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Longitudinal retinal changes in MOGAD

Short title: Longitudinal retinal changes in MOGAD

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Abstract

Objective: Patients with myelin oligodendrocyte glycoprotein antibody (MOG-IgG) associated disease (MOGAD) suffer from severe optic neuritis (ON) leading to retinal neuro-axonal loss, which can be quantified by optical coherence tomography (OCT). We assessed whether ON-independent retinal atrophy can be detected in MOGAD.

Methods: Eighty MOGAD patients and 139 healthy controls (HC) were included. OCT data was acquired with 1) Spectralis spectral domain OCT (MOGAD (N=66) and HC (N=103)) and 2) Cirrus HD-OCT (MOGAD (N=14) and HC (N=36)). Macular combined ganglion cell and inner plexiform layer (GCIPL) and peripapillary retinal nerve fibre layer (pRNFL) were quantified.

Results: At baseline, GCIPL and pRNFL were lower in MOGAD eyes with a history of ON (MOGAD-ON) compared with MOGAD eyes without a history of ON (MOGAD-NON) and HC ($p<0.001$). MOGAD-NON eyes had lower GCIPL volume compared to HC ($p<0.001$) in the Spectralis, but not in the Cirrus cohort. Longitudinally (follow-up up to 3 years), MOGAD-ON with ON within the last 6-12 months before baseline exhibited greater pRNFL thinning than MOGAD-ON with an ON >12 months ago ($p<0.001$). The overall MOGAD cohort did not exhibit faster GCIPL thinning compared with HC.

Interpretation: Our study suggests the absence of attack-independent retinal damage in MOGAD. Yet, ongoing neuroaxonal damage or oedema resolution seems to occur for up to 12 months after ON, which is longer than what has been reported with other ON forms. These findings support that the pathomechanisms underlying optic nerve involvement and the evolution of OCT retinal changes after ON is distinct in MOGAD.

Introduction

Patients with myelin oligodendrocyte glycoprotein antibody (MOG-IgG) associated disease (MOGAD) often suffer from severe and recurrent optic neuritis episodes (ON), which can lead to significantly impaired visual acuity and visual quality of life.[1–4] In neuropathological studies, MOGAD is characterized by multiple sclerosis (MS)-like pathology, with an immune response directed against myelin and oligodendrocytes leading to complement deposition and inflammatory demyelination.[3,5–8] Yet, MOGAD is considered a distinct entity from MS. In recent years, it has been shown that ON in MOGAD is often associated with extreme optic disc and retinal nerve fibre layer (RNFL) oedema in the acute phase with subsequent marked retinal neurodegeneration.[2,7,9,10]

Assumptions regarding the dynamics of retinal layer thickness changes following ON in less common aetiologies like MOGAD are often made based on studies in MS. In MS, inner retinal layer thinning appears to be predominantly complete by ~ 6 months after ON.[11,12] Furthermore, it has been well established in MS that accelerated progressive inner retinal layer thinning (compared with normal aging) occurs independently of clinical episodes of ON.[13,14] In an exploratory, longitudinal, multicentre study on the long-term course of adult MOGAD employing optical coherence tomography (OCT), we previously observed ON-independent thinning of the peripapillary RNFL (pRNFL) in MOGAD, but no significant thinning was observed in the macular composite ganglion cell and inner plexiform layer (GCIPL).[2] This phenomenon was mainly detectable in eyes of patients with relapses (including contralateral ON) shortly before study entry, but it was unclear when and why this occurred. This could suggest 1) a prolonged neurodegenerative process of the retina after the insult, 2) a prolonged time-course of resolution of severe oedema, 3) retinal damage induced by relapse-treatment (such as high-dose steroids) 4) a combination of these effects.

Hence, we initiated a large international multicentre study of retinal imaging in MOGAD to date to clarify whether 1) subclinical inner retinal layer thinning independent of ON exists in MOGAD and 2) if previous recent ON > 6 months before baseline may account for such findings.

Materials and methods

Study design and population

The study presented here is as an international, multicentre, retrospective, longitudinal study. Cross-sectional and longitudinal analyses of the available data were performed. We enrolled 85 MOGAD patients and 139 healthy controls (HC). Some of the patients had already been described in previous cross-sectional[4,9,10] and longitudinal analyses[2]. Parts of the data were acquired via the *Collaborative Retrospective Study on retinal OCT in Neuromyelitis Optica* (CROCTINO) study within the Guthy-Jackson Charitable Foundation network.[15,16] For participating centers and contributors, please refer to Supplementary Table 1 and Supplementary Table 2 respectively. Inclusion criteria were 1) a diagnosis of MOGAD according to the suggested criteria by Jarius et al.[17] with evidence of MOG-IgG as well as clinical MOGAD symptomatology, 2) age of at least 18 years, 3) follow-up (F/U) of at least one year between at least two examinations, 4) OCT ring scan (pRNFL) and/or macular volume scans with at least 3 mm diameter for each visit, and 5) patients must not have had a clinical episode of ON within 6 months of the baseline scan and during the course of the study. The risk of overlooked subclinical ON prior to baseline or subclinical ON during F/U was further minimized by excluding patients with a baseline absolute inter-eye-difference in the pRNFL of $\geq$ 7µm or a change in the inter-eye difference during follow-up of $\geq$ 7µm, respectively, in accordance with the threshold proposed by Nolan et al.[18] - as well as confirmatory using a baseline percentage inter-eye-difference in the GCIPL of $\geq$ 5% (data not shown). Additionally, the presence of clinical/functional data during the F/U period and at date of OCT acquisition (expanded disability status scale (EDSS), type and number of attacks, treatment etc.) were recorded. Any other neurological or ophthalmological comorbidities (glaucoma, diabetes mellitus, retinal surgery, retinal disease, refractive error > 6 dioptres) potentially influencing OCT results were classified as exclusion criteria. For detection of MOG-IgG serum, serum samples from all patients were analysed at least once with established cell-based assays at the discretion of the respective centre using laboratory cut-offs.[19] Written informed consent was obtained from all patients participating in the study. Local ethics committees approved the study protocol in accordance with the Declaration of Helsinki (1964) as amended.

Optical coherence tomography

Data of high-resolution OCT images from two different spectral domain (SD) OCT instrument types were included: Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany) from eleven centres and Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA, US) from two centres. OCT quality control was performed according to OSCAR-IB criteria.[20,21] Segmentation and analysis were performed semi-automatically using software provided by the OCT manufacturer and controlled by the responsible OCT experts at the respective centres.

Two cohorts were studied in the present work: 1) Spectralis Spectral-Domain (SD) OCT cohort; (*Spectralis cohort*) 2) Cirrus HD-OCT cohort (*Cirrus cohort*). All centres using Spectralis SD OCT applied the automatic real-time (ART) function for image averaging. In this cohort, pRNFL thickness and volumes of GCIPL and inner nuclear layer (INL) were obtained. GCIPL and INL were calculated as cylinders 3 mm in diameter around the fovea from a macular volume scan (25° x 30°, 61 vertical B-scans or 20° x 20°, 25 vertical B-scans). pRNFL was measured with the eye tracker activated using ring scans around the optic nerve (12°, 1536 A-scans) or the innermost ring of a star-and-ring scan around the optic nerve (12°, 768 A-scans). For Cirrus HD-OCT, peripapillary scans were acquired using the Optic Disc Cube 200 x 200 protocol (which covers a 6 x 6 mm^2 area centred on the optic disc) and the pRNFL thickness measurements were obtained using the conventional software on the device, as previously described. Macular scans were obtained using the Macular Cube 512 × 128 Cirrus protocol centred on the fovea, and the GCIPL segmentation and measurement was performed using conventional Cirrus HD-OCT software, which measures the GCIPL thickness in an elliptical annulus around the fovea (the vertical inner and outer radii of 0.5mm and 2.0mm, respectively, that are stretched 20% in the horizontal axis). INL was not available in the Cirrus group.

Statistical methods

All statistical analyses and graphical representations were performed with R version 4.1.0.[22] Statistical significance was established at $p<0.05$. All parameters are described as mean ± standard deviation (SD), if not stated otherwise. OCT parameter comparisons were performed using linear mixed effect models for baseline comparisons (with group, age and sex as fixed effects, and subject and centre as random effects), longitudinal within-group analyses (with F/U time, age at baseline and sex as fixed effects, and centre and [subject/subject-eye] as random effects) and longitudinal between-group comparisons (with [F/U time*group], age at baseline and sex as fixed effects, and centre and [subject/subject-eye] as random effects).

Results

Cohort description and F/U data

In the Spectralis cohort, we included 66 MOGAD patients (126 eyes) from nine centers and 103 HCs (206 eyes) from six centers. The Spectralis MOGAD group included 69 (55%) eyes of 43 patients (65%) with a history of ON (MOGAD-ON) with a median of 1 ON per eye (range 1 - 5) (not available for N=1) and a median of 25 (IQR 11 - 84) months from most recent ON to OCT (not available for N=7). Fifty-seven eyes had no history of ON (MOGAD-NON) (45%). Due to different study protocols, F/U data were only available for 86 eyes of 43 MOGAD patients.

In the Cirrus cohort, we included 14 MOGAD patients (27 eyes) and 36 HC (72 eyes) from two centers. The Cirrus MOGAD group included 22 (81%) MOGAD-ON eyes of 13 patients with a median of 1 attack (range 1 - 6) and a median of 15 (IQR 9 - 23) months from time of most recent ON to OCT. In contrast to the Spectralis cohort, only five (17%) eyes were MOGAD-NON. F/U data were available for all MOGAD patients and HC. We excluded possible subclinical ON episodes prior to baseline in non-ON eyes based on the inter-eye pRNFL difference (supplementary analyses 1). We had retrospective data on the lesion location of the ON episodes for a subset of our cohort (supplementary table 3) Characteristics are described in further detail for a subset of this cohort in Chen et al. 2022.[23] The demographic and clinical characteristics of all included patients are shown in table 1.

Cross-sectional comparisons of OCT measures between groups

First, we analysed group differences at baseline between MOGAD-ON, MOGAD-NON and HC eyes (Table 2, Figure 1). For both (Spectralis and Cirrus) cohorts, pRNFL and GCIPL thicknesses were significantly lower in MOGAD-ON compared with MOGAD-NON and with HC. In the Spectralis cohort, INL volume was higher in MOGAD-ON compared with MOGAD-NON and HC ($p<0.001$). In both cohorts, eyes that had experienced a single ON episode (MOGAD-1-ON) had markedly lower pRNFL and GCIPL thicknesses compared with MOGAD-NON. This difference was accentuated in eyes with 2 (MOGAD-2-ON) or >2 episodes (MOGAD-3-ON) (table 3).

When comparing MOGAD-NON eyes with HC, the Spectralis cohort had a lower GCIPL (MOGAD-NON; 0.57 ± 0.07 mm^3, HC: 0.62 ± 0.05 mm^3, $p<0.001$) and pRNFL (MOGAD-NON: 94.9 ± 12.4µm, HC: 99.1 ± 8.9 µm, $p=0.008$), but the comparisons were not significantly

different in the Cirrus cohort. To better understand this effect in the Spectralis cohort, we compared MOGAD-NON eyes with (N=12) and without a history of contralateral ON (N=45). The two groups had comparable GCIPL (0.57 ± 0.07 mm^3 for both). Yet, MOGAD-NON eyes with a history of contralateral ON had lower pRNFL thickness (90.1 ± 14.2 µm) compared with MOGAD-NON without a history of contralateral ON (96.2 ± 11.7 µm), although the comparison was not statistically significant (p=0.20). Similar findings (but in a lower sample size) were observed in the Cirrus cohort for MOGAD-NON eyes with a history of contralateral ON (N=3, pRNFL: 95.7 ± 4.0 µm, GCIPL: 79.3 ± 7.6 µm) compared with MOGAD-NON eyes without a history of contralateral ON (N=2, pRNFL: 101.5 ± 2.1µm, GCIPL: 87.5 ± 0.7 µm).

Longitudinal analysis of OCT measure change

Within the Spectralis cohort we observed longitudinally significant pRNFL thinning (p<0.001), which was not accompanied by significant progressive GCIPL reduction (p=0.86, table 4, figure 2). For the Cirrus cohort, we found longitudinally significant pRNFL (p=0.001) and GCIPL thinning (p=0.002) within MOGAD (combining MOGAD-ON and MOGAD-NON). Compared with HC this progressive thinning was only significant for pRNFL in the Spectralis cohort, but not significantly faster compared with HC for GCIPL in either cohorts or for pRNFL in the Cirrus cohort.

In the Spectralis cohort, relapses other than ON attacks during F/U did not appear to have augmenting influence on rates of pRNFL atrophy (data not shown). Furthermore, we compared MOGAD-ON with an ON 6 - 12 months before baseline versus MOGAD-ON with an ON > 12 months before baseline. In both cohorts, the longitudinal pRNFL thinning was more pronounced in MOGAD-ON with an ON 6 - 12 months before baseline compared with MOGAD-ON > 12 months before baseline (Spectralis: B=-0.10, SE=0.02, p<0.001 | Cirrus: B=1.63, SE=0.43, p<0.001). GCIPL thinning did only differ between groups in the Cirrus cohort (Spectralis: B<0.001, SE<0.001, p=0.58 | Cirrus: B=-0.74, SE=0.25, p=0.005). Additional analyses of ON and non-ON eyes from both cohorts can be found in supplementary analyses 2.

Discussion

This analysis aimed to evaluate whether subclinical neuro-axonal degeneration occurs independently of disease activity in MOGAD and found no evidence of subclinical progressive neurodegeneration or of relapse-independent retinal neurodegeneration in MOGAD compared with HC. In contrast, the analyses suggest a prolonged influence of ON attacks on retinal measurements and a slowed remission of oedematous changes that occurs over 12 months after an ON attack. This was confirmed in two distinct cohorts with two different OCT devices respectively – although to a different extent.

Previous cross-sectional studies have shown conflicting results on whether MOGAD-ON patients have a more favourable outcome regarding neuroaxonal content compared with ON patients with other demyelinating conditions. This is of major interest because it may have direct implications for the use of medication to prevent relapses.[3,9,10,24,25] Confirming previous reports, we were able to show consistently severe neuroaxonal retinal degeneration after MOGAD-ON. The pRNFL and GCIPL degeneration depended on the number of ONs with higher ON-numbers causing more neuroaxonal damage. Yet, both cohorts showed the greatest decrease in pRNFL and GCIPL after the first ON, whereas subsequent ONs appeared to lead to less absolute change.[26] These data are in line with the experience with ON in MS and in aquaporin-4-antibody (AQP4-IgG) positive neuromyelitis optica spectrum disorder (NMOSD). An explanation for the different extent of inner retinal layer thinning after initial ON vs subsequent ON attacks is most likely accounted for by a "basement effect" (i.e. approaching maximal possible atrophy of the retinal layer, due to other constituents of these layers including glial cells, blood vessels and extracellular matrix), but more aggressive and early acute therapy or preventative immunotherapy may also contribute.[2]

In this study, we were able to gain valuable further insights into ON-mediated retinal neuro-axonal degeneration in MOGAD. However, uncertainty remains as to whether ON-independent retinal neuroaxonal degeneration occurs in MOGAD. The Spectralis and Cirrus cohorts showed some longitudinal loss of neuroaxonal tissue, but the rates of change did not differ from HC. Furthermore, when eyes with ON within 6 - 12 months of the baseline OCT were excluded, there was no significant longitudinal pRNFL thinning. Considering the influence of potential chiasmal crossover effects and previous ON episodes shown by our analyses, we currently do not assume a neuroaxonal retinal degeneration independent of relapses.[2] Nevertheless, chiasmal crossover from contralateral ON is considered a rare event in MOGAD-ON and some uncertainty remains.[27]

Subgroup analyses showed that the group of MOGAD patients with ON within 6 - 12 months before baseline exhibited significantly faster pRNFL thinning compared to those with ON >12 months before baseline. The most likely explanation for this finding may be ongoing resolution of pRNFL swelling due to edema and/or ongoing neurodegeneration. Based on our data, we recommend at least 12 months of stable disease before inclusion of participants in OCT studies investigating longitudinal ON-independent change in MOGAD. In addition, our findings support that pRNFL thickness change following MOGAD-ON may follow different kinetics compared to MS.[12,28,29] Also, other non-ON relapses during F/U could affect this outcome, for example via trans-synaptic degeneration or generalized subclinical inflammatory activity.

Our data underscore the previously proposed distinctiveness of MOGAD compared with MS suggesting that the assumptions drawn from MS are not necessarily suitable to explain changes in MOGAD. Our findings are also different from AQP4-IgG positive NMOSD, an astrocytopathy, which has been proposed to have a primary antibody-associated retinopathy supported by animal and clinical studies.[16,26,30–33] Interestingly, prior studies have reported that longitudinal GCIPL and pRNFL atrophy occurs in AQP4-IgG positive NMOSD independent of ON attacks,[16,26,31] which has also been consistently shown in MS.[34] This is in contrast to the data presented here in our MOGAD cohort and is supported by the fact that the retina does not contain myelin-producing oligodendrocytes and expression of MOG has not been detected, making primary retinopathy due to MOG-IgG unlikely. Yet, a direct comparison to prove these distinct features of retinal pathology might be valuable in the future.

This international, multicentre, and largest longitudinal OCT analysis in MOGAD to date has overcome previous limitations of smaller studies through collaboration of expert centres worldwide. However, limitations exist: The data were acquired retrospectively and on two different OCT devices – with longitudinal HC data not available for all of them. All MOGAD patients were included regardless of clinical presentation and regime of immunosuppressive treatment. Thus, there is a large heterogeneity of associated clinical phenotypes that improves the generalizability of the results. Due to the rarity of the disease, the sample size is also relatively small, despite being the largest study of this topic to date. As a result, outliers may have a greater impact on the results and the robustness of results, especially longitudinally, might be impacted.

In conclusion, our longitudinal analysis of inner retinal layer thickness changes in MOGAD presented here reflects the heterogeneity of the scientific data with a broad classification of MOGAD-ON. By using two OCT devices, we could confirm a relapse-dependent, longitudinal pRNFL decrease in MOGAD up to 12 months after ON. However, we did not find evidence for subclinical relapse-independent neuroaxonal retinal degeneration. This analysis demonstrates a retinal phenotype in MOGAD-ON, which is distinct from AQP4-IgG positive NMOSD and MS. This delineation supports the classification of MOGAD as a distinct disease entity and is a further argument for the creation of MOGAD-specific treatment regimens.[35] In preparation of future prospective studies of ON-independent retinal changes, it is recommended to restrict analyses to patients with ON relapses > 12 months before baseline to minimize relapse-dependent effects.

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Author contributions

FCO, ESS, JC, FP, and JH contributed to the concept and design of the study. HGZ, SM, SvS, CC, LC, AJG, MRY, TJS, AG, AUB, EV, AF, PAC, ShS, LP, ADC, OO, SP, EPF, PSR, GB, TZ, TK, OA, MR, PA, IA, BK, LA, NA, KS, RM, CFT, ACC, PV, BSD, EHML contributed to the acquisition and analysis of data. FCO and ESS drafted the text and prepared the figures. Other contributors of the CROCTINO study group and their institutional affiliations are included in Supplementary Table 2.

Potential conflicts of interest

AUB is cofounder and shareholder of Nocturne. He is named as inventor on several patent applications regarding OCT image analysis. The other authors have nothing to report.

Data Availability

The data supporting the findings of this study are available within the article and from the corresponding author by reasonable request.

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Figure legends

Figure 1: Boxplots for baseline OCT thicknesses by group measured by Spectralis (A, C) and Cirrus (B, D) for healthy controls (HC, left), MOGAD eyes without a history of ON (NON, middle) and MOGAD eyes with a history of ON (ON, right). Boxplots overlayed with individual values as dots display A) pRNFL (Spectralis), B) pRNFL (Cirrus), D) GCIPL (Spectralis), D) GCIPL (Cirrus).

Abbreviations: GCIPL: ganglion cell and inner plexiform layer, HC: healthy controls, MOGAD: myelin oligodendrocyte glycoprotein antibody associated disease, NON: MOGAD eyes without a history of ON, OCT: optical coherence tomography, ON: MOGAD eyes with a history of ON, p: p-value, pRNFL: peripapillary retinal nerve fibre layer thickness.

Figure 2: Longitudinal OCT thicknesses by group measured by Spectralis (A, C) and Cirrus (B, D) for HC (continuous line) and MOGAD (dashed line). Lines (thin) for individual eye-based trajectories overlayed with predicted line for mixed linear effect model (thick) for A) pRNFL (Spectralis), B) pRFNL (Cirrus), C) GCIPL (Spectralis), D) GCIPL (Cirrus). Plotted for maximum F/U for GCIPL.

Abbreviations: GCIPL: ganglion cell and inner plexiform thickness, HC: healthy controls, MOGAD: myelin oligodendrocyte glycoprotein antibody associated disease, NON: MOGAD eyes without a history of ON, OCT: optical coherence tomography, pRNFL: peripapillary retinal nerve fibre layer thickness.

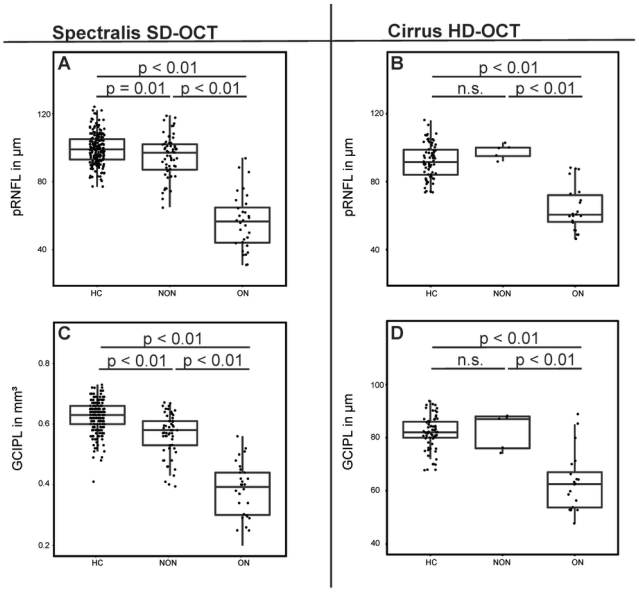
Table legends

Table 1: Cohort description for MOGAD patients and HC for Cirrus (left) and Spectralis cohort (right).
Abbreviations: EDSS: expanded disability status scale, HC: healthy controls, MOGAD: myelin oligodendrocyte glycoprotein antibody associated disease, N: number, OCT: optical coherence tomography, ON: optic neuritis episode, SD: standard deviation.

Table 2: Baseline comparisons of OCT thicknesses between HC, MOGAD-ON and MOGAD-NON for Cirrus and Spectralis cohort
Abbreviations: B: estimate, MOGAD-ON: eyes with a history of ON, MOGAD-NON: eyes without a history of ON, HC: healthy controls, MOGAD: myelin oligodendrocyte glycoprotein antibody associated disease, p: p-value, SD: standard deviation, SE: standard error, GCIPL: ganglion cell and inner plexiform layer, pRNFL: peripapillary retinal nerve fibre layer thickness, INL: inner nuclear layer.

Table 3: Baseline comparisons of OCT thicknesses between MOGAD-ON with different numbers of ON episodes for Cirrus and Spectralis cohort
Abbreviations: B: estimate, MOGAD-ON: eyes with a history of ON, MOGAD-NON: eyes without a history of ON, MOGAD-1-ON: eyes with a history of 1 ON, MOGAD-2-ON: eyes with a history of 2 ONs, MOGAD-3-ON: eyes with a history of 3 or more ONs, MOGAD: myelin oligodendrocyte glycoprotein antibody associated disease, p: p-value, SD: standard deviation, SE: standard error, GCIPL: ganglion cell and inner plexiform layer, pRNFL: peripapillary retinal nerve fibre layer thickness, INL: inner nuclear layer.

Table 4: Longitudinal changes of OCT thicknesses for Cirrus and Spectralis cohort
Abbreviations: B: estimate, HC: healthy controls, MOGAD: myelin oligodendrocyte glycoprotein antibody associated disease, p: p-value, SD: standard deviation, SE: standard error, GCIPL: ganglion cell and inner plexiform layer, pRNFL: peripapillary retinal nerve fibre layer thickness, INL: inner nuclear layer.



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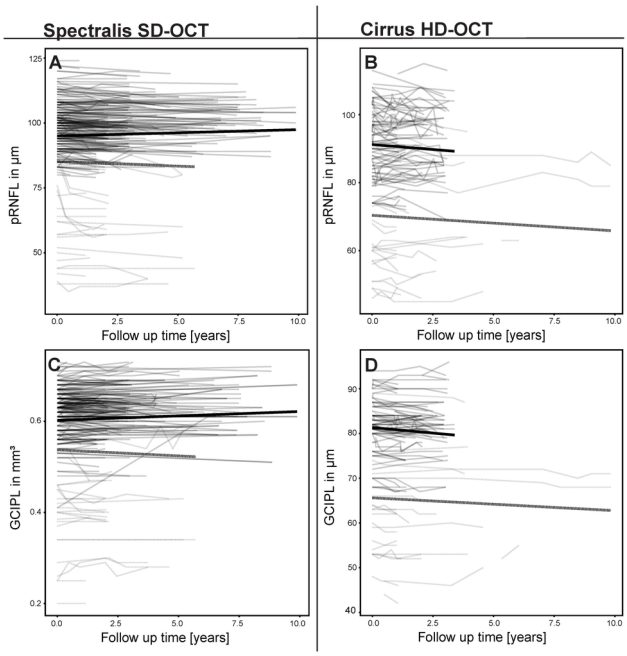

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	CIRRUS COHORT		SPECTRALIS COHORT	
	HC	**MOGAD**	**HC**	**MOGAD**
Subjects [N]	36	14	103	66
Eyes [N]	72	27	206	126
Age [years, mean ± SD]	44 ± 12	45 ± 14	36 ± 14	38 ± 14
Sex [male, N (%)]	13 (36)	5 (36)	41 (40)	32 (49)
Ethnicity [N (%)]				
- Asian	0 (0)	0 (0)	0 (0)	12 (18)
- Caucasian	36 (100)	14 (100)	103 (100)	53 (80)
- Other or Unknown	0 (0)	0 (0)	0 (0)	1 (2)
Follow-up time [months, median (IQR)]]	31 (22 – 36)	27 (13 – 36)	35 (23 – 65)	25 (15 - 36)
Time since disease onset [years, median (IQR)]	.	3 (1 – 5)	.	3 (1 – 8)
EDSS [median (min-max)]	.	1.5 (1.0 – 2.0)	.	2.0 (1.0 – 2.5)
Patients with a history of ON [N (%)]	.	13 (93)	.	43 (65)
Eyes with a history of ON [N (%)]	.	22 (81)	.	69 (55)
Time since last ON [months, median (IQR)]	.	15 (9 - 23)	.	25 (11 - 84)

Table 1: Cohort description for MOGAD patients and HC for Cirrus (left) and Spectralis cohort (right).
Abbreviations: EDSS: expanded disability status scale, HC: healthy controls, MOGAD: myelin oligodendrocyte glycoprotein antibody associated disease, N: number, OCT: optical coherence tomography, ON: optic neuritis episode, SD: standard deviation

	HC	MOGAD		HC vs. MOGAD-ON			HC vs. MOGAD-NON			MOGAD-ON vs. MOGAD-NON		
		NON	ON	B	SE	p	B	SE	p	B	SE	p
CIRRUS COHORT												
N	72	5	22									
pRNFL [µm, mean ± SD]	91.9 ± 10.3	98.0 ± 4.4	64.2 ± 13.3	-26.9	3.4	<0.001	6.1	5.3	0.26	-35.2	6.2	<0.001
GCIPL [µm, mean ± SD]	81.9 ± 6.2	82.6 ± 7.0	63.3 ± 11.1	-18.5	2.5	<0.001	-0.3	3.4	0.93	-17.6	5.2	0.003
SPECTRALIS COHORT												
N	206	57	69									
pRNFL [µm, mean ± SD]	99.1 ± 8.9	94.9 ± 12.4	64.3 ± 21.3	-36.0	2.3	<0.001	-4.6	1.7	0.008	-29.5	2.9	< 0.001
GCIPL [mm^3, mean ± SD]	0.62 ± 0.05	0.57 ± 0.07	0.43 ± 0.11	-0.18	0.01	<0.001	-0.05	0.01	<0.001	-0.130	0.015	< 0.001
INL [mm^3, mean ± SD]	0.27 ± 0.02	0.27 ± 0.03	0.29 ± 0.04	0.03	<0.01	<0.001	-0.01	0.004	0.18	0.019	0.004	<0.001

Table 2: Baseline comparisons of OCT thicknesses between HC, MOGAD-ON and MOGAD-NON for Cirrus and Spectralis cohort

Abbreviations: B: estimate, MOGAD-ON: eyes with a history of ON, MOGAD-NON: eyes without a history of ON, HC: healthy controls, MOGAD: myelin oligodendrocyte glycoprotein antibody associated disease, p: p-value, SD: standard deviation, SE: standard error, GCIPL: ganglion cell and inner plexiform layer, pRNFL: peripapillary retinal nerve fibre layer thickness, INL: inner nuclear layer.

	MOGAD-ON			MOGAD-1-ON vs. MOGAD-NON			MOGAD-2-ON vs. MOGAD-1-ON			MOGAD-3-ON vs. MOGAD-2-ON		
	1	2	≥3	B	SE	p	B	SE	p	B	SE	p
CIRRUS COHORT												
N	12	3	7									
pRNFL [µm, mean ± SD]	68.3 ± 15.0	54.3 ± 7.4	61.3 ± 9.6	-7.6	2.0	0.012	-13.6	3.0	0.02	-4.7	5.3	0.43
GCIPL [µm, mean ± SD]	65.8 ± 12.7	54.3 ± 7.1	62.8 ± 6.4	-3.9	1.5	0.044	-10.6	2.5	0.02	-1.0	1.0	0.49
SPECTRALIS COHORT												
N	37	19	12									
pRNFL [µm, mean ± SD]	72.0 ± 20.1	57.1 ± 19.9	49.4 ± 14.1	-23.4	3.4	< 0.001	-11.0	5.5	0.05	-2.9	7.1	0.68
GCIPL [mm^3, mean ± SD]	0.5 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	-0.11	0.02	<0.001	-0.05	0.03	0.07	-0.06	0.04	0.21

Table 3: Baseline comparisons of OCT thicknesses between MOGAD-ON with different numbers of ON episodes for Cirrus and Spectralis cohort

Abbreviations: B: estimate, MOGAD-ON: eyes with a history of ON, MOGAD-NON: eyes without a history of ON, MOGAD-1-ON: eyes with a history of 1 ON, MOGAD-2-ON: eyes with a history of 2 ONs, MOGAD-3-ON: eyes with a history of 3 or more ONs, MOGAD: myelin oligodendrocyte glycoprotein antibody associated disease, p: p-value, SD: standard deviation, SE: standard error, GCIPL: ganglion cell and inner plexiform layer, pRNFL: peripapillary retinal nerve fibre layer thickness, INL: inner nuclear layer.

	MOGAD (within group)			MOGAD vs. HC		
	B	SE	p	B	SE	P
CIRRUS COHORT (HC [N=72] MOGAD [N=27])						
pRNFL [µm/year]	-0.371	0.106	0.001	-0.256	0.170	0.13
GCIPL [µm/year]	-0.205	0.063	0.002	-0.045	0.081	0.58
SPECTRALIS COHORT (HC [N=206] MOGAD [N=86])						
pRNFL [µm/month]	-0.080	0.012	<0.001	-0.098	0.015	<0.001
GCIPL [mm^3/month]	< 0.001	< 0.001	0.86	<0.001	<0.001	0.09
INL [mm^3/month]	-0.002	0.005	0.65	-0.004	0.004	0.32

Table 4: Longitudinal changes of OCT thicknesses for Cirrus and Spectralis cohort

Abbreviations: B: estimate, HC: healthy controls, MOGAD: myelin oligodendrocyte glycoprotein antibody associated disease, p: p-value, SD: standard deviation, SE: standard error, GCIPL: ganglion cell and inner plexiform layer, pRNFL: peripapillary retinal nerve fibre layer thickness, INL: inner nuclear layer,