Optical coherence tomography and visual evoked potentials in pediatric MS

ABSTRACT

Objective: To determine the relative ability of optical coherence tomography (OCT) and pattern-reversal visual evoked potentials (pVEPs) to detect visual pathway involvement in pediatric-onset MS.

Methods: Pediatric-onset MS participants (onset <18 years) and healthy controls (HCs) underwent OCT (Cirrus HD-OCT) and pVEPs. Retinal nerve fiber layer (RNFL), ganglion cell layer to inner plexiform layer (GCL-IPL), and P100 pVEP latency were measured. Generalized estimating equation models were used to compare the groups, adjusting for age and intereye correlations.

Results: Twenty-four pediatric MS participants, 14 with a history of remote (>6 months) optic neuritis (ON) in one eye (8 participants) or both the eyes (6 participants), and 24 HCs were enrolled. RNFL thinning (<83 μm, 2 SDs below HC eyes) occurred in 50% of ON eyes vs 5% of non-ON eyes. Prolonged VEP latency (>109 msec) occurred in 58% of ON eyes and 55% of non-ON eyes. A clinical history of ON predicted RNFL (p = 0.001) and GCL-IPL thinning, whereas prolonged pVEP latency in children with MS occurred independent of ON history.

Conclusions: OCT and pVEPs provide complementary but distinct insights. OCT is sensitive to retinal changes in the context of clinical ON, whereas pVEPs are useful to detect disseminated lesions of the visual pathway in children with MS. Neurrol Neuroimmunol Neuroinflamm 2017;4: e356; doi: 10.1212/NXI.0000000000000356

GLOSSARY
ETDRS = Early Treatment Diabetic Retinopathy Study; GCL-IPL = ganglion cell layer to inner plexiform layer; GEE = generalized estimating equation; HC = healthy control; OCT = optical coherence tomography; ON = optic neuritis; pVEP = pattern-reversal visual evoked potential; RNFL = retinal nerve fiber layer; VA = visual acuity.

Optical coherence tomography (OCT) and pattern-reversal visual evoked potentials (pVEPs) assess the structural and functional integrity of the visual pathway. Although OCT and pVEPs are well-substantiated tools to evaluate MS in adults, less is known about the comparative utility of these tools in pediatric-onset MS. Importantly, because OCT interrogates retinal injury and pVEPs assess visual pathway pathology, these tools may inform differently. Prior studies evaluating VEP alone in children with optic neuritis (ON) have demonstrated prolonged latencies and/or reduced amplitudes in 83% of children with acute ON.1 PVEPs are abnormal in 56% of children with confirmed MS at the time of their first attack, even if this attack did not include clinical ON.2 In OCT studies, thinning of the retinal nerve fiber layer (RNFL) and the ganglion cell layer (GCL) occurs after ON, with maximal thinning in the ON eye recorded at 6 months post-ON.3 In adults with MS, thinning of the retina has also been documented in the absence of ON, although thinning in non-ON eyes in pediatric MS has been variably detected.4–6 In pediatric-onset MS, the likelihood of an OCT or VEP abnormality in MS eyes,
with or without ON, has not been calculated. We sought to compare OCT and pVEPs in a cohort of pediatric-onset MS participants, with and without a history of ON, in order to inform on the relative utility of these tests in the pediatric context.

**METHODS** Pediatric-onset MS participants (whose first attack occurred prior to age 18 years) were recruited for this cross-sectional study from The Children’s Hospital of Philadelphia (CHOP) between November, 2013, and July, 2015. Healthy controls (HCs) were recruited through local advertisement. Healthy participants without neurologic, ocular, or systemic disease were eligible provided they had a normal corrected visual acuity (VA) (defined as 47 or more letters correct using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, which is approximately 20/25 using Snellen acuity).

The diagnosis of MS was confirmed using the 2010 McDonald criteria.1 Prior ON was confirmed by history and documentation of reduced high-contrast VA, red desaturation, pain with ocular movement, and/or visual field defect. A chart review was performed to abstract the maximum VA deficit, presence of optic disc edema, color vision loss, pain with eye movements, and findings on confrontation visual field examination as recorded at the time of ON. MRI of the orbits (if available), brain, and spine were reviewed for all participants to confirm ON and MS diagnoses. The subsequent development of optic nerve pallor, as adjudicated by a neurologist or neuro-ophthalmologist, was documented. None of the participants had active acute ON at the time of evaluation, and all were at least 6 months from an acute attack of ON. Eyes were categorized as ON eyes, fellow eyes (the unaffected eye in a participant with unilateral ON), or non-ON eyes (no history of ON in either eye).

All study procedures occurred on the same day, beginning with the measurement of high-contrast VA using the ETDRS VA chart with the participant’s own corrective lenses or glasses if needed. Although we did not perform cycloplegic refraction, all participants had their refractive error for each eye recorded using an autorefractor (VisuRef; Carl Zeiss Meditec, Inc., Dublin, CA) as a refractive error can affect OCT results.6,8 Refractive errors did not exceed 4 diopters.

Spectral domain OCT was obtained in a dark room without windows by a single trained technician using Cirrus HD-OCT (Model 5000, software version 6.5; Carl Zeiss Meditec, Inc.) at 27,000 A-scans per second. Participants underwent the Optic Disc Cube (200 × 200 scans) and Macular Cube (512 × 128) protocols for each undilated eye while fixating on landmarks positioned nasally or centrally to the Optic Disc Cube and Macular Cube, respectively. The technician verified that the images were focused and centered with uniform illumination and assessed for artifacts as recommended by the OSCAR-IB Consensus Criteria for Retinal OCT Quality Assessment.19 Only scans meeting these criteria and having a signal strength ≥7 were used for the analysis. Segmentation was performed using the built-in automatic segmentation algorithm of the OCT system. Inspection of the resulting Macular Cube cross sections revealed no evidence for eccentric fixation as the fovea was always centered at fixation. RNFL thickness measured from an interpolated 1.7-mm-radius circle centered on the optic nerve head obtained from the Optic Disc Cube scan. GCL to inner plexiform layer thickness (GCL-IPL) was obtained from analysis of the parfoveal and perifoveal retina of the Macular Cube scan.
Table 1 Demographics

|                  | MS (N = 24) | Healthy controls (N = 24) | p Value |
|------------------|-------------|---------------------------|---------|
| Mean age, y (range) | 17.5 (11-24) | 15.4 (8-22)               | 0.046   |
| Sex (F:M)        | 14:10       | 16:8                      | 0.105   |
| Race, n (%)      |             |                           | 0.152   |
| Caucasian        | 15 (62.5)   | 13 (56.5)                 |         |
| African American | 9 (37.5)    | 5 (21.7)                  |         |
| Asian            | 0 (0)       | 2 (8.7)                   |         |
| Unknown/mixed    | 0 (0)       | 3 (13.0)                  |         |
| Ethnicity, n (%) |             |                           | 0.259   |
| Hispanic         | 3 (12.5)    | 1 (4.2)                   |         |
| Non-Hispanic     | 21 (87.5)   | 20 (83.3)                 |         |
| Unknown/not reported | 0          | 3 (8.3)                   |         |
| Mean disease duration, y (range) | 2.4 (0.3-7.7) | NA                        | NA      |
| Mean duration from last episode of optic neuritis, y (range) | 2.9 (0.5-6.0) | NA                        | NA      |
| EDSS, median (range) | 1 (0-3.5)  | NA                        | NA      |

Abbreviations: EDSS = Expanded Disability Status Scale; NA = not applicable.

Table 2 Mean OCT and VEP values

|                  | Healthy eyes (N = 48) | All eyes (N = 48) | p Value* vs control eyes | Non-ON eyes (N = 20) | p Value* vs control eyes | Fellow eyes (N = 8) | p Value* vs control eyes | ON eyes (N = 20) | p Value* vs control eyes |
|------------------|-----------------------|-------------------|--------------------------|----------------------|--------------------------|---------------------|--------------------------|------------------|--------------------------|
| RNFL (SD)        | 100 (8), N = 47       | 90 (14), N = 48   | 0.002                    | 100 (10), N = 20     | 0.193                    | 87 (12), N = 8      | 0.001                    | 81 (12), N = 20   | 0.001                    |
| GCL-IPL (SD)     | 83 (8), N = 45        | 76 (9), N = 46    | 0.001                    | 79 (9), N = 20       | 0.103                    | 77 (10), N = 7      | 0.032                    | 72 (9), N = 18    | 0.001                    |
| VEP latency (SD) | 101 (4), N = 35       | 115 (17), N = 30  | <0.001                   | 119 (17), N = 11     | <0.001                   | 108 (6), N = 7      | <0.001                   | 115 (20), N = 12  | 0.001                    |

Abbreviations: GCL-IPL = ganglion cell layer to inner plexiform layer; OCT = optical coherence tomography; ON = optic neuritis; pVEP = pattern-reversal visual evoked potential; RNFL = retinal nerve fiber layer.

*Generalized estimating equation models were used to compare each group with healthy eyes, adjusting for age and intereye correlations.

†The clinical features of the MS participants who underwent pVEPs (N = 30 eyes) did not differ from the patients who did not complete this test (N = 18 eyes). There was no difference between the groups with respect to the number of ON eyes (p = 0.580), the age at testing (p = 0.811), disease duration (p = 0.937), or mean high-contrast letter acuity scores (p = 0.1435).
Table 3 Proportions with abnormal findings

| Proportions of patients with | HC eyes (N = 48) | All eyes | MS (N = 48) |
|-----------------------------|------------------|---------|-------------|
| Visual acuity deficit       |                  |         |             |
| Pallor present              |                  |         |             |
| RNFL abnormal (<83 μm)      |                  |         |             |
| GCL-IPL abnormal (<71 μm)   |                  |         |             |
| VEP latency prolonged (>109 msec) |         |         |             |

Abbreviations: GCL-IPL = ganglion cell layer to inner plexiform layer; HC = healthy control; ON = optic neuritis; RNFL = retinal nerve fiber layer; VEP = visual evoked potential.

One HC had normal high-contrast visual acuity (47 letters correct in each eye) but had an RNFL of 82 and 81 μm in the right and left eyes. The GCL-IPL and VEP latencies for this individual were within the normal range. One HC had prolonged VEP latencies (112 and 116 msec in the right and left eyes), despite normal high-contrast visual acuity (59 and 60 letters), RNFL, and GCL-IPL thicknesses.

DISCUSSION OCT and VEP provide valuable, but different information in pediatric-onset patients with MS. OCT confirms the history of ON, but unlike the findings in adult MS, OCT infrequently identifies retinal abnormalities in pediatric-onset patients with MS who have not experienced clinical evidence of optic nerve involvement. Only 5% of our patients with MS demonstrated RNFL thinning and 10% had GCL-IPL thinning in the absence of prior ON. By contrast, prolonged pVEP latency occurred

Table 4 Capacity of OCT and VEP to correctly identify MS eyes with and without ON compared with healthy eyes

|                         | MS-ON eyes compared with HC eyes | MS fellow eyes (non-ON eye) vs HC eyes | MS non-ON eyes vs healthy controls |
|-------------------------|----------------------------------|--------------------------------------|----------------------------------|
|                         | RNFL thinning, % | GCL-IPL thinning, % | Prolonged VEP latency, % | RNFL thinning, % | GCL-IPL thinning, % | Prolonged VEP latency, % | RNFL thinning, % | GCL-IPL thinning, % | Prolonged VEP latency, % |
| Sensitivity             | 50 | 33 | 58 | 25 | 13 | 43 | 4 | 10 | 55 |
| Specificity             | 96 | 100 | 94 | 96 | 100 | 94 | 96 | 100 | 94 |
| Positive predictive value | 83 | 100 | 78 | 50 | 100 | 60 | 33 | 100 | 75 |
| Negative predictive value | 82 | 79 | 87 | 88 | 88 | 89 | 70 | 71 | 87 |

Abbreviations: GCL-IPL = ganglion cell layer to inner plexiform layer; HC = healthy control; OCT = optical coherence tomography; ON = optic neuritis; RNFL = retinal nerve fiber layer; VEP = visual evoked potential.
in 53% of patients with MS, a finding that was not influenced by a history of ON.

Our data are aligned with adult studies in which VEP abnormalities are more frequently seen than RNFL thinning in non-ON eyes.\textsuperscript{12,13} Our VEP results are also similar to a prior study in which 48 of the 85 (56%) pediatric patients with MS demonstrated VEP prolongation more than 2.5 SDs beyond control mean latencies and/or reduced amplitudes.\textsuperscript{2} Also in line with our findings, another study of 14 pediatric patients with MS reported no difference in VEP latencies between MS-ON eyes and MS non-ON eyes (\(p = 0.524\)) or between MS-ON eyes and MS fellow eyes (\(p = 0.654\)).\textsuperscript{5}

OCT has been reported in 54 pediatric patients with MS collectively between 3 prior studies, all of which reported a significant decrease in mean RNFL thickness among MS-ON eyes compared with HC eyes.\textsuperscript{4,6} In this study, we demonstrated a mean reduction of 19 \(\mu\)m in RNFL thickness among pediatric MS-ON eyes vs HCs, which is comparable with a meta-analysis of adult OCT data which revealed a mean RNFL loss of 20.38 \(\mu\)m (95% CI \(-22.86\) to \(-17.91\)) among 956 MS-ON eyes vs 1,107 HC eyes.\textsuperscript{14}

Although the comparison of mean scores enables the identification of population differences, such data do not necessarily inform on the utility of testing for the individual patient. In our cohort, only 50% of children with MS and a history of ON will have reduced RNFL that is 2 SDs below the mean for HCs; this proportion of children with abnormal RNFL results in MS-ON eyes is substantiated by 2 previous pediatric MS OCT studies based on their published mean data.\textsuperscript{4,6} Although OCT parameters in half of the MS-ON eyes may fall within a normal reference range, intereye differences in RNFL and GCL-IPL thicknesses may help the clinician in identifying a remote history of ON.

In this study, the mean RNFL thickness in MS non-ON eyes was equal to the mean of HCs. We did not replicate findings of 2 other OCT studies of pediatric MS participants in which mean RNFL thickness was reduced in non-ON eyes, findings that were interpreted as supportive of a more degenerative global MS pathology.\textsuperscript{4,5} Using intereye differences in OCT measures, we did identify 3 patients with MS without a history of ON whose intereye differences exceeded the intereye variability seen in our control cohort. However, 2 of these 3 patients had RNFL and GCL-IPL values above the normative mean (despite the intereye differences), rendering it difficult to propose evidence of non-ON global MS-related injury in our cohort.

There are several important caveats to our work. The rarity of pediatric MS limits sample size. We did not perform formal cycloplegic refractions, an important issue given that severe myopia is associated with a thinner retina, and VA testing and VEPs ideally should be performed with the patient’s best refractive correction. To mitigate this concern at least in part, we used an autorefractor to estimate the refractive error and none of the patients had severe myopia (\(>-4.00\)). Furthermore, nearly all of our patients with MS had visual acuities near or equal to 20/40, and all HCs by inclusion criteria had 20/20 VA in each eye, making even mild uncorrected myopia unlikely to have been a factor in this study.

These results can inform clinical decision making. For a patient with suspected or confirmed MS who describes a remote history of vision loss, an abnormal OCT (defined either by absolute or intereye measures that deviate substantially from normative values) may be used to support a prior episode of ON. However, a normal OCT does not exclude the possibility of prior ON. VEP abnormalities detect dissemination of disease in patients being investigated for MS and are informative even in the absence of ON.

**Table 5** Intereye differences for OCT and VEP metrics

| Metric                | HC             | MS             | \(p\) Value |
|-----------------------|----------------|----------------|------------|
| RNFL, mean difference, \(\mu m\) | 2.3 (SD 1.7) [range 0–6] | 7.6 (SD 7.1) [range 0–30] | 0.0011 |
| GCL-IPL, mean difference, \(\mu m\) | 0.7 (SD 0.8) [range 0–2] | 5.1 (SD 6.0) [range 0–24] | 0.0012 |
| VEP latency, mean difference, msec | 1.5 (SD 1.3) [range 0.2–5] | 13.3 (SD 13.6) [range 0.8–45.4] | 0.0012 |

Abbreviations: GCL-IPL = ganglion cell layer to inner plexiform layer; HC = healthy control; OCT = optical coherence tomography; RNFL = retinal nerve fiber layer; VEP = visual evoked potential.

**AUTHOR CONTRIBUTIONS**

Amy T. Waldman: study concept/design, acquisition of data, statistical analysis, interpretation of data, drafting/revising the manuscript for content, including medical writing for content, obtaining funding, and study supervision and coordination. Grant T. Liu: contribution to study concept/design, interpretation of data, drafting/revising the manuscript for content, including medical writing for content. William Gaetz, Tomas S. Aleman, and Brenda L. Banwell: interpretation of data and drafting/revising the manuscript for content, including medical writing for content and obtaining funding, and study supervision and coordination. Geraldine Liu: acquisition of data, analysis and interpretation of data, statistical analysis, and drafting/revising the manuscript for content. Amy M. Lavery: acquisition of data, analysis and interpretation of data, statistical analysis, and drafting/revising the manuscript for content. Amy T. Waldman: study concept/design, acquisition of data, statistical analysis, interpretation of data, drafting/revising the manuscript for content, including medical writing for content, and study supervision and coordination. Grant T. Liu: contribution to study concept/design, interpretation of data, and drafting/revising the manuscript for content. William Gaetz, Tomas S. Aleman, and Brenda L. Banwell: interpretation of data and drafting/revising the manuscript for content, including medical writing for content.

**STUDY FUNDING**

This study was supported by the NIH (NINDS) (K23NS069806, PI: A. Waldman).
DISCLOSURE
A.T. Waldman received travel funding from Novartis; receives publishing royalties from UpToDate; and holds stock or stock options in Pfizer and Spark Therapeutics.
G.T. Liu serves on the editorial board for Journal of Neuro-Ophthalmology; receives royalties from Elsevier. A.M. Lavery reports no disclosures. G. Liu’s spouse receives royalties from Elsevier. W. Gaetz reports no disclosures. T.S. Aleman received research support from NIH. B.L. Banwell served on the scientific advisory board for Biogen, Sanofi, Eli Lilly, and Novartis; received travel funding and/or speaker honoraria from Biogen, Merck Serono, Teva, and Bayer; serves on the editorial board for Neurology®; consulted for Biogen Idec, Eli Lilly, Sanofi, and Novartis; has spoken at an event supported by the Consortium of MS Centers; and received research support from Multiple Sclerosis Society of Canada, Multiple Sclerosis Scientific Research Foundation, and National Multiple Sclerosis Society. Go to Neurology.org/nn for full disclosure forms.

Received January 27, 2017. Accepted in final form March 24, 2017.

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Optical coherence tomography and visual evoked potentials in pediatric MS
Amy T. Waldman, Grant T. Liu, Amy M. Lavery, et al.
*Neurol Neuroimmunol Neuroinflamm* 2017;4;
DOI 10.1212/NXI.0000000000000356

This information is current as of June 5, 2017
