AQP4-IgG and MOG-IgG Related Optic Neuritis—Prevalence, Optical Coherence Tomography Findings, and Visual Outcomes: A Systematic Review and Meta-Analysis

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Background: Optic neuritis (ON) is a cardinal manifestation of multiple sclerosis (MS), aquaporin-4 (AQP4)-IgG-, and myelin oligodendrocyte glycoprotein (MOG)-IgG-associated disease. However, the prevalence of AQP4-IgG seropositivity and MOG-IgG seropositivity in isolated ON is unclear, and studies comparing visual outcomes and optical coherence tomography (OCT)-derived structural retinal measures between MS-ON, AQP4-ON, and MOG-ON eyes are limited by small sample sizes.

Objectives: (1) To assess the prevalence of AQP4-IgG and MOG-IgG seropositivity among patients presenting with isolated ON; (2) to compare visual outcomes and OCT measures between AQP4-ON, MOG-ON, and MS-ON eyes.

Methods: In this systematic review and meta-analysis, a total of 65 eligible studies were identified by PubMed search. Statistical analyses were performed with random effects models.

Results: In adults with isolated ON, AQP4-IgG seroprevalence was 4% in non-Asian and 27% in Asian populations, whereas MOG-IgG seroprevalence was 8 and 20%, respectively. In children, AQP4-IgG seroprevalence was 0.4% in non-Asian and 15% in Asian populations, whereas MOG-IgG seroprevalence was 47 and 31%, respectively.

AQP4-ON eyes had lower peri-papillary retinal nerve fiber layer (pRNFL; \(-11.7 \, \mu m, \, 95\% \, CI: \,-15.2 \, to \,-8.3 \, \mu m\)) and macular ganglion cell + inner plexiform layer (GCIPL; \(-9.0 \, \mu m, \, 95\% \, CI: \,-12.5 \, to \,-5.4 \, \mu m\)) thicknesses compared with MS-ON eyes.

Similarly, pRNFL (\(-11.2 \, \mu m, \, 95\% \, CI: \,-21.5 \, to \,-0.9 \, \mu m\)) and GCIPL (\(-6.1 \, \mu m, \, 95\% \, CI: \,-10.8 \, to \,-1.3 \, \mu m\)) thicknesses were lower in MOG-ON compared to MS-ON eyes, but did not differ between AQP4-ON and MOG-ON eyes (pRNFL: \(-1.9 \, \mu m, \, 95\% \, CI: \,-9.1 \, to \, 5.4 \, \mu m\); GCIPL: \(-2.6 \, \mu m, \, 95\% \, CI: \,-8.9 \, to \, 3.8 \, \mu m\)). Visual outcomes were worse in AQP4-ON compared to both MOG-ON (mean logMAR difference: 0.60, 95% CI: 0.39 to 0.81) and MS-ON eyes (mean logMAR difference: 0.68, 95% CI: 0.40 to 0.96) but were similar in MOG-ON and MS-ON eyes (mean logMAR difference: 0.04, 95% CI: 0.05 to 0.14).
**INTRODUCTION**

Optic neuritis (ON) is a cardinal manifestation of inflammatory conditions of the central nervous system (CNS), including multiple sclerosis (MS), aquaporin-4 (AQP4)-IgG-, and myelin oligodendrocyte glycoprotein (MOG)-IgG-associated disease (1–3). Early recognition of the underlying etiology of ON has important therapeutic implications, given that treatment approaches vary between these conditions, and therapies that are efficacious in MS may exacerbate or be ineffective in AQP4-IgG- or MOG-IgG-associated disease (4, 5). Furthermore, visual prognosis appears to differ between these conditions, with AQP4-IgG-associated ON (AQP4-ON) typically characterized by worse visual outcomes in comparison to MS-associated ON (MS-ON) and MOG-IgG-associated ON (MOG-ON) (6–8). In patients presenting with classic neuromyelitis optica (NMO) or acute disseminated encephalomyelitis (ADEM)-like phenotypes, clinical suspicion for AQP4-IgG- or MOG-IgG-associated disease is high, but diagnosis may be challenging and delayed in limited forms, such as isolated ON. Notably, the reported prevalence of AQP4-IgG and MOG-IgG seropositivity among patients presenting with isolated ON varies significantly between studies, and the available literature suggests that seropositivity for these antibodies is more common in non-white populations with ON (9, 10).

Optic nerve injury results in thinning of the retinal nerve fiber layer (RNFL), which is mainly composed of the unmyelinated axons of the retinal ganglion cells (RGCs), and the ganglion cell layer, which contains the cell bodies of the RGCs (1). Optical coherence tomography (OCT) is an imaging technique that utilizes near-infrared light to obtain high-resolution images of the retina in vivo and enables the quantitative evaluation of individual retinal layers, allowing assessment of the integrity of the RGC axons [peri-papillary RNFL thickness (pRNFL)] and RGC cell bodies [composite thickness of the macular ganglion cell + inner plexiform layer (GCIPL)] (11, 12). OCT studies have generally demonstrated increased severity of pRNFL and GCIPL thinning following AQP4-ON and MOG-ON eyes, compared to MS-ON (8). However, given the rarity of AQP4-IgG- and MOG-IgG-associated disease, OCT studies have examined relatively small numbers of participants, not permitting an in-depth characterization and comparison of the retinal neuro-axonal injury that occurs in these conditions.

The primary objectives of this systematic review and meta-analysis were as follows: (1) To determine the seroprevalence of AQP4-IgG and MOG-IgG among patients presenting with isolated ON, and to explore variation in prevalence by geographical location/ethnicity. (2) To assess pRNFL and GCIPL thicknesses in AQP4-ON and MOG-ON eyes (including comparisons to MS-ON and healthy controls), and to investigate whether distinct patterns of retinal injury are associated with AQP4-ON or MOG-ON. (3) To compare visual outcomes between AQP4-ON, MOG-ON, and MS-ON eyes.

**METHODS**

The present systematic review and meta-analysis is reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (13, 14).

**Search Strategy and Study Selection**

The PubMed electronic database was queried using search algorithms (available in detail in Supplementary Table 1) including the following keywords: “mog,” “myelin oligodendrocyte glycoprotein,” “nmo,” “neuromyelitis optica,” “aquaporin 4,” “aqp4,” “aquaporin-4,” “optic neuritis,” “optic coherence tomography,” “retina,” “nerve fiber layer,” “ganglion cell,” “vision,” “visual outcome,” and “disability.” Databases were last accessed on October 29, 2019.

All retrieved studies were imported into the Covidence platform for study eligibility screening and inclusion. The studies were screened independently by two reviewers (AGF and LM), and in cases of disagreement, another reviewer (ESS) was consulted.

For our first study objective (assessing the prevalence of AQP4-IgG and MOG-IgG seropositivity in isolated ON), we identified all studies that reported the frequency of AQP4-IgG and/or MOG-IgG seropositivity in a cohort of patients presenting with an initial episode of isolated (monosymptomatic) unilateral or bilateral ON. Study exclusion criteria included the following: (1) studies that did not report the number of

**Conclusions:** AQP4-IgG- and MOG-IgG-associated disease are important diagnostic considerations in adults presenting with isolated ON, especially in Asian populations. Furthermore, MOG-IgG seroprevalence is especially high in pediatric isolated ON, in both non-Asian and Asian populations. Despite a similar severity of GCIPL and pRNFL thinning in AQP4-ON and MOG-ON, AQP4-ON is associated with markedly worse visual outcomes.

**Keywords:** optic neuritis (ON), optical coherence tomography (OCT), neuromyelitis optica (NMO), neuromyelitis optica spectrum disorder (NMOSD), visual acuity, retina, aquaporin-4 (AQP4) IgG, myelin oligodendrocyte glycoprotein (MOG) IgG associated disease
patients with pre-existing diagnoses of MS or neuromyelitis optica spectrum disorder (NMOSD) or with prior episodes of neurological dysfunction, (2) \( n < 10 \) participants, and (3) unclear criteria for participant inclusion or inclusion only of selected high-risk patient subgroups (e.g., bilateral or recurrent ON, normal brain MRI). As secondary analyses, we also identified studies reporting the prevalence of AQP4-IgG and MOG-IgG seropositivity in patients presenting with recurrent isolated (unilateral or bilateral) ON or bilateral simultaneous/rapidly sequential ON.

For our second study objective (comparison of OCT measures between AQP4-ON, MOG-ON, and MS-ON eyes), we identified studies that reported OCT measures from patients with AQP4-ON and/or MOG-ON and included data permitting at least one of the following comparisons: (1) AQP4-ON vs. healthy control (HC) eyes, (2) MOG-ON vs. HC eyes, (3) AQP4-ON vs. MOG-ON eyes, (4) AQP4-ON vs. MS-ON eyes, and (5) MOG-ON vs. MS-ON eyes. Comparison of MS-ON vs HC eyes was not performed as this was not the focus of our study and this has been reported in a recent large meta-analysis (15).

Similarly, for our third study objective (comparison of visual outcomes in AQP4-ON, MOG-ON, and MS-ON eyes), studies were included that reported visual outcomes in AQP4-ON and/or MOG-ON and included data permitting at least one of the following comparisons: (1) AQP4-ON vs. MOG-ON, (2) AQP4-ON vs. MS-ON, and (3) MOG-ON vs. MS-ON.

For our analyses of OCT and visual outcomes, we only included articles with assessments of ON eyes performed at least 3 months after an episode of acute ON. For studies that collected the data necessary for our analyses but did not report the results in a manner appropriate for our purposes (e.g., not separating eyes by ON history, reporting combined estimates for AQP4-IgG seropositive and seronegative NMOSD patients), corresponding authors were contacted and were asked to provide additional information. If this information was not made available, these studies were excluded. Additional unpublished data from the cohorts included in the manuscripts was occasionally provided, at the discretion of the corresponding authors. For the OCT component, studies were also excluded if they did not utilize spectral-domain OCT.

When two or more similar studies (fulfilling inclusion criteria) were reported from the same institution or author with unclear participant overlap between studies, authors were contacted to provide clarification. When unable to obtain this information, the publication with the highest number of participants was included in the analysis. Case reports, reviews, or studies published in a non-English language were excluded. Reference lists of relevant review articles were also examined to identify studies that may have been missed during the initial database search.

**Data Extraction and Outcomes**

Two investigators (AGF and LM) independently conducted the data extraction, and any discrepancies were resolved by consensus.

For assessment of the prevalence of AQP4-IgG and MOG-IgG in isolated ON, we recorded the total number of patients presenting with an isolated ON in each study (excluding patients with a prior neurological history), and the number of patients that tested positive for AQP4-IgG or MOG-IgG.

The main outcome measures for OCT analyses were the thicknesses (\( \mu m \)) of the pRNFL and the macular GCIPL [or macular ganglion cell layer complex (GCC), which additionally includes the macular RNFL] of eyes with a history of ON, and this information was recorded for each group as the mean \( \pm SD \). Additional data on quadrantal pRNFL thicknesses were collected, if available. For studies that reported OCT measures as median/interquartile range and the corresponding authors had not provided the mean \( \pm SD \), a normal distribution was assumed to calculate the SD. If macular OCT measures were reported as volumes, they were converted to thicknesses according to the formula: Thickness = Volume/Surface Area. For macular measures, the region of interest varied between studies (e.g., perifoveal area of 3 or 6 mm in diameter, including or excluding the foveal subfield); thus, the surface area was calculated separately for each study, depending on the utilized protocol. While not a primary focus of this study, we also recorded (when available) the prevalence of microcystoid macular pathology (MMP; also referred to as microcystic macular edema in the literature) in AQP4-ON and MOG-ON eyes (16–18).

For visual outcomes, the main outcome measures were the logarithm of the minimum angle of resolution (logMAR) in eyes with a history of ON and the percentage of affected eyes with high-contrast visual acuity (VA) worse than 20/200. For MOG-IgG serostatus, only studies that reported using cell-based assays (CBAs) for testing were included, whereas for AQP4-IgG serostatus, studies utilized a variety of assays, including CBAs, indirect tissue immunofluorescence, enzyme-linked immunosorbent assay (ELISA) or fluorescence-based immunoprecipitation assay (FIPA).

Data were extracted from cross-sectional cohorts and from a single time point from longitudinal studies (typically the baseline assessment).

**Data Synthesis and Statistical Analysis**

For all study objectives, studies of pediatric participants were examined separately.

We estimated the pooled AQP4-IgG and MOG-IgG prevalence in isolated ON separately for Asian and non-Asian populations, given the divergence of prevalence between studies in these populations, and evidence supporting higher prevalence of NMOSD in Asian populations (10). Given the relatively low prevalence of these disorders in some of the included studies (estimates close to 0%), we utilized the variance-stabilizing double arcsine transformation method (19).

OCT measures were handled as continuous variables. Results are presented as mean differences between the groups of interest. OCT measures from different spectral-domain OCT devices were analyzed together, similar to a prior large meta-analysis in MS, given that, at a group level, it appears that data are comparable across devices and segmentation algorithms (15, 20). In terms of macular OCT measures, the GCIPL and GCC were analyzed together, given that the GCC accounts for the majority of the thickness of the GCC. Additionally, we estimated the pooled prevalence of MMP in AQP4-ON and MOG-ON eyes.
| Study                  | Time period | Study setting | Adult/pediatric | Age                  | Female sex | Race               | AQP4-IgG positive | MOG-IgG positive | Bilateral ON | Important considerations                  |
|-----------------------|-------------|---------------|-----------------|----------------------|------------|--------------------|------------------|-----------------|-------------|------------------------------------------|
| Carnero et al.        | 2009–2015   | Argentina     | Adult            | Mean (±SD): 31.6 (±11.1) in AQP4-IgG positive, 38.4 (±12.9) in AQP4-IgG negative | 47%        | –                  | Tissue-based indirect IF | –               | 32%         | –                                        |
| Chen et al. (40)      | 1988–1991   | Multicenter–USA | Adult (18–45)    | Mean (±SD): 32.8 (±6.9) | 76%        | 85% Caucasian     | CBA              | CBA             | 0%          | Recruited only patients with unilateral ON |
| Chen et al. (41)      | 2015–2016   | China         | Pediatric        | Range: 5–18, Mean (±SD): 11.8 (±3.3) in MOG-ON, 16.9 (±0.8) in AQP4-ON | 70%        | –                  | CBA              | CBA             | 63%         | –                                        |
| Cobo-Calvo et al. (22)| 2014–2016   | France        | Mixed adult pediatric | Median (range): 16.8 (1.7–64.9) for MOG-ON | 52%        | 93% Caucasian in MOG-IgG positive | CBA              | CBA             | 22% in MOG-IgG positive | –            |
| Dale et al. (23)      | –           | Australia     | Pediatric        | Median (range): 8 (1.3–15.3) | 51%        | –                  | ELISA            | CBA             | 67%         | –                                        |
| Deschamps et al. (42) | 2014–2016   | France        | Mixed adult pediatric | Range: 16–57 | 75%        | –                  | CBA              | CBA             | 10%         | MOG AQP4 only tested if patient did not meet diagnostic criteria for MS |
| Ducloyer et al. (24)  | 2017–2018   | France        | Adult            | Mean (±SD): 35.6 (±13.8) | 68%        | –                  | CBA              | –               | 15%         | –                                        |
| Hacoohen et al. (25)  | 2009–2011   | UK France     | Pediatric        | Range: 1.3–15.8 | 57%        | –                  | CBA              | –               | –           | –                                        |
| Jarius et al. (26)    | –           | Multicenter–Europe | Mixed adult pediatric | Median (range): 34 (14–72) | 75%        | 96% Caucasian     | FIPA             | –               | 22%         | –                                        |
| Kim et al. (28)       | 2013–2014   | South Korea   | Adult            | Mean (±SD): 38.7 (±11.5) in AQP4-IgG positive, 42.3 (±14.7) in AQP4-IgG negative | 67%        | Asian              | CBA              | –               | 7%          | –                                        |
| Kim et al. (27)       | 2007–2016   | South Korea   | Adult            | Mean (±SD): 43 (±13) | 63%        | –                  | CBA              | –               | 21%         | –                                        |
| Liu et al. (29)       | 2014–2016   | China         | Adult            | Range: 18–72 | 80%        | –                  | CBA              | CBA             | 20%         | –                                        |
| Petzold et al. (30)   | 1995–2007   | UK            | Adult            | Range: 15–71 | 67%        | –                  | CBA              | CBA             | –           | –                                        |
| Rostasy et al. (31)   | 2004–2010   | Germany Austria | Pediatric        | Median (range): 13 (2–18) | 73%        | –                  | CBA              | CBA             | 8%          | –                                        |

(Continued)
| Study | Time period | Study setting | Adult/pediatric | Age | Female sex | Race | AQP4-IgG assay | MOG-IgG assay | Bilateral ON | Important considerations |
|-------|-------------|---------------|-----------------|-----|------------|------|----------------|---------------|--------------|--------------------------|
| Soelberg et al. (32) | 2014–2016 | Denmark | Mixed adult pediatric | Median (range): 38 (16–66) | 69% | 100% Caucasian | CBA | CBA | 8% | – |
| Song et al. (33) | 2016–2017 | China | Pediatric | Mean (±SD): 10.6 (±4.4) | 56% | – | – | CBA | 52% | – |
| Storoni et al. (34) | 2009–2010 | UK | Adult | – | – | 61% Caucasian 14% African 15% Asian 10% Other | FIPA | – | – | – |
| Waters et al. (35) | 2004–2017 | Canada | Pediatric | Median (IQR): 10.8 (6.2–13.9) | 51% | – | – | CBA | CBA | – | – |
| Zhao et al. (36) | 2015–2016 | China | Adult | Mean (±SD): 31.3 (±5.3) for MOG-ON 40.7 (±15.3) for AQP4-ON 31.3 (±13.2) for other | 71% | – | CBA | CBA | 25% | – |
| Zhou et al. (39) | 2013–2014 | China | Mixed adult pediatric | Range: 13–73 | 66% | – | CBA | – | 26% | – |
| Zhou et al. (37) | 2009–2010 | China | Adult | Median (range): 36.8 (18–73) | 66% | – | CBA | – | 24% | – |
| Patients with recurrent isolated ON | | | | | | | | | | |
| Benoïlid et al. (43) | 2010–2011 | France | Adult | Mean (±SD): 33.1 (±14.8) | 73% | 97% Caucasian | CBA | – | 33% | – |
| de Seze et al. (44) | 2005–2007 | France | Adult | Mean (±SD): 35.4 (±11.9) | 92% | – | Tissue-based indirect IF | – | – | – |
| Jarius et al. (26) | – | Multicenter - Europe | Mixed adult pediatric | Median (range): 34 (14–72) | 75% | 96% Caucasian | FIPA | – | 22% | – |
| Jitprapaikulsan et al. (45) | 2010–2017 | USA | Mixed adult pediatric | Range: 12–72 | 72% | 83% Caucasian | CBA | CBA | 22% | – |
| Li et al. (46) | 2008–2013 | China | Adult | Mean (±SD): 39.0 (±15.4) | 75% | – | CBA | – | 23% | – |
| Martinez-Hernandez et al. (47) | 2005–2014 | Spain | Mixed adult pediatric | Median (range): 28 (5–65) | 71% | – | CBA | – | 45% | Only recruited patients with normal or nonspecific MRI findings |

AQP4, aquaporin 4; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; ON, optic neuritis; CBA, cell-based assay; FIPA, Fluorescence based immunoprecipitation assay; IF, immunofluorescence; ELISA, enzyme-linked immunosorbent assay; MRI, magnetic resonance imaging; IQR, interquartile range; SD, standard deviation.
For studies reporting VA measurements in logMAR format, logMAR was handled as a continuous variable and results are presented as mean differences between groups of interest. For studies reporting visual outcomes as percentage of eyes with VA worse than 20/200, we calculated the relative risk of this unfavorable visual outcome (i.e., VA < 20/200). Studies reporting visual outcomes in any other formats were included in the qualitative, but not the quantitative, synthesis.

All analyses were performed with random effects models, since the heterogeneity was expected to be high due to varying OCT devices, differing scan protocols and macular regions of interest, and differences in the demographic and clinical characteristics of the participants across studies. To minimize the impact of the study heterogeneity, we did not compare OCT measures or visual outcomes across studies; rather, we estimated between-group differences in each study and then performed a pooled analysis of these estimated differences. We assessed for heterogeneity between the included studies using the I² estimate. I² > 75% was considered to indicate significant heterogeneity.

Statistical analyses were performed with Stata version 16 (StataCorp, College Station, TX). For the meta-analysis of prevalence, the Stata package “metaprop” was used (21).

RESULTS
Prevalence of AQP4-IgG and MOG-IgG Seropositivity in Monosymptomatic ON
Study Selection and Study Characteristics
A PubMed search identified 1,187 records. Of these, 197 articles were selected and assessed for eligibility at the full-text level. After careful evaluation, 21 studies, comprising 1,876 patients, were included that met the inclusion criteria (22–42). The detailed flow chart is presented in Supplementary Figure 1. For our secondary analysis in patients with recurrent ON, six studies, comprising 510 patients, were included that met our inclusion criteria (26, 43–47). There was an insufficient number of studies/participants to analyze the prevalence of AQP4-IgG or MOG-IgG seropositivity among patients presenting with isolated bilateral simultaneous or sequential ON. The included studies are summarized in Table 1.
AQP4-IgG Prevalence in Monosymptomatic ON
The pooled prevalence of AQP4-IgG seropositivity in adults with isolated ON (Figure 1) was 4% in non-Asian cohorts (95% CI: 0 to 11%) and 27% in Asian cohorts (95% CI: 19 to 36%). In pediatric cohorts (Figure 2), similar to adults, AQP4-IgG seroprevalence was again higher in Asian cohorts (15%; 95% CI: 9 to 23%), whereas in the three available studies of non-Asian populations, the prevalence of AQP4-IgG seropositivity was 0.4% (95% CI: 0 to 3.2%).

MOG-IgG Prevalence in Monosymptomatic ON
The prevalence of MOG-IgG seropositivity in adults with isolated ON (Figure 3) was 8% in non-Asian cohorts (95% CI: 4 to 13%) and 20% in Asian cohorts (95% CI: 16 to 24%). In pediatric cohorts (Figure 4), in contrast to adults, MOG-IgG seroprevalence was higher in non-Asian populations (47%; 95% CI: 36 to 58%) relative to Asian populations (31%; 95% CI: 22 to 40%), but both had higher prevalence compared to adults.

AQP4-IgG and MOG-IgG Prevalence in Recurrent Isolated ON
In non-Asian cohorts, the prevalence of AQP4-IgG seropositivity in patients with recurrent isolated ON (Figure 5) was 16% (95% CI: 12 to 21%). Only one study reported the frequency of AQP4-IgG seropositivity in Asian patients with recurrent ON (41%; 95% CI: 31 to 51%). For MOG-IgG, we were able to identify only two studies fulfilling the inclusion criteria; based on these studies (Figure 6), the prevalence of MOG-IgG seropositivity in non-Asian cohorts with recurrent ON was 15% (95% CI: 11 to 19%). No eligible pediatric studies were identified.

OCT Findings in AQP4-ON and MOG-ON
Study Selection and Study Characteristics
A PubMed search identified 351 records. Of these, 98 articles were selected and assessed for eligibility at the full-text level. After careful evaluation, 31 studies were included that met the inclusion criteria (8, 29, 33, 36, 41, 48–73). The detailed flow chart is presented in Supplementary Figure 2. The included studies, comprising a total of 814 HC eyes, 611 AQP4-ON eyes, 237 MOG-ON eyes, and 361 MS-ON eyes, are summarized in Table 2.

OCT Measures in Adult ON
As expected, pRNFL and GCIPL thicknesses were lower in AQP4-ON and MOG-ON eyes, as compared with HC eyes (Supplementary Figures 3, 4). The pooled mean pRNFL difference for AQP4-ON eyes was $-38.0 \mu m$ (95% CI: $-46.5$ to $-29.6 \mu m$) and $-35.7 \mu m$ (95% CI: $-43.1$ to $-28.4 \mu m$) for MOG-ON eyes. The pooled mean GCIPL difference was $-25.8 \mu m$ (95% CI: $-29.1$ to $-22.5 \mu m$) for AQP4-ON eyes and $-26.7 \mu m$ (95% CI: $-32.6$ to $-20.8 \mu m$) for MOG-ON eyes. AQP4-ON eyes had lower pRNFL ($-11.7 \mu m$; 95% CI: $-15.2$ to $-8.3 \mu m$) and GCIPL ($-9.0 \mu m$; 95% CI: $-12.5$ to $-5.4 \mu m$) thicknesses compared with MS-ON (Figure 7), but there were no differences in these OCT measures between AQP4-ON and
MOG-ON eyes (pRNFL: −1.9 µm; 95% CI: −9.1 to 5.4 µm; GCIPL: −2.6 µm; 95% CI: −8.9 to 3.8 µm; Figure 8). Similar to AQP4-ON, when comparing MOG-ON to MS-ON eyes (Figure 9), we found that MOG-ON eyes had lower pRNFL (−11.2 µm; 95% CI: −21.5 to −0.9 µm) and GCIPL thicknesses (−6.1 µm; 95% CI: −10.8 to −1.3 µm).

When examining quadrantal pRNFL thicknesses, we did not observe any differences between AQP4-ON and MOG-ON (Supplementary Figure 5). However, AQP4-ON was associated with lower nasal, inferior, and superior quadrant pRNFL thicknesses compared with MS-ON (Supplementary Figure 6), but no difference was observed in temporal pRNFL thickness between AQP4-ON and MS-ON eyes (−1.4 µm, 95% CI: −5.9 to 3.1 µm). All quadrantal pRNFL thicknesses were lower in MOG-ON compared to MS-ON eyes (Supplementary Figure 7), but these findings did not achieve statistical significance, likely due to the small sample size.

The prevalence of MMP in ON eyes was reported in a small number of studies. The pooled prevalence of MMP was 15% in AQP4-ON eyes (95% CI: 7 to 24%; n = 7 studies) and 21% in MOG-ON eyes (95% CI: 11 to 32%; n = 6 studies), which is higher compared to the reported prevalence of MMP in MS-ON eyes (~6%) (16, 17).

OCT Measures in Pediatric ON

We were able to identify four studies reporting OCT findings in pediatric ON, and OCT measures could be pooled for three studies (33, 41, 67). Similar to adults, pRNFL thickness did not differ between pediatric AQP4-ON and MOG-ON eyes (7.4 µm, 95% CI: −5.9 to 32.0 µm; Supplementary Figure 8). Further comparisons between groups of interest were not possible based on the available data.

Visual Outcomes in AQP4-ON and MOG-ON

Study Selection and Study Characteristics

A PubMed search identified 624 records. Of these, 202 articles were selected and assessed for eligibility at the full-text level. After careful evaluation, 35 studies were included that met the inclusion criteria (8, 29, 30, 33, 36, 39, 41, 45, 47, 48, 51–54, 57, 59, 63, 65, 66, 68, 69, 71, 72, 74–85). The detailed flow chart is presented in Supplementary Figure 9.

The included studies with their baseline characteristics are summarized in Table 3. In our quantitative synthesis, we included 26 studies comprising 747 AQP4-ON eyes, 426 MOG-ON eyes, and 524 MS-ON eyes.
Visual Outcomes in Adult ON
AQP4-ON eyes had worse high contrast VA when compared to both MOG-ON (mean logMAR difference: 0.60, 95% CI: 0.39 to 0.81) and MS-ON (mean logMAR difference: 0.68, 95% CI: 0.40 to 0.96; Figures 10, 11). Visual outcomes did not differ between MOG-ON and MS-ON (mean logMAR difference: 0.04, 95% CI: −0.05 to 0.14; Figure 12). Moreover, the risk of a poor visual outcome (VA ≤ 20/200) was higher for AQP4-ON compared to MOG-ON [relative risk (RR): 5.39, 95% CI: 2.95 to 9.86; Figure 10] and compared to MS-ON (RR: 3.76, 95% CI: 1.71 to 8.25; Figure 11).

Nine studies were excluded from our quantitative synthesis, since the visual outcomes were not presented in a format that was consistent with the other studies. The findings of the studies are presented in Supplementary Table 2. Importantly, all these studies reported that visual outcomes were markedly better in MOG-ON eyes, as compared with AQP4-ON eyes, in line with the results from the quantitative synthesis.

Visual Outcomes in Pediatric ON
We were able to identify three studies reporting visual outcomes in pediatric ON associated with seropositivity for AQP4-IgG and MOG-IgG (33, 41, 63). Similar to adults, the risk of a poor visual outcome (VA ≤ 20/200) was higher for AQP4-ON compared to MOG-ON (RR: 20.11, 95% CI: 4.79 to 84.34), but the sample sizes of the studies were rather small (Supplementary Figure 10).

DISCUSSION
The present systematic review and meta-analysis revealed variable patterns of seroprevalence of AQP4-IGG and MOG-IgG among patients presenting with isolated ON, with overall higher seroprevalence of both antibodies among Asian populations. Moreover, MOG-IgG-associated ON accounted for a large proportion of pediatric isolated ON (over a third of cases), and high MOG-IgG seroprevalence was noted across the pediatric populations included in our study. Furthermore, despite a similar severity of GCIPL and pRNFL thinning in AQP4-ON and MOG-ON, AQP4-ON was associated with markedly worse visual outcomes, compared to both MOG-ON and MS-ON.

Overall, our results support the idea that AQP4-IgG- and MOG-IgG-associated disorders are not rare entities in Asian populations and are important diagnostic considerations during the initial evaluation of ON in these populations. Notably, cohorts from China comprised the vast majority of the Asian cohorts in our study. However, relatively high seroprevalence of AQP4-IgG and/or MOG-IgG in ON has been reported in several studies (that did not however fully fulfill our inclusion criteria) from Japan, Thailand, Malaysia, and additional Chinese centers (74, 77, 86–89). Importantly, while population-based studies support the notion that Eastern Asian populations have a higher prevalence of NMOSD compared to Caucasian populations, MOG-IgG-associated disease does not appear to exhibit a...
significant racial preponderance based on data from existing hospital-based studies (90). This suggests that our findings of high AQP4-IgG seroprevalence in ON in Asian populations are likely accounted for by both a higher prevalence of NMOSD and a lower prevalence of MS, whereas for MOG-IgG seroprevalence, the latter may be a more important factor. A noteworthy exception to our finding of overall lower seroprevalence of AQP4-IgG seropositivity in non-Asian populations was the study by Carnero-Contentti et al. (39), which enrolled patients from Buenos Aires, Argentina, and reported an AQP4-IgG seroprevalence of 30% among patients with ON (39). This finding is unexpected, given evidence supporting that the relative frequency of NMO vs. MS in Buenos Aires is low, and similar to that observed in Caucasian populations (91). Notably, this study did not report the ethnic/racial composition of the cohort, and it is possible that referral bias or other factors, which we were unable to detect on our review of the manuscript, contributed to this observation. While the frequency of AQP4-IgG and MOG-IgG seropositivity in ON appears to be lower in non-Asian populations, it remains crucial to consider these entities, especially in patients with atypical characteristics including recurrent or bilateral ON, longitudinally extensive optic nerve lesions, peri-neuritis (MOG-IgG), chiasmal/optic tract involvement (AQP4-IgG >> MOG-IgG), and/or poor visual recovery (AQP4-IgG) (6, 92). As expected, we found markedly higher seroprevalence of AQP4-IgG and MOG-IgG in recurrent isolated ON; however, the number of available studies was small, and mainly limited to non-Asian adult populations.
| Study                | Time period | Study setting | Adult/ pediatric | Age                  | Female sex | Race          | Device                | Protocol/ROI | MMP       | Macular measure |
|---------------------|-------------|---------------|------------------|----------------------|------------|---------------|-----------------------|--------------|-----------|-----------------|
| Akaishi et al.       | 2005–2013   | Japan         | Mixed adult pediatric | Mean (±SD): 37.5 (±18.2) in MOG-ON 30 (±9.9) in MS-ON 44.2 (±14.5) in AQP4-ON | 75%        | –             | Topcon (OCT-2000) | –            | –         | GCC             |
| Chen et al.          | 2015–2016   | China         | Pediatric        | Range: 5–18          | 58%        | –             | Zeiss (Cirrus) Optic disc cube 200x200 Macular cube 512x128 | –            | n/a       |
| Deschamps et al.     | 2011–2016   | France        | Mixed adult pediatric | Range: 16–63         | 94% in AQP4-ON 56% in MOG-ON | –             | Heidelberg Engineering (Spectralis) | –            | n/a       |
| Eye et al.           | –           | UK Ireland    | Pediatric        | Median: 8.5 in AQP4-ON MOG-ON 13 in MS-ON | 62%        | –             | Heidelberg Engineering (Spectralis) | –            | n/a       |
| Havla et al.         | 2013–2015   | Germany       | Adult            | Mean (±SD): 41.4 (±14.0) in MOG-ON 39.9± 12.5 in MS-ON 48.3± 8.9 in AQP4-ON 41.5± 13.8 in HC | 46% MOG-ON/MS-ON/HC 79% in AQP4-ON | –             | Heidelberg Engineering (Spectralis) | Optic disc: 12‘ 3.4 mm 50ART Macula: 25 vertical scans RDt: 3mm ETDRS perifoveal rim | 13% of AQP4-ON eyes 46% of MOG-ON eyes 0% of MS-ON eyes |
| Hokari et al.        | 2000–2013   | Japan         | Adult            | Median (IQR): 47 (39–62) in AQP4-ON 38 (30–47) in MS-ON | 97%        | –             | Optovue (RTVue-100) | –            | –         | GCC             |
| Hu et al.            | 2013–2015   | China         | Mixed adult pediatric | Mean (±SD): 26.0 (±10.2) in AQP4-ON 28.3 (±3.2) in HC | –          | Zeiss (Cirrus) Optic disc cube 200 x 200 Macular cube 512 x 128 | –             | GCIP     |
| Lim et al.           | 1993–2012   | Korea         | Adult            | Mean (±SD): 30.9 (±11.2) in AQP4-ON 33.7 (±14.8) in MS-ON | 73%        | –             | –                       | –            | n/a       |
| Liu et al.           | 2014–2016   | China         | Adult            | Range: 18–72         | 80%        | Zeiss (Cirrus) Optic disc cube 120 ART 1536 A scans per B scan. Macula: 20 x 20 degree raster scan 25 horizontal scans (ART79; 512 A scans per B scan) | –             | n/a       |
| Martinez-Lapiscina et al. | –           | Spain         | Adult            | Median (IQR): 34.9 [19.4–43.8] in AQP4-ON 54.4 [33.4–58.1] in MOG-ON | 66% in AQP4-ON 50% in MOG-ON | –             | Heidelberg Engineering (Spectralis) | –            | GCIP     |
| Mekhasingharak et al. | 2015–2016   | Thailand      | Adult            | Range: 19–76         | 92%        | Zeiss (Cirrus) Optic disc cube 200x200 Macular cube 512x128 | –             | GCIP     |
| Narayan et al.       | 2009–2018   | USA           | Pediatric        | Mean (±SD): 14.1 (±4.6) in AQP4-ON 18 (±4.9) in MOG-ON | 86%        | –             | Zeiss (Cirrus) Optic disc cube 200x200 Macular cube 512x128 | –            | n/a       |
| (Continued)                                                     |             |               |                  |          |               |                        |              |           |                 |

(Continued)
| Study            | Time period | Study setting | Adult/pediatric | Age | Female sex | Race | Device | Protocol/ROI | MMP | Macular measure |
|------------------|-------------|---------------|-----------------|-----|------------|------|--------|-------------|-----|-----------------|
| Oertel et al.    | –           | Germany UK    | Adult           | Mean (±SD): 47.3 (±14.4) in AQP4-ON 43.1 (±9.8) in HC | 84% in AQP4-ON 79% in HC | 76% Caucasian 10% African-Caribbean 8% Asian 2% Middle Eastern 2% mixed 2% unknown | Heidelberg Engineering (Spectralis) | Multiple protocols ROI: 3mm cylinder | – | GCIPL |
| Outteryck et al. | –           | France        | Mixed adult pediatric | Mean (±SD): 44.1 (±9.7) in AQP4-ON 39.7 (±11.3) in MS-ON 38.1 (±12.2) in HC | 79% in HC 62.5% in MOG-ON | 79% in HC 69% in MS-ON 68% in HC | Heidelberg Engineering (Spectralis) | Multiple protocols ROI: 3mm cylinder | 30% of MOG-ON eyes | GCIPL |
| Pache et al.     | –           | Germany Denmark | Adult           | Mean (±SD): 44.0 (±15.2) in MOG-ON 43.2 (±13.9) in AQP4-ON | 97% | 100% Caucasian | Heidelberg Engineering (Spectralis) | – | 19% of AQP4-ON eyes 22% of MOG-ON eyes | GCIPL |
| Pandit et al.    | –           | India         | Mixed adult pediatric | Median (range): 21 (6–53) | 43% | South Asian | Heidelberg Engineering (Spectralis) | Optic disc: 12° 768 or 1536 A-scans 16≤ART≤100. Macula: 25° x 30° 61 vertical or horizontal B-scans 768 A-scans per B-scan 9 ≤ ART ≤ 15 | 21% of MOG-ON eyes | GCC |
| Peng et al.      | –           | China         | Mixed adult pediatric Excluded patients with AQP4-IgG seropositive NMO (only isolated AQP4-ON) | Range: 17–66 | 74% | – | Heidelberg Engineering (Spectralis) | ROI: 6mm ETDRS rim excluding central 1mm | – | GCIPL |

(Continued)
| Study                  | Time period | Study setting | Adult/pediatric | Age                | Female sex | Race  | Device                      | Protocol/ROI                      | MMP          | Macular measure |
|------------------------|-------------|---------------|-----------------|--------------------|------------|-------|-----------------------------|-----------------------------------|--------------|-----------------|
| Shen et al. (69, 71)   | 2015–2017   | Australia     | Adult           | Mean (±SD): 48.2 (±18.1) in AQP4-ON/MOG-ON, 43.6 (±10.1) in MS-ON, 39.6 (±14) in HC | 68%        | –     | Heidelberg Engineering (Spectralis) | Optic disc: 3.50 mm Macula: radial star-like scan ROI: Central macular region (2 mm diameter), 6 slices of the star-like scan. | –            | GCIPPL          |
| Song et al. (69)       | 2016–2017   | China         | Pediatric       | Mean (±SD): 10.6 (±4.4) | 56%        | –     | Zeiss (Cirrus)              | –                                  | –            | GCIPPL          |
| Sotiriou et al. (69)   | 2008–2018   | USA           | Adult           | Mean (±SD): 43.7 (±12.7) in AQP4-ON, 43.8 (±13.3) in MOG-ON, 41.5 (±12.6) in MS, 41.5 (±14.1) in HC | 78%        | 61%  | Zeiss (Cirrus)              | Optic disc cube 200 x 200, Macular cube 512 x 128 | 19% of AQP4-ON eyes, 11% of MOG-ON eyes, 6% of MS-ON eyes | –            | GCIPPL          |
| Srikajan et al. (72)   | 2009–2015   | Thailand      | Adult           | Mean (±SD): 36.7 (±14.0) in AQP4, 34.4 (±13.5) in MS | 94%        | –     | Zeiss (Cirrus)              | –                                  | –            | n/a             |
| Stiebel-Kalish et al. (59) | 2003–2015  | Israel        | Mixed adult and pediatric | Mean (±SD): 46.3 (±17.6) in AQP4-ON, 41.7 (±9.4) in MOG-ON | 69%        | –     | Zeiss (Cirrus)              | Optic disc cube 200x200           | –            | n/a             |
| Tian et al. (60)       | 2013–2014   | China         | Adult           | Mean (±SD): 30.5 (±16.7) in MS-ON, 40.5 (±13.8) in AQP4-ON, 32.0 (±13.8) in HC | 66%        | –     | Optovue (RTVue-100)         | Optic disc: 4 circular scans (1,024 A-scans/scan), 3.45 mm | –            | n/a             |
| vonGlehn et al. (70)   | 2011–2012   | Brazil        | Mixed adult and pediatric | Range: 14–76 | 85%        | –     | Heidelberg Engineering (Spectralis) | -                                  | –            | n/a             |
| Zhang et al. (61)      | 2012–2017   | China         | Mixed adult and pediatric | Range: 15–74 | 74%        | –     | Zeiss (Cirrus)              | Optic disc: 3.45mm                  | -            | n/a             |
| Zhao et al. (36)       | 2015–2016   | China         | Mixed adult and pediatric | Mean (±SD): 31.3 (±15.3) in MOG-ON, 40.7 (±15.3) in AQP4-ON | 78%        | –     | Optovue (RTVue-100)         | Optic disc: 3.45mm, 4 circular scans (1024 A-scans/scan) | -            | GCIPPL          |
A similar finding was expected in bilateral ON; however, there was an insufficient number of studies/participants eligible to systematically study this. Finally, in children with isolated ON, our results show that MOG-IgG is very commonly detected, across both Asian and non-Asian populations. However, AQP4-IgG seropositivity was exceedingly rare among non-Asian pediatric populations, but relatively common (15%) in Asian pediatric cohorts. The causes of these ethnic and age disparities are poorly understood, but it is likely that there is a genetic component, although environmental factors may also play a role (93, 94).

An important consideration is the fact that the included studies recruited very few patients of African ancestry. This is a critical point since NMOSD occurs frequently in individuals of African ancestry, and African-Americans/Europeans with NMOSD are more likely to experience severe attacks with poor recovery and appear to have higher mortality (95–97). Nevertheless, the frequency of AQP4-IgG and MOG-IgG seropositivity in isolated ON in these populations could not be investigated in the present meta-analysis.

Furthermore, we have found that AQP4-ON and MOG-ON eyes exhibited similarly severely decreased pRNFL and macular GCIPL thicknesses after ON, which was greater than that observed in MS-ON eyes. When examining quadrantal pRNFL thicknesses, we were unable to identify any quadrantal patterns of retinal injury that were specific to MOG-ON. However, when comparing AQP4-ON and MS-ON, AQP4-ON was associated with decreased inferior, superior, and nasal pRNFL thickness, but the temporal pRNFL did not appear to differ between the two groups. This finding suggests that the temporal pRNFL is relatively preserved in AQP4-ON or disproportionately affected in MS-ON. Temporal preponderance of pRNFL damage in MS-ON compared to AQP4-ON was also reported in a study by Schneider et al. (98), which, however, did not fulfill inclusion criteria for our meta-analysis. The pathophysiology underlying the observed differences is not clear; however, the arcuate fibers (located in the superior and inferior quadrants) are commonly injured in vascular optic neuropathies (99). This pattern of quadrantal thinning may suggest that vascular compromise is a mechanism of tissue injury in AQP4-ON. Notably, retinal vascular alterations have been reported in vivo in NMO and pathologic studies have identified prominent vascular fibrosis and hyalinization in NMO lesions (99, 100).

Interestingly, and in line with our prior observations (8), we found that, despite a similar severity of pRNFL and GCIPL thinning in AQP4-ON and MOG-ON, visual outcomes clearly diverged between these two entities, with MOG-ON eyes having relatively preserved visual acuity, whereas AQP4-ON eyes experienced markedly worse visual outcomes compared to both MOG-ON and MS-ON. The biological underpinnings of this observation remain unclear. AQP4-IgG-associated disease is recognized as an autoimmune astrocytopathy with secondary demyelination (101). In pathologic studies, a spectrum of changes in astrocytes has been described, including astrocyte necrosis and dystrophic astrocytic profiles (101). AQP4 is highly expressed in the retina, predominantly in retinal astrocytes and Müller glial cells; it is therefore conceivable that AQP4-IgG may cause...
direct retinal injury. Interestingly, foveal thinning and altered foveal morphology have been reported in AQP4-IgG seropositive eyes without a history of ON, suggesting that subclinical direct retinal involvement may occur in AQP4-IgG-associated disease (102–104). In a pathological study of human retinas, AQP4-IgG seropositivity was associated with loss of AQP4 immunoreactivity on Müller cells, while intravitreal AQP4-IgG injection in mice resulted in reduced AQP4 expression by Müller cells, reactive retinal gliosis and loss of RGCs (53, 105). Notably, AQP4 deletion renders Müller cells incapable of handling osmotic stress and may induce an inflammatory response in the retina (106). These findings suggest that the poor visual prognosis in AQP4-ON may be partially mediated by alterations in the dynamics of astrocyte and Müller cell function.

MMP has also been proposed as a factor that is associated with poor outcomes following ON, since MMP eyes have worse visual outcomes and more severe GCIPL and pRNFL thinning (16–18). However, when accounting for GCIPL thickness and ON etiology, MMP does not appear to be independently associated with visual acuity, suggesting that MMP may represent a marker of optic neuropathy severity, rather than a direct contributor to visual dysfunction following ON (8). The prevalence of MMP was reported by a small number of studies included in our meta-analysis but appeared to be overall similar in AQP4-ON (15%) and MOG-ON (21%) and higher in both compared to the reported prevalence in MS-ON (∼6%). Further work is needed to clarify the pathoetiology of MMP and whether MMP is causally associated with poor visual outcomes after ON.

FIGURE 7 | Forest plot of the mean difference in global pRNFL and GCIPL thickness between AQP4-ON and MS-ON. The SD-OCT devices used are indicated as H (Spectralis, Heidelberg Engineering; Heidelberg, Germany), O (RTVue, Optovue Inc; Fremont, CA, USA), and T (3D OCT-2000, Topcon Corporation; Tokyo, Japan), Z (Cirrus, Carl Zeiss Meditec; Dublin, CA, USA).
Furthermore, we observed an impressive discordance between structural and functional outcomes in MOG-ON; even though MOG-ON was associated with severe pRNFL and GCIPL thinning, high-contrast visual acuity was remarkably preserved and did not differ from MS-ON. Contrary to AQP4, MOG is not expressed in the human retina; therefore, the observed inner retinal thinning is expected to be due to secondary change due to retrograde degeneration and not primary retinal pathology. The pathophysiology underlying the observed structure-function mismatch in MOG-ON is unclear; however, an important consideration is that, with OCT, we are not able to visualize the histological composition of each retinal layer. Therefore, it is conceivable that the relative contributions of the RGCs and their axons to GCIPL and RNFL thicknesses differ between AQP4-ON and MOG-ON, despite a similar severity of retinal layer thinning. In fact, the glial content of the RNFL is considerable and microglia constitute a significant component of the inner plexiform layer, whose thickness is measured as a composite with the ganglion cell layer as GCIPL (107, 108). Given the markedly different pathogenic mechanisms in these disorders, it is conceivable that the observed discrepancies may be related to differences in glial activation and migration, resulting in differing compositions of the pRNFL and the GCIPL and, consequently, different functional capacity of the retina. Another important consideration is that there is a floor effect present for OCT measures, and a single AQP4-ON or MOG-ON attack can lead to marked pRNFL and GCIPL atrophy, while subsequent attacks may not lead to appreciable changes in inner retinal layer.
thicknesses, despite worsening visual function (109). Analyses comparing visual and structural measures between groups after a single attack of ON would be useful to address this issue; however, the vast majority of studies included in our meta-analysis did not report OCT or visual acuity separately for patients with single and recurrent ON. However, since both AQP4-ON and MOG-ON frequently relapse, we do not expect that this may have significantly affected our findings when comparing outcomes in AQP4-ON vs. MOG-ON, although this may have influenced comparisons with MS-ON (6).

In this meta-analysis, we also attempted to examine OCT findings and visual outcomes in pediatric ON associated with AQP4-IgG and MOG-IgG seropositivity. However, this population has not been studied extensively and a systematic review of the literature revealed only four studies, with small numbers of participants (33, 41, 63, 67). OCT measures could be pooled for three of these, two of which included Asian children (33, 41). Therefore, our meta-analysis is clearly underpowered to study characteristics of pediatric AQP4-ON and MOG-ON. Nevertheless, the OCT findings and visual outcomes appear to be similar to those observed in adults. The inclusion of pediatric cases should be an important consideration for future studies, especially since MOG-IgG antibodies are commonly detected in children with ON.

Despite the strengths of the present report, several limitations must be acknowledged. Firstly, the majority of the included prevalence studies were performed at tertiary academic referral centers, with clinical expertise in neuro-ophthalmology. Therefore, it is conceivable that the patients who were recruited in these studies are not a representative sample of patients presenting with isolated ON and are likely enriched for cases with increased severity or atypical characteristics. Thus, it is possible that our results may overestimate the true prevalence rate of these disorders in the general population due to referral bias. This issue should also be considered when interpreting the OCT and visual outcomes, since patients with more severe attacks of ON and poor recovery are potentially more likely to be referred to a tertiary center for further management, and mild cases with favorable outcomes may be underrepresented in the existing literature. Furthermore, between-study heterogeneity was considerable in almost all pooled analyses of OCT measures or visual outcomes. A potential source of heterogeneity in analyses of OCT measures is the fact that the included studies...
| References                        | Time period | Study setting          | Adult/pediatric       | Age                                      | Female sex | Race               | Visual outcome–considerations |
|----------------------------------|-------------|------------------------|-----------------------|------------------------------------------|------------|--------------------|-------------------------------|
| Akaishi et al. (48, 74, 75)       | 2005–2013   | Japan                  | Mixed adult and pediatric | Mean (±SD): 37.5 (±18.2) in MOG-ON, 30 (±9.9) in MS-ON, 44.2 (±14.5) in AQP4-ON | 75%        | -                  | Outcome at eye level          |
| Chen et al. (41)                  | 2015–2016   | China                  | Pediatric             | Range: 5–18                              | 58%        | -                  | Outcome at eye level          |
| Cobo-Calvo et al. (76)            | 2014–2017   | France                 | Adult                 | Median (range): 36.5 (19–76.8) in MOG-ON, 39.3 (18.2–85) in AQP4-ON | 69%        | 86% Caucasian      | Outcome at patient level      |
| Contentti et al. (39)             | 2009–2015   | Argentina              | Adult                 | Mean (±SD): 31.6 (±11.1) in AQP4-ON, 38.4 (±12.9) in other | 70%        | -                  | Outcome at patient level      |
| Deschamps et al. (51)             | 2011–2016   | France                 | Mixed adult and pediatric | Range: 16–63                             | 94% in AQP4-ON, 56% in MOG-ON | -                  | Outcome at eye level          |
| Eyre et al. (63)                  | -           | UK, Ireland            | Pediatric             | Median: 8.5 in AQP4-ON and MOG-ON, 13 in MS-ON | 62%        | -                  | Outcome at eye level          |
| Falcão-Gonçalves et al. (63)      | 2004–2016   | Brazil                 | Adult                 | Median (IQR): 31.6 (22.6–37.4) in AQP4-ON, 27.2 (23.2–37.4) in MS-ON | 80%        | -                  | Outcome at eye level          |
| Havla et al. (62)                 | 2013–2015   | Germany, France        | Adult                 | Mean (±SD): 41.4 (±14.0) in MOG-ON, 39.9 (±12.5) in MS-ON, 48.3 (±8.9) in AQP4-ON, 41.5 (±13.8) in HC | 46% in MOG-ON/MS-ON, 79% in AQP4-ON | -                  | Outcome at eye level          |
| Hokari et al. (53)                | 2000–2013   | Japan                  | Adult                 | Median (IQR): 47 (39–62) in AQP4-ON, 38 (30–47) in MS-ON | 97%        | -                  | Outcome for number of attacks, not eyes |
| Ishikawa et al. (77)              | 2015–2018   | Japan                  | Mixed adult and pediatric | Range: 3–87                              | 84% in AQP4-ON, 51% in MOG-ON | -                  | Outcome at patient level      |
| Jitprapaikulsan et al. (45)       | 2000–2017   | USA                    | Mixed adult and pediatric | Range: 5–72                              | 72%        | 83% Caucasian      | Outcome at patient level      |
| Kim et al. (78)                   | -           | South Korea            | Adult                 | Mean (±SD): 39.4 (±12.0) in AQP4-ON, 35.2 (±10.0) in MS-ON | 78%        | -                  | Outcome at eye level          |
| Kitley et al. (79)                | 2010–2013   | UK                     | Adult                 | Mean (±SD): 32.3 (±17.1) in MOG-ON, 44.9 (±14.8) in AQP4 | 44% in MOG-ON, 90% in AQP4-ON | 66% Caucasian | Outcome at patient level |
| Lim et al. (65)                   | 1993–2012   | Korea                  | Adult                 | Mean (±SD): 30.9 (±11.2) in AQP4-ON, 33.7 (±14.8) in MS-ON | 73%        | -                  | Outcome at eye level          |
| Liu et al. (29)                   | 2014–2016   | China                  | Adult                 | Range: 18–72                              | 80%        | -                  | Outcome at eye level          |
| Martinez-Lapiscina et al. (66)    | -           | Spain                  | Adult                 | Median (IQR): 34.9 [19.4–43.8] in AQP4-ON, 54.4 [53.4–58.1] in MOG-ON | 66% in AQP4-ON, 50% in MOG-ON | -                  | Outcome at eye level          |

(Continued)
| References | Time period | Study setting | Adult/pediatric | Age | Female sex | Race | Visual outcome–considerations |
|------------|-------------|---------------|-----------------|-----|------------|------|-----------------------------|
| Martinez-Hernandez et al. (47) | 2005–2014 | Spain | Mixed adult and pediatric | Range: 5–65 | 71% | - | Outcome at patient level |
| Mekhasingharak et al. (54) | 2015–2016 | Thailand | Adult | Range: 19–76 | 92% | - | Outcome at eye level |
| Merle et al. (84) | - | Martinique | Adult | Mean (±SD): 47.5 (±10.5) in AQP4-ON, 44.5 (±10.1) in MS-ON | 87% | - | Outcome at eye level |
| Outteryck et al. (69) | - | France | Adult | Mean (±SD): 44.1 (±9.7) in AQP4-ON, 39.7 (±11.3) in MS-ON, 38.1 (±12.2) in HC | 78% in AQP4-ON, 69% in MS-ON, 68% in HC | - | Outcome at eye level |
| Pache et al. (57) | - | Germany, Denmark | Adult | Mean (±SD): 44.0 (±15.2) in MOG-ON, 43.2 (±13.9) in AQP4-ON | 97% | 100% Caucasian | Outcome at eye level |
| Peng et al. (85) | 2014–2015 | China | Adult | Mean (±SD): 33 (±12), Range: 30–51 | 74% | - | Outcome at eye level |
| Petzold et al. (30) | 1995–2007 | UK | Mixed adult and pediatric | Range: 15–71 | 67% | - | Outcome at eye level |
| Piccolo et al. (60) | 2008–2014 | UK | Mixed adult and pediatric | Range: 3–59 | 78% | - | Outcome at patient level |
| Ramanathan et al. (61) | 2001–2014 | USA, Australia | Mixed adult and pediatric | Median (range): 15 (3–58) | 82% | - | Outcome at patient level |
| Sepulveda et al. (82) | 2013–2015 | Spain | Mixed adult and pediatric | Median (range): 39 (10–77) | 87% | - | Outcome at patient level |
| Shen et al. (69) and You et al. (71) | 2015–2017 | Australia | Adult | Mean (±SD): 48.2 (±16.1) in AQP4-ON/MOG-ON, 43.6 (±10.1) in MS-ON | 68% | - | Outcome at eye level |
| Song et al. (33) | 2016–2017 | China | Pediatric | Mean (±SD): 10.6 (±4.4) | 56% | - | Outcome at eye level |
| Sotrichos et al. (6) | 2008–2018 | USA | Adult | Mean (±SD): 43.7 (±12.7) in AQP4-ON, 43.8 (±13.3) in MOG-ON, 41.5 (±12.6) in MS-ON, 41.5 ±14.1 in HC | 78% | - | Outcome at eye level |
| Srikajon et al. (72) | 2009–2015 | Thailand | Adult | Mean (±SD): 36.7 (±14.0) in AQP4-ON, 34.4 (±13.5) in MS-ON | 94% | - | Outcome at eye level |
| Stiebel-Kalish et al. (59) | 2003–2015 | Israel | Mixed adult and pediatric | Mean (±SD): 46.3 (±17.6) in AQP4-ON, 41.7 (±9.4) in MOG-ON | 69% | - | Outcome at eye level |
| Zhao et al. (36) | 2015–2016 | China | Mixed adult and pediatric | Mean (±SD): 31.3 (±15.3) in MOG-ON, 40.7 (±15.3) in AQP4-ON | 78% | - | Outcome at eye level |
utilized a variety of spectral-domain OCT devices, as well as scanning and segmentation protocols. Moreover, participants’ demographics and clinical characteristics varied considerably between studies and it is likely that there is variability in the phenotype, disease course, and outcomes among different racial or age groups. To minimize the impact of these differences on our results, we did not compare OCT measures or visual outcomes across studies; rather, we estimated the differences in retinal layer thicknesses or logMAR between groups that were included in the same study and performed a pooled analysis of these estimated differences. In analyses of OCT measures and visual outcomes, we were also notably unable to account for the number of ON attacks, since some studies included patients with a single event, while others recruited patients with multiple ON episodes. It is expected that the number of ON episodes has an impact on OCT findings and final visual acuity, especially since recurrent ON is common in cases of AQP4-ON and MOG-ON; this should be a consideration in future studies. Additionally, even though we attempted to analyze findings in adult ON separately from pediatric ON, some studies (noted in Tables 1–3) recruited mixed adult and pediatric or adolescent populations; this is an important

![FIGURE 10](image-url)
consideration when attempting to draw conclusions regarding potential differences in the characteristics of these disease entities between these age groups. Finally, AQP4-IgG serostatus was determined using a variety of assays, including ELISA in some studies, which is known to have an inferior performance in terms of sensitivity and specificity compared to CBAs (110, 111). This is a relevant point, since the use of an assay with suboptimal diagnostic accuracy may have led to misclassification of patients. Nevertheless, the majority of studies included in our meta-analysis (including 79% of studies assessing the prevalence of AQP4-IgG in ON) utilized CBA to determine the AQP4-IgG serostatus of their participants. MOG-IgG serostatus was determined exclusively using CBAs with full-length human MOG, given that MOG-IgG detected by ELISA or Western blot lacks disease specificity. Notably, commonly used MOG-IgG CBAs demonstrate overall good agreement for high-positive and negative samples, although agreement is lower for borderline results, and this is another factor that could potentially influence diagnostic accuracy in the included studies (112).

**CONCLUSIONS**

Our systematic review and meta-analysis provides a comprehensive overview of the epidemiology and structural and functional outcomes in ON associated with AQP4-IgG and MOG-IgG seropositivity. Our findings support the idea that AQP4-IgG- and MOG-IgG-related disease are more common causes of ON in Asian vs. non-Asian populations and that
MOG-IgG seroprevalence is especially high in pediatric ON, and we provide estimates of seroprevalence in these groups. We have also shown that MOG-ON and AQP4-ON are associated with similar severity of retinal thinning; however, visual outcomes appear to be markedly worse in AQP4-ON. Future studies should seek to investigate the pathoetiology of these findings, as well as to provide insights regarding optimal acute and chronic treatment strategies for these disorders.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

AF and ES: study conception and design, data acquisition, analysis and interpretation, drafting, and revision of the manuscript for important intellectual content. LM: data acquisition and interpretation and revision of the manuscript for important intellectual content. SS and PC: data interpretation and revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.540156/full#supplementary-material

Supplementary Figure 1 | Study selection for our first study objective (assessing the prevalence of AQP4-IgG and MOG-IgG seropositivity in isolated ON).

Supplementary Figure 2 | Study selection for our second study objective (comparison of OCT measures between AQP4-ON, MOG-ON and MS-ON eyes).

Supplementary Figure 3 | Forest plot of the mean difference in global pRNFL and GCIPL thickness between AQP4-ON and HC.

Supplementary Figure 4 | Forest plot of the mean difference in global pRNFL and GCIPL thickness between MOG-ON and HC.

Supplementary Figure 5 | Forest plot of the mean difference in quadrantal pRNFL thicknesses between AQP4-ON and MOG-ON.

Supplementary Figure 6 | Forest plot of the mean difference in quadrantal pRNFL thicknesses between AQP4-ON and MS-ON.

Supplementary Figure 7 | Forest plot of the mean difference in quadrantal pRNFL thicknesses between MOG-ON and MS-ON.

Supplementary Figure 8 | Forest plot of the mean difference in global pRNFL thickness between AQP4-ON and MOG-ON in pediatric ON.

Supplementary Figure 9 | Study selection for our third study objective (assessment of the visual outcome in AQP4-ON, MOG-ON and MS-ON eyes).

Supplementary Figure 10 | Forest plot of the relative risk of a poor visual outcome (VA worse than 20/200) in AQP4-ON vs MOG-ON in pediatric ON.

Supplementary Table 1 | Search terms.

Supplementary Table 2 | Visual outcome in AQP4-ON, MOG-ON and MS-ON; qualitative synthesis.
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Conflict of Interest: SS had received consulting fees from Medical Logix for the development of CME programs in neurology and had served on scientific advisory boards for Biogen, Genzyme, Genentech Corporation, EMD Serono, and Celgene. SS was the PI of investigator-initiated studies funded by Genentech Corporation and Biogen and received support from the Race to Erase MS foundation. SS had received equity compensation for consulting from JuneBrain LLC, a retinal imaging device developer. SS was also the site investigator of a trial sponsored by MedDay Pharmaceuticals. PC had received consulting fees from Disarm Therapeutics and Biogen and was PI on grants to JHU from Biogen and Annexon. ES had served on scientific advisory boards for Viela Bio and Genentech.

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