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The prevalence and prognostic value of myelin oligodendrocyte glycoprotein antibody in adult optic neuritis

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ABSTRACT

Background and objective: Adult demyelinating optic neuritis (ON) with positive myelin-oligodendrocyte glycoprotein antibody (MOG-Ab) has distinct clinical features. This study aimed to investigate the point prevalence, relationship with steroid dependency and prognosis value of MOG-Ab in adult ON.

Methods: Clinical data analysis was undertaken in adults with ON admitted between December 2014 and January 2016. Patients were classified into three groups based on aquaporin-4 antibody (AQP4-Ab) and MOG-Ab status: AQP4-ON, MOG-ON and seronegative-ON.

Results: A total of 158 adults with ON (190 eyes) were assessed, including 31 MOG-ON (19.6%), 67 AQP4-ON (42.4%) and 60 seronegative-ON (38.0%) cases. The female-to-male ratio was significantly lower in MOG-ON (1.8:1) than that in AQP4-ON (8.6:1) groups ($p = .005$). The median age, percentage of bilateral ON and visual loss at the nadir at onset was similar among the three groups. Thirty-eight eyes (76%) in the MOG-ON group showed good visual recovery (> 20/40) in the final visit, which is statistically better than that in the AQP4-ON and seronegative-ON groups ($p < .001$ and $p = .006$, resoectively). Fifteen adults with ON (9.5%) showed dependency on steroid, which was particularly prominent in the MOG-ON group (11/31, 35.5%) and rarely presented in the AQP4-ON (2, 3.0%) and seronegative-ON (2, 3.3%) groups. Results suggested less loss of pRNFL in MOG-ON than that in AQP4-ON group ($p < .001$), and a larger proportion of canalicular segment involved in MOG-ON adults ($p = .007$ and $p < .001$).

Conclusion: MOG-ON had the smallest proportion of acute demyelinating ON in Chinese adults. One third of adults with MOG-ON predominantly showed a substantial dependency on steroids and relapse on steroid reduction or cessation, which rarely presented in AQP4-ON and seronegative-ON adults.

1. Introduction

Adult optic neuritis (ON) has been reported to have distinctive clinical characteristics and prognosis from ON in children [1,2]. As an inflammatory demyelinating disorder of the optic nerve, ON is either regarded as an isolated optic neuropathy or is associated with various central nervous system (CNS) demyelinating diseases such as neuromyelitis optica (NMO) spectrum disorder [3,4]. Aquaporin-4 (AQP4) antibody was the first validated diagnostic biomarker; the diagnostic specificity for NMO is almost 91% [5,6]. Several studies recently indicated that NMO and neuromyelitis optica spectrum disorder (NMOSD) patients with negative AQP4 antibodies present with antibodies against the myelin-oligodendrocyte glycoprotein (MOG), showing a potential value as a new biomarker [7,8].

AQP4-Ab was reported to be the smallest proportion of adult ON in France [9], whereas the prevalence of MOG-Ab in Asian ON adults is still unclear. In recent years, some studies reported the distinct characteristics of MOG antibody-positive patients from those of other ON phenotypes [10–12]. A small cohort study demonstrated that five out of eight MOG-ON patients had corticosteroid dependency in Greece [13]. The potential relationship between MOG-Ab and corticosteroid dependency in adults with ON remains a further investigation.

The prevalence and particular clinical characteristics of MOG-ON in Asian adults remained unclear and had not been reported due to the small overall number of MOG-ON adults in cohorts and racial diversity. Therefore, compared to other ON phenotypes, we predominantly analysed the point prevalence, relationship with steroid dependency and prognostic value of MOG-ON in Chinese adults.

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2. Materials and methods

2.1. Patient enrolment

We identified 402 patients with demyelinating diseases in the Chinese People's Liberation Army General Hospital (PLAGH) between December 2015 and January 2017, and 158 ON patients who were ≥ 18 years of age with at least one year of follow-up were enrolled in our study.

The diagnosis of ON was based on the Optic Neuritis Treatment Trial (ONTT) [4] and the detailed inclusion criteria are the following: (1) initiated with ON, presenting with acute or subacute visual loss; (2) age of ON onset ≥18 years; (3) at least two of the following conditions: ocular pain during eye movement, afferent pupillary defect, abnormal visual evoked response, dyschromatopsia and field defect. Patients with any of the following were excluded [14]: unknown AQP4-Ab or MOG-Ab serum status, existing multiple sclerosis (MS), or NMO prior to the first onset of ON or incomplete clinical and follow-up data. MS and NMO were diagnosed according to the current international criteria: (1) MS: fulfilling the 2017 McDonald criteria for the diagnosis of MS [15]; (2) NMO: fulfilling the 2015 International Panel for NMO diagnosis criteria [16].

2.2. Serum and cerebrospinal fluid (CSF) tests

All enrolled patients underwent serum tests for AQP4 antibodies and MOG antibodies with cell-based assay (CBA). Samples were tested at a branch of the Euroimmun Medical Diagnostic Laboratory in China, using a fixed cell-based indirect immunofluorescence test (Euroimmun, Lübeck, Germany) and qualitative analyses using confocal microscopy.

All adults underwent the hospital's routine standard blood analysis and necessary diagnostic tests of serum, including anti-nuclear antibody (ANA), Sjögren's syndrome A and B antibodies (anti-SSA and anti-SSB); histocompatibility complex-B27 (HLA-B27); thyroglobulin antibodies (TGAb); thyroid peroxidase antibodies (TPOAb) and rheumatoid factor (RF) in the hospital.

2.3. Neuro-ophthalmic examinations

All ON adults were investigated according to the hospital's routine standard investigation protocol for ON, with detailed ophthalmic examinations by ophthalmologists Zhou H·F, Sun M.M, Song H.L. The best-corrected visual acuity (BCVA) was evaluated using a Snellen chart. The decimal BCVA was converted to the logarithm of the minimal angle of resolution (logMAR) for statistical analyses, where logMAR = −logBCVA.

Orbital magnetic resonance imaging (MRI) was performed on all enrolled adults. Spinal MRI was carried out on patients with positive neurological signs. T2-weighted imaging and post-contrast T-weighted imaging were used for image collection and evaluation. The optic nerve was divided into five segments: intraorbital, canalicular, intracranial segments, optic chiasm and tract [17]. Data of the peripapillary retinal nerve fibre layer (pRNFL) measurements in spectral domain optical coherence tomography (SD-OCT) examinations were obtained using high-definition SD-OCT (Carl Zeiss Meditec, Dublin, CA, USA) at least three months after the initial attack.

All ON adults in the acute phase were treated with intravenous methylprednisolone (1000 mg daily) over 3–5 consecutive days, followed by oral prednisolone (starting dose 1 mg/kg/d) with variable durations (at least 3 months), based on individual clinician preference and ON subtype [18].

2.4. Statistical analysis

Statistical analyses were performed using SPSS statistical software for Windows, version 23.0 (IBM Corporation, New York, USA, 2015). Categorical variables among the three groups were analysed with a Chi-square test, where appropriate, between-group comparisons were performed using Fisher's exact test followed by Bonferroni's correction. For numeric data, multiple comparisons were performed using non-parametric Kruskal-Wallis test, where appropriate, non-parametric Kruskall-Wallis test was further used to make between-group comparisons, and then with the Bonferroni's correction. A value of $P < .05$ was considered statistically significant.

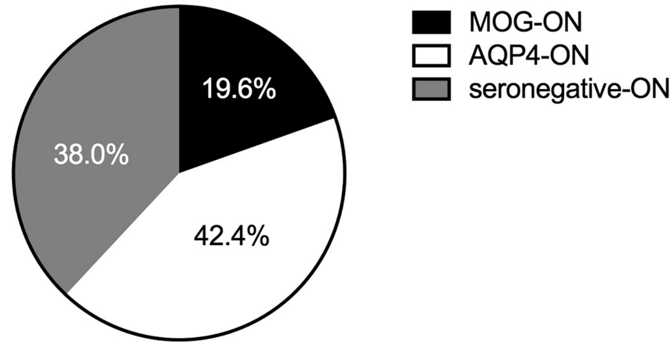

Fig. 1. Proportion of different ON subtypes in our adult cohort.

3. Results

3.1. Demographic and clinical characteristics

We finally enrolled 158 ON adults (190 eyes), including 31 (19.6%) MOG-ON, 67 (42.4%) AQP4-ON and 60 (38.0%) seronegative-ON adults (Fig. 1). Their demographics and characteristics are presented in Table 1. No adult patients were positive for both antibodies. The female-to-male ratio was significantly lower in MOG-ON (1.8:1) than that in AQP4-ON (8.6:1) groups ($p = .005$), but no significant difference was found in the seronegative-ON (3.3:1) group ($p = .322$). The median age and percentage of bilateral ON at onset was similar among the three groups. Twenty-one MOG-ON (67.7%) and 38 seronegative-ON (63.3%) patients appeared more likely to have optic disc swelling ($p = .002$ and $p = .001$, respectively). Only 12.9% (4/31) of patients had accompanying autoimmune antibodies in the MOG-ON group, in contrast to the AQP4-ON (34/67, 50.7%) and seronegative-ON (5/60, 8.3%) groups ($p < .001$ and $p = .713$).

3.2. Visual outcomes and clinical prognosis

Table 2 presents the visual outcome and clinical prognosis of the three groups. Visual loss at the nadir during the first episode in the MOG-ON group was similar to that in AQP4-ON and seronegative-ON groups ($p = .179$) (Fig. 2). During the follow-up, 38 eyes (76%) in the MOG-ON group showed good visual recovery (> 20/40) in the final visit, which is statistically better than that in AQP4-ON and seronegative-ON groups ($p < .001$ and $p = .006$) (Fig. 3). The follow-up duration showed no statistical difference among the three groups. Median number of ON attacks in the MOG-ON group was more than that in seronegative-ON ($p = .001$), but similar to the AQP4-ON group ($p = .179$). The percentage of ON patients with relapsing course in MOG-ON and AQP4-ON groups were more than that in the seronegative-ON group ($p = .002$ and $p < .001$). MOG-ON adults had the highest annualised relapse rates (ARR) among the three groups ($p = .001$ and $p = .005$). During the follow up period, about 1/3 of patients with seronegative ON had bilateral involvement (23/60, 38.3%) compared to 61.3% in the MOG-ON group ($p = .047$) and 71.6% in the AQP4-ON group ($p < .001$). Only two MOG-ON adults developed NMO during the observation period.

A total of 15 ON adults (9.5%) showed an intense dependency on

Table 1
Demographic and clinical characteristics in MOG-ON, AQP4-ON and seronegative-ON adults.

	MOG-ON	AQP4-ON	Seronegative-ON	*P*	[a]*P*	[b]*P*	[c]*P*
No. of patients, n (%)	31 (19.6)	67 (42.4)	60 (38.0)				
No. of eyes	40	76	74				
Female, n (%)	20 (64.5)	60 (89.6)	46 (76.7)	0.012	0.005*	0.322	0.059
Age at onset, median (range), y	39.61 (18–63)	36.91 (18–72)	37.97 (18–65)	0.606			
Bilateral ON at onset, n (%)	9 (29.0)	9 (13.4)	14 (23.3)	0.152			
Previous infection, n (%)	9 (29.0)	9 (13.4)	14 (23.3)	0.152			
Ocular pain, n (%)	20 (64.5)	29 (43.3)	31 (51.7)	0.144			
Optic disc swelling, n (%)	21 (67.7)	22 (32.8)	38 (63.3)	< 0.001	0.002*	0.818	0.001*
Duration from attack to nadir, median (range), d	6.47 (3 – 10)	5.96 (1–19)	7.38 (1 – 20)	0.357			
Abnormal autoimmune antibody, n (%)	4 (12.9)	34 (50.7)	5 (8.3)	< 0.001	< 0.001*	0.713	< 0.001*
ANA	4 (12.9)	25 (37.3)	4 (6.7)	< 0.001	0.017	0.437	< 0.001*
Anti-SSA/Anti-SSB	0 (0)	18 (26.9)	2 (3.3)	< 0.001	0.001*	0.546	< 0.001*
Anti-TGAb/Anti-TPOAb	0 (0)	10 (14.9)	0 (0)	< 0.001	0.028		0.002*
HLA -B27	0 (0)	3 (4.5)	0 (0)	0.226			
Anti-dsDNA	0 (0)	3 (4.5)	0 (0)	0.226			
RF	1 (3.2)	3 (4.5)	0 (0)	0.250			

P, comparison among three ON subgroups. A p value < .05 was considered significant.
A *p value < 0.017 was considered significant after Bonferroni's correction for multiple comparisons.
ANA, anti-nuclear antibodies; SSA and SSB, Sjögren's syndrome A and B antibodies; HLA−B27, histocompatibility complex-B27; TGAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies; dsDNA, double-stranded DNA; RF, rheumatoid factor.
[a] *P*, MOG-ON versus AQP4-ON.
[b] *P*, MOG-ON versus seronegative-ON.
[c] *P*, AQP4-ON versus seronegative-ON.

steroid, tending to relapse when the steroid dose was reduced. We noted that this trend was particularly prominent in the MOG-ON group (11/31, 35.5%), but rarely presented in AQP4-ON (2, 3.0%) and seronegative-ON (2, 3.3%) groups ($p < .001$ and $p < .001$). Fig. 4 presents features of the 15 steroid-dependent ON (11 MOG-ON, 2 AQP4-ON and 2 seronegative-ON) adults. They were predominantly prone to relapse during the later period of oral prednisone treatment, especially at doses < 30 mg or within one month of stopping treatment. The range of susceptible dose was 2.5–30 mg, and the average duration interval between steroid stop and relapse was 11 days.

3.3. CSF and OCT measurements

Table 3 demonstrates the results of laboratory, MRI distribution and pRNFL thickness. Compared with the AQP4-ON group, lower CSF IgG levels were observed in the MOG-ON group ($p < .001$). Eighty-six eyes were analysed for OCT measurements, including 19 eyes in MOG-ON patients, 37 eyes in AQP4-ON patients and 30 eyes in seronegative-ON adults. The pRNFL measurements showed an average of 72.40 ± 9.20, 60.74 ± 12.23 and 67.59 ± 15.90 μm, suggesting less loss of pRNFL in MOG-ON adults when compared to AQP4-ON group ($p < .001$). The HD-OCT system automatically analysed pRNFL thickness in the superior, temporal, inferior and nasal quadrants, and we found that the thickness of the superior and inferior quadrants showed significantly less loss when compared to AQP4-ON adults ($p < .001$ and $p < .001$), but the thickness of the temporal and nasal quadrants had no significant difference.

Table 2
Comparison of visual outcome and clinical prognosis among patients with MOG-ON, AQP4-ON and seronegative-ON.

	MOG-ON	AQP4-ON	Seronegative-ON	*P*	[a]*P*	[b]*P*	[c]*P*
No. of patients	31	67	60				
BCVA at first onset, eyes, n	40	76	74				
VA > 20/40	2 (5.0)	3 (3.9)	2 (2.7)	0.885			
20/40 ≥ VA ≥ 20/200	10 (25.0)	15 (19.7)	13 (17.6)	0.944			
VA < 20/200	28 (70.0)	58 (76.3)	59 (79.7)	0.505			
Mean ± SD (logMAR)	1.99 ± 0.94	2.04 ± 0.99	1.82 ± 0.88	0.179			
BCVA at last follow-up, eyes, n	50	115	83				
VA > 20/40	38 (76.0)	37 (32.2)	40 (48.2)	< 0.001	< 0.001*	0.002*	0.027
20/40 ≥ VA ≥ 20/200	5 (10.0)	23 (20.0)	16 (19.3)	0.274			
VA < 20/200	7 (14.0)	55 (47.8)	27 (32.5)	< 0.001	< 0.001*	0.023	0.040
Mean ± SD (logMAR)	0.37 ± 0.63	1.17 ± 1.01	0.75 ± 0.85	< 0.001	< 0.001*	0.006*	0.005*
Follow-up, mean ± SD	37.79 ± 41.71	44.10 ± 43.38	31.43 ± 28.05	0.612			
ON attack number, median (range)	2.38 (1–6)	2.90 (1 – 10)	1.49 (1–4)	< 0.001	0.179	0.001*	< 0.001*
Bilateral ON at last follow-up, n (%)	19 (61.3)	48 (71.6)	23 (38.3)	0.001	0.247	0.047	< 0.001*
Relapsing ON, n (%)	21 (67.7)	55 (82.1)	20 (33.3)	< 0.001	0.126	0.002*	< 0.001*
ARR (mean ± SD)	1.14 ± 0.73	0.64 ± 0.30	0.46 ± 0.35	< 0.001	< 0.001*	0.014*	0.005*
Conversion to NMO, n (%)	2 (6.5)	15 (22.4)	0 (0)	< 0.001	0.083	0.114	< 0.001*
Steroid dependency, n (%)	11 (35.5)	2 (3.0)	2 (3.3)	< 0.001	< 0.001*	< 0.001*	1.000

P, comparison among three ON subgroups. A p value < .05 was considered significant.
A *p value < .017 was considered significant after Bonferroni's correction for multiple comparisons. BCVA, best corrected visual acuity; ARR, annualised relapse rate.
[a] *P*, MOG-ON versus AQP4-ON.
[b] *P*, MOG-ON versus seronegative-ON.
[c] *P*, AQP4-ON versus seronegative-ON.

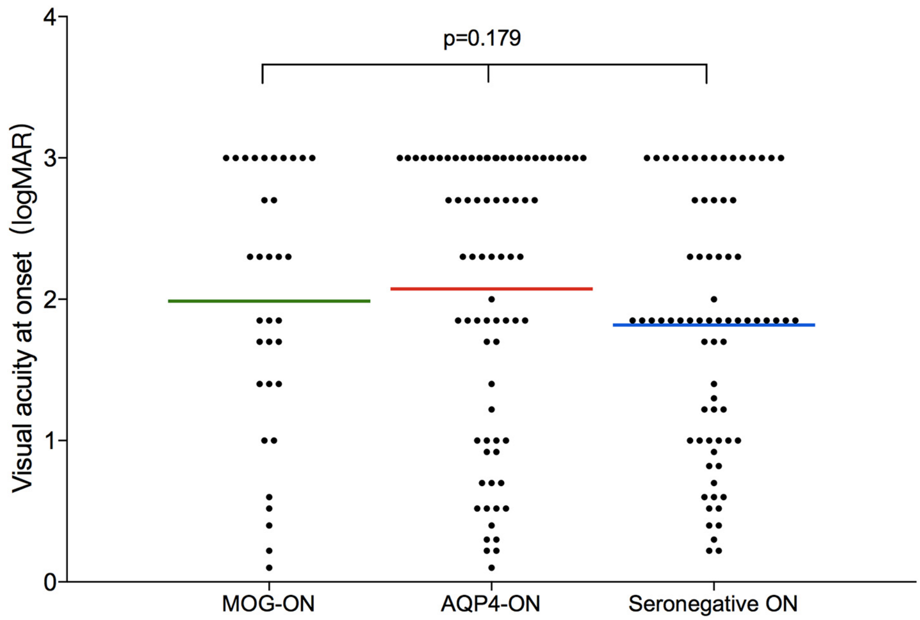

Fig. 2. Worst visual acuity at onset in the acute phase of the three groups (Non-parametric Kruskal-Wallis test was used to compare among three ON subgroups. A *p* value < .05 was considered significant.)

3.4. Orbital MRI distribution

Orbital MRI was performed in the acute stage of the initial attack. Those whose MRIs were obtained at other hospitals were excluded due to differences in apparatus. In total, 89 cases (104 eyes) were assessed in this cohort, including 21 eyes in the MOG-ON group, 42 eyes in the AQP4-ON group and 41 eyes in the seronegative-ON group. Table 3 presents the detailed distribution of ON-lesions in the acute phase of the initial attack. No significant difference was found in the proportion of involved intraorbital segmentsg among the three groups. The proportion of involved canalicular segment in the MOG-ON group was more than that in the other two groups ($p = .007$ and $p < .001$) (Fig. 5).

4. Discussion

In this single-centre cohort study, MOG-ON (31/158, 19.6%) had the smallest proportion and AQP4-ON (67/158, 42.4%) included a relatively higher proportion of acute demyelinating ON in Chinese adults. This result conflicts with a previous study in France, which reported an estimated prevalence of 10% for MOG-ON and 4.5% for AQP4-ON (the smallest proportion) [9]. The difference of prevalence could be explained by the effects of various ethnicities and latitude. Meanwhile, a study from Japan showed a similar rate of 25%–30% for MOG-ON in total patients, but the result was not evaluated respectively by age [19].

In our cohort, MOG-ON adults showed a significantly lower female predominance than AQP4-ON adults (65% vs 90%) did, which was accordant with previous studies of Caucasians [12,20]. Our previous

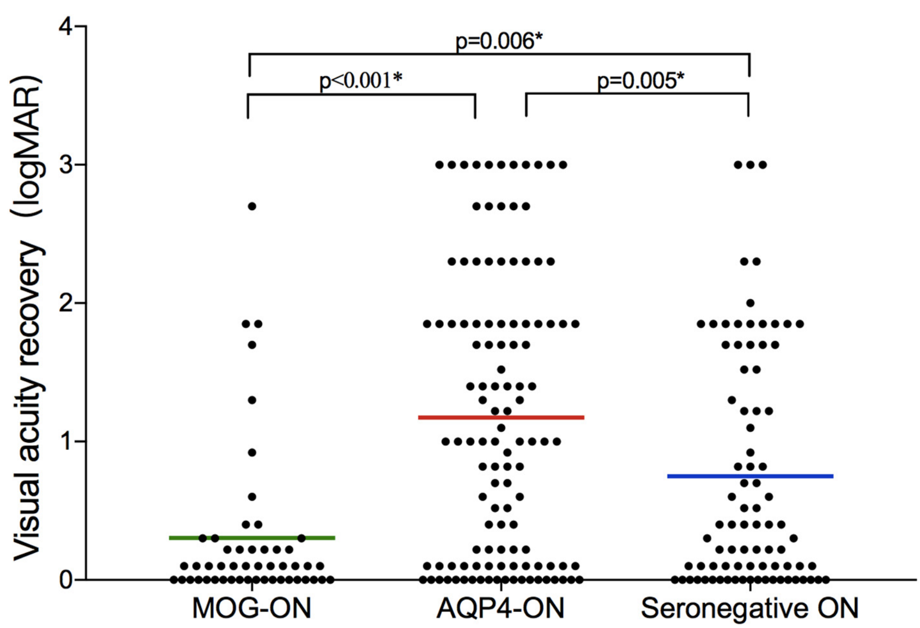

Fig. 3. Final visual acuity in the chronic phase at the last follow-up visit of the three groups (Non-parametric Kruskal-Wallis test was used to make between-group comparisons, followed by Bonferroni's correction. A p value < .017 was considered significant.)

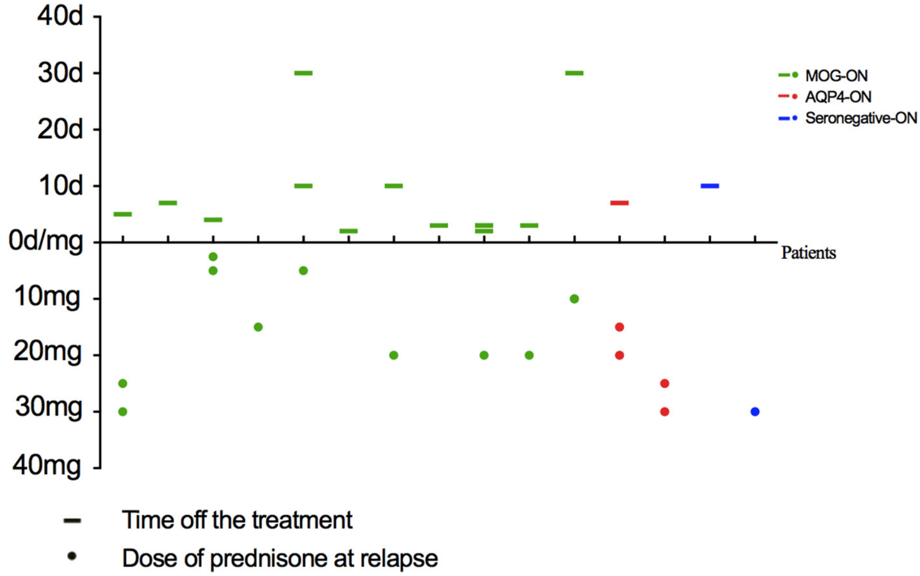

Fig. 4. Fifteen steroid-dependent adults (11 MOG-ON, 2 AQP4-ON and 2 seronegative-ON) who were more likely to relapse on steroid reduction or cessation during later period of oral prednisone treatment.

study suggested that MOG-ON patients had a younger age of disease onset than the AQP4-ON group (20.2 vs 35.6 years), which contained both children and adults, whereas we found no significant difference of mean age at onset among the three groups in our adult cohort [21]. According to our study, 61.3% of MOG-ON adults had bilateral ON during the follow-up, which is more than the seronegative-ON (38.3%) group, but similar to the AQP4-ON (71.6%) group. Thirty-eight eyes (76%) in the MOG-ON group showed good visual recovery (VA > 20/40) in the final visit, and the mean final visual acuity was statistically better than in the other two groups, which was consistent with other studies of Caucasians and Asians [21,22].

Notably, 9.5% (15/158) of ON adults showed an intense dependency on steroid, which was particularly prominent in MOG-ON adults (11/31, 35.5%) but rarely presented in AQP4-ON (2, 2.99%) and seronegative-ON (2, 2.33%) groups. Similar to our results, a study in Australasia indicated that a total of 103/146 episodes had a relationship with steroid tapering in the relapsing MOG antibody-positive patients [18]. Chalmoukou [13] also observed that five out of eight MOG-ON patients had corticosteroid dependency in Greece. Besides, Ramanathan et al. reported two MOG-ON paediatric cases with corticosteroid dependency [23]. To our knowledge, our study was the first to report the relevant proportion of steroid-dependent adults in each ON subgroup in China. Because the high proportion of steroid-dependent patients in MOG-ON adults, steroids should be considered to be reduced gradually at a lower speed, and immunosuppressors or maintenance oral prednisone could be actively considered.

Orbital MRI plays an essential role in the diagnosis and to differentiate subtypes of ON [24]. Previous studies seldom elaborated on the lesion position of the optic nerve in ON patients. In our cohort, 95.2% of eyes in the MOG-ON group affected the intraorbital segment, whereas a larger proportion of involved canalicular segment were found than in the other two groups. Only 2 eyes involved the optic chiasm in MOG-

Table 3
Comparison of laboratory, orbital MRIs and pRNFL thickness among adults with MOG-ON, AQP4-ON and seronegative-ON.

	MOG-ON	AQP4-ON	Seronegative-ON	*P*	[a]*P*	[b]*P*	[c]*P*
MRI distribution, eyes, n	21	42	41				
Orbital, n (%)	20 (95.2)	39 (92.9)	37 (90.2)	0.803			
Canalicular, n (%)	18 (85.7)	21 (50.0)	15 (36.6)	0.001	0.007*	< 0.001*	0.270
Intracranial, n (%)	8 (38.1)	12 (28.6)	6 (14.6)	0.101			
Optic chiasm, n (%)	2 (9.5)	8 (19.0)	3 (7.3)	0.292			
Tract, n (%)	0 (0)	3 (14.0)	1 (2.4)	0.528			
CSF examination							
CSF white cells count (No/mm3)	3.12 ± 3.46	2.69 ± 2.65	1.78 ± 2.91	0.003	0.654	0.039	0.001*
CSF protein (mg/L)	309.68 ± 92.46	372.66 ± 143.64	341.26 ± 94.74	0.098			
CSF IgG level (mg/dl)	2.12 ± 0.93	3.87 ± 2.71	2.60 ± 1.46	< 0.001	< 0.001*	0.134	0.003*
pRNFL (μm), eyes, n	19	37	30				
Average thickness (mean ± SD)	72.40 ± 9.20	60.74 ± 12.23	67.59 ± 15.90	< 0.001	< 0.001*	0.076	0.016*
Superior thickness (mean ± SD)	86.60 ± 15.01	69.74 ± 21.32	82.02 ± 24.61	< 0.001	< 0.001*	0.212	0.003*
Inferior thickness (mean ± SD)	89.60 ± 18.47	68.04 ± 21.07	80.27 ± 28.05	< 0.001	< 0.001*	0.046	0.022
Temporal thickness (mean ± SD)	50.60 ± 16.92	46.05 ± 10.44	47.95 ± 14.89	0.545			
Nasal thickness (mean ± SD)	57.95 ± 9.43	53.89 ± 9.23	56.05 ± 8.20	0.044	0.033	0.507	0.067

P, comparison among three ON subgroups. A *p* value < .05 was considered significant.
A **p* value < .017 was considered significant after Bonferroni's correction for multiple comparisons. CSF, cerebrospinal fluid; pRNFL, peripapillary retinal nerve fibre layer.
[a] *P*, MOG-ON versus AQP4-ON.
[b] *P*, MOG-ON versus seronegative-ON.
[c] *P*, AQP4-ON versus seronegative-ON.

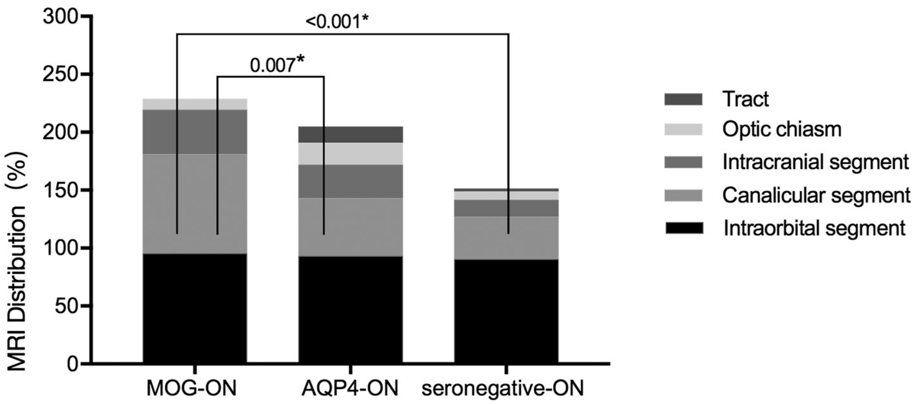

Fig. 5. Distribution of ON lesions in each sub-segment among three groups of ON adults.

ON adults. This finding was consistent with the study by S Ramanathan et al. [25], which reported that MOG-ON tended to involve the anterior optic pathway, whereas AQP4-ON involved the posterior optic pathway. Akaishi et al. [19] also indicated that the wider range of AQP4-ON lesions was the strongest predictor of its final visual outcome. The underlying mechanism of MRI diversity in different ON subtypes and the prognostic value of MRI in MOG-ON remain to be further investigated.

Our study also had some limitations. First, this study is a single-centre cohort study, which has a selection bias as the exclusion criteria. Otherwise, we could not describe the relationship between the titre of MOG-Ab/AQP4-Ab and prognosis or relapse of ON. Thus, more investigations with prospective studies with a large cohort are required.

MOG-ON had the smallest proportion of acute demyelinating ON in Chinese adults. The unique characteristic of steroid dependency was predominantly presented in MOG-ON adults, with one third of them showing substantial dependency on steroids and relapse on steroid reduction or cessation, which rarely presented in AQP4-ON and seronegative-ON groups.

Conflicts of interest

All the authors declare that there is no conflict interest.

Ethical statement

This work was approved by the PLAGH Ethics Committee and was conducted according to the Declaration of Helsinki in its latest applicable version. All individuals participated in this work after voluntarily providing written informed consent.

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