Multiple Sclerosis and Related Disorders 61 (2022) 103761

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

Progressive retinal changes in pediatric multiple sclerosis

Giulia Longoni [a,b], Robert A. Brown [c], Ade Oyefiade [a], Renisha Iruthayanathan [a], Colin Wilbur [a,b], Shahriar Shams [a], Austin Noguera [a], Stephanie A. Grover [a], Julia O'Mahony [a], Luke Chung [a], Michael J. Wan [d], Jean K. Mah [e], Fiona Costello [e], Douglas L. Arnold [c,f], Ruth Ann Marrie [g], Amit Bar-Or [h], Brenda Banwell [i], Donald Mabbott [a], Arun Y. Reginald [d], E. Ann Yeh [a,b,*]

[a] Department of Neurosciences and Mental Health, The Hospital for Sick Children, Toronto, ON, Canada
[b] Department of Pediatrics, Division of Neurology, University of Toronto, Toronto, ON, Canada
[c] McConnell Brain Imaging Centre, Montreal Neurological Institute and Hospital, McGill University, Montreal, QC, Canada
[d] Department of Ophthalmology and Visual Sciences, The University of Toronto, Toronto, ON, Canada
[e] Departments of Clinical Neurosciences and Surgery, Cumming School of Medicine, University of Calgary, AB, Canada
[f] Department of Neurology and Neurosurgery, Montreal Neurological Institute and Hospital, McGill University, Montreal, QC, Canada
[g] Departments of Internal Medicine and Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Canada
[h] Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[i] Division of Neurology, The Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

ARTICLE INFO

Keywords:
Optical coherence tomography (OCT)
Pediatric multiple sclerosis
Pediatric acquired demyelinating disorders

ABSTRACT

Objectives To determine to what extent acute demyelinating episodes *versus* chronic degenerative phenomena drive retinal neuroaxonal damage in pediatric acquired demyelinating syndromes (ADS).

Methods We acquired optical coherence tomography (OCT) data (follow-up range: 2 weeks – 5 years, at variable intervals from presentation) in pediatric participants who had multiple sclerosis (MS), monophasic ADS, or were healthy. Multivariable mixed effects models were used to assess the association of the number of demyelinating episodes (either optic neuritis [ON], or non-ON relapses) with changes in retinal nerve fiber layer (RNFL) or ganglion cell layer-inner plexiform layer (GCIPL) thickness.

Results 64 OCT sans from 23 MS, and 33 scans from 12 monophasic ADS participants were compared with 68 scans from 62 healthy participants. The first ON episode had the biggest impact on RNFL or GCIPL thickness in monophasic ADS (RNFL: -7.9 μm, CI=5.5, $p = 0.0056$; GCIPL: -8.4 μm, CI=4.4, $p = 0.0002$) and MS (RNFL: -16 μm, CI = 3.7, $p < 10^{-6}$; GCIPL: -15 μm, CI = 2.6, $p < 10^{-6}$). Non-ON relapses were also associated with small but significant retinal thickness reductions in MS (RNFL: -2.6 μm/relapse, CI = 1.4, $p = 0.0003$; GCIPL: -2.8 μm/relapse, CI = 0.89, $p < 10^{-6}$). MS participants showed progressive GCIPL thinning independent of acute demyelinating episodes (-2.7 μm/year, CI = 1.9, $p = 0.0058$).

Conclusions We showed a prominent impact of early ON episodes on OCT measures of neuroaxonal structure in patients with ADS. We also demonstrated negative effects of non-ON relapses, and the presence of chronic retinal neurodegenerative changes, in youth with MS.

1. Introduction

In MS, the inner layers of the retina are subject to widespread inflammatory and degenerative changes (Green et al., 2010) which can be estimated quantitatively and non-invasively by OCT. Decreased peripapillary RNFL or macular ganglion GCIPL thickness, as measured using OCT, are considered to be reliable markers of chronic retinal neuroaxonal damage (Petzold et al., 2017).

Abbreviations: ADEM, acute disseminated encephalomyelitis; ADS, acquired demyelinating syndromes; AQP4, aquaporin 4; CI, 95% confidence interval; DMT, disease-modifying treatment; Eq., equation; GCIPL, ganglion cell layer-inner plexiform layer; GCIPLT, GCIPL thickness; MOG, myelin oligodendrocyte glycoprotein; *N*, number; OCT, optical coherence tomography; ON, optic neuritis; RNFL, retinal nerve fiber layer; RNFLT, RNFL thickness; TM, transverse myelitis.

* Corresponding author at: Department of Pediatrics, Division of Neurology, University of Toronto, Toronto, ON, Canada.
E-mail address: ann.yeh@sickkids.ca (E.A. Yeh).

https://doi.org/10.1016/j.msard.2022.103761
Received 21 October 2021; Received in revised form 16 March 2022; Accepted 21 March 2022
Available online 23 March 2022

The OCT literature in pediatric MS is, to date, scant. As in adults, profound RNFL and GCIPL thickness reductions have been consistently demonstrated in children after an acute episode of ON (Costello et al., 2015; Graves et al., 2016; Waldman et al., 2013; Yeh et al., 2014, 2009). Recent longitudinal MRI studies described a progressive loss of brain tissue integrity in pediatric MS,(Aubert-Broche et al., 2014; Longoni et al., 2017) and conceivably similar phenomena could be hypothesized to occur within the retina.

On the other hand, transient episodes of CNS inflammation in the absence of chronic disease (monophasic ADS) are not expected to be associated with progressive retinal pathology. Even a single episode of transient hemispheric inflammation has, however, been shown to lead to permanent disruption of brain white matter integrity and failure of normal brain growth (Aubert-Broche et al., 2014, 2017; Longoni et al., 2017), but the long-term effect of monophasic CNS inflammation on retinal structures is unknown.

Longitudinal studies could thus potentially allow a quantification of the distinct effects of acute demyelinating episodes *versus* chronic degenerative phenomena on the retina in this population.

We aimed to longitudinally evaluate retinal neuroaxonal injury in children with pediatric-onset MS and monophasic ADS compared to a healthy control population, and, further, to assess how episodes of inflammation of the optic nerve or of other CNS locations influence these dynamics.

2. Materials and methods

2.1. Participants

This was a n exploratory longitudinal analysis of prospectively collected observational data (2010–2018) from children and adolescents enrolled at the Hospital for Sick Children (SickKids) (Toronto, Canada) or at the Alberta Children's Hospital (Calgary, Canada) (Fig. 1) in the prospective Canadian Pediatric Acquired Demyelinating Disease Study (Banwell et al., 2011) or in a longitudinal Registry of pediatric patients with acquired demyelination at the Hospital for Sick Children. Participants from the first cohort were enrolled at the time of clinical presentation (ADS) and were imaged with OCT as close to the time of incident demyelination as practical, and subsequently at 3, 6, and 12 months, then yearly afterwards and at the time of further demyelinating episodes. The separate cohort of participants from the Hospital for Sick Children were assessed at regular intervals at the time of clinic visits or at the time of further demyelinating episodes.

Inclusion criteria were: (i) a diagnosis of MS or monophasic ADS (Krupp et al., 2013); (ii) age <18 years at the time of enrollment; and (iii) at least two standardized OCT time points acquired at variable intervals from the first acute neurological presentation which passed quality control (Tewarie et al., 2012). Exclusion criteria were a history of (i) other neurological conditions or major medical comorbidities; (ii) coexisting ocular pathologies; (iii) refractive error ± 6 diopters; (iv) an MS relapse in the previous 30 days; or (v) monophasic ADS with less than two years of follow-up. Anti-MOG antibodies were tested in a subset of patients as detailed in Table 1. ON was defined as an acute episode of optic nerve inflammation confirmed by clinical and/or neurophysiological evaluation, according to standard definitions (Petzold et al., 2014). Eyes from participants with and without a clinical history of ON were included. For those with a history of ON, all measurements obtained within −15 and +90 days from the episode were excluded from the current analysis, to eliminate most of the confounding effect of acute (pre-clinical or clinical) retinal changes (Costello et al., 2015). Age- and sex-matched healthy participants were recruited from the community in Toronto and Calgary through local advertisement. Only a small number of these ($n = 6$) had OCT measurements from two

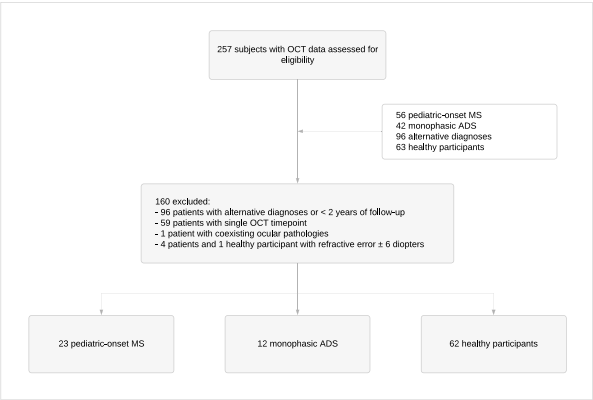

Fig. 1. Study flow diagram.

Table 1
Clinical and demographic characteristics of the three study groups.

	MS		Monophasic ADS		Healthy participants
Number of participants	23		12 °		62
Female sex, n (%)	16 (69)		3 (25)		27 (44)
Tested for MOG-Ab (no. of MOG-Ab positive)	7/23 (1)		5/12 (3)		0/62 (n/a)
Tested for AQP4-Ab (no. of AQP4-Ab positive)	5/23 (0)		7/12 (0)		0/62 (n/a)
Taking DMT, n (%) *	20 (88)		_		_
Total number of OCTs	136		66		136
Median number of OCTs per participant (range)	2 (2–6)		2.5 (2–5)		1 (1–2)
Median OCT follow-up (range) [years] §	0.8 (0.04–4.4)		1.6 (0.8–5.3)		0.0 (0.0–1.5)
Median age at incident demyelination (range) [years]	13.6 (5.9–17 0.4)		8.3 (2.7–13.9)		_
Median time from incident demyelination at study entry (range) [years]†	1.3 (0.01–11.1)		1.9 (0.5–5.0)		_
Distribution of OCT observations according to the number of previous eye-specific episodes of ON (number of eye-time points (%))	**0 ONs**	$n =$ 88 (69)	**0 ONs**	$n =$ 36 (55)	_
	1 ON	$n =$ 34 (27)			
	≥ 2 ONs	$n = 6$ (5)	**1 ON**	$n =$ 30 (45)	
Distribution of OCT observations according to the number of previous non-ON relapses *post* incident demyelination (number of eye-time points (%))	**0 relapses**	$n =$ 80 (63)	_		_
	1 relapse	$n =$ 24 (19)			
	2 relapses	$n =$ 4 (3)			
	3 relapses	$n =$ 6 (5)			
	4 relapses	$n =$ 14, (11)			

° Seven isolated ON, three isolated TMs, one ADEM, and one other polyfocal CNS syndrome without encephalopathy.
* Twenty of the MS participants (88%) received disease-modifying treatment for part or the whole study follow-up (glatiramer acetate, $n =$ seven; interferon β−1a, $n =$ seven; dimethyl fumarate, $n =$ six; natalizumab, $n =$ four; interferon β−1b; $n =$ three; peginterferon β−1a; $n =$ three; cyclophosphamide, $n =$ two; teriflunomide, $n =$ one; rituximab, $n =$ one; alemtuzumab, $n =$ one).
§ "OCT follow-up" refers to the elapsed time between the first and last OCT scan analyzed.
† "Study entry" refers to the time of the first OCT.

time points. See Fig. 1 for a study flow diagram.

2.2. Clinical evaluation and history

Demographic and clinical information including sex, age and time from incident demyelination at study entry, number of clinical episodes of ON as well as the date and affected eye for each episode, number and date of MS relapses, the use of DMT, and comorbidities were collected using a standardized case report form.

2.3. OCT data acquisition and processing

In both centers, all scans were performed by trained personnel using a spectral domain OCT (SD-OCT) Cirrus scanner (Carl Zeiss Meditec 4000, software version 7.0.3.19). Scanning was performed using the Optic Disc Cube 200 × 200 scan protocol for evaluation of the peripapillary RNFLT, and the Macular Cube 512 × 128 scan protocol for that of GCIPLT. Signal strength equal to or above 6 (out of 10) was considered adequate for analysis. Peripapillary RNFLT was assessed by quadrants, and the average of all quadrants was reported as the mean RNFLT in micrometers (μm). GCIPLT was measured in sextants and averaged to provide a mean GCIPLT [μm]. GCIPLT and RNFLT were derived from data generated by the manufacturer's fully automated segmentation software. Segmentation results were reviewed to ensure accuracy, with manual correction by trained OCT technicians where necessary.

2.4. Standard protocol approvals, registrations, and patient consents

Ethics approval was received from the Research Ethics Board at the Hospital for Sick Children (REB# 1000005356 and 1000053920) and the University of Calgary (REB# 151111 and 151297). Written informed consent was obtained from all guardians and informed assent from all participants before study initiation.

2.5. Statistical analysis

Statistical analysis was performed using custom software written in Python (Python Software Foundation, python.org) and R (R Core Team, 2017) using the Scientific Python package (Scipy, www.scipy.org), the RPy2 module (RPy2, rpy.sourceforge.net) the lme4 package, and SPSS (IBM Corp. Version 26.0. Armonk, NY). We conducted a preliminary analysis comparing the GCIPLT and RNFLT between the two sites and between groups of the two sites after adjusting for *age at measure* and *sex*, and they did not differ (RNFLT: corrected model F 7.5, $p = 3.4 \times 10^{-7}$; *site:* F 2.4, $p = 0.13$; *site*group*: F 0.1, $p = 0.34$; GCIPLT: corrected model F 7.9, $p = 1.5 \times 10^{-7}$; *site:* F 2.2, $p = 0.14$; *site*group*: F 1.3, $p = 0.27$). Therefore, participants from both sites were pooled for subsequent analyses.

Our main model (**Eqs. (1) and (2), Appendix e-1**) assessed each eye from each participant longitudinally using mixed effects models with random effects for *eye* (right and left) nested within *subject* to account for inter-eye and intra-eye correlation over repeated measurements. RNFLT and GCIPLT changes over time in each *group* (healthy participants as reference group*)* were modeled with fixed effects for *age at study entry* (study entry = time of first OCT), *time from incident demyelination at study entry* (for MS or patients with monophasic ADS), *time from study entry, number of eye-specific ON episodes as of each OCT time point*, and their interactions, as detailed in **Appendix e-1**. The number of ON episodes was categorized as zero, one, or greater than one (eyes of patients without previous ON, and unaffected eyes of patients with previous unilateral ON - "fellow eyes"- were not distinguished). Our analysis accounted for the number of ON episodes for each patient-eye as measured in the interval from presentation to each OCT visit (rather than a cumulative number over the study for each patient). The number of non-ON relapses at the time of each OCT visit was categorized as zero or more than zero.

As the main model did not include terms estimating the effect of *time from incident demyelination at study entry* on RNFLT or GCIPLT of MS or monophasic ADS separately (assessing the presence of possible chronic changes *before* study start in either group), this was assessed in two *ad hoc* models (**Eqs. (3) and (4), Appendix e-1**), including similar fixed and random effects included in Eqs. (1) and (2).

Finally, we assessed the within-eye association between RNFLT and GCIPLT over time in our whole study population, to investigate whether the changes were concordant or not (**Eq. (5), Appendix e-1).**

Chi-squared tests comparing the log-likelihoods of the models (Eq. (1) to (5)) with null models tested whether the model as a whole had significant explanatory power. Results were corrected for multiple comparisons (Bonferroni correction for five independent tests, with adjusted p for the F test of overall significance of each model = 0.01) and reported where significant. Residual plots were inspected to ensure models' accuracy. **Appendix e-1** includes a detailed explanation of the statistical analysis.

4. Results

4.1. Demographic and clinical characteristics

We analyzed 64 OCT scans from 23 participants with pediatric MS, 33 OCT scans from 12 participants with monophasic ADS, and 68 OCT scans from 62 healthy participants. See Table 1 for detailed clinical and demographical data. The full model fits are displayed in **Appendix e-2**.

***RNFL or GCIPLT changes associated with acute demyelinating episodes (*Fig. 2 *Intercepts)*.**

RNFLT (Eq. (1)). The average RNFLT for a control of average age at study start (14 years) was 100.5 μm. On multivariable analysis, eyes of monophasic ADS or MS participants who had never experienced ON had RNFL that were not significantly thinner than that of healthy participants (monophasic ADS: −9.8 μm, CI=11; MS: −6.1 μm, CI = 6.5, $p = 0.084$, *versus* healthy participants). Monophasic ADS or MS eyes with one episode of ON had decreased RNFL compared to eyes with zero episodes of ON (monophasic ADS: −7.9 μm, CI = 5.5, $p = 0.0056$; MS: −16 μm, CI = 3.7, $p < 10^{-6}$, *versus* eyes of the corresponding disease group with zero ON episodes). However, on average, eyes of MS participants that experienced multiple additional ON episodes did not have significantly lower RNFLT compared to eyes with one ON episode (−0.58 μm, CI = 6.0, $p = 0.85$). Each non-ON disease relapse after incident demyelination in the MS group was associated with an average RNFL decrement of −2.6 μm/ relapse (CI = 1.4, $p = 0.0003$).

GCIPLT (Eq. (2)). GCIPLT averaged 85 μm in the eyes of healthy participants. In patient eyes with no previous history of ON, GCIPLT was similar to that of healthy controls (monophasic ADS: −5.2 μm, CI = 8.3; MS: −2.2 μm, CI = 3.9, $p = 0.33$, *versus* healthy participants). However, GCIPLT was significantly lower after the first episode of ON (monophasic ADS: −8.4 μm, CI = 4.4, $p = 0.0002$; MS: −15 μm, CI = 2.6, $p < 10^{-6,}$ *versus* eyes of the corresponding disease group with zero ON episodes). The occurrence of additional ON episodes after the first was not associated with significant additional GCIPL thickness decrements (0.21 μm, CI = 4.5, $p = 0.93$, *versus* eyes with one ON episode) in the MS group. Each non-ON relapse after incident demyelination was associated with an average GCIPL thickness decrement of −2.8 μm (CI = 0.89, $p < 10^{-6}$).

***Progressive RNFL or GCIPLT changes independent of acute demyelinating episodes (*Fig. 2*- Trajectories)*.**

RNFLT. RNFLT of MS participants was associated with time from incident demyelination (−2.8 μm/year; CI = 1.5, $p = 0.0004$), indicating ongoing RNFLT decline independent of ON episodes or disease relapses before study entry (Eq. (3)). During the study period, however, neither monophasic ADS nor MS eyes for any of the ON or relapse categories showed significant progressive RNFL changes independent of clinical ON episodes or non-ON relapses (Eq. (1)).

GCIPLT. As with RNFLT, GCIPLT before study entry was decreased in

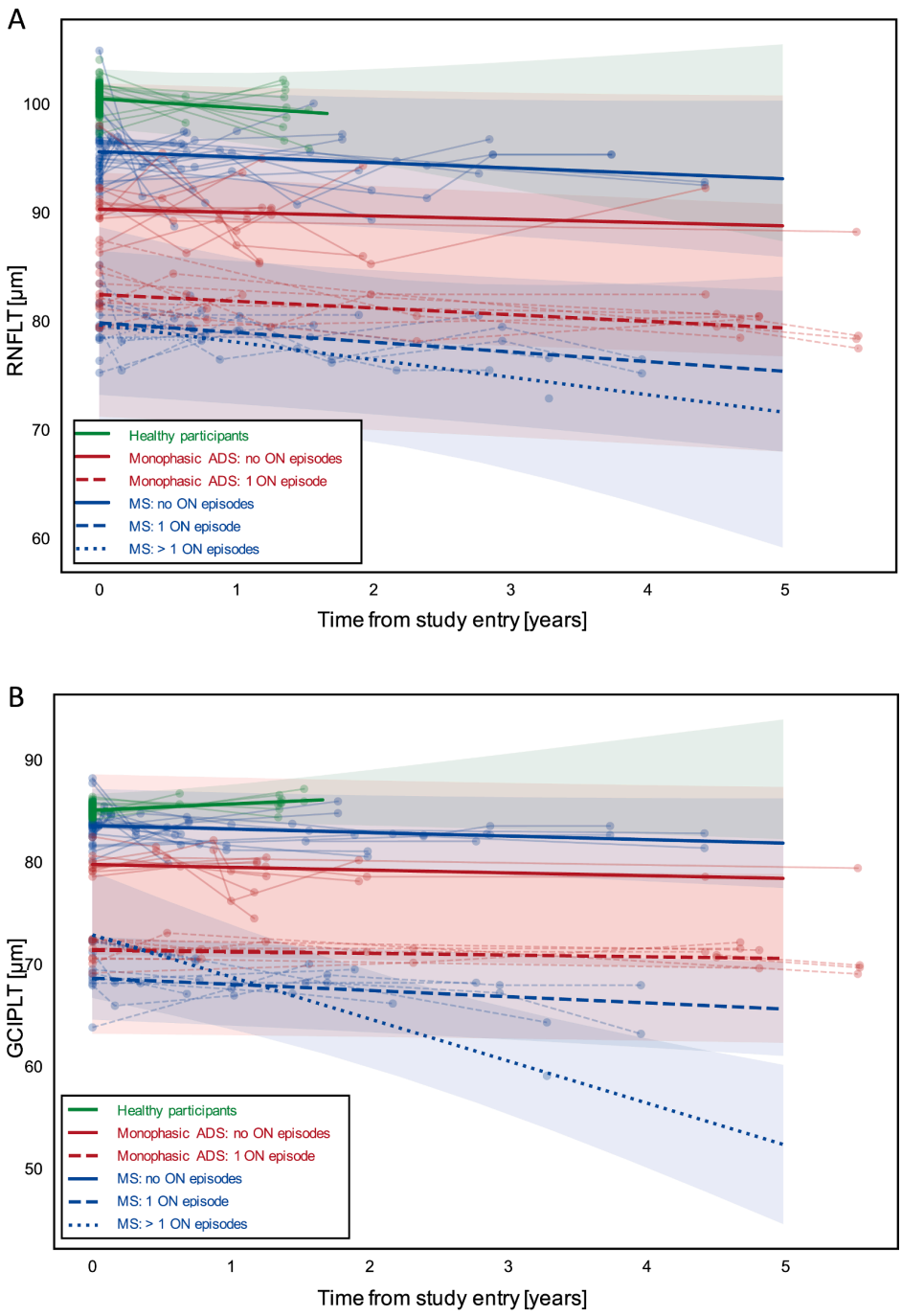

Fig. 2. RNFL and GCIPL trajectories. Evolution of RNFLT (A) and GCIPLT (B) in pediatric-onset multiple sclerosis (blue), monophasic ADS (red), and healthy participants (green), according to the number of ON episodes at the time of their OCT scan. Points connected by light lines are individual participants. Heavy lines show trajectories predicted by the model for each group. Shaded areas are 95% confidence intervals. Both RNFLT and GCIPLT drop significantly after the first episode of ON, in both MS and monophasic ADS participants. The MS group show decreasing GCIPLT over time after multiple (> 1) episodes of ON (For interpretation of the references to color in this figure legend when reproduced in black and white, the reader is referred to the web version of this article.).

relation to time from incident demyelination (−1.5 µm/year; CI = 0.83, $p = 0.0005$) in MS participants (Eq. (4)). Interestingly, MS eyes with multiple previous episodes of ON showed ongoing GCIPL thinning (−2.7 µm/ year, CI = 1.9, $p = 0.0058$) while multiple previous non-ON relapses were not associated with subsequent significant ongoing GCIPL thinning. However, each non-ON relapse was associated with progressively slower GCIPL changes over time (= attenuated atrophy rates) [0.55 µm-slower yearly thinning *versus* eyes of MS participants with one less previous relapse, CI = 0.41, $p = 0.0089$]. Monophasic ADS did not show significant progressive GCIPLT changes (Eq. (2)).

Longitudinal relationship between RNFLT and GCIPLT.

Within the same eye and over time, RNFLT was strongly associated with GCIPLT (+1.1 µm for each one-µm increase of GCIPLT, CI = 0.074, $p < 10^{-6}$) (Eq. (5)).

5. Discussion

In this longitudinal study we found chronic, progressive reductions of GCIPLT through time in youth with MS, beginning after multiple (> one) episodes of ON. While we detected a pronounced impact of the first

episode of ON on RNFLT or GCIPLT in MS participants, subsequent episodes were associated with much smaller decreases in thickness. In addition, we observed small but significant reductions of both retinal layers' thicknesses in association with every non-ON relapse after incident demyelination.

Monophasic ADS are a heterogeneous group of disorders characterized by transient and non-recurrent CNS inflammation, not meeting the diagnostic criteria for MS (Thompson et al., 2018). These may include ADEM-like phenotypes, ON, acute TM, brainstem or cerebellar syndromes, hemispheric-related syndromes, or their combination. Monophasic ADS participants who experienced ON showed pronounced decrease in both retinal layers' thicknessess, but ongoing degenerative changes independent of ON episodes were not found. Only a small proportion of patients were tested for MOG antibody. This precluded us from a separate evaluation of MOG-positive patients, in whom clinical events may be separated by many years, and a chronic biology has not yet been ascertained.

RNFLT or GCIPLT were not significantly affected in MS or monophasic ADS in the absence of previous episodes of ON.

These results are consistent with those of our previous cross-sectional study from 2009, where partially overlapping study cohorts were included (Yeh et al., 2009). Results from other previous studies investigating subclinical OCT changes in pediatric MS patients (either distinguishing or not between eyes of MS patients without a history of ON in either eye or fellow eyes) are generally in agreement with this finding (Graves et al., 2016; Waldman et al., 2013, 2017; Yilmaz et al., 2012). While the small sample size of both our MS and healthy participant cohorts limits the power of our study, our results suggest a relative preservation of retinal layer thicknesses in pediatric MS or monophasic ADS in the absence of previous ON episodes and supports the notion of acute optic nerve inflammation as one of the major determinants of axonal loss and neurodegeneration within the retina of these patients.

Pronounced retinal layer changes occurred in both MS and monophasic ADS in association with the first episode of ON.

In accordance with previous literature (Graves et al., 2016; Waldman et al., 2013; Yeh et al., 2014; Yilmaz et al., 2012) we observed markedly reduced RNFL or GCIPL thickness associated with the first episode of ON in youth with MS. Importantly, affected eyes of monophasic ADS participants also showed significant retinal injury. Our models did not detect significant further incremental RNFL or GCIPL thickness decrements associated with each additional episode of ON in children with MS. However, our analysis included only six OCT visits from MS participants with two or more episodes of ON, decreasing our ability to detect significant changes in this group. We previously evaluated the additive effect of multiple episodes of ON in a group of children with various ADS (including 16 children with MS) (Yeh et al., 2014). Compared to control eyes, RNFL showed a linear trend of 9 μm decrements with each additional episode of ON, while GCIPL thickness did not show significant incremental reductions (Yeh et al., 2014). The discrepancy with our current results for the RNFLT may derive from the different statistical approaches. Where we previously evaluated average decrements across ON episodes, we have now specifically estimated the decrements associated with each additional ON episode. Our data suggest a non-linear effect of multiple ON episodes on retinal thicknesses, and this should be taken into account in future studies on larger cohorts. Another reason for discrepancy may derive from combining MS and other ADS in the same group in our previous study (Yeh et al., 2014).

Ongoing degeneration occurred within both RNFL and GCIPL of pediatric MS participants before study entry.

In participants with MS, our models (Eqs. (4) and (5)) predicted ongoing RNFLT and GCIPLT decline independent of ON episodes or relapses before the time of study entry. This was unexpected in the context of absence of significant RNFLT or GCIPLT decline independent of acute attacks *after* study start. These results may be partly explained by a slowing of retinal layers' thinning with increasing disease duration in participants with MS (the role of DMT initiation on retinal layers' changes will need to be elucidated in future studies).

Ongoing degeneration occurred within the GCIPLT of pediatric MS participants after multiple previous ON episodes.

We found a progressive decrease of GCIPL thickness over time in eyes of youth with MS after multiple episodes of ON. These results may be explained by ongoing subclinical episodes of optic nerve inflammation, a delayed effect of multiple previous ON episodes on the GCIPL, or suggest the instauration of neurodegenerative phenomena within the retina. The exact mechanisms of progressive retinal injury will have to be elucidated in future studies including pathological evidence.

Non-ON disease relapses were associated with moderate discrete incremental GCIPL and RNFL thickness reductions in children with MS.

The association between GCIPL thickness reductions and non-ON disease relapses is in keeping with previous findings in adults with MS that showed an association of retinal injury with increased brain inflammatory disease activity (Gordon-Lipkin et al., 2007; Green et al., 2010; Knier et al., 2016a, 2016b; Oh et al., 2015; Ratchford et al., 2013; Saidha et al., 2012) This may reflect neuroaxonal degeneration from distant lesions within the optic radiations (Jindahra et al., 2009), or different mechanisms related to diffuse brain inflammation. Our interpretation of this finding, which may support the view of OCT as a surrogate marker of disease activity in pediatric MS, is limited by the lack of MRI-derived measures of disease burden in MS patients, such that we could not establish the contribution of posterior visual pathway lesions leading to GCIPL thickness reduction by retrograde and/or trans-synaptic degeneration from post-geniculate lesions. Interestingly, GCIPL showed attenuated atrophy rates in children with MS after multiple non-ON disease relapses. This is consistent with previous longitudinal studies showing a slower GCIPL thinning in adult patients with higher number of previous relapses (Balk et al., 2016; Ratchford et al., 2013), and may hint at a diminished tendency for inflammatory damage over the course of the disease, or at a gradual depletion of retinal structures available for neurodegeneration. Of note, our results of decreased retinal layers' thicknesses with each episode of non-ON relapse, in the absence of significant thickness reductions associated with episodes of ON following the first one, may be explained by the different statistical approach used to evaluate the effect of ON and non-ON relapses. As previously mentioned, we evaluated the specific effect of each sequential (0, 1, >1) ON episode on retinal thicknesses, while the decrements associated with each non-ON relapse were evaluated using a linear trend (*averaging* the effect of subsequent non-ON relapses). These results, however, may also be explained by the low rate of MS participants with multiple ON, and the higher number of MS participants with non-ON relapses. Therefore, these findings need to be interpreted with caution.

Our analysis is limited by the relatively small sample size with limited longitudinal follow-up for participants with MS or monophasic ADS, and by the lack of longitudinal OCT sampling for healthy controls. These factors may have reduced our statistical power. The small sample size also prevented us from evaluating the effects of the presence of MOG-antibodies, disease-modifying treatment, or sexual dimorphism on retinal outcomes. Furthermore, the lack of standardized brain imaging precluded us from evaluating the relationship between retinal outcome and brain volume in pediatric MS.

In pediatric MS and monophasic ADS, axonal loss and neurodegeneration within the retina are predominantly related to the first episode of acute optic nerve inflammation. Progressive degenerative phenomena at the level of the GCIPL, which proceed independently of further clinical episodes of ON or non-ON relapses, also occur in children with pediatric MS. These findings indicate an increased pathogenicity of early inflammatory episodes on retinal structures, they confirm a link between retinal and global brain injury in pediatric MS, and possibly suggest an exhaustion of the retinal compensatory ability after repeated inflammatory bouts. This may have important implications for treatment strategies in this population of children.

Data availability

Anonymized data will be shared by request from any qualified investigator.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

This work was supported by the Ontario Institute for Regenerative Medicine (OIRM), the Stem Cell Network, the National Multiple Sclerosis Society (NMSS), and The Multiple Sclerosis Scientific Research Foundation (MSSRF).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.103761.

References

Aubert-Broche, B., Fonov, V., Narayanan, S., Arnold, D.L., Araujo, D., Fetco, D., Till, C., Sled, J.G., Banwell, B., Collins, D.L., Canadian Pediatric Demyelinating Disease, N., 2014. Onset of multiple sclerosis before adulthood leads to failure of age-expected brain growth. Neurology 83 (23), 2140–2146.

Aubert-Broche, B., Weier, K., Longoni, G., Fonov, V.S., Bar-Or, A., Marrie, R.A., Yeh, E.A., Narayanan, S., Arnold, D.L., Verhey, L.H., Banwell, B., Collins, D.L., Canadian Pediatric Demyelinating Disease, N., 2017. Monophasic demyelination reduces brain growth in children. Neurology 88 (18), 1744–1750.

Balk, L.J., Cruz-Herranz, A., Albrecht, P., Arnow, S., Gelfand, J.M., Tewarie, P., Killestein, J., Uitdehaag, B.M., Petzold, A., Green, A.J., 2016. Timing of retinal neuronal and axonal loss in MS: a longitudinal OCT study. J. Neurol. 263 (7), 1323–1331.

Banwell, B., Bar-Or, A., Arnold, D.L., et al., 2011. Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: a prospective national cohort study. Lancet Neurol. 10, 436–445.

Costello, F., Pan, Y.I., Yeh, E.A., Hodge, W., Burton, J.M., Kardon, R., 2015. The temporal evolution of structural and functional measures after acute optic neuritis. J. Neurol. Neurosurg. Psychiatr. 86 (12), 1369–1373.

Gordon-Lipkin, E., Chodkowski, B., Reich, D.S., Smith, S.A., Pulicken, M., Balcer, L.J., Frohman, E.M., Cutter, G., Calabresi, P.A., 2007. Retinal nerve fiber layer is associated with brain atrophy in multiple sclerosis. Neurology 69 (16), 1603–1609.

Graves, J.S., Chohan, H., Cedars, B., Arnow, S., Yiu, H., Waubant, E., Green, A., 2016. Sex differences and subclinical retinal injury in pediatric-onset MS. Mult. Scler. 447–455.

Green, A.J., McQuaid, S., Hauser, S.L., Allen, I.V., Lyness, R., 2010. Ocular pathology in multiple sclerosis: retinal atrophy and inflammation irrespective of disease duration. Brain 133 (Pt 6), 1591–1601 a journal of neurology.

Jindahra, P., Petrie, A., Plant, G.T., 2009. Retrograde trans-synaptic retinal ganglion cell loss identified by optical coherence tomography. Brain 132 (Pt 3), 628–634 a journal of neurology.

Knier, B., Berthele, A., Buck, D., Schmidt, P., Zimmer, C., Muhlau, M., Hemmer, B., Korn, T., 2016a. Optical coherence tomography indicates disease activity prior to clinical onset of central nervous system demyelination. Mult. Scler. 22 (7), 893–900.

Knier, B., Schmidt, P., Aly, L., Buck, D., Berthele, A., Muhlau, M., Zimmer, C., Hemmer, B., Korn, T., 2016b. Retinal inner nuclear layer volume reflects response to immunotherapy in multiple sclerosis. Brain 139 (11), 2855–2863 a journal of neurology.

Krupp, L.B., Tardieu, M., Amato, M.P., Banwell, B., Chitnis, T., Dale, R.C., Ghezzi, A., Hintzen, R., Kornberg, A., Pohl, D., Rostasy, K., Tenembaum, S., Wassmer, E., Group, f.t.I.P.M.S.S., 2013. International pediatric multiple sclerosis study group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult. Scler. J. 19 (10), 1261–1267.

Longoni, G., Brown, R.A., MomayyezSiahkal, P., Elliott, C., Narayanan, S., Bar-Or, A., Marrie, R.A., Yeh, E.A., Filippi, M., Banwell, B., Arnold, D.L., Canadian Pediatric Demyelinating Disease, N., 2017. White matter changes in paediatric multiple sclerosis and monophasic demyelinating disorders. Brain 1300–1315 a journal of neurology.

Oh, J., Sotirchos, E.S., Saidha, S., Whetstone, A., Chen, M., Newsome, S.D., Zackowski, K., Balcer, L.J., Frohman, E., Prince, J., Diener-West, M., Reich, D.S., Calabresi, P.A., 2015. Relationships between quantitative spinal cord MRI and retinal layers in multiple sclerosis. Neurology 84 (7), 720–728.

Petzold, A., Balcer, L.J., Calabresi, P.A., Costello, F., Frohman, T.C., Frohman, E.M., Martinez-Lapiscina, E.H., Green, A.J., Kardon, R., Outteryck, O., Paul, F., Schippling, S., Vermersch, P., Villoslada, P., Balk, L.J., Ern-Eye, I., 2017. Retinal layer segmentation in multiple sclerosis: a systematic review and meta-analysis. Lancet Neurol. 16 (10), 797–812.

Petzold, A., Wattjes, M.P., Costello, F., Flores-Rivera, J., Fraser, C.L., Fujihara, K., Leavitt, J., Marignier, R., Paul, F., Schippling, S., Sindic, C., Villoslada, P., Weinshenker, B., Plant, G.T., 2014. The investigation of acute optic neuritis: a review and proposed protocol. Nat. Rev. Neurol. 10 (8), 447–458.

R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

Ratchford, J.N., Saidha, S., Sotirchos, E.S., Oh, J.A., Seigo, M.A., Eckstein, C., Durbin, M. K., Oakley, J.D., Meyer, S.A., Conger, A., Frohman, T.C., Newsome, S.D., Balcer, L.J., Frohman, E.M., Calabresi, P.A., 2013. Active MS is associated with accelerated retinal ganglion cell/inner plexiform layer thinning. Neurology 80 (1), 47–54.

Saidha, S., Sotirchos, E.S., Ibrahim, M.A., et al., 2012. Microcystic macular oedema, thickness of the inner nuclear layer of the retina, and disease characteristics in multiple sclerosis: a retrospective study. Lancet Neurol. 11 (11), 963–972.

Tewarie, P., Balk, L., Costello, F., Green, A., Martin, R., Schippling, S., Petzold, A., 2012. The OSCAR-IB consensus criteria for retinal OCT quality assessment. PLoS One 7 (4), e34823.

Thompson, A.J., Banwell, B.L., Barkhof, F., Carroll, W.M., et al., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 17 (2), 162–173.

Waldman, A.T., Hiremath, G., Avery, R.A., Conger, A., Pineles, S.L., Loguidice, M.J., Talman, L.S., Galetta, K.M., Shumski, M.J., Wilson, J., Ford, E., Lavery, A.M., Conger, D., Greenberg, B.M., Ellenberg, J.H., Frohman, E.M., Balcer, L.J., Calabresi, P.A., 2013. Monocular and binocular low-contrast visual acuity and optical coherence tomography in pediatric multiple sclerosis. Mult. Scler. Relat. Disord. 3 (3), 326–334.

Waldman, A.T., Liu, G.T., Lavery, A.M., Liu, G., Gaetz, W., Aleman, T.S., Banwell, B.L., 2017. Optical coherence tomography and visual evoked potentials in pediatric MS. Neurol. Neuroimmunol. Neuroinflamm. 4 (4), e356.

Yeh, E.A., Marrie, R.A., Reginald, Y.A., Buncic, J.R., Noguera, A.E., O'Mahony, J., Mah, J.K., Banwell, B., Costello, F., Canadian Pediatric Demyelinating Disease Network, 2014. Functional-structural correlations in the afferent visual pathway in pediatric demyelination. Neurology 83 (23), 2147–2152.

Yeh, E.A., Weinstock-Guttman, B., Lincoff, N., Reynolds, J., Weinstock, A., Madurai, N., Agarwal, N., Buch, P., Karpinski, M., Ramanathan, M., 2009. Retinal nerve fiber thickness in inflammatory demyelinating diseases of childhood onset. Mult. Scler. 15 (7), 802–810.

Yilmaz, U., Gucuyener, K., Erin, D.M., Yazar, Z., Gurkas, E., Serdaroglu, A., Tepe, N., Demir, E., 2012. Reduced retinal nerve fiber layer thickness and macular volume in pediatric multiple sclerosis. J. Child Neurol. 27 (12), 1517–1523.