients (Table 5, Fig. 1). No significant differences were noted between pediatric versus young and middle-aged patients ($p = .614$ and $p = .405$, respectively) in the MRIs of orbital and canalicular segment lesions. The proportion of patients experiencing intracranial optic nerve involvement was higher in the pediatric cohort than the young and middle-aged cohorts (45.4 vs. 21.2 vs 36.7%, respectively, $p = .014$). These subgroups had almost the same incidence of chiasma involvement based on MRI imaging (12.3 vs. 9.7 vs. 11.1%, respectively, $p > 0.999$). Furthermore, only two pediatric patients (3.5%) displayed optic tract involvement.

4. Discussion

In this single-center study, we evaluated the aged-based clinical features and outcomes of MOG-ON in Chinese patients, and found that 52.7% (58/110) of all MOG-ON patients were pediatric. MOG-Ab-related disease has an earlier age of onset, an observation that is supported by two recent studies from Korea and Australia. [13,14] Our previous study [10] reported that the onset in MOG-ON occurs sooner than AQP4-ON (5–63 years old vs. 8–72, respectively), but only

Table 2
Demographics and clinical characteristics in different MOG-ON subgroups.

	Pediatric	Young	Middle-aged	*P* value
No. of patients, n (%)	58 (52.7)	34 (30.9)	18 (16.4)	
No. of eyes	99	59	30	
Mean age at onset (range)	10.1 (2–17)	30.2 (18–46)	53.0 (47–67)	< 0.001
Female (%)	29 (50.0)	21 (61.8)	13 (72.2)	0.204
Bilaterality at first onset, n (%)	27 (46.6)	11 (32.4)	6 (33.3)	0.333
Ocular pain, n (%)	39 (67.2)	29 (85.3)	15 (83.3)	0.135
Optic disc swelling, n (%)	41 (48.2)	22 (50.0)	10 (41.7)	0.797
Abnormal autoimmune antibodies, n (%)	9 (15.5)	7 (20.6)	5 (27.8)	0.481
ANA	0 (0.0)	3 (8.8)	3 (16.6)	
ACA	1 (1.7)	1 (2.9)	0 (0.0)	
ANCA	0 (0.0)	0 (0.0)	0 (0.0)	
Anti-SSA/ Anti-SSB	1 (1.7)	0 (0.0)	2 (11.1)	
ACL/ β2-GPI	3 (5.2)	1 (2.9)	2 (11.1)	
APF	1 (1.7)	0 (0.0)	1 (5.6)	
RF	0 (0.0)	0 (0.0)	0 (0.0)	
HLA-B27	2 (3.4)	1 (2.9)	0 (0.0)	
ATAs/anti-TPOAb	1 (1.7)	1 (2.9)	2 (11.1)	
No. of lumbar punctures	43	28	15	
CSF white cell count, mean ± SD (n/mm3)	8.7 ± 20.6	2.4 ± 3.0	2.9 ± 3.6	0.165
White cell counts elevated	9 (20.9)	1 (3.6)	2 (13.3)	0.111
CSF protein, mean ± SD (g/L)	303.1 ± 105.4	342.8 ± 116.4	345.2 ± 95.4	0.222
Protein elevated	8 (18.6)	8 (28.6)	5(33.3)	0.370
CSF IgG level, mean ± SD (mg/dL)	2.16 ± 1.24	2.30 ± 1.09	2.37 ± 1.00	0.780
IgG level elevated	4 (9.3)	5 (17.9)	1 (6.7)	0.492

*$p < .05$, **$p < .01$. ANA, antinuclear antibody; ACA, anticentromere antibody; ANCA, antineutrophil cytoplasmic antibodies; ACL, anticardiolipin antibody; β2-GPI, anti-β2-glycoprotein I; anti-SSA and SSB, anti-Sjögren's syndrome A and B; APF, antiperinuclear factor; RF, rheumatoid factor; HLA-B27, human leukocyte antigen-B27; ATAs, anti-thyroglobulin antibodies; anti-TPOAb, anti-thyroid peroxidase autoantibody; CSF, cerebrospinal fluid; ON, optic neuritis.

enrolled 20 patients with MOG-ON. The clinical features of age-based MOG-ON in Chinese patients have remained vague and required further study. To our knowledge, the present study is the largest report on the age-based clinical characteristics in Chinese MOG-ON patients.

In our MOG-ON cohort, 57.3% patients were female. This is consistent with previous studies, which a variable MOG-ON prevalence in female patients of 38% to 75% [15–17]. In our study, we observed a similar proportion of female patients in the pediatric and young subgroups (50% vs. 61.8%), and slightly more in the middle-aged group (72.2%, $p = .204$). Our recent study reported that 48.0% patients were female in the pediatric MOG-ON subgroup, however we only enrolled 25 new pediatric MOG-ON patients. Overall, pain associated with movement was present in 75.5% (83/110) of patients, optic disc edema was noted in 47.4% (73/154) of patients, abnormal autoimmune antibodies were found in 19.1% (21/110) of patients, and 40.0% (44/110) of patients experienced bilateral involvement, all similar percentages to

Table 3
Comparison of visual outcomes and clinical prognosis in different MOG-ON subgroups.

	Pediatric	Young	Middle-aged	P value
No. of patients	58	34	18	
BCVA at nadir at first onset, eyes, n	83	45	24	0.561
≤0.1	66 (79.5)	33 (73.3)	20 (83.3)	
0.1–0.5	12 (14.5)	7 (15.6)	4 (16.7)	
≥0.5	5 (6.0)	5 (11.1)	0 (0.0)	
BCVA recovery at first onset, eyes, n	83	45	24	0.03
≤0.1	2(2.4)	2 (4.4)	5 (20.8)	
0.1–0.5	0 (0)	2 (4.4)	0 (0)	
≥0.5	81 (97.6)	41 (91.1)	19 (79.2)	
BCVA recovery at last follow-up, eyes, n	99	59	30	< 0.001**
≤0.1	5 (5.1)	5 (8.5)	4 (13.3)	
0.1–0.5	1 (1.0)	7 (11.9)	6 (20.0)	
≥0.5	93 (93.9)	47 (79.7)	20(66.7)	
LogMAR at nadir at first onset, mean ± SD	1.55 ± 0.82	1.64 ± 1.05	1.86 ± 0.86	0.337
LogMAR recovery at first onset, mean ± SD	0.06 ± 0.23	0.12 ± 0.34	0.58 ± 0.99	< 0.001**
LogMAR recovery at last follow-up, mean ± SD	0.12 ± 0.37	0.22 ± 0.41	0.56 ± 0.87	< 0.001**
Recurrent ON in follow-up, n (%)	27 (46.6)	23 (67.6)	8(44.4)	0.110
Relapse after steroid reduction or cessation, n (%)	10(17.2)	14(41.2)	4(22.2)	0.456
Time of first to second attack (months)	14.14 ± 16.25	25.65 ± 34.38	22.19 ± 49.27	0.422
Relapse times in follow-up, mean ± SD	1.24 ± 2.25	2.21 ± 2.66	1.39 ± 2.52	0.179
Follow-up, month, median (range)	23 (6–128)	27(6–217)	24(8–161)	0.951
Patients with a follow-up of at least 12 months, n	46	28	14	
Patients with relapsing at least 12 months, n (%)	26(56.5)	21(75.0)	8(57.1)	0.254
Patients with monophasic at least 12 months, n (%)	20(43.5)	7(25.0)	6(42.9)	0.254
ARR, mean ± SD	0.32 ± 0.50	0.73 ± 0.87	0.49 ± 1.08	0.036*
ADEM-ON	6(10.3)	0(0)	0(0)	0.066
Conversion to NMOSD, n (%)	2 (3.4)	7 (20.6)	0 (0)	0.010*

*$p < .05$, **$p < .01$. ON, optic neuritis; BCVA, best corrected visual acuity; ARR, annualised relapse rate; NMOSD, neuromyelitis optica spectrum disorder; ADEM, acute disseminated encephalomyelitis; LogMAR, logarithm of the minimum angle of resolution.

Table 4
Comparison of pRNFL and macular GCIPL thickness in different MOG-ON subgroups.

	Pediatric	Young	Middle-aged	P value
pRNFL (μm), eyes (n)	57	38	10	
Average thickness (mean ± SD)	68.68 ± 12.63	68.68 ± 14.24	68.30 ± 11.10	0.996
Superior quadrant (mean ± SD)	85.35 ± 20.07	82.03 ± 22.81	82.20 ± 16.20	0.723
Nasal quadrant (mean ± SD)	57.89 ± 7.58	60.61 ± 12.01	56.10 ± 7.64	0.261
Inferior quadrant (mean ± SD)	85.68 ± 22.65	84.45 ± 23.69	88.20 ± 20.90	0.895
Temporal quadrant (mean ± SD)	44.98 ± 14.40	48.58 ± 15.64	46.50 ± 8.90	0.497
GCIPL (μm), eyes (n)	57	38	10	
Average thickness (mean ± SD)	59.74 ± 7.57	59.00 ± 8.62	57.10 ± 6.37	0.608
Superior quadrant (mean ± SD)	61.04 ± 8.66	59.79 ± 9.68	58.10 ± 5.88	0.567
Nasal superior quadrant (mean ± SD)	57.93 ± 8.52	57.55 ± 10.91	55.20 ± 5.53	0.692
Nasal inferior quadrant (mean ± SD)	57.30 ± 7.85	56.92 ± 8.43	55.30 ± 7.03	0.766
Inferior quadrant (mean ± SD)	58.54 ± 7.08	58.74 ± 8.06	56.90 ± 7.26	0.781
Temporal inferior quadrant (mean ± SD)	62.05 ± 7.56	60.45 ± 9.08	59.50 ± 7.89	0.505
Temporal superior quadrant (mean ± SD)	61.28 ± 8.45	60.68 ± 9.40	58.30 ± 6.70	0.604

pRNFL, peripapillary retinal nerve fiber layer; GCIPL, ganglion cell-inner plexiform layer.

what has been reported in previous studies. [9,10,14]

In this MOG-ON cohort, 119 eyes (78.3%) were 0.1 or worse at the initial attack, and 160 eyes (85.1%) were 0.5 or better at the final visit, again consistent with previous reports. [9,18] At the final visit, 93 eyes (93.9%) had better visual recovery (≥0.5) in the pediatric group compared with the young (47, 79.7%) and middle-aged groups (20, 66.7%; $p < .001$). In previous studies, patients with MOG-ON frequently experienced recurrent disease [8]. In our study, 52.7% of patients experienced at least one episode of recurrence of ON, and 25.5% of patients were diagnosed CRION [19], similar to the findings of Chen. [9] The pediatric group had a lower annual recurrence rate than the young and middle-aged groups, and the ARR in young patients is similar to previous reports of adult MOG-ON. [20]

MOG-Abs can be detected in children with AQP4-Ab seronegative NMOSD, recurrent optic neuritis, transverse myelitis, and multiphasic acute disseminated encephalomyelitis [21,22], and a proportion of these children will experience a relapse in disease [23,24]. In our study, 46.6% of the children in the MOG-ON cohort presented with a relapsing form. ADEM followed by ON is a rare, but distinct clinical phenotype in children [3]. In our cohort, six children had an ON attack during an episode of ADEM. This is similar to a previous study [25] in which a higher proportion of pediatric-onset patients fulfilled the diagnostic criteria of ADEM compared to adult-onset patients. Finally, only two patients in the pediatric group developed NMOSD within the follow-up period. Because of the relatively short follow-up duration, the conversion rate for ADEM and NMOSD must be confirmed in further longitudinal studies. None of the MOG-ON patients were diagnosed with multiple sclerosis (MS). Another study similarly found that MOG-Ab-positive patients generally do not meet the clinical or radiographic criteria for MS. [26]

OCT measurements, such as of pRNFL and mGCIPL thickness, are frequently used as structural markers of axonal loss in ON patients and to differentiate between ON subtypes [27,28]. OCT studies showed that pRNFL atrophy developed within 6 months in ON patients, and that pRNFLthickness remained stable after 6 months [29]. Our study found no significant differences between age subgroups in terms of OCT measurements after 6 months of onset. We propose that this may be due to differences in follow-up times and the relapse rates in our cohort.

In our cohort, optic nerve MRI scans showed perineural enhancement in 52.0%, extensive longitudinal in 87.7%, and chiasmal in 11.3% of the patients, and only two patients (1.9%) displayed optic tract involvement. These results were similar to the values found in previous studies [9,30] where MRI lesions in MOG-ON patients tended to involve extensive longitudinal and perineural enhancement, with some extending to the optic chiasma and the tract. The intracranial portion of the optic nerve was involved in more pediatric patients than young and middle-aged patients ($p = .014$).

This study had several limitations. First, this was a single-center study, which can introduce selection bias, interfering with the cause and effect relationship. Second, this was a retrospective cohort, with variable investigations, descriptions, and follow-up, and often limited data was available for analysis. For example, SD-OCT data was available to review in 105 out of 188 eyes (55.9%). Third, MOG Ab titers were measured within 1 month of ON onset or relapse, and no relationship between titer and prognosis was discerned. Therefore, prospective studies in multiple centers and involvement of patients of varied ethnicities are required to clarify the influence of onset age on the final prognosis of patients with MOG-ON.

5. Conclusion

Based on the results of this study, pediatric ON is the most common MOG-ON subgroup in our single-center cohort. Pediatric patients had different clinical features, including earlier age of onset, better recovery of visual acuity, lower annual rates of relapse, and more intracranial optic nerve involvement than young and middle-aged patients. Age of

Table 5
Comparison of optic nerve MRIs in different MOG-ON subgroups.

	Total	Pediatric	Young	Middle-aged	P value
No. of patients (eyes)	106 (179)	57 (97)	31 (52)	18 (30)	
Perineural enhancement, n (%)	93 (52.0)	50 (51.5)	25 (48.1)	18 (60.0)	0.578
Length involved more than half, n(%)	157 (87.7)	85 (87.6)	45 (86.5)	27 (90.0)	0.899
Orbital, n (%)	171 (95.5)	94 (96.9)	49 (94.2)	28 (93.3)	0.614
Canalicular, n (%)	123 (68.7)	69 (71.1)	32 (61.5)	22 (73.3)	0.405
Intracranial, n (%)	66 (36.9)	44 (45.4)	11 (21.2)	11 (36.7)	0.014*
Chiasmal, n (%)	12 (11.3)	7 (12.3)	3 (9.7)	2 (11.1)	> 0.999
Optic tract, n (%)	2 (1.9)	2 (3.5)	0 (0)	0 (0)	0.682

MRI, magnetic resonance imaging.
* $p < .05$.

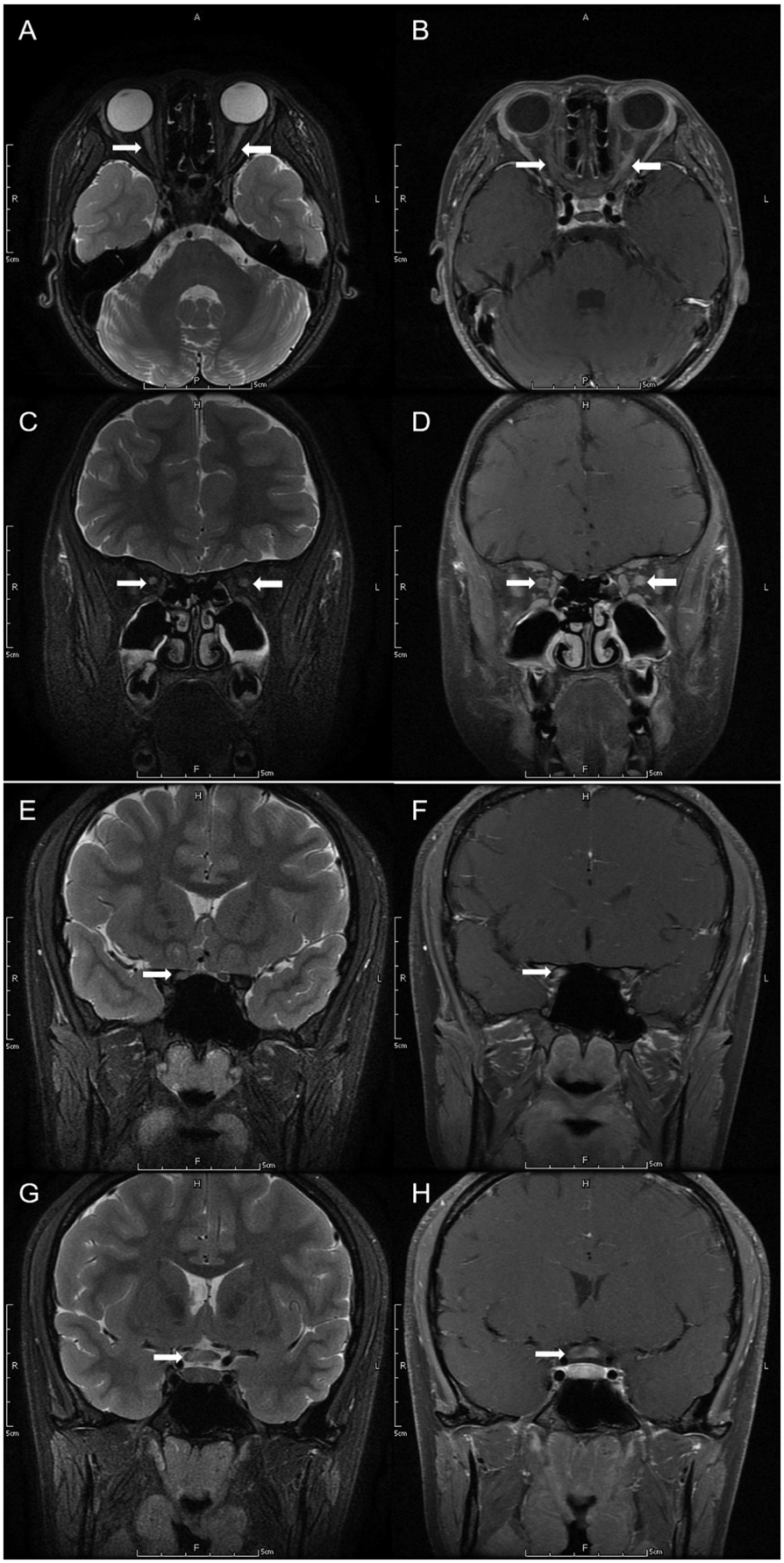

Fig. 1. Optic nerve abnormalities detected by MRI in patients with MOG-ON. (A-D) Images from a 5-year-old girl with MOG-ON showing bilateral prominent enhancement of optic nerve and sheath (perineural enhancement), extending along almost the entire nerve (white arrows). (A) Axial T2-weighted Image. (B) T1 postcontrast Image. (C) Coronal T2-weighted Image. (D) T1 postcontrast image. (*E*-H) Images from a 14-year-old girl with MOG-ON showing longitudinally extensive right optic nerve lesion extending from the chiasm (white arrows). (E) Coronal T2-weighted Image showing extensive T2 high signal in the right canalicular optic nerve. (F) T1 postcontrast image showing lesion in the right canalicular optic nerve with marked postcontrast enhancement. (G) Coronal T2 weighted image showing extensive T2 high signal in the chiasm. (H) T1 postcontrast image showing lesion in the chiasm with marked postcontrast enhancement.

onset may be a predictor for determining visual prognosis in MOG-ON patients.

Contributors

HS, HZ, and MY are co-first authors and contributed equally. Study was designed and conducted by HS, HZ, MY, QX, and SW. Collection, analysis, management, and interpretation of the data was performed by HS, HZ, MY and MS. Manuscript was prepared by HS, HZ, and MY. Critical revision of the manuscript was performed by QX and SW. Review and final approval of the manuscript was performed by all the authors.

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Competing interests

None declared.

Patient consent

Obtained.

Ethics approval

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References

[1] The clinical Profile of Optic Neuritis, Experience of the optic neuritis treatment trial. Optic neuritis study group, arch, Ophthalmology 109 (12) (1991) 1673–1678.
[2] A. Toosy, D. Mason, D. Miller, Optic neuritis, Lancet Neurol. 13 (1) (2014) 83–99.
[3] P. Huppke, K. Rostasy, M. Karenfort, B. Huppke, R. Seidl, S. Leiz, M. Reindl, J. Gärtner, Acute disseminated encephalomyelitis followed by recurrent or monophasic optic neuritis in pediatric patients, Mult. Scler. 19 (7) (2013) 941–946.
[4] T. Kezuka, H. Ishikawa, Diagnosis and treatment of anti-myelin oligodendrocyte glycoprotein antibody positive optic neuritis, Jpn. J. Ophthalmol. 62 (2) (2018) 101–108.
[5] S. Jarius, J. Frederikson, P. Waters, F. Paul, G. Akman-Demir, R. Marignier, D. Franciotta, K. Ruprecht, B. Kuenz, P. Rommer, W. Kristoferitsch, B. Wildemann, A. Vincent, Frequency and prognostic impact of antibodies to aquaporin-4 in patients with optic neuritis, J. Neurol. Sci. 298 (1–2) (2010) 158–162.
[6] S. Jarius, K. Ruprecht, I. Kleiter, N. Borisow, N. Asgari, K. Pitarokoili, F. Pache, O. Stich, L. Beume, M. Hümmert, C. Trebst, M. Ringelstein, O. Aktas, A. Winkelmann, M. Buttmann, A. Schwarz, H. Zimmermann, A. Brandt, D. Franciotta, M. Capobianco, J. Kuchling, J. Haas, M. Korporal-Kuhnke, S. Lillevang, K. Fechner, K. Schanda, F. Paul, B. Wildemann, M. Reindl, MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin, J. Neuroinflammation 13 (1) (2016) 279.
[7] J. Chen, W. Tobin, M. Majed, J. Jitprapaikulsan, J. Fryer, J. Leavitt, E. Flanagan, A. McKeon, S. Pittock, Prevalence of myelin Oligodendrocyte glycoprotein and Aquaporin-4-IgG in patients in the optic neuritis treatment trial, JAMA Ophthalmol. 136 (4) (2018) 419–422.
[8] F. Pache, H. Zimmermann, J. Mikolajczak, S. Schumacher, A. Lacheta, F. Oertel, J. Bellmann-Strobl, S. Jarius, B. Wildemann, M. Reindl, A. Waldman, K. Soelberg, N. Asgari, M. Ringelstein, O. Aktas, N. Gross, M. Buttmann, T. Ach, K. Ruprecht, F. Paul, A. Brandt, MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 4: afferent visual system damage after optic neuritis in MOG-IgG-seropositive versus AQP4-IgG-seropositive patients, J. Neuroinflammation 13 (1) (2016) 282.
[9] J. Chen, E. Flanagan, J. Jitprapaikulsan, A. López-Chiriboga, J. Fryer, J. Leavitt, B. Weinshenker, A. McKeon, J. Tillema, V. Lennon, W. Tobin, B. Keegan, C. Lucchinetti, O. Kantarci, C. McClelland, M. Lee, J. Bennett, V. Pelak, Y. Chen, G. VanStavern, O. Adesina, E. Eggenberger, M. Acierno, D. Wingerchuk, P. Brazis, J. Sagen, S. Pittock, Myelin Oligodendrocyte glycoprotein antibody (MOG-IgG)-positive optic neuritis: clinical characteristics, radiologic clues and outcome, Am J. Ophthalmol. 195 (2018) 8–15.
[10] Y. Zhao, S. Tan, T. Chan, Q. Xu, J. Zhao, D. Teng, H. Fu, S. Wei, Clinical features of demyelinating optic neuritis with seropositive myelin oligodendrocyte glycoprotein antibody in Chinese patients, Br. J. Ophthalmol. 102 (10) (2018) 1372–1377.
[11] K. Schulze-Bonsel, N. Feltgen, H. Burau, L. Hansen, M. Bach, Visual acuities "hand motion" and "counting fingers" can be quantified with the freiburg visual acuity test, Invest. Ophthalmol. Vis. Sci. 47 (3) (2006) 1236–1240.
[12] M. Storoni, I. Davagnanam, M. Radon, A. Siddiqui, G. Plant, Distinguishing optic neuritis in neuromyelitis optica spectrum disease from multiple sclerosis: a novel magnetic resonance imaging scoring system, J. Neuroophthalmol. 33 (2) (2013) 123–127.
[13] J.W. Hyun, M.R. Woodhall, S.H. Kim, I.H. Jeong, B. Kong, G. Kim, Y. Kim, S.P. Min, S.R. Irani, P. Waters, Longitudinal analysis of myelin oligodendrocyte glycoprotein antibodies in CNS inflammatory diseases, J. Neurol. Neurosurg. Psychiatry 88 (10) (2017) 811–817.
[14] S. Ramanathan, S. Mohammad, E. Tantsis, T. Nguyen, V. Merheb, V. Fung, O. White, S. Broadley, J. Lechner-Scott, S. Vucic, A. Henderson, M. Barnett, S. Reddel, F. Brilot, R. Dale, Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination, J. Neurol. Neurosurg. Psychiatry 89 (2) (2018) 127–137.
[15] D. Sato, D. Callegaro, M. Lana-Peixoto, P. Waters, F. de Haidar Jorge, T. Takahashi, I. Nakashima, S. Apostolos-Pereira, N. Talim, R. Simm, A. Lino, T. Misu, M. Leite, M. Aoki, K. Fujihara, Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders, Neurology 82 (6) (2014) 474–481.
[16] J. Kitley, P. Waters, M. Woodhall, M. Leite, A. Murchison, J. George, W. Küker, S. Chandratre, A. Vincent, J. Palace, Neuromyelitis optica spectrum disorders with aquaporin-4 and myelin-oligodendrocyte glycoprotein antibodies: a comparative study, JAMA Neurol. 71 (3) (2014) 276–283.
[17] A. Pröbstel, G. Rudolf, K. Dornmair, N. Collongues, J. Chanson, N. Sanderson, R. Lindberg, L. Kappos, J. de Seze, T. Derfuss, Anti-MOG antibodies are present in a subgroup of patients with a neuromyelitis optica phenotype, J. Neuroinflammation 12 (2015) 46.
[18] H. Nakajima, M. Motomura, K. Tanaka, A. Fujikawa, R. Nakata, Y. Maeda, T. Shima, A. Mukaino, S. Yoshimura, T. Miyazaki, H. Shiraishi, A. Kawakami, A. Tsujino, Antibodies to myelin oligodendrocyte glycoprotein in idiopathic optic neuritis, BMJ Open 5 (4) (2015) e007766.
[19] A. Petzold, G. Plant, Chronic relapsing inflammatory optic neuropathy: a systematic review of 122 cases reported, J. Neurol. 261 (1) (2014) 17–26.
[20] R. Matsuda, T. Kezuka, A. Umazume, Y. Okunuki, H. Goto, K. Tanaka, Clinical profile of anti-myelin oligodendrocyte glycoprotein antibody seropositive cases of optic neuritis, Neuroophthalmology 39 (5) (2015) 213–219.
[21] E.M. Hennes, M. Baumann, K. Schanda, B. Anlar, B. Bajer-Kornek, A. Blaschek, S. Brantner-Inthaler, K. Diepold, A. Eisenkā, T. Gotwald, Prognostic relevance of MOG antibodies in children with an acquired demyelinating syndrome, Neurology 89 (9) (2017) 900–908.
[22] M. Baumann, E.M. Hennes, K. Schanda, M. Karenfort, B. Kornek, R. Seidl, K. Diepold, H. Lauffer, I. Marquardt, J. Strautmanis, Children with multiphasic disseminated encephalomyelitis and antibodies to the myelin oligodendrocyte glycoprotein (MOG): extending the spectrum of MOG antibody positive diseases, Mult. Scler. 22 (14) (2016) 1821.
[23] Y. Hacohen, Y.Y. Wong, C. Lechner, M. Jurynczyk, S. Wright, B. Konuskan, J. Kalser, A.L. Poulat, H. Maurey, E. Ganelincohen, Disease course and treatment responses in children with relapsing myelin Oligodendrocyte glycoprotein antibody-associated disease, JAMA Neurol. 75 (4) (2018) 478–487.
[24] S. Ramanathan, S. Mohammad, E. Tantsis, T.K. Nguyen, V. Merheb, F. Vsc, O.B. White, S. Broadley, J. Lechner-Scott, S. Vucic, Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination, J. Neurol. Neurosurg. Psychiatry 89 (2) (2018) 127–137.
[25] C. Lu, C. Chen, X. Zhong, X. Sun, H. Zhu, X. Li, Y. Hui, Y. Shu, Y. Chang, X. Hu, Different features between pediatric-onset and adult-onset patients who are seropositive for MOG-IgG: a multicenter study in South China, J. Neuroimmunol. 321 (2018) 83.
[26] S. Ramanathan, K. Prelog, E. Barnes, E. Tantsis, S. Reddel, A. Henderson, S. Vucic, M. Gorman, L. Benson, G. Alper, C. Riney, M. Barnett, J. Parratt, T. Hardy, R. Leventer, V. Merheb, M. Nosadini, V. Fung, F. Brilot, R. Dale, Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis, Mult. Scler. 22 (4) (2016) 470–482.
[27] C. Peng, W. Wang, Q. Xu, S. Zhao, H. Li, M. Yang, S. Cao, H. Zhou, S. Wei, Structural alterations of segmented macular inner layers in Aquaporin4-antibody-positive optic neuritis patients in a Chinese population, PLoS One 11 (6) (2016) e0157645.
[28] G. Zhao, Q. Chen, Y. Huang, Z. Li, X. Sun, P. Lu, S. Yan, M. Wang, G. Tian, Clinical characteristics of myelin oligodendrocyte glycoprotein seropositive optic neuritis: a cohort study in Shanghai, China, J. Neurol. 265 (1) (2018) 33–40.
[29] I. Gabilondo, E. Martínez-Lapiscina, E. Fraga-Pumar, S. Ortiz-Perez, R. Torres-Torres, M. Andorra, S. Llufriu, I. Zubizarreta, A. Saiz, B. Sanchez-Dalmau, P. Villoslada, Dynamics of retinal injury after acute optic neuritis, Ann. Neurol. 77 (3) (2015) 517–528.
[30] S. Jarius, K. Ruprecht, I. Kleiter, N. Borisow, N. Asgari, K. Pitarokoili, F. Pache, O. Stich, L. Beume, M. Hümmert, M. Ringelstein, C. Trebst, A. Winkelmann, A. Schwarz, M. Buttmann, H. Zimmermann, J. Kuchling, D. Franciotta, M. Capobianco, E. Siebert, C. Lukas, M. Korporal-Kuhnke, J. Haas, K. Fechner, A. Brandt, K. Schanda, O. Aktas, F. Paul, M. Reindl, B. Wildemann, MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome, J. Neuroinflammation 13 (1) (2016) 280.