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ORIGINAL COMMUNICATION

# Comparison of the retinal vascular network and structure in patients with optic neuritis associated with myelin oligodendrocyte glycoprotein or aquaporin-4 antibodies: an optical coherence tomography angiography study

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## Abstract

**Objective** To compare the retinal vascular network and structure of optic neuritis associated with myelin oligodendrocyte glycoprotein antibodies (MOG-ON) or aquaporin-4 antibodies (AQP4-ON).

**Methods** Nineteen patients with MOG-ON (29 eyes), 24 patients with AQP4-ON (43 eyes), and 25 healthy participants (50 eyes) were enrolled. The best-corrected visual acuity (BCVA), mean deviation (MD), retinal nerve fiber layer (RNFL) thickness, parafoveal ganglion cell and inner plexiform layer (GCIPL) thickness, and vessel densities in the peripapillary and parafoveal areas were measured.

**Results** The BCVA, RNFL thickness, GCIPL thickness, and vessel densities in the peripapillary and parafoveal areas were significantly decreased in the AQP4-ON and MOG-ON eyes compared with healthy controls (all $P < 0.05$). There were no significant differences in the MD, RNFL thickness, GCIPL thickness, or vessel densities between the AQP4-ON and MOG-ON eyes (all $P > 0.05$). However, the BCVA was significantly worse in AQP4-ON eyes than in MOG-ON eyes ($P = 0.001$). The peripapillary vessel density was significantly correlated with the BCVA and MD in AQP4-ON eyes and with MD in MOG-ON eyes (all $P < 0.05$).

**Conclusions** MOG-ON and AQP4-ON are associated with severe visual dysfunction, as well as retinal structural and vascular damage. The extent of visual dysfunction was strongly correlated with the peripapillary vessel density. Although we found no significant difference in the MD between MOG-ON and AQP4-ON, which are characterized by comparable vascular and structural damage within the peripapillary and parafoveal areas, the BCVA was worse in AQP4-ON eyes than in MOG-ON eyes.

**Keywords** Optic neuritis · Myelin oligodendrocyte glycoprotein · Aquaporin-4 · Optical coherence tomography angiography · Vessel density

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## Introduction

Optic neuritis (ON) is a frequent manifestation in patients with neuromyelitis optica spectrum disorders (NMOSD) that causes neuroaxonal damage to the optic nerve and retina, and ultimately leads to visual impairment [1, 2]. Aquaporin-4 (AQP4)-antibody (Ab)-positive NMOSD is one of the most common types of NMOSD in China, and we recently reported that 64.1% of patients with this type experienced ON at least once during their disease course [3]. With the introduction of highly specific cell-based assays, antibodies against MOG (MOG-IgG) have been detected in some AQP4-Ab-seronegative patients with NMOSD, and studies have suggested that MOG-ON is associated with more favorable visual outcomes after ON compared with AQP4-ON [4–6]. Moreover, Sotirchos et al. [7] reported that AQP4-IgG seropositivity is associated with worse visual outcomes after ON compared with that in patients with MOG-ON, even among patients with similar thinning of the macular ganglion cell and inner plexiform layer (GCIPL).

The recent development of optical coherence tomography angiography (OCTA) has offered ophthalmologists the opportunity to scan retinal blood vessels non-invasively [8]. Using this technique, several studies have revealed marked changes of the retinal vessels in eyes affected by retinal or optic nerve diseases [9–11]. Furthermore, we recently reported that the retinal vessel density was decreased in AQP4-ON eyes [12]. However, little is known about the changes in the structure and vascularity of retinal blood vessels in MOG-ON and AQP4-ON, and whether there are differences between these disorders. Therefore, the aims of the study were to investigate the characteristics of the retinal vasculature in MOG-ON and AQP4-ON eyes, and to identify any differences between these two disorders.

## Methods

### Participants

Nineteen patients with MOG-ON (29 eyes; only eyes with ON were included), 24 age-matched patients with AQP4-ON (43 eyes, only eyes with ON were included) and 25 healthy participants were enrolled between June 2015 and June 2017 at the Neuromyelitis Optica-Multiple Sclerosis Clinic at Huashan Hospital of Fudan University and the Eye and ENT Hospital of Fudan University (Shanghai, China). The study was approved by the Ethics Committee of the Eye and ENT Hospital of Fudan University and performed in accordance with the Declaration of Helsinki and its amendments. Written informed consent was obtained from all participants.

All of the subjects underwent comprehensive ophthalmologic examinations, which included best-corrected visual acuity (BCVA) using a Snellen chart and converted into logarithms of the minimum angle of resolution (logMAR) for analysis, slit-lamp biomicroscopy, refraction measurement using an auto-refractor, calculation of the spherical equivalence as the spherical diopter plus one-half of the cylindrical dioptric power, dilated fundus examination, and measurement of intraocular pressure using a noncontact tonometer. The central visual field was assessed using a Humphrey Field Analyzer 750 with a Swedish Interactive Thresholding Algorithm standard 30-2 test program (Carl Zeiss Meditec, Dublin, CA), and the mean deviation (MD) was determined. The reliability criteria comprised false-positive and false-negative rates of $< 33\%$ and fixation loss of $< 20\%$.

Patients and control subjects with any of the following were excluded: presence of corneal scarring, cataract or obvious vitreous opacity that can affect the transparency of refracting media; history of eye trauma or eye surgery; signs of myopic degeneration or pathologic forms of myopia; other ophthalmic diseases such as retinal vein occlusion, diabetic retinopathy, hypertensive retinopathy, age-related macular degeneration, glaucoma, non-arteritic anterior ischemic optic neuropathy, congenital eye disorders, and other fundus diseases; diagnosis of diabetes mellitus, hypertension, migraine, or other systemic diseases; treatment with intravenous or high doses of oral steroids within 30 days of enrollment; long-term treatment with antihypertensive or antiarrhythmic medications; and history of hydroxychloroquine, ethambutol, or tamoxifen administration.

Patients with MOG-ON or AQP4-ON were eligible if they satisfied the following criteria: best-corrected visual acuity (BCVA) of $\geq$ 20/400 in the eye with the best eyesight; no episodes of ON within 6 months before enrollment; refraction error between $+1.00$ and $-6.00$; cooperation with OCTA and visual field examinations; and seropositivity for MOG-Ab or AQP4-Ab. All the patients underwent clinical neurological examinations with the Expanded Disability Status Scale on the same day as OCTA. History of ON was defined as an acute loss of vision lasting $> 24$ h that was associated with decreased high-contrast visual acuity, eye movement pain, impaired color vision and/or visual field, or optic nerve enhancement on magnetic resonance imaging.

### Detection of MOG-Ab and AQP4-Ab

Patient sera were tested for anti-MOG and anti-AQP4 antibodies at the Euroimmun Medical Diagnostic Laboratory (China) using a fixed-cell-based indirect immunofluorescence test based on BIOCHIPs (EUROIMMUN AG, Lübeck, Germany).

### OCTA acquisition and processing

Both eyes underwent OCTA scans at the same visit using a spectral-domain system (RTVue-XR Avanti, Optovue, Fremont, CA, USA), as previously described [12]. The quality of the OCTA images was evaluated by two independent ophthalmologists blinded to the participants' diagnostic category/group. Poor-quality images with a signal strength index of < 40 and images with residual motion artifacts were rejected.

The radial peripapillary capillary network was visualized on scans within a 0.75-mm-wide elliptical annular region extending from the optic disc boundary. The vasculature within the internal limiting membrane and the nerve fiber layer was automatically analyzed using the software. The parafoveal capillary network was visualized on scans within the annular zone (1–3 mm diameter) around the foveal center. The superficial capillary layer was defined as a layer extending 3 μm below the internal limiting membrane to the outer boundary of the inner plexiform layer. The software automatically calculated the thickness of the parafoveal GCIPL across the parafoveal region to the depth of the superficial capillary layer. Vessel densities were automatically calculated by the software as the relative area of the target region (percent) occupied by large vessels and microvessels [8]. The RNFL and macular thicknesses were also measured automatically using the system. The RNFL thickness was measured across a circular region with a diameter of 3.45 mm centered on the optic disc.

### Statistical analyses

Statistical analyses were performed using IBM SPSS V.20.0 (SPSS, Inc., Chicago, IL, USA). The demographic and ophthalmic data were compared between the study groups using the Kruskal–Wallis test and Fisher's exact test as appropriate. The ophthalmologic and OCT parameters were compared between the study groups using generalized estimating equations (GEE) with adjustment for intrasubject inter-eye differences. The GEE results are reported as regression coefficients (β) with the standard error (SE). Correlations between OCTA parameters and spectral-domain OCT parameters, and between OCTA parameters and clinical parameters were also determined using the GEE models. Statistical significance was set at $P < 0.05$.

## Results

### Demographic and clinical characteristics

A total of 24 AQP4-ON patients (43 eyes), 19 MOG-ON patients (29 eyes), and 25 healthy controls (50 eyes) were included in this study, and their demographic and clinical characteristics are summarized in Table 1. All of the patients

**Table 1** Demographic and clinical characteristics of patients with AQP4-ON, MOG-ON and healthy controls

| | Healthy controls | AQP4-ON | MOG-ON | *P* |
|---|---|---|---|---|
| Number of participants | 25 | 24 | 19 | – |
| Number of eyes | 50 | 43 | 29 | - |
| Females, *n* (%) | 20 (80) | 23 (96) | 12 (63) | **0.000** |
| Age (years, mean ± SD) | 39 ± 8 | 40 ± 10 | 36 ± 15 | 0.235 |
| Episodes of ON, median (range) | – | 2 (1–4) | 2 (1–5) | 0.752 |
| Disease duration, months (median [range]) | – | 27 (6–81) | 43 (6–192) | 0.591 |
| VFSS (median [range]) | – | 2.5 (1–4) | 1 (1–4) | **0.000** |
| EDSS score (median [range]) | – | 3 (1–6) | 1 (1–7.5) | **0.000** |
| Spherical equivalence (D) | − 0.78 ± 1.42 | − 0.89 ± 1.69 | − 1.38 ± 2.18 | 0.308 |
| IOP (mmHg) | 15 ± 2 | 15 ± 2 | 16 ± 2 | 0.362 |
| Regimens for preventing relapse, *n* | | | | |
| Azathioprine | – | 13 | 12 | |
| Mycophenolate mofetil | – | 2 | 2 | |
| Cyclophosphamide | – | 1 | 0 | |
| Tacrolimus | – | 1 | 1 | |
| Rituximab | – | 1 | 0 | |
| None | – | 6 | 4 | |

Values in bold are significant at $P < 0.05$

*MOG-ON* myelin oligodendrocyte glycoprotein antibody-associated optic neuritis, *AQP4-ON* aquaporin-4 antibody-associated optic neuritis, *SD* standard deviation, *ON* optic neuritis, *VFSS* Visual Functional System Score, *EDSS* Expanded Disability Status Scale, *D* diopters, *IOP* intraocular pressure

were treated with high-dose intravenous methylprednisolone following by tapering schedule in the acute stage. Regimens to prevent relapse in patients with MOG-ON were azathioprine ($n=12$), mycophenolate mofetil ($n=2$), and tacrolimus ($n=1$); the other four patients were not receiving any preventive regimens at the time of the study for various reasons. Regimens to prevent relapse in patients with AQP4-ON were azathioprine ($n=13$), mycophenolate mofetil ($n=2$), cyclophosphamide ($n=1$), tacrolimus ($n=1$), and rituximab ($n=1$); the other six patients were not receiving any preventive regimens at the time of the study for various reasons. The mean age was not significantly different among the three groups. The AQP4-ON group comprised a higher proportion of females compared with the MOG-ON group ($P<0.05$). The EDSS and VFSS scores were significantly higher in the AQP4-ON group than in the MOG-ON group, although the number of episodes of ON did not differ significantly between these two groups. The mean spherical equivalence and IOP were not significantly different among the three groups.

### Comparisons of visual function, retinal structure, and vessel densities among AQP4-ON, MOG-ON and healthy control eyes

The OCT and visual function data are compared among the AQP4-ON, MOG-ON, and healthy eyes in Table 2 and Fig. 1. The BCVA was significantly decreased in the AQP4-ON eyes ($0.36\pm0.52$ logMAR, $P<0.001$) and the MOG-ON eyes ($0.09\pm0.20$ logMAR, $P=0.014$) compared with that in healthy eyes $0.00\pm0.04$ logMAR). Although the BCVA was worse in the AQP4-ON eyes than in the MOG-ON eyes ($P=0.001$; Table 2; Fig. 1), the MD was not significantly different between the AQP4-ON eyes ($-9.97\pm12.21$ dB) and the MOG-ON eyes ($-7.52\pm9.07$ dB, $P=0.359$; Table 2). The RNFL thickness, GCIPL thickness, and vessel densities in the peripapillary and parafoveal areas were significantly decreased in the AQP4-ON and MOG-ON eyes compared with those in the healthy eyes (all $P<0.05$; Table 2; Fig. 1), but there were no significant differences in these parameters between the AQP4-ON eyes and the MOG-ON eyes (all $P>0.05$; Fig. 1). We also compared these parameters after matching eyes based on the number of ON episodes. The ocular characteristics were similar between the AQP4-ON and MOG-ON eyes, except for BCVA. BCVA was not significantly different between the MOG-ON and healthy eyes ($P=0.286$, Figure S2).

### Correlations between OCTA parameters and visual function in patients with MOG-ON and AQP4-ON.

We also performed multivariable analyses to determine the correlations between OCTA parameters and visual functions (BCVA and MD) in MOG-ON eyes and AQP4-ON eyes. In the adjusted GEE models, we found that the MD was positively correlated with the peripapillary vessel density ($\beta=0.0.898$, SE $=0.312$, $P=0.004$, Table 3) in MOG-ON eyes and peripapillary vessel density ($\beta=1.416$, SE $=0.383$, $P=0.000$, Table 3) in AQP4-ON eyes, but not with the other parameters. The BCVA was significantly correlated with the peripapillary vessel density in the AQP4-ON eyes ($\beta=-0.038$, SE $=0.01$, $P=0.000$, Table 3), but not in the MOG-ON eyes ($P>0.05$, Table 3).

## Discussion

In this study, we detected evidence of visual dysfunction and retinal structural and vasculature damage in eyes affected by MOG-ON or AQP4-ON. Notably, the extent of visual dysfunction was strongly correlated with the peripapillary vessel density in the MOG-ON eyes and AQP4-ON eyes. We also found that with a similar extent of vascular and structural damage within the peripapillary and parafoveal areas, the MD was similar in both groups, but BCVA was significantly worse in AQP4-ON eyes than in MOG-ON eyes.

Several studies have described retinal damage in MOG-ON and AQP4-ON eyes [12–14]. The thinner RNFL and

**Table 2** Comparisons of visual function and OCT parameters among the three groups

| | Healthy control | AQP4-ON | MOG-ON | *P* |
|---|---|---|---|---|
| Number of eyes | 50 | 43 | 29 | - |
| BCVA, logMAR | $0.00\pm0.04$ | $0.36\pm0.52$ | $0.09\pm0.20$ | $<0.001$ |
| MD (dB) | – | $-9.97\pm12.21$ | $-7.52\pm9.07$ | 0.359 |
| Peripapillary vessel density (%) | $64.62\pm2.50$ | $51.39\pm9.05$ | $51.43\pm7.18$ | $<0.001$ |
| Parafoveal vessel density (%) | $52.13\pm2.86$ | $46.91\pm3.56$ | $45.94\pm3.40$ | $<0.001$ |
| Average RNFL thickness (μm) | $107.86\pm8.33$ | $75.93\pm24.04$ | $77.45\pm17.20$ | $<0.001$ |
| Average GCIPL thickness (μm) | $122.22\pm7.39$ | $100.42\pm16.78$ | $97.07\pm12.30$ | $<0.001$ |

*MOG-ON* myelin oligodendrocyte glycoprotein antibody-associated optic neuritis, *AQP4-ON* aquaporin-4 antibody-associated optic neuritis, *BCVA* best-corrected visual acuity, *MD* mean deviation, *GCIPL* ganglion cell and inner plexiform layer, *RNFL* retinal nerve fiber layer

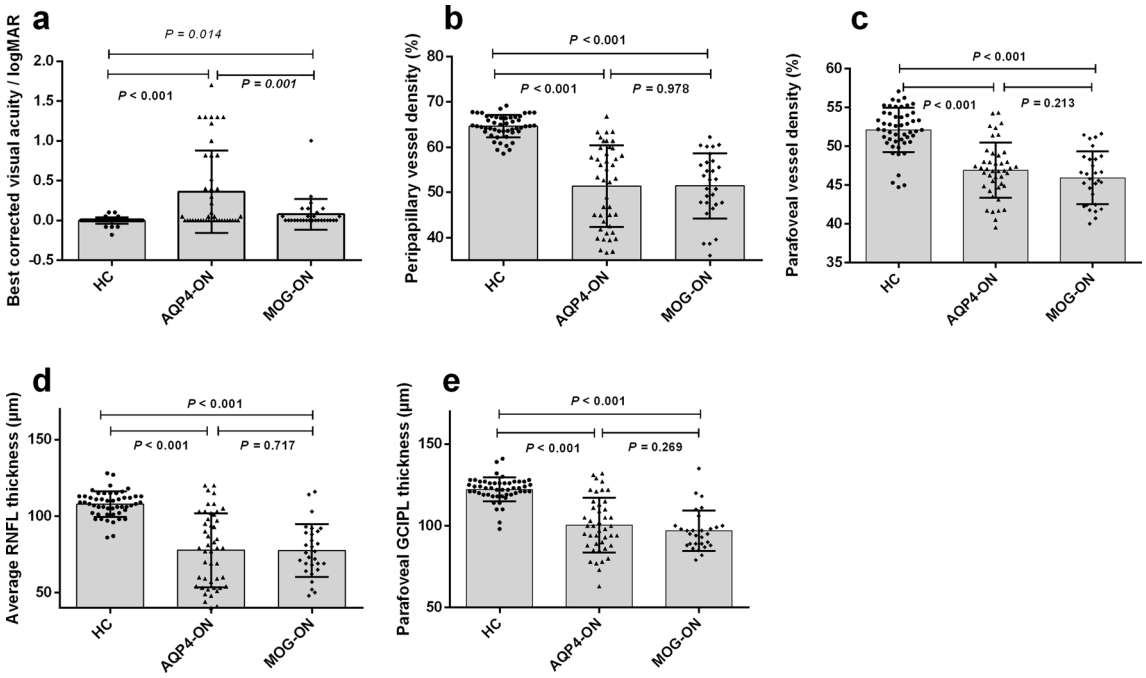


**Fig. 1** Comparisons of visual function, retinal structure, and vessel densities among the AQP4-ON, MOG-ON and healthy control eyes. **a** Best-corrected visual function. **b** Peripapillary vessel density. **c** Parafoveal vessel density. **d** RNFL thickness. **e** Parafoveal GCIPL thickness. Boxes are means ± standard deviation, with individual values shown as symbols. *AQP4-ON* aquaporin-4 antibody-associated optic neuritis, *GCIPL* ganglion cell and inner plexiform layer, *HC* healthy control, *MOG-ON* myelin oligodendrocyte glycoprotein antibody-associated optic neuritis, *RNFL* retinal nerve fiber layer

**Table 3** Correlations between OCTA parameters and visual function in MOG-ON and AQP4-ON eyes

| | AQP4-ON | | | | | | MOG-ON | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BCVA | | | MD | | | BCVA | | | MD | | |
| | *β* | SE | *P* | *β* | SE | *P* | *β* | SE | *P* | *β* | SE | *P* |
| Peripapillary vessel density (%) | −0.038 | 0.01 | **0.000** | 0.898 | 0.312 | **0.004** | 0.012 | 0.007 | 0.074 | 1.416 | 0.383 | **0.000** |
| Parafoveal vessel density (%) | −0.006 | 0.019 | 0.750 | 0.270 | 0.508 | 0.595 | 0.008 | 0.010 | 0.389 | −0.367 | 0.356 | 0.302 |
| RNFL thickness (μm) | −0.004 | 0.004 | 0.328 | 0.078 | 0.106 | 0.461 | 0.002 | 0.002 | 0.288 | -0.292 | 0.534 | 0.057 |
| GCIPL thickness (μm) | 0.008 | 0.004 | 0.053 | −0.164 | 0.096 | 0.089 | -0.005 | 0.003 | 0.130 | −0.074 | 0.152 | 0.627 |

*BCVA* best-corrected visual acuity, *GCIPL* ganglion cell and inner plexiform layer, *RNFL* retinal nerve fiber layer, *MOG-ON* myelin oligodendrocyte glycoprotein antibody-associated optic neuritis, *AQP4-ON* aquaporin-4 antibody-associated optic neuritis

GCIPL detected in our patients is consistent with the results of prior studies showing marked structural damage in MOG-ON and AQP4-ON eyes [5, 7]. We also revealed that the peripapillary and parafoveal vessel densities were significantly decreased in both groups. The mechanism involved in ON-associated retinal vascular network rarefaction is unclear. One possible explanation is that the blood supply requirements are decreased following ON-related retinal damage. The vascular plexuses within the retina are supplied by the central retinal artery, a branch of the ophthalmic artery. The retinal microvascular networks supply the inner retinal layers (i.e., RNFL and GCIPL). Considering that ON and optic neuropathy cause atrophy of the RNFL and GCIPL, a rational explanation for the decreased retinal vessel density in ON eyes may be due to their lower metabolic demand. The simultaneous decreases in the inner retinal thickness and retinal vessel density in MOG-ON eyes and AQP4-ON eyes may support these hypotheses.

The retinal nerve fibers and vessels converge at the optic disc. Therefore, the vessels and structure within the peripapillary area reflect the average damage across the entire retina, unlike the parafoveal area. Previously, Li et al. [15] reported that visual stimulation increases neural activity and cerebral blood flow under normal physiologic conditions, suggesting that perfusion of the central nervous system may be sensitive to changes in neural activity. Costello et al. [16] reported

that in eyes with multiple sclerosis-associated ON and an RNFL thickness of > 75 µm, the MD was not significantly correlated with the RNFL thickness. Their findings suggest that RNFL thinning does not adequately reflect the functional status of retinal ganglion cells. In our study, we found that visual function (BCVA and MD) was significantly correlated with the peripapillary vessel density after adjusting for other variables. This finding suggests that peripapillary retinal perfusion may be more sensitive to the changes in visual stimulation and retinal ganglion cell activity.

When we compared the visual function and structural characteristics between the AQP4-ON eyes and MOG-ON eyes, we found that the BCVA was lower in AQP4-ON eyes than in MOG-ON eyes, but there were no significant differences in the retinal thicknesses or vessel densities between the two groups. Similar results were reported by Sotirchos et al. [5]. We also found no significant differences in the retinal vasculature and MD between the two groups. A One eye with MOG-ON experienced a new episode of ON during the follow-up, and we recorded data before (at least 6 months after the previous episode ON), during the episode of ON, and 6 months after the episode (Figure S1). In the phase of ON, the papilledema may affect the result of peripapillary vessel density and RNFL thickness (Figure S1 e, g), so we excluded the results within 6 months after ON for analyzis. We found that the peripapillary vessel density, parafoveal vessel density, RNFL thickness and GPIPL thickness was reduced after ON, the BCVA recovered to the lever before ON, but the MD was not recovered to the lever before ON. The reason visual acuity was worse in AQP4-ON eyes than in MOG-ON eyes, despite comparable retinal vasculature and structural damage, remains unclear. However, these findings may be due to the distinct pathophysiologies of MOG-ON and AQP4-ON. MOG-ON involves an autoimmune response specific to MOG, which is expressed on myelin sheaths, whereas the retina contains unmyelinated neurons lacking MOG [17]. Consequently, the retinal damage and reduced numbers of nerve fibers and ganglion cells in MOG-ON may be due to retrograde degenerative processes, which reduce the retina's metabolic requirements. The reduced metabolic demand leads to a reduction in retinal perfusion via autoregulatory mechanisms. Remarkably, however, a reduction in RNFL thickness was observed in two fellow eyes without clinical evidence of prior ON [5]. The mechanisms underlying this finding require further investigation. In contrast, AQP4-ON is characterized by autoimmune astrocytopathy. AQP4 is highly expressed in retinal Müller cells, the cell bodies of which are located in the inner nuclear layer, while astrocytes are mainly located in the RNFL, particularly in the end-feet membranes facing the blood vessels [18, 19]. Müller cells are involved in multiple homeostatic functions within the retina, and a decrease in AQP4 immunoreactivity on retinal Müller cells has been demonstrated in AQP4-ON eyes [20]. Deletion of AQP4 decreases the capacity of Müller cells to withstand osmotic stress and induces retinal inflammation, and selective ablation of Müller cells causes photoreceptor apoptosis and vascular retinal abnormalities [21, 22]. Therefore, in addition to retrograde degenerative processes, direct damage to the vascular and cone cells, which are essential for central visual acuity and are mainly located in the fovea, may occur in AQP4-ON and contribute to the worse BCVA. The RNFL and GCIPL thicknesses reflect damage to retinal ganglion cells. Because the macular fovea is normally avascular, the oxygen and nutritional demands of the fovea are ordinarily met by vessels within the parafoveal area and partially by the choroidal vascular system. Thus, the RNFL, GCIPL, and retinal vessel density may not reflect the severity of damage to the cone cells within the fovea. This may explain why the MD was similar but the BCVA was worse in AQP4-ON eyes than in MOG-ON eyes, despite the similar extent of vascular and structural damage within the peripapillary and parafoveal areas. Functional studies of cones, using multifocal electroretinography, for example, in MOG-ON and AQP4-ON eyes are needed to confirm our hypothesis.

Our study has several limitations. First, we enrolled relatively small numbers of patients with MOG-ON and AQP4-ON. Thus, independent validation of our results in other cohorts is warranted. Second, the cross-sectional nature of the study limited our ability to evaluate the implications of changes in the implications of progression of MOG on the changes in retinal microvasculature.

In conclusion, our study provides compelling evidence that MOG-ON and AQP4-ON are associated with severe RNFL, GCIPL, peripapillary vessel, and parafoveal vessel damage. We also revealed that the extent of visual dysfunction is strongly correlated with the peripapillary vessel density. In AQP4-ON eyes and MOG-ON eyes, in which the extent of vascular and structural damage within the peripapillary and parafoveal areas was similar, the MD was not significantly different between the two groups, but the BCVA was worse in AQP4-ON eyes. Further studies are needed to confirm and expand on our findings, and to identify potential new therapeutic targets for ON.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00415-021-10609-3.

**Authors' contributions** CQ and MW had full access to all of the data, and take responsibility for the integrity of the data and the accuracy of the data analyses. Concept and design: CQ and MW. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: JY and YH (Wenghang Wong). Critical revision of the manuscript for important intellectual content: CQ and MW. Statistical analysis: JY. Administrative, technical, or material support: CQ and MW. Supervision: CQ and MW.

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**Availability of data and material** The research data used to support the findings of this study are included within the article.

## Declarations

**Conflicts of interest** The authors have no proprietary or commercial interests regarding any of the content discussed in this article.

**Ethics approval** The study was approved by the Ethics Committee of the Eye and ENT Hospital of Fudan University.

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