[Original article: 2 tables; 2 figures]

Retinal nerve fibre layer thinning is associated with worse visual outcome after optic neuritis in children with relapsing demyelinating syndromes

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ABBREVIATIONS

Ab-ON	Antibody-associated optic neuritis
AQP4-Ab	Aquaporin-4 antibody
HCVA	High-contrast visual acuity
IQR	Interquartile range
logMAR	Logarithm of the minimum angle of resolution
MOG-Ab	Myelin oligodendrocyte glycoprotein antibody
MS-ON	Multiple-sclerosis-associated optic neuritis
NMOSD	Neuromyelitis optical spectrum disorder
OCT	Optical coherence tomography
RDS	Relapsing demyelinating syndrome
RNFL	Retinal nerve fibre layer
VEP	Visual evoked potentials

[Abstract]

AIM Optic neuritis may be monophasic or occur as part of a relapsing demyelinating syndrome (RDS), such as multiple sclerosis, aquaporin-4 antibody (AQP4-Ab) neuromyelitis

optical spectrum disorder (NMOSD), or myelin oligodendrocyte glycoprotein antibody (MOG-Ab)-associated disease. The aims of this study were to test whether clinical, electrophysiological, and microstructural parameters differ in multiple-sclerosis-associated optic neuritis (MS-ON) and antibody-associated optic neuritis (Ab-ON); to identify the clinical and paraclinical characteristics of children suffering worse long-term visual outcome of RDS-optic neuritis; and to explore the relationship between RNFL thickness and clinical parameters in RDS-optic neuritis.

METHOD Forty-two children with optic neuritis were retrospectively studied: 22 with multiple sclerosis (MS-ON) and 20 with antibody-associated demyelination (Ab-ON: MOG-Ab=16 and AQP4-Ab=4). Clinical and paraclinical features were analysed.

RESULTS Complete recovery of visual acuity was reported in 25 out of 42 children; eight out of 38 (21%) suffered moderate or severe visual impairment (logarithm of the minimum angle of resolution [logMAR]>0.5) in their worse eye, including four out of 38 who were blind (logMAR>1.3) in their worse eye (two with multiple sclerosis, two with AQP4-Ab NMOSD). None of the children with MOG-Ab were blind. Recurrence of optic neuritis was more common in the Ab-ON group than the MS-ON group (15 out of 20 vs seven out of 22, p=0.0068). Retinal nerve fibre layer (RNFL) thickness at baseline inversely correlated with visual acuity at final follow-up (r=−0.42, p=0.0023). There was no significant relationship between the number of episodes of optic neuritis and mean RNFL (r=−0.18, p=0.3), nor any significant relationship between the number of episodes of optic neuritis and visual impairment (r=0.03, p=0.8).

INTERPRETATION In children with RDS, long-term visual impairment inversely correlated with RNFL thickness, but not with the number of relapses of optic neuritis. Optical coherence tomography may have a role in assessing children with optic neuritis to monitor disease activity and inform treatment decisions.

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What this paper adds

- Forty per cent of children with relapsing demyelinating syndromes (RDS) suffer long-term visual impairment after optic neuritis.
- Relapse of optic neuritis, occurring more frequently in the non-multiple-sclerosis group.
- Thinning of the retinal nerve fibre layer, as visualized by optical coherence tomography (OCT), is associated with worse visual outcome.
- OCT can be used alongside clinical parameters in children with RDS as an objective measure of neuroretinal loss.

[Main text]

Optic neuritis, defined as inflammation of one or both optic nerves in association with visual dysfunction, is one of the most common presentations of acquired central nervous system (CNS) demyelination in childhood, with an incidence of approximately 0.2 per 100 000.[1]

Core deficits in visual acuity, colour perception, and visual field are commonly accompanied by ocular pain and headache.[2] Sixty per cent to 77% of children suffer severely decreased visual acuity (worse than logarithm of the minimum angle of resolution [logMAR] 1.0 or Snellen 20/200) in the acute phase.[3–5] Optic neuritis may occur in isolation (idiopathic optic neuritis) or be associated with a relapsing demyelinating syndrome (RDS), such as multiple sclerosis, aquaporin-4 antibody (AQP4-Ab) neuromyelitis optical spectrum disorder (NMOSD), and myelin oligodendrocyte glycoprotein antibody (MOG-Ab)-associated disease. Frequent involvement of the optic nerve in RDS may be caused by the more permeable blood–brain barrier at the optic nerve compared with other CNS sites.[6]

Optical coherence tomography (OCT) and electrodiagnostic tests can be useful paraclinical parameters in patients with optic neuritis.[7] OCT may detect structural retinal changes, such as retinal nerve fibre layer (RNFL) and ganglion cell layer thinning, and the development of microcystic macular oedema and retinal damage.[8] OCT may help to differentiate between multiple sclerosis and NMOSD, with more severe retinal damage and hence greater RNFL thinning detected after optic neuritis in patients with AQP4-Ab NMOSD.[9] Studies performed in adult cohorts have shown that RNFL thickness is reduced in both optic neuritis and non-optic-neuritis eyes compared with healthy individuals,[10] and predicts visual function after optic neuritis,[11] and disease activity[12] and disability[13] in multiple sclerosis.

Electrodiagnostic tests, particularly visual evoked potentials (VEP), may reveal loss of functional integrity in the optic pathway owing to demyelination. VEP is a distinct measure of visual function from high-contrast visual acuity (HCVA) and the two can be discrepant, especially in cases of optic atrophy. VEP correlates with other measures of visual function, such as contrast sensitivity and low-contrast letter acuity. VEP can also be used to identify clinically silent optic neuritis;[14] a recent study of 24 patients with paediatric-onset

multiple sclerosis detected prolonged VEP latency in 58% of eyes with optic neuritis, but also in 55% of non-optic-neuritis eyes, highlighting that subclinical involvement of the optic nerve is common in children with multiple sclerosis.[15] The prognostic value of both OCT and VEP in predicting future optic neuritis relapse and long-term visual outcome in children with RDS is yet to be evaluated.

Full recovery of HCVA occurs in most children presenting with optic neuritis,[2,16] but subtle deficits may persist, particularly in low contrast and colour vision.[2] Furthermore, in a subset of patients with AQP4-Ab-positive NMOSD and MOG-Ab-associated disease, frequent attacks are often associated with accumulating damage and functional impairment of vision, with severe impairment (functional blindness) in 18% (Kitley et al.)[17] and 36% (Pach et al.)[18] of patients respectively. In adults, high-dose corticosteroid treatment hastens the recovery from acute optic neuritis,[19] but does not influence final visual outcome or the risk of subsequent multiple sclerosis.[20] Encouraging results from randomized controlled trials of phenytoin[21] and erythropoietin[22] in optic neuritis suggest that neuroprotective agents, besides immunotherapy, may be of use in acute demyelination, and OCT may be used to provide outcome measures to test the efficacy of medications.

The aims of this study were to (1) test whether clinical, electrophysiological, and microstructural parameters differ in multiple-sclerosis-associated optic neuritis (MS-ON) and antibody-associated optic neuritis (Ab-ON); (2) identify the clinical and paraclinical characteristics of children suffering worse long-term visual outcome of RDS-optic neuritis; and (3) explore the relationship between RNFL thickness and clinical parameters in RDS-optic neuritis.

METHOD

Participants

Children presented to three UK and Ireland Childhood CNS Inflammatory Demyelination Working Group centres: Great Ormond Street Hospital, Evelina London Children's Hospital, and Birmingham Children's Hospital. The diagnosis of RDS was defined as two or more episodes of acquired CNS demyelination lasting longer than 24 hours, involving the optic nerve, brain, or spinal cord, associated with T2-weighted lesions on magnetic resonance imaging (MRI). In this retrospective study, we included children with a history of at least one episode of optic neuritis and the after RDS diagnoses: multiple sclerosis, AQP4-Ab NMOSD, and MOG-Ab-associated demyelination. Patients with antibody-negative RDS were excluded. A diagnosis of optic neuritis was confirmed by an experienced neuro-ophthalmologist on the basis of history of reduced HCVA, red desaturation, pain with ocular movement, and/or visual field defect. Complete visual recovery was defined by normal HCVA, normal colour vision, and normal visual fields.

All investigations were undertaken as part of the routine diagnostic protocols of participating centres. MRI of the brain and spinal cord was performed in all cases. Within 1 month of an acute demyelination event, clinically symptomatic children underwent testing for serum AQP4-Ab and MOG-Ab (not cerebrospinal fluid), as part of routine assessments of children with demyelinating diseases, performed at the clinical neuroimmunology service at the Oxford Radcliffe Hospital Trust, Oxford, UK, using live cell-based assays.[23,24]

Assessments of visual function were done by ophthalmology departments at the three centres, including HCVA measured by the logMAR and colour vision measured by Ishihara plates. Electrodiagnostic tests methods for children have been described previously.[25] In brief, monocular VEP were recorded from occipital midline referred to a mid-frontal electrode according to International Society for Clinical Electrophysiology of Vision standards[26] and were acquired and analysed using a Espion E3 system (Diagnosys LLC, Cambridge, UK). Pattern reversal and onset VEP were produced by high-contrast, black and

white checks ranging in side length from 400′, 200′, 100′, 50′, 25′, 12.5′, and 6.25′, presented in a 30° stimulus field. Flash VEP were produced in response to flash strength 4 from a hand-held Grass strobe presented at 30cm from the patient. OCT was performed using the SPECTRALIS system (Heidelberg Engineering Ltd, Hertfordshire, UK). The mean RNFL thickness was calculated across the inferior, superior, nasal, and temporal segments.

Standard protocol approval

This study was approved by Great Ormond Street Hospital Research and Development Department (reference 16NC10).

Statistical analysis

Statistical analysis was performed using commercially available software GraphPad Prism 6 (GraphPad Software Inc, La Jolla, CA, USA) and R version 3.3.2 (https://www.R-project.org/). As the AQP4-ON group comprised only four children, myelin oligodendrocyte glycoprotein-associated optic neuritis and AQP4-ON were combined together as Ab-ON for statistical analysis. To compare variables between MS-ON and Ab-ON, non-parametric statistical tests (Mann–Whitney tests) were used for continuous distributions, and Fisher's exact tests for nominal data. We explored the association between RNFL thickness and clinical parameters in all patients together using Spearman's rank correlation coefficient. Owing to the limited sample sizes, *p* values were used sparingly, using an arbitrary level of 5% significance (two-tailed).

RESULTS

Baseline characteristics and clinical features

A total of 42 children (all under the age of 18y) with a history of at least one episode of optic neuritis were identified. Twenty-two patients had multiple sclerosis and 20 had Ab-positive optic neuritis (AQP4-Ab-positive NMOSD=4, MOG-Ab-associated disease=16). Demographics and clinical features at onset of optic neuritis are summarized in Table I. Twenty out of 42 children suffered severe visual impairment during the acute episode (logMAR≥1.0, i.e. Snellen 20/200 or worse). The main differences between MS-ON and Ab-ON disease were older age at presentation in MS-ON (13y MS-ON vs 8y Ab-ON, $p<0.0001$) and more frequent finding of abnormal MRI brain in MS-ON than Ab-ON (21 out of 22 [95%] MS-ON vs two out of 20 [10%] Ab-ON, $p<0.0001$) (Table I).

Clinical outcomes

Median length of follow-up from first clinical presentation was 4 years (interquartile range [IQR] 3–7). Clinical parameters at final follow-up are summarized in Table II. Recurrence of optic neuritis was more common in the Ab-ON group than in the MS-ON group (15 out of 20 Ab-ON vs seven out of 22 MS-ON, $p=0.0068$); in particular, 13 out of 16 patients who were MOG-Ab-positive had recurrent optic neuritis. The total number of optic neuritis relapses was also higher in children with Ab-ON (median 1, range 0–10) compared with MS-ON (median 0, range 0–6) ($p=0.029$) (Fig. 1a).

By the end of follow-up, 71 out of 84 (85%) eyes had been affected by clinically apparent episodes of optic neuritis; of these, 63 out of 71 (89%) had ophthalmology follow-up assessments, at a median interval of 2.1 years (range 0.4–10.3). Median logMAR in eyes with a history of optic neuritis at final follow-up was 0.02 (IQR 0.00–0.18) (Fig. 1b). Twelve out of 42 children had persisting impairment of colour vision, defined as more than one error on Ishihara plate testing. Overall, a complete functional recovery of vision occurred in 25 out of 42 children; eight out of 38 had at least moderately impaired vision (logMAR>0.5) in their

worse eye, including four out of 38 who were blind (logMAR>1.3) in their worse eye. Children with AQP4-Ab were more likely to be blind in at least one eye than children who were AQP4-Ab negative (two out of four vs two out of 34, p=0.043); none of the children with MOG-Ab were blind.

Electrophysiological outcomes

Electrodiagnostic tests, including VEP, were performed in 24 out of 42 children; three were excluded as they were done during the acute phase of optic neuritis, leaving 21 out of 42 children with electrodiagnostic tests included in the study, performed at a median interval of 1.68 years after first presentation with optic neuritis (range 0.2–8.4). VEP was abnormal in 22 out of 33 eyes with a clinical history of optic neuritis and two out of nine eyes without a history of optic neuritis. Electrophysiological parameters are summarized in Table II.

Microstructural outcomes

OCT was performed in 31 out of 42 children. Assessments were performed outside the acute phase of optic neuritis at a median interval of 1.81 years after first presentation with optic neuritis (range 0.2–10.3). Retinal microstructural parameters are summarized in Table II. Abnormal RNFL thinning in at least one segment was observed in 33 out of 51 (64.7%) eyes with a history of optic neuritis and one out of 11 eyes without a history of optic neuritis. Median RNFL thickness in eyes with optic neuritis (averaged across all four segments) was 76μm (IQR 65.3–84) versus 100.8μm (IQR 89.3–107) in non-optic-neuritis eyes (p=0.0002) (Table II). Serial OCT was performed in nine out of 31 cases (five MOG-Ab, four multiple sclerosis) (Table III). The mean decline in RNFL (over a median interval of 1.88y, range 0.31–3.48) was 2.06μm (SD 6.02) (p=0.17, paired t test).

The Ab-ON group had a higher rate of optic nerve atrophy, as determined by disc pallor, compared with the MS-ON group (17 out of 20 vs 12 out of 22, p=0.047).

Correlation between RNFL thickness, number of relapses, and final visual outcome

Among eyes with optic neuritis there was an inverse correlation between mean RNFL thickness and visual impairment (logMAR) (r=−0.41, p=0.0081) (Fig. 2b). There was no significant relationship between the number of optic neuritis episodes and mean RNFL (r=−0.18, p=0.3), nor any significant relationship between number of optic neuritis episodes and visual impairment (r=0.03, p=0.8).

DISCUSSION

In this large cohort of children with RDS and optic neuritis, 48% had a non-multiple-sclerosis phenotype, and optic neuritis occurred more frequently in the antibody-mediated group compared with those with multiple sclerosis. Clinical characteristics at presentation of optic neuritis such as pain, bilateral involvement, and severity of acute visual loss did not differ between groups, and were similar to a historical cohort from the same three tertiary centres, comprising children with monophasic, idiopathic optic neuritis.[3] Although lacking statistical significance because of the small numbers of patients with AQP4-Ab NMOSD, it is notable that 75% of AQP4-ON presented with bilateral involvement (compared with 36% of MS-ON), and 75% of AQP4-ON caused severe visual loss at nadir (compared with 45% of MS-ON). Interestingly, relapses of optic neuritis occurred more frequently in children with antibody-mediated disease, in keeping with recent reports of adults in which patients with MOG-Ab were more likely to have multiple relapses of optic neuritis.[18,27] Nevertheless, complete visual recovery occurred in 56% of children with MOG-Ab in our cohort, and none were registered blind. HCVA at final follow-up did not differ significantly between groups,

although it is notable that children with AQP4-Ab NMOSD suffered worse visual recovery even after a single episode of optic neuritis, with four of the seven worse eyes in the study belonging to patients with AQP4-Ab NMOSD, and two out of four AQP4-ON patients registered blind at final follow-up. Interestingly, we did not identify any significant decline in RNFL over time in those undergoing serial OCT, suggesting that an attack of severe optic neuritis, often the first, may be the more important determinant of microstructural damage in RDS than subsequent milder relapses.

A key finding in this study was the absence of any correlation between number of relapses and visual outcome, alongside a significant correlation between RNFL thinning and worse visual outcome. We detected RNFL thinning on OCT in 56% of MS-ON eyes and 75% of Ab-ON eyes, similar to a recent study identifying RNFL thinning in 50% of children with multiple sclerosis and a history of optic neuritis.[15] OCT offers an opportunity to monitor disease activity and progression non-invasively; in adults with multiple sclerosis, RNFL thinning is a sensitive and specific predictor of clinical disease activity, independent of lesion accumulation on brain MRI.[28] However, it is not yet part of routine clinical practice across all paediatric centres, and robust control data in healthy children remain limited, as is standardization of RNFL measurements, particularly in the acute phase of optic neuritis when swelling may complicate some automated RNFL measures. In this cohort, RNFL did not differ between groups, but RNFL thinning was associated with poorer visual outcome, in keeping with a previous study of paediatric ADS.[29] In that study, which included children without any clinical episodes of optic neuritis, RNFL thinning was found to differ by number of optic neuritis episodes in the group analysis; in the present study, in which all children had at least one clinical episode of optic neuritis, the lack of correlation observed between relapse rate and final visual outcome suggests that RNFL thinning (indicating pre-existing ganglion cell fibre loss) may be a more sensitive parameter for monitoring disease activity and

prompting treatment escalation than the relapse rate in children with a clinical history of optic neuritis.

Our finding of clinically silent disease by electrodiagnostic tests – that is, abnormal VEP in 'non-optic-neuritis' eyes – is consistent with previous reports[14,15] and provides further support to the recent Magnetic Resonance Imaging In Multiple Sclerosis (MAGNIMS) recommendation that the inclusion of optic nerve disease identified clinically, radiologically, or electrophysiologically would increase the sensitivity of dissemination-in-space criteria for multiple sclerosis.[30] There was a low rate of VEP normalization in eyes with optic neuritis across all groups, even in those with recovered HCVA; the time course of remyelination after optic neuritis has yet to be fully elucidated. Longitudinal analysis may be more informative in understanding the disease pathobiologies in the different groups. We hypothesized different pathobiological conditions may produce different patterns of optic nerve involvement, but we did not detect differences in RNFL thickness between the segments, possibly because of the small numbers.

A major limitation of our study was its retrospective nature, with inconsistent visual assessments, which were performed clinically and not as part of a research protocol. Low-contrast visual acuity and symbol digit modalities were not routinely assessed at follow-up and it is possible that some subtle functional impairment may have been missed.[31] The paucity of normative paediatric OCT data, especially longitudinally, should also be acknowledged. Additionally, our study design and the small numbers were not optimal for evaluation of treatment effect. Using electrodiagnostic tests, we detected clinically silent disease in a proportion of children with multiple sclerosis, but not in antibody-mediated optic neuritis, highlighting the need for further prospective studies with standardized longitudinal analysis of microstructural and electrophysiological parameters to increase our understanding of the disease pathobiologies. Nevertheless, this study shows that overall clinical relapse of

optic neuritis does not adversely affect visual outcome in most children and indeed can be clinically silent in a proportion of children as evaluated by electrodiagnostic tests. As we have shown that OCT correlates with final visual outcome, it may offer clinical utility as a tool in assessing children with optic neuritis, as an objective measure of neuroretinal loss in RDS, and as a surrogate endpoint to evaluate the benefit of neuroprotective agents.

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Table I: Demographics and clinical features at initial presentation with optic neuritis

	AQP4-Ab-positive NMOSD (*n*=4)	MOG-Ab associated disease (*n*=16)	Ab-ON (including AQP4-Ab and MOG-Ab cases) (*n*=20)	MS-ON (*n*=22)	*p**
Median age (IQR) at optic neuritis onset, y	8.5 (5.25–12.25)	8 (6.75–9.25)	8 (6–10.25)	13 (11.75–14)	<0.0001
Sex (F:M, % female)	3:1 (75)	9:7 (56)	12:8 (60)	14:8 (64)	1.0
Ethnicity, white (%)	1/4 (25)	10/16 (63)	11/20 (55)	6/22 (27)	0.1
History of previous CNS demyelinating events (%)	2/4 (50)	5/16 (31)	7/20 (35)	5/22 (23)	0.5
Median total number (range) of previous CNS demyelinating events	0.5 (0–1)	0 (0–2)	0 (0–2)	0 (0–4)	1.0
Painful optic neuritis (%)	1/4 (25)	9/16 (56)	10/20 (50)	10/22 (45)	1.0
Bilateral optic neuritis (%)	3/4 (75)	9/16 (56)	12/20 (60)	8/22 (36)	0.2
Several visual impairments at nadir (logMAR≥1.0) (%)	3/4 (75)	7/16 (44)	10/20 (50)	10/22 (45)	1.0
Abnormal MRI brain (%)	1/4 (25)	1/16 (6)	2/20 (10)	21/22 (95)	<0.0001

AQP4-Ab, aquaporin-4 antibody; NMOSD, neuromyelitis optical spectrum disorder; MOG-Ab, myelin oligodendrocyte glycoprotein antibody; Ab-ON, antibody-associated optic neuritis; MS-ON, multiple-sclerosis-associated optic neuritis; IQR, interquartile range; CNS, central nervous system; logMAR, logarithm of the minimum angle of resolution; MRI, magnetic resonance imaging.

Table II: Clinical, microstructural, and electrophysiological outcomes

	AQP4-Ab-positive NMOSD (*n*=4)	MOG-Ab-associated disease (*n*=16)	Ab-ON (including AQP4-Ab and MOG-Ab cases) (*n*=20)	MS-ON (*n*=22)	*p**
Recurrence of optic neuritis (%)	2 (50)	13 (81)	15 (75)	7 (32)	0.0068
Median total number (range) of optic neuritis relapses	0.5 (0–4)	1 (0–10)	1 (0–10)	0 (0–6)	0.029
Disc pallor at baseline	4 (100)	13 (81)	17 (85)	12(55)	0.047
Impaired colour vision in worse affected eye (Ishihara <17/17) (%)	1 (25)	3 (19)	4 (20)	4 (18)	1
Median logMAR (IQR) high-contrast visual acuity in worse affected eye	1.1 (0–2.2)	0.1 (0.02–0.11)	0.1 (0–0.21)	0 (0–0.23)	0.3
Complete functional recovery in both eyes (%)	2 (50)	9 (56)	11 (55)	14 (64)	0.8
At least moderately impaired vision (logMAR>0.5) in worse eye (%)	2 (50)	2 (13)	4 (20)	4 (18)	1
Blind (logMAR>1.3) in worse eye (%)	2 (50)	0 (0)	2 (10)	2 (9)	1
Eyes with optic neuritis	*n*=8	*n*=29	*n*=37	*n*=34	n/a
Median (IQR) high-contrast visual acuity	0.5 (0–1.81)	0.06 (0–0.1)	0.06 (0–0.21)	0.01 (0–0.17)	0.3
Abnormal RNFL thinning (%)	4/4 (100)	14/20 (70)	18/24 (75)	15/27 (56)	0.24
Median (IQR) RNFL thickness, µm	—	73 (54.1–84.2)	73 (54.1–84.2)	78 (68.8–85.6)	0.3
Median (IQR) inferior RNFL thickness, µm	—	99 (63–112.2)	99 (63–112.2)	99 (85.5–110.5)	0.44
Median (IQR) superior RNFL thickness, µm	—	94.5 (73–108.3)	94.5 (73–108.3)	100 (91.5–109.5)	0.21
Median (IQR) nasal RNFL thickness, µm	—	50 (42.3–64.3)	50 (42.3–64.3)	56 (50–63)	0.28
Median (IQR) temporal RNFL thickness, µm	—	45.5 (39–50.8)	45.5 (39–50.8)	48 (37.5–60)	0.45
Abnormal VEP (%)	2/2 (100)	7/13 (54)	9/15 (60)	13/18 (72)	0.7
Non-optic-neuritis eyes	*n*=0	*n*=3	*n*=3	*n*=10	n/a
Median logMAR (IQR) high-contrast visual acuity	—	0 (0–0.01)	0 (0–0.01)	0 (0–0)	n/a
Abnormal RNFL thinning (%)	—	0/2 (0)	0/2 (0)	1/9 (11)	1
Median (IQR) RNFL thickness, µm	—	110.9 (110.8–110.9)	110.9 (110.8–110.9)	95.5 (87.4–100.9)	n/a
Median (IQR) inferior RNFL thickness, µm	—	153 (145–161)	153 (145–161)	119 (107–127.5)	n/a
Median (IQR) superior RNFL thickness, µm	—	133.5 (125.3–141.8)	133.5 (125.3–141.8)	127 (115–132)	n/a
Median (IQR) nasal RNFL thickness, µm	—	84.5 (83.8–85.2)	84.5 (83.8–85.2)	75 (63–77)	n/a
Median (IQR) temporal RNFL thickness, µm	—	72.5 (71.8–73.3)	72.5 (71.8–73.3)	67 (60.5–68)	n/a
Abnormal VEP (%)	—	1/3 (33)	1/3 (33)	1/6 (17)	1

AQP4-Ab, aquaporin-4 antibody; NMOSD, neuromyelitis optical spectrum disorder; MOG-Ab, myelin oligodendrocyte glycoprotein antibody; Ab-ON, antibody-associated optic neuritis; MS-ON, multiple-sclerosis-associated optic neuritis; logMAR, logarithm of the minimum angle of resolution; IQR, interquartile range; n/a, not applicable; RNFL, retinal nerve fibre layer; VEP, visual evoked potentials.

Table III: Serial optical coherence tomography

	MOG-Ab-associated disease (*n*=5)	MS-ON (*n*=4)	*p**
Eyes with optic neuritis	*n*=9	*n*=6	n/a
Abnormal RNFL thinning (%)	9/9 (100%)	4/6 (67%)	0.15
Median (IQR) RNFL thickness, μm	65.3 (47.5–70.8)	76.8 (59.6–83.4)	0.14
Change in mean RNFL thickness from baseline (SD), μm	−4.4 (6.9)	−0.83 (3)	
Non-optic neuritis eyes	*n*=1	*n*=2	n/a
Abnormal RNFL thinning (%)	0/1 (0%)	1/2 (50%)	n/a
Median (IQR) RNFL thickness, μm	119.3	90.3 (88.5–92)	n/a
Change in mean RNFL thickness from baseline (SD), μm	8.5	−0.3 (2.1)	n/a

MOG-Ab, myelin oligodendrocyte glycoprotein antibody; MS-ON, multiple-sclerosis-associated optic neuritis; n/a, not applicable; RNFL, retinal nerve fibre layer; IQR, interquartile range; SD, standard deviation.

Figure 1: Clinical outcome of patients with optic neuritis. (a) Total number of optic neuritis relapses at final follow-up (median follow-up time 4y) in individuals with antibody-associated optic neuritis (Ab-ON) and multiple-sclerosis-associated optic neuritis (MS-ON). (b) High-contrast visual acuity at final follow-up in Ab-ON and MS-ON eyes. Aquaporin-4 antibody (square), myelin oligodendrocyte glycoprotein antibody (circle), multiple sclerosis (triangle). logMAR, logarithm of the minimum angle of resolution.

Figure 2: Correlation of retinal nerve fibre layer (RNFL) thickness with clinical parameters. (a) Total number of clinical relapses. (b) Correlation between mean RNFL thickness and visual impairment in eyes with optic neuritis. MOG-ON, myelin oligodendrocyte glycoprotein-associated optic neuritis; MS-ON, multiple-sclerosis-associated optic neuritis; logMAR, logarithm of the minimum angle of resolution.