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Inter-Ocular Difference in Retinal Nerve Fiber Layer Thickness Predicts Optic Neuritis in Pediatric-Onset Multiple Sclerosis

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Introduction

Optical coherence tomography (OCT) can be used to quantifiably estimate retinal thickness in ophthalmologic and neurologic conditions including multiple sclerosis (MS). In particular, quantification of the retinal nerve fiber layer (RNFL), which consists of the unmyelinated axonal fibers of the optic nerve, provides insight into active or prior injury to the optic nerve. OCT-derived measurements of RNFL thickness are primarily compared to normative values supplied by the manufacturer's reference database to make inferences about the presence of underlying pathology (1). Using this approach, RNFL thickness values are usually considered abnormal if they fall below the lower 5^{th} or 1^{st} percentiles. RNFL measurements demonstrate excellent reproducibility (1). The presence of RNFL thinning has shown good sensitivity and specificity for confirming remote optic neuritis (ON) in the context of MS (2).

Documenting a prior ON event can be useful in the diagnostic evaluation of a child with possible MS. Yet, while ON is a common symptom in POMS, studies have demonstrated that only 50% of pediatric ON eyes may show RNFL thinning following a clinical ON attack (2–4). Thus, ON pathology may be missed by OCT if RNFL thickness is in the normal range. Regarding the prevalence of measurable retinal insult after ON, pediatric ON and POMS are rare disorders; therefore, OCT studies have generally been limited by small sample sizes. For example, among five published OCT studies on POMS, each reported less than 28 participants, of whom only a portion had ON (2–6). The largest study included 53 POMS participants (27 ON eyes) (7). There is also discordance among these studies regarding the prevalence of RNFL thinning in non-ON eyes.

Beyond relying on age-related normative values for RNFL thickness in individual eyes, the field would benefit from data that documents what amount of interocular difference (IOD) in RNFL thickness would be indicative of a prior ON attack in a POMS patient. We previously demonstrated in a single-center cohort of 24 POMS participants using Cirrus OCT that considering the RNFL IOD helped detect an additional 12.5% of POMS-ON participants who had failed to demonstrate RNFL thinning in the affected eye (2). In an international adult MS cohort, an RNFL IOD greater than 5μm was shown to predict remote unilateral ON (8). To improve the diagnostic yield of RNFL measurements, we first determined the frequency of RNFL thinning in ON and non-ON eyes in a large multicenter POMS cohort. We then explored whether considering the RNFL IOD improves detection of remote ON.

Methods

PERCEPTION group

We developed the PEdiatric Research Collaboration ExPloring Tests in Ocular Neuroimmunology (PERCEPTION) to address the gaps in knowledge regarding visual outcome metrics and their interpretation in pediatric neuroinflammatory diseases. For the present study, children with POMS had been enrolled at 4 academic centers (Boston Children’s Hospital, Children’s Hospital of Philadelphia [CHOP], University of California San Francisco [UCSF], and University of Texas Southwestern/Children’s Dallas). The centers were chosen based on their respective visual sciences research interests with expertise in both pediatric neurology and neuro-ophthalmology. The study is approved by the respective Institutional Review Boards at each center. All participants gave informed written consent, and child assent was obtained.

Participants

Youth with POMS whose first attack occurred <18 years of age were enrolled. POMS diagnosis was confirmed by the 2017 McDonald criteria (9). Children with other neuroinflammatory diseases or radiographic isolated syndrome (abnormal MRI suggestive of MS with no clinical attacks) were excluded from the current study. Clinical ON was defined as having visual impairment lasting >24 hours, accompanied by pain with eye movement, abnormal color vision, and/or a central scotoma; ON history was confirmed by medical records. POMS-ON participants were excluded if their most recent ON attack occurred <6 months prior to the OCT scan. POMS non-ON participants were defined as those that

did not have a clinical history of ON in either eye. For participants with a history of unilateral ON, the unaffected eye is defined as the fellow eye. In children, RNFL thickness is greater than in adults; thus, pediatric values cannot be abstracted from adult cohorts (10). Therefore, to obtain the appropriate normative data, a healthy control cohort with no history of known ocular disease affecting the visual pathway were also enrolled. Healthy controls were recruited at 3 of the 4 centers (all centers except Boston Children's Hospital) by local advertisement.

Optical coherence tomography (OCT)

Spectral domain OCT was obtained by trained technicians at each site using Spectralis (Heidelberg, Germany, software version 6.12) at 40,000 A-scans per second. Participants underwent an RNFL scan using the Nsite Analytics™ RNFL protocol for each undilated eye. The technician verified that the images were focused and centered with uniform illumination and assessed for artifacts. All Spectralis OCT scans were reviewed to ensure acceptable quality, as defined by the OSCAR-IB guidelines (11). OCT data from UCSF has been previously published (7). All OCT data is reported as recommended by the APOSTEL guidelines (12).

Database

Data were managed and stored using the research-focused electronic web-based data capture system REDCap (13), hosted at CHOP under an agreement with the software's development consortium, led by Vanderbilt University.

Statistical analyses

Demographic features were compared using Student's t-test for age and the test of proportions for sex. The mean, median, standard deviation (SD), and range of RNFL thickness and RNFL IOD values were calculated. RNFL thinning was defined as <2 SD below the mean for the control participants. Based on a recently published international collaboration in adults, an abnormal RNFL IOD was defined as >5μm (8). RNFL thickness values were compared between groups using a generalized estimating equation (GEE, using an independent covariance matrix to account for intra-subject inter-eye relationships). RNFL IOD values were compared between groups using multivariate linear regression. Linear regression was also used to investigate the relationship between RNFL IOD and a history of remote ON within the POMS cohort.

In a sensitivity analysis, we explored other cutoffs for abnormal RNFL IOD values to determine whether our results are concordant with previously published adult studies. We calculated the sensitivity and specificity of different RNFL IOD cutoffs to predict remote ON and created a receiver operating characteristic (ROC) curve to determine the cutoff that maximized both specificity and sensitivity. The area under the curve (AUC) was calculated to determine the capacity of the test (the consideration of RNFL IOD values) to distinguish POMS-ON subjects from POMS subjects with no history of remote ON. Statistical analyses were performed using Stata Statistical Software (STATA, Version 12.1, College Station, TX, USA: StataCorp LP), and the ROC curve and AUC calculation were performed using

GraphPad Prism (Version 8.3.0, La Jolla, CA, USA, GraphPad Software Inc.). Statistical significance was defined as $p<0.05$.

Results

Participants

Across the four sites, 157 participants with POMS (mean age 15.2 years, SD 3.2) and 33 healthy controls (mean age 13.6 years, SD 5.0) were enrolled (Table 1). The difference in age between the groups was significant ($p=0.016$), although there was no relationship between age and RNFL thickness in the healthy controls ($p=0.584$). There was no difference in sex between the POMS and control cohorts ($p=0.139$). A clinical history of ON was reported in 67 POMS participants (90 eyes) (Table 1). Additional clinical information for the POMS group is provided in Table 1.

In the healthy control cohort, the mean RNFL thickness was 104.0μm (SD 9.0, range 86–130, Table 2); accordingly, abnormal RNFL thickness was defined as <86μm (<2 SD from the control mean).

RNFL thickness

Of the 90 eyes with remote ON, 45 (50%) demonstrated RNFL thickness <86μm (Fig. 1). In the 224 non-ON eyes, 24 (11%) had RNFL thickness <86μm (Fig. 1). As a group, mean RNFL thickness was reduced in the pooled eyes of POMS participants compared to eyes from controls ($p<0.001$, Table 2). As expected, POMS eyes with a history of ON (both eyes of participants with bilateral ON and the affected eyes of unilateral ON participants) had thinner RNFL values compared to healthy controls ($p<0.001$, Table 2). Compared to healthy controls, POMS participants with no history of remote ON (neither unilateral nor bilateral) demonstrated reduced RNFL thickness ($p<0.001$, Table 2), suggesting the presence of subclinical injury. Likewise, the fellow eyes of POMS participants with a history of unilateral ON also demonstrated RNFL thinning compared to control eyes ($p=0.001$, Table 2). There was no difference in RNFL thickness between fellow unaffected eyes and the eyes of participants with no history of remote ON (neither unilateral nor bilateral) ($p=0.735$). Within the POMS group, as anticipated, the RNFL thickness of eyes affected by ON was thinner than those not affected ($p<0.001$).

We acknowledge that a proportion of the participants were previously published (7). When removed, the mean RNFL thickness among non-ON eyes (96.8μm, SD 11.6) and clinical ON eyes (83.0μm, SD 21.4) was unchanged.

RNFL IOD

RNFL IOD was greater in POMS participants than in controls ($p=0.006$, Table 2). Compared to controls, RNFL IOD was greater for POMS participants with a clinical history of both unilateral ($p<0.001$) and bilateral ($p=0.003$) ON. However, there was no difference in RNFL IOD between POMS participants with no history of ON and controls ($p=0.087$, Table 2).

RNFL IOD as an indicator of remote ON

RNFL IOD was abnormal (>5μm) in 62 (39%) POMS participants (Fig. 1). Of these individuals, 40 (65%) had a history of remote ON. Among participants with a history of clinical ON but RNFL thickness values ≥86μm in both eyes (N=33), 14 (42%) individuals were identified as having ON by IOD criteria (having an RNFL IOD >5μm, Fig. 1). Of the 14 additional ON participants identified by IOD criteria, 10 had unilateral ON and 4 had bilateral ON. Using both RNFL thickness and IOD as criteria for remote ON, 48 (72%) participants with a clinical history of ON had unilateral or bilateral RNFL thinning <86μm and/or an RNFL IOD >5μm.

We also explored RNFL thickness and IOD in those POMS participants without a clinical history of ON (N=90) (Fig. 1). Bilateral or unilateral RNFL thinning <86μm occurred in 12 (13%) non-ON POMS participants or 20 of 180 (11%) eyes. An RNFL IOD >5μm occurred in 22 (24%) non-ON POMS participants. Together, 27 (30%) POMS participants with no clinical history of ON had unilateral or bilateral RNFL thinning <86μm and/or an abnormal RNFL IOD. In contrast, only 3 (9%) healthy control subjects had RNFL IOD >5μm; of those subjects, two had an IOD of 6 and one had an IOD of 7μm.

The area under the ROC curve, the capacity of the test to distinguish patients with a history of remote ON vs. those without, was 0.76 (Fig. 2). In predicting ON history, an RNFL IOD cutoff of 5μm had a sensitivity of 60% and specificity of 76%. An IOD cutoff of 6μm had a slightly lower sensitivity (55%) and higher specificity (86%), but the difference between the two (specificity – sensitivity = 31%) was nearly double that for a cutoff of 5μm (specificity – sensitivity = 16%), suggesting that an IOD cutoff of 5μm is preferable. In comparison, the sensitivity for an IOD cutoff of 4μm was 69% with a specificity of 74%; a cutoff of 4μm therefore achieved the smallest difference between sensitivity and specificity for all IOD cutoffs (specificity – sensitivity = 5%). Thus, an IOD cutoff of 4μm had the greatest capacity to distinguish POMS patients with remote ON vs. those without an ON history; however, both cutoffs of 4μm and 5μm yield similar specificities. For consistency with prior adult studies and ease of implementation across the age span, we recommend a cutoff of 5μm.

Within the POMS group, RNFL IOD was associated with a history of ON (either bilateral or unilateral) and unilateral ON (both $p<0.001$). The relationships remained significant when age and sex were included in the model.

Discussion

Mean RNFL thinning below normative ranges in POMS is not an obligate finding after an ON attack. This study confirms our observation, as only 50% of POMS-ON eyes demonstrated RNFL thinning below the normal range for age-matched controls (<86μm) (2). The value of OCT in identifying a history of clinical ON in POMS is enhanced when RNFL IOD is considered in addition to RNFL thickness values in individual eyes. Our findings have clinical implications for improved diagnostic yield when using OCT to confirm ON history in POMS.

We defined an RNFL IOD >5μm as indicative of disease based on a large adult cohort (8) that included 368 healthy and 1,530 MS participants. Nolan-Kenney and colleagues determined that an RNFL IOD threshold of 5μm maximized sensitivity and specificity for identifying a history of unilateral ON. The narrow IOD in our control population (mean 2.4μm, SD 2.0) further supports the use of 5μm as a cutoff. The adult study also explored IOD cutoffs for ganglion cell and inner plexiform layer thickness (GCL-IPL); however, our multicenter cohort did not uniformly collect such data for analysis.

While the presence of RNFL thinning is not a universal finding in POMS, the magnitude of average RNFL thinning in POMS-ON eyes compared to control eyes (mean loss of 22.1μm) was similar to adults with MS. A meta-analysis using time-domain OCT demonstrated a loss, on average, of 20.4μm in RNFL thickness (95% confidence interval [CI] 17.9μm to 22.9μm) among adult MS-ON eyes (14). The same study reported an average loss of RNFL thickness in adult MS non-ON eyes of 7.1μm (95% CI 5.5μm to 8.7μm) compared to controls, which is similar to our POMS cohort (mean loss of 6.3μm).

We further explored the OCT parameters in POMS participants with no history of clinical ON. Although these participants did not have a clinical attack suggestive of ON, their RNFL thickness values were significantly thinner than controls; 30% had RNFL thinning (<86μm) and/or an abnormal IOD (>5μm). These participants may have experienced subclinical ON, as demonstrated in a previous POMS studies (7).

There are several caveats to our work. First, we defined ON history by review of medical records for clinical symptoms. For this study, we did not require a dedicated MRI of the orbits at the time of the clinical symptoms to confirm the diagnosis of ON. It is possible that a higher proportion of ON participants would have RNFL thinning if a stricter definition (such as the presence of an enhancing ON lesion) was utilized. The Pediatric Optic Neuritis Prospective Outcomes Study (15) defined their cohort based on the presence of an enhancing optic nerve lesion using a dedicated MRI of the orbits with fat-saturated sequences and will be able to specifically address the proportion of participants demonstrating RNFL thinning after an MRI-confirmed attack in the future. While Nolan-Kenney et al. only considered the use of RNFL IOD to detect monocular ON (8), we chose to also include POMS participants with a history of bilateral involvement to mimic “real world” experiences. Most ON occurrences in POMS are unilateral, although both eyes can be affected at different times; therefore, while an individual attack may be considered unilateral, a patient who experienced unilateral attacks in each eye, regardless of whether the attacks temporally coincided, would be considered to have a clinical history of bilateral ON.

Our study is limited by the inclusion of retrospective data, including a previously published cohort. Graves et al. reported subclinical RNFL thinning in POMS non-ON eyes (7), which could have influenced the proportion of abnormal eyes in the current study; however, when these participants were removed from the analyses, there was no change in the mean RNFL values.

Our findings suggest that in POMS, the value of OCT as a tool to detect a history of clinical ON is enhanced when RNFL IOD is considered in addition to monocular RNFL thickness

values. In clinical practice, RNFL IOD should be considered when interpreting OCT results, especially for POMS patients who may have experienced clinical symptoms but have RNFL thickness values for each eye within the normal range.

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Conflicts of interest statement:

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Emmanuelle Waubant is site Principal Investigator for ongoing trials with Genentech and Biogen. She has research funding from NIH, PCORI, NMSS, and Race to Erase MS. She has received honoraria for lectures from Medscape, The Corpus, and AAN and for consulting work from Jazz Pharmaceuticals, Emerald, and DBV. She is co-chief editor for MSARD.

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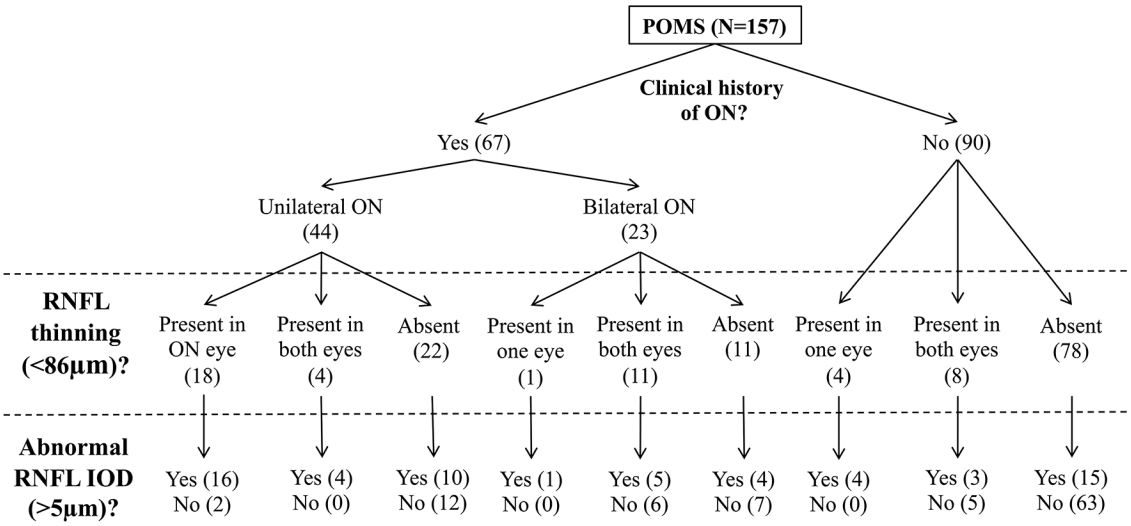

FIG. 1.

RNFL IOD as an Indicator of Remote ON in POMS

POMS = pediatric-onset multiple sclerosis; ON = optic neuritis; RNFL = retinal nerve fiber layer; IOD = interocular difference; numbers in parentheses = number of participants

Diagram demonstrating the number of pediatric-onset multiple sclerosis (POMS) patients (with and without optic neuritis) with retinal nerve fiber layer (RNFL) thinning (<86µm) and an interocular difference (IOD) greater than 5µm. In patients with a clinical history of optic neuritis (ON), RNFL thinning was not present in all affected eyes. The IOD can help the clinician identify optic nerve pathology. The presence of RNFL thinning or an abnormal IOD in those without a clinical ON history suggests a subclinical insult.

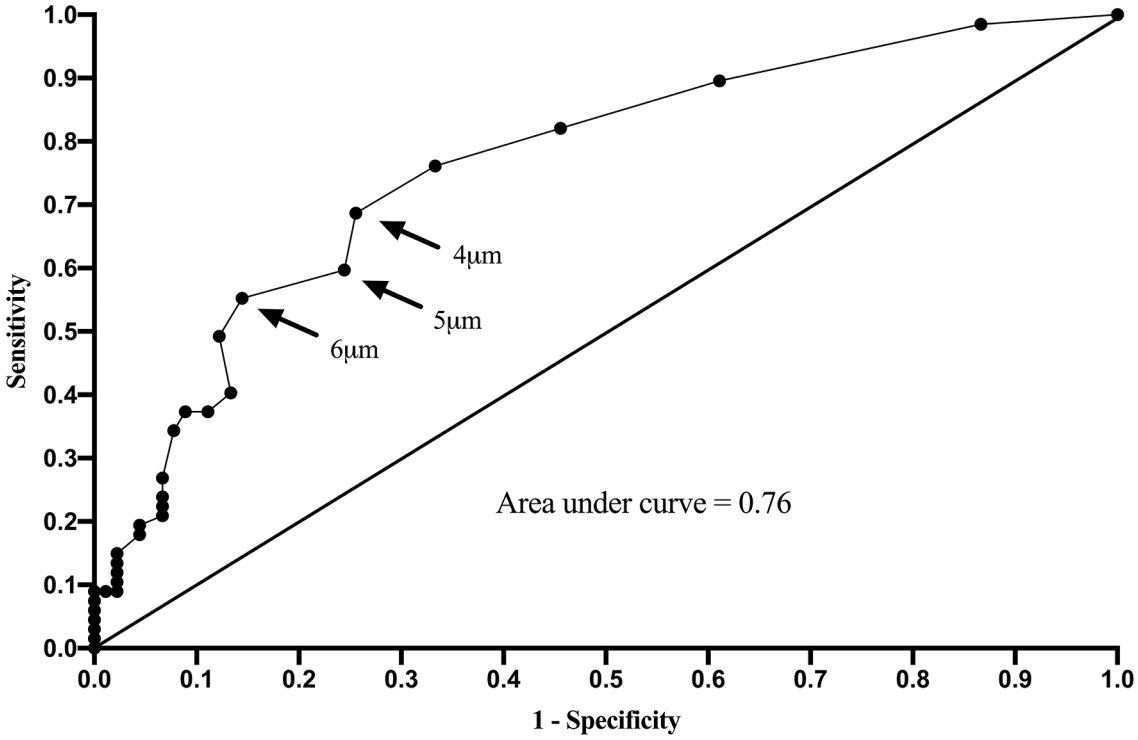

FIG. 2.

Receiver Operating Characteristic Curve for Retinal Nerve Fiber Layer Interocular Difference

The sensitivity and specificity of each potential retinal nerve fiber layer (RNFL) interocular difference (IOD) cutoff for identifying remote optic neuritis (ON) was calculated. For each IOD cutoff, the sensitivity was plotted against (1 – specificity) to generate a receiver operating characteristic (ROC) curve. The area under the curve (AUC), the capacity of the test to distinguish patients with a history of remote ON vs. those without, was 0.76. The optimal IOD cutoff at which sensitivity and specificity are closest is 4μm; however, both cutoffs of 4μm and 5μm yield similar specificities.

TABLE 1.

Demographic, clinical, and OCT data for healthy controls and POMS participants

		Healthy Controls (N = 33)	POMS (N = 157)	p-value
Age (years), mean (SD)		13.6 (5.0)	15.2 (3.2)	0.016[a]
Sex, N (% female)		18 (55%)	101 (64%)	0.139[b]
Time since clinical onset (years), median (range)		N/A	1.0 (0.02–14.2)	N/A
History of ON (bilateral or unilateral), N (%)		N/A	67 (43%)	N/A
	Unilateral ON, N (% ON participants)	N/A	44 (66%)	N/A
	Bilateral ON, N (% ON participants)	N/A	23 (34%)	N/A

[a]Age compared using Students t-test

[b]Sex compared using the test of proportions

POMS = pediatric-onset multiple sclerosis; ON = optic neuritis; N/A = not applicable; N = number of subjects; SD = standard deviation

TABLE 2.

Absolute RNFL thickness and IOD in healthy controls and POMS participants

	Healthy Controls		POMS			p-value
	N	**Result**	**Group**	**N**	**Result**	
RNFL thickness (μm), mean (SD, range)	66 eyes	104.0 (9.0, 86–130)	All	314 eyes	92.9 (17.5, 36–127)	<0.001
			Subjects with no history of ON in either eye	180 eyes	97.7 (13.4, 40–127)	<0.001
			ON eyes	92 eyes	81.9 (21.1, 36–119)	<0.001
			Fellow eyes	42 eyes	96.9 (13.2, 67–124)	0.001
RNFL IOD (μm), mean (SD, range)	33 subjects	2.4 (2.0, 0–7)	All	157 subjects	6.9 (9.4, 0–65)	0.006
			Subjects with no history of ON in either eye	90 subjects	4.0 (5.2, 0–28)	0.087
			Unilateral ON	44 subjects	12.3 (12.4, 1–65)	<0.001
			Bilateral ON	23 subjects	8.5 (10.9, 0–42)	0.003

RNFL = retinal nerve fiber layer; N = number of eyes or subjects; POMS = pediatric-onset multiple sclerosis; ON = optic neuritis; IOD = interocular difference; SD = standard deviation. P-values for group comparisons between healthy controls and POMS were calculated using univariate generalized estimating equations (GEE, using an independent covariance matrix to account for intra-subject inter-eye relationships) for RNFL thickness values and linear regression for RNFL IOD.