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

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1	Abstract
2	Background: Optic neuritis (ON) may be monophasic or occur as part of a relapsing demyelinating
3	syndrome (RDS), such as MS, AQP4-Ab neuromyelitis optical spectrum disorder (NMOSD) or MOG-
4	Ab-associated disease.
5	
6	Methods: 42 children were retrospectively studied; 22 with MS (MS-ON) and 20 with Ab-associated
7	demyelination (Ab-ON: MOG-Ab=16 and AQP4-Ab=4). Clinical and paraclinical features were analysed.
8	
9	Results: Complete recovery of visual acuity (VA) was reported in 25/42 (60%) children; 8/38 (21%)
10	suffered moderate or severe visual impairment (logMAR>0.5) in their worst eye, including 4/38 (11%)
11	who were blind (logMAR>1.3) in their worst eye (2 MS, 2 AQP4-Ab NMOSD). None of the children with
12	MOG-Ab were blind. Recurrence of ON was more common in the Ab-ON vs MS-ON group (15/20 vs
13	7/22, p=0.0068). RNFL thickness at baseline inversely correlated with total number of ON episodes
14	(r=0.38, p=0.0062) and VA at final follow-up (r=-0.42, p=0.0023). There was no correlation between
15	number of ON episodes and visual outcome.
16	
17	Conclusion: In children with RDS, long-term visual impairment inversely correlated with RNFL
18	thickness, but not with number of ON relapses. OCT may have a role in the assessment of children with
19	ON to monitor disease activity and inform treatment decisions.
20	
21	
22	What this paper adds:
23	 40% of children with relapsing demyelinating syndromes (RDS) suffer long-term visual
24	impairment following optic neuritis (ON).
25	Relapse of ON, occurring more frequently in the non-MS group, is not correlated with final
26	visual outcome.
27	• Thinning of the retinal nerve fibre layer, as visualised by optical coherence tomography (OCT),
28	is associated with worse visual outcome.
29	OCT can be used alongside clinical parameters in children with RDS as an objective measure
30	of neuroretinal loss.
31	
32	

34 Introduction

35 Optic neuritis (ON), defined as inflammation of one or both optic nerves in association with visual 36 dysfunction, is one of the commonest presentations of acquired CNS demyelination in childhood, with 37 an incidence of approximately 0.2 per 100,000¹. Core deficits in visual acuity (VA), colour perception 38 and visual field are commonly accompanied by ocular pain and headache². 60-77% of children suffer 39 severely decreased VA (worse than logMAR 1.0 or Snellen 20/200) in the acute phase³⁻⁵. ON may 40 occur in isolation (idiopathic ON) or be associated with a relapsing demyelinating syndrome (RDS), 41 such as multiple sclerosis (MS), aquaporin-4 antibody (AQP4-Ab) neuromyelitis optica spectrum 42 disorder (NMOSD) and myelin oligodendrocyte glycoprotein (MOG) Ab-associated disease. Frequent

involvement of the optic nerve in RDS may be due to the more permeable blood-brain barrier at the
 optic nerve compared to other CNS sites⁶.

45

46 Optical coherence tomography (OCT) and electrodiagnostic tests can be useful paraclinical parameters 47 in patients with optic neuritis⁷. OCT may detect structural retinal changes, such as retinal nerve fibre 48 layer (RNFL) and ganglion cell layer thinning, and the development of microcystic macular oedema and 49 retinal damage. OCT may help to differentiate between MS and NMOSD, with more severe retinal 50 damage and hence greater RNFL thinning detected following optic neuritis in patients with AQP4-Ab 51 NMOSD⁸. Studies carried out in adult cohorts have shown that RNFL thickness is reduced in both ON 52 and non-ON eyes compared to healthy controls⁹, and predicts visual function after ON¹⁰, and disease 53 activity¹¹ and disability¹² in MS.

54

55 Electrodiagnostic tests, particularly visual evoked potentials (VEP), may reveal loss of functional 56 integrity in the optic pathway due to demyelination. VEP is a distinct measure of visual function from 57 high-contrast VA (HCVA) and the two can be discrepant, especially in cases of optic atrophy. VEP 58 correlates with other measures of visual function, such as contrast sensitivity and low contrast letter 59 acuity. VEP can also be used to identify clinically silent ON13: a recent study of 24 patients with 60 paediatric-onset MS detected prolonged VEP latency in 58% of ON eyes, but also in 55% of non-ON 61 eves, highlighting that subclinical involvement of the optic nerve is common in children with MS¹⁴. The 62 prognostic value of both OCT and VEP in predicting future ON relapse and long-term visual outcome in 63 children with RDS is yet to be evaluated.

64

Full recovery of HCVA occurs in the majority of children presenting with ON^{2, 15}, but subtle deficits may

66 persist, particularly in low contrast and colour vision². Furthermore, in a subset of patients with AQP4-

67 Ab positive NMOSD and MOG-Ab-associated disease, frequent attacks are often associated with

68 accumulating damage and functional impairment of vision, with severe impairment (functional

blindness) in 18%¹⁶ and 36%¹⁷ of patients respectively. In adults, high-dose corticosteroid treatment

70 hastens the recovery from acute ON¹⁸, but does not influence final visual outcome or the risk of

- 71 subsequent MS¹⁹. Encouraging results from randomized-controlled trials of phenytoin²⁰ and
- rythropoietin²¹ in ON suggest that neuroprotective agents, besides immunotherapy, may be of utility in
- acute demyelination and OCT may be used to provide outcome measures to test the efficacy of
- 74 medications.
- 75
- The aims of this study were to (1) test whether clinical, electrophysiological and microstructural
- parameters differ in MS-ON and Ab-ON; (2) identify the clinical and paraclinical characteristics of
- children suffering worse long-term visual outcome of RDS-ON; and (3) explore the relationship between
- 79 RNFL thickness and clinical parameters in RDS-ON.
- 80

81 Patients and methods

82 Participants

83 Children presented to three UK & Ireland Childhood CNS Inflammatory Demyelination Working Group 84 (UK-CID) centres: Great Ormond Street Hospital, Evelina London Children's Hospital, and Birmingham 85 Children's Hospital. The diagnosis of RDS was defined as two or more episodes of acquired CNS 86 demyelination lasting >24 hours, involving the optic nerve, brain or spinal cord, associated with T2 87 lesions on MRI. In this retrospective study, we included children with history of at least one episode of 88 ON and the following RDS diagnoses: MS, AQP4-Ab NMOSD and MOG-Ab-associated demyelination. 89 Patients with antibody-negative RDS were excluded. A diagnosis of ON was confirmed by an 90 experienced neuro-ophthalmologist on the basis of history of reduced HCVA, red desaturation, pain with 91 ocular movement, and/or visual field defect. Complete visual recovery was defined by normal HCVA, 92 normal colour vision and normal visual fields. 93 94 All investigations were undertaken as part of the routine diagnostic protocols of participating centres. 95 MR imaging of the brain and spinal cord was undertaken in all cases. Within 1 month of an acute 96 demyelination event, clinically symptomatic children underwent testing for serum AQP4-Ab and MOG-97

- Ab (not CSF), as part of routine assessments of children with demyelinating diseases, performed at the
 Clinical Neuroimmunology service at the Oxford Radcliffe Hospital Trust, using live cell-based assays²².
- 99

- 100
- 101 Assessments of visual function were carried out by ophthalmology departments at the three centres,
- 102 including HCVA measured by the logarithm of the minimum angle of resolution (logMAR) and colour
- 103 vision measured by Ishihara plates. Electrodiagnostic tests (EDT) methods for children have been
- 104 described previously²⁴. In brief, monocular VEPs were recorded from Oz referred to a mid-frontal
- 105 electrode according to International Society for Clinical Electrophysiology of Vision (ISCEV) standards²⁵
- 106 and were acquired and analysed using a Espion E3 system (Diagnosys LLC, Cambridge UK). Pattern
- 107 reversal and onset VEPs were produced by high contrast, black and white checks ranging in side length

- 108 from 400', 200',100', 50', 25',12.5' and 6.25', presented in a 30 degree stimulus field. Flash VEPs were
- 109 produced in response to flash strength 4 from a hand held Grass strobe presented at 30cm from the
- 110 patient. OCT was performed using the SPECTRALIS® system (Heidelberg Engineering Ltd.
- 111 Hertfordshire, UK). The mean RNFL thickness was calculated across the inferior, superior, nasal and
- 112 temporal segments.
- 113
- 114 Standard Protocol Approvals, Registrations, and Patient Consents
- 115 This study was approved by Great Ormond Street Hospital Research and Development Department
- 116 (reference: 16NC10).
- 117

118 Statistical analysis

- 119 Statistical analysis was performed using commercially available software GraphPad Prism 6 (GraphPad
- 120 Software Inc) and R 3.3.2. As the AQP4-ON group comprised only four children, MOG-ON and AQP4-
- 121 ON were combined together as antibody-associated ON (Ab-ON) for statistical analysis. To compare
- 122 variables between MS-ON to Ab-ON, non-parametric statistical tests (Mann-Whitney tests) were used
- 123 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
- 125 correlation coefficient. Owing to the limited sample sizes, p-values were used sparingly, using an
- arbitrary level of 5% significance (two-tailed).
- 127

128 **Results**

- 129 Baseline characteristics and clinical features at presentation with ON
- 130 A total of 42 children (all under the age of 18 years) with a history of at least one episode of ON were
- 131 identified. 22 patients had MS and 20 had Ab-positive ON (AQP4-Ab positive NMOSD = 4, MOG-Ab-
- associated disease = 16). Demographics and clinical features at onset of ON are summarised in Table
- 133 1. 20/42 (48%) children suffered severe visual impairment during the acute episode (logMAR >= 1.0, i.e.
- 134 20/200 or worse). The main differences between MS-ON and Ab-ON disease were older age at
- presentation in MS-ON (13 years MS-ON vs 8 years Ab-ON, p<0.0001), and more frequent finding of
- 136 abnormal MRI brain in MS-ON than Ab-ON (21/22 (95%) MS-ON vs 2/20 (10%) Ab-ON (p<0.0001)
- 137 (Table 1).

- 139 Clinical outcomes
- 140 Median length of follow up from first clinical presentation was 4 years (IQR 3-7). Clinical parameters at
- 141 final follow up are summarised in Table 2a. Recurrence of ON was more common in the Ab-ON group
- 142 compared to the MS-ON group (15/20 (75%) Ab-ON vs 7/22 (32%) MS-ON, p=0.0068); in particular,
- 143 13/16 (81%) MOG-Ab positive patients had recurrent ON. The total number of ON relapses was also

higher in Ab-ON children (median 1, range 0-10) compared to MS-ON (median 0, range 0-6) (p=0.029)(Figure 1a).

146

- By the end of follow up, 71/84 (85%) eyes had been affected by clinically apparent episodes of optic
- neuritis; of these 63/71 (89%) had ophthalmology follow up assessments, at a median interval of 2.1
- 149 years (range 0.4-10.3). Median logMAR in eyes with a history of ON at final follow up was 0.02 (IQR
- 150 0.00-0.18) (Figure 1b). 12/42 (29%) children had persisting impairment of colour vision, defined as >1
- 151 error on Ishihara plate testing. Overall a complete functional recovery of vision occurred in 25/42 (60%)
- 152 children; 8/38 (21%) had at least moderately impaired vision (logMAR>0.5) in their worst eye, including
- 4/38 (11%) who were blind (logMAR>1.3) in their worst eye. Children with AQP4-Ab were more likely to
 be blind in at least one eye than AQP4-Ab negative children (2/4 vs 2/34, p=0.043); none of the children
- 155 with MOG-Ab were blind.
- 156

157 Electrophysiological outcomes

158 Electrodiagnostic tests (EDT), including VEP, were carried out in 24/42 children (57%); three were

excluded as they were carried out during the acute phase of ON, leaving 21/42 children (50%) with EDT

160 included in the study, performed at median 1.68 years interval after first presentation with ON (range

161 0.2-8.4). VEP was abnormal in 22/33 (67%) eyes with a clinical history of ON and 2/9 (22%) eyes

162 without a history of ON. Electrophysiological parameters are summarised in Table 2a.

163

164 Microstructural outcomes

OCT was carried out in 31/42 (74%) children. Assessments were performed outside the acute phase of
 ON at a median 1.81 years interval after first presentation with ON (range 0.2-10.3). Retinal

167 microstructural parameters are summarised in Table 2a. Abnormal RNFL thinning in >=1 segment was

168 observed in 33/51 (64.7%) eyes with a history of ON and 1/11 (9%) eyes without a history of ON.

169 Median RNFL thickness in ON eyes (averaged across all four segments) was 76µm (IQR 65.3-84µm)

170 versus 100.8μm (IQR 89.3-107μm) in non-ON eyes (p=0.0002) (Table 2a). Serial OCT was performed

171 in 9/31 (29%) cases (5 MOG-Ab, 4 MS) (Table 2b). The mean decline in RNFL (over a median interval

172 of 1.88 years, range 0.31-3.48) was 2.06µm (±6.02 µm SD) (p=0.17, paired t test).

173

174 The Ab-ON group had a higher rate of optic nerve atrophy as determined by disc pallor compared to the 175 MS-ON group (17/20 vs 12/22, p=0.047).

- 176
- 177 Correlation between RNFL thickness, number of relapses and final visual outcome
- 178 Among ON eyes there was an inverse correlation between mean RNFL thickness and visual impairment
- 179 (logMAR) (r=-0.41, p=0.0081) (Figure 2b). There was no significant relationship between number of ON

episodes and mean RNFL (r=-0.18, p=0.3), nor any significant relationship between number of ON
 episdes and visual impairment (r=0.03, p=0.8).

182

183 Discussion

184 In this large cohort of children with RDS and ON, 48% of children had a non-MS phenotype; ON 185 occurred more frequently in the antibody-mediated group compared to those with MS. Clinical 186 characteristics at ON presentation such as pain, bilateral involvement and severity of acute visual loss 187 did not differ between groups, and were similar to a historical cohort from the same three tertiary 188 centres, comprising children with monophasic, idiopathic ON³. Although lacking statistical significance 189 due to small numbers of patients with AQP4-Ab NMOSD, it is notable that 75% of AQP4-ON presented 190 with bilateral involvement (compared to 36% of MS-ON), and 75% of AQP4-ON caused severe visual 191 loss at nadir (compared to 45% of MS-ON). Interestingly, relapses of ON occurred more frequently in 192 children with antibody-mediated disease, inkeeping with recent reports in adults in which patients with 193 MOG-Ab were more likely to have multiple ON relapses^{17, 26}. Nevertheless, complete visual recovery 194 occurred in 56% of children with MOG-Ab in our cohort, and none were registered blind. HCVA at final 195 follow up did not differ significantly between groups, although it is notable that children with AQP4-Ab 196 NMOSD suffered worse visual recovery even after a single episode of ON, with 4 of the 7 worst eyes in 197 the study belonging to patients with AQP4-Ab NMOSD, and 2/4 (50%) AQP4-ON patients registered 198 blind at final follow up. We did not identify any significant decline in RNFL over time in those undergoing 199 serial OCT, suggesting a severe first attack of ON may be the more important determinant of 200 microstructural damage in RDS than subsequent relapses.

201

202 A key finding in this study was the absence of any correlation between number of relapses and visual 203 outcome, alongside a significant correlation between RNFL thinning and worse visual outcome. We 204 detected RNFL thinning on OCT in 56% of MS-ON eyes and 75% of Ab-ON eyes, similar to a recent 205 study identifying RNFL thinning in 50% of children with MS and a history of ON¹⁴. OCT offers an 206 opportunity to monitor disease activity and progression non-invasively; in adults with MS, RNFL thinning 207 is a sensitive and specific predictor of clinical disease activity, independent of lesion accumulation on 208 MRI brain²⁷. However it is not yet part of routine clinical practice across all paediatric centers, and 209 robust control data in healthy children remains limited, as is standardization of RNFL measurements, 210 particularly in the acute phase of ON when swelling may complicate some automated RNFL measures. 211 In this cohort RNFL did not differ significantly between groups, but RNFL thinning was associated with 212 poorer visual outcome. in keeping with a previous study of paediatric RDS (Yeh et al Multiple Sclerosis 213 2009; 15: 802-810). In that study, which included children without any clinical episodes of ON, RNFL 214 thinning was found to differ by number of ON episodes in the group analysis; in the present study, in 215 which all children had >=1 clinical episode of ON, the lack of correlation observed between relapse rate 216 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 escalationthan the relapse rate, in children with a clinical history of ON.

219

Our finding of clinically-silent disease by EDT – i.e. abnormal VEP in "non-ON" eyes – is consistent with previous reports^{13, 14} and provides further support to the recent MAGNIMS recommendation that the inclusion of optic nerve disease identified clinically, radiologically or electrophysiologically would increase the sensitivity of dissemination-in-space criteria for MS²⁸. There was a low rate of VEP normalisation in ON eyes across all groups, even in those with recovered HCVA; the time course of remyelination after ON has yet to be fully elucidated. Longitudinal analysis may be more informative in understanding the disease pathobiologies in the different groups.

227

228 A major limitation of our study is its retrospective nature, with inconsistent visual assessments, which 229 were performed clinically and not as part of a research protocol. Low-contrast VA and symbol digit 230 modalities were not routinely assessed at follow up and it is possible that some subtle functional 231 impairment may have been missed²⁹. The paucity of normative paediatric OCT data, especially 232 longitudinally, should also be acknowledged. Additionally, our study design and the small numbers are 233 not optimal for evaluation of treatment effect. Using electrodiagnostic tests we detected clinically silent 234 disease in a proportion of children with MS, but not in antibody mediated ON, highlighting the need for 235 further prospective studies with standardised longitudinal analysis of microstructural and 236 electrophysiological parameters to increase our understanding of the disease pathobiologies. 237 Nevertheless, this study shows that overall clinical relapse of ON does not adversely affect visual 238 outcome in most children. As OCT correlates with final visual outcome, it may offer clinical utility as a 239 tool in the assessment of children with ON; as an objective measure of neuroretinal loss in RDS; and as 240 a surrogate endpoint to evaluate the benefit of neuroprotective agents. 241 242 Funding 243 This research is supported by the NIHR University College London Hospitals Biomedical Research 244 Centre (OC) and the NIHR Great Ormond Street Hospital Biomedical Research Centre (YH, CH).

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- 246

247 Figure legend

Figure 1: Clinical outcome of patients with optic neuritis. (A) Total number of ON relapses at final-

follow up (median follow-up time 4 years) in Ab-ON and MS-ON cases. (B) High contrast visual acuity at

250 final follow up in Ab-ON and MS-ON eyes. AQP4-Ab (square), MOG-Ab (circle), MS (triangle).

- **Figure 2:** Correlation of retinal nerve fibre layer thickness (RNFL) with clinical parameters. (A) total
- 253 number of clinical relapses (B) Correlation between mean RNFL thickness and visual impairment in ON
- 254 eyes.

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

Table 1: Demographics and clinical features at initial presentation with ON

Table 2a: Clinical, microstructural and electrophysiological outcomes

	AQP4-Ab	MOG-Ab-	Ab-ON	MS-ON	p-value*
	positive	associated	(including	(n=22)	
	NMOSD	disease (n=16)	AQP4-Ab		
	(n=4)		and MOG-		
			Ab cases)		
			(n=20)		
Recurrence of ON (%)	2 (50%)	13 (81%)	15 (75%)	7 (32%)	0.0068
Total number of ON	0.5 (0-4)	1 (0-10)	1 (0-10)	0 (0-6)	0.029
relapses; median (range)					
Disc pallor when?	4 (100%)	13 (81%)	17 (85%)	12(55%)	0.047
Baseline?(%)					
Impaired colour vision in	1 (25%)	3 (19%)	4 (20%)	4 (18%)	1
worst affected eye					
(Ishihara <17/17) (%)					
High contrast visual acuity	1.1 (0-2.2)	0.1 (0.02-0.11)	0.1 (0-0.21)	0 (0-0.23)	0.3
in worst affected eye,					
logMAR; median (IQR)					
Complete functional	2 (50%)	9 (56%)	11 (55%)	14 (64%)	0.8
recovery in both eyes (%)					

At least moderately	2 (50%)	2 (13%)	4 (20%)	4 (18%)	1
impaired vision					
(logMAR>0.5) in worst eye					
(%)	2(500/)	0 (00()	2 (100/)	2 (00()	1
Blind (logMAR>1.3) in	2 (50%)	0 (0%)	2 (10%)	2 (9%)	1
worst eye (%)	0				
ON eyes	n=8	n=29	n=37	n=34	n/a
High contrast visual	0.5 (0-1.81)	0.06 (0-0.1)	0.06 (0-0.21)	0.01 (0-0.17)	0.3
acuity, logMAR;					
median (IQR)	4/4 (4000()	44/00 (700/)	40/04 (750/)	45/07 (500()	0.04
Abnormal RNFL	4/4 (100%)	14/20 (70%)	18/24 (75%)	15/27 (56%)	0.24
thinning (%)					
Mean RNFL thickness,	-	73 (54.1-84.2)	73 (54.1-	78 (68.8-	0.3
μm; median (IQR)			84.2)	85.6)	
Inferior RNFL	-	99 (63-112.2)	99 (63-	99 (85.5-	0.44
thickness, μm; median			112.2)	110.5)	
(IQR)					
Superior RNFL	-	94.5 (73-	94.5 (73-	100 (91.5-	0.21
thickness, μm; median		108.3)	108.3)	109.5)	
(IQR)					
Nasal RNFL thickness,	-	50 (42.3-64.3)	50 (42.3-	56 (50-63)	0.28
μm; median (IQR)			64.3)		
Temporal RNFL	-	45.5 (39-50.8)	45.5 (39-	48 (37.5-60)	0.45
thickness, μm; median			50.8)		
(IQR)					
Abnormal VEP (%)	2/2 (100%)	7/13 (54%)	9/15 (60%)	13/18 (72%)	0.7
Non-ON eyes	n=0	n=3	n=3	n=10	n/a
High contrast visual	-	0 (0-0.01)	0 (0-0.01)	0 (0-0)	n/a
acuity, logMAR;		· · · ·	· · · ·	· · ·	
median (IQR)					
Abnormal RNFL	-	0/2 (0%)	0/2 (0%)	1/9 (11%)	1
thinning (%)		()		(
Mean RNFL thickness,	-	110.9 (110.8-	110.9	95.5 (87.4-	n/a
μm; median (IQR)		110.9)	(110.8-	100.9)	
		,	110.9)	,	
Inferior RNFL	-	153 (145-161)	153 (145-	119 (107-	n/a
thickness, μm; median			161)	127.5)	
(IQR)			,	121.0)	
Superior RNFL	-	133.5 (125.3-	133.5	127 (115-	n/a
thickness, µm; median		141.8)	(125.3-	132)	170
(IQR)			141.8)	102)	
Nasal RNFL thickness,	-	84.5 (83.8-	84.5 (83.8-	75 (63-77)	n/a
μm; median (IQR)		85.2)	85.2)	10(00-11)	11/0
Temporal RNFL		72.5 (71.8-	72.5 (71.8-	67 (60.5-68)	n/a
thickness, μm; median	-	`	•	07 (00.0-00)	11/a
•		73.3)	73.3)		
(IQR)		1/2 (220/)	1/2 /220/ \	1/6 (170/)	1
Abnormal VEP (%)	-	1/3 (33%)	1/3 (33%)	1/6 (17%)	1

Table 2b: Serial optical coherence tomography

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

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