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Monocular and binocular low-contrast visual acuity and optical coherence tomography in pediatric multiple sclerosis

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Abstract

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Conflict of Interest

The authors declare no conflict of interest.

Background—Low-contrast letter acuity and optical coherence tomography (OCT) capture visual dysfunction and axonal loss in adult-onset multiple sclerosis (MS), and have been proposed as secondary outcome metrics for therapeutic trials. Clinical trials will soon be launched in pediatric MS, but such outcome metrics have not been well-validated in this population.

Objectives—To determine whether MS onset during childhood and adolescence is associated with measurable loss of visual acuity and thinning of the retinal nerve fiber layer (RNFL), whether such features are noted only in the context of clinical optic nerve inflammation (optic neuritis, ON) or are a feature of MS even in the absence of optic nerve relapses, and to define the optimal methods for such detection.

Study design—Cross-sectional study

Methods—Monocular and binocular high- and low-contrast letter acuity and contrast sensitivity were assessed in a cross-sectional cohort of children (ages 5 to 17 years) with MS (N=22 patients, 44 eyes; 8 patients with a history of ON) and disease-free controls (N=29 patients; 58 eyes) from three academic centers. Binocular summation was determined by calculating the number of letters correctly identified using the binocular score minus the better eye score for each visual test. RNFL thickness was measured using OCT (Stratus OCT-3). Results were analyzed in terms of “eyes” as: MS ON+, MS ON–, and control eyes. Generalized estimating equation (GEE) regression models were used to compare patients to controls.

Results—Traditional high-contrast visual acuity scores did not differ between MS ON+, MS ON–, and controls eyes. MS ON+ eyes had decreased monocular ($p<0.001$) and decreased binocular ($p=0.007$) low-contrast letter acuity (Sloan 1.25% contrast charts) scores. Monocular visual acuity did not differ when comparing MS ON– and control eyes. The magnitude of binocular summation using low-contrast charts was similar for pediatric MS participants and controls and was not diminished in children with a history of ON. While the mean RNFL thickness for all MS eyes ($103\pm17\ \mu\text{m}$) trended lower when compared to corresponding measures in control eyes ($109\pm9\ \mu\text{m}$, $p=0.085$), we confirmed a highly significant reduction in mean RNFL thickness in MS eyes with a history of ON ($86\pm22\ \mu\text{m}$, $p<0.001$). RNFL thickness of MS ON– eyes in pediatric MS patients ($109\pm11\ \mu\text{m}$) did not differ from controls ($p=0.994$).

Conclusions—Low-contrast letter acuity detects subtle visual loss in MS patients with prior ON, consistent with incomplete recovery, a finding further supported by RNFL loss in ON affected eyes. In MS patients with prior unilateral ON, binocular acuity is decreased; however, the magnitude of binocular summation is preserved, unlike adult-onset MS who exhibit a reduced capacity for visual compensation in the context of unilateral injury. Also unlike findings in adult-onset MS, we did not demonstrate RNFL thinning in ON– eyes of children and adolescents with MS. Further validation is required to confirm whether neurodegeneration of visual pathways occurs in the absence of relapse, and thus whether OCT will serve as a sensitive metric for such pathology in the pediatric and adolescent MS context.

Keywords

multiple sclerosis; optic neuritis; pediatric; demyelinating disease

1. Introduction

Children with multiple sclerosis (MS) are at risk for visual impairment, and optic neuritis (ON) is the presenting feature of MS in 25% of pediatric-onset patients (Banwell et al. 2009; Chitnis et al., 2009). In clinical practice, visual acuity is measured by high-contrast Snellen acuity charts. However, such assessment may underestimate subtle, clinically impactful deficits in vision (Mowry et al., 2009). Low-contrast acuity assessments have been shown to have higher sensitivity and can detect reduced contrast acuity even in the absence of a

clinically evident episode of optic neuritis in adult-onset MS patients (Balcer et al., 2000, 2003). Only one study to date has evaluated the diagnostic sensitivity of low contrast visual acuity testing (2.5% contrast) in a heterogeneous cohort of pediatric patients with demyelinating diseases (Yeh et al., 2009). Low-contrast letter acuity scores were decreased in pediatric MS eyes, even among eyes not affected by ON, and the number of letters read correctly correlated with optical coherence tomography (OCT) measures of retinal nerve fiber layer (RNFL) thickness.

Unilateral reduction in visual acuity in otherwise healthy individuals results in acuity deficits in the affected eye that are more than compensated for when the patient uses binocular vision, a phenomenon termed “binocular summation” (Pineles et al., 2011). Binocular summation occurs when the binocular visual acuity is greater than the monocular acuity for the better eye, whereas binocular inhibition occurs when the binocular visual acuity score is worse than the monocular score for the better eye. In adults with MS who have experienced unilateral ON, binocular summation is impaired, and some adults with MS and ON experience binocular inhibition (Pineles et al., 2011). It is unknown whether pediatric MS patients with unilateral ON demonstrate impaired binocular summation or binocular inhibition, or whether the young age of these patients permits an enhanced compensatory mechanism that abrogates the impact of unilateral visual loss. Damage to the anterior visual axis in early childhood is known to profoundly influence visual development, as illustrated by studies of amblyopia in children; however, the impact of milder visual loss in later childhood as is typically experienced by pediatric MS patients has not been studied.

Letter acuity (high- and low-contrast) is only one means to evaluate the integrity of visual function. OCT, which provides a non-invasive quantification of retinal thickness, has emerged as a valuable new tool to assess the severity of axonal damage in MS (Fisher et al., 2006). OCT has also been shown to be sensitive to subclinical optic nerve involvement, with demonstration of thinning of the RNFL even in clinically unaffected eyes (ON– eyes) of adult-onset MS patients (Fisher et al., 2006).

We sought to determine whether MS onset during childhood and adolescence is associated with measurable loss of visual acuity and thinning of the retinal nerve fiber layer, whether such features are noted only in the context of a history of clinical optic nerve inflammation (optic neuritis, ON) or are a feature of MS even in the absence of optic nerve relapses. We evaluated the sensitivity of low-contrast acuity and OCT in the eyes of pediatric and adolescent MS patients with a history of ON (MS ON+), eyes unaffected by ON (MS ON–), and compared these findings to the eyes of healthy pediatric and adolescent controls. Further, we evaluated the capacity for binocular summation in children with and without a history of ON as a means of evaluating whether MS onset in children is associated with a greater capacity for binocular visual compensation as seen in adults with MS.

2. Materials and Methods

2.1. Participants

In this cross-sectional study, children and adolescents with relapsing-remitting MS between age 5 and 17 years and healthy age-matched pediatric controls were recruited from three academic centers: Children's Hospital of Philadelphia, Johns Hopkins University, and University of Texas Southwestern Medical Center between November, 2006, and June, 2011. Healthy children were recruited from Neurology and Ophthalmology clinics. Controls were eligible if their best corrected visual acuity was 20/20 (for children 6 years and older) or 20/25 (for 5-year-old children) or better, as assessed using standard Snellen acuity charts, and if they reported no known neurologic, ocular, or systemic disease.

The diagnosis of MS was conferred according to the 2005 McDonald criteria (Polman et al., 2005; Krupp et al., 2007). A history of ON was established provided there was clear documentation of an acute relapse lasting more than 24 hours and associated with decreased high-contrast letter acuity, pain with eye movement, color desaturation, and/or visual field abnormalities, with or without optic nerve swelling or enhancement visualized by magnetic resonance imaging.

For MS patients, each eye was classified as MS ON+ (presence of ON) or MS ON- (absence of ON) (Table 1). When considering both eyes, patients were classified as having MS ON+/MS ON- if only one eye had experienced ON, MS ON- if the patient had no history of ON, and MS ON+/MS ON+ if both eyes had experienced prior ON.

For subjects with unilateral optic neuritis (MS ON+/MS ON-), the MS ON- eyes were further defined as “MS fellow eyes”, and were considered separately from the eyes of children who had no history of ON in either eye (MS ON- eyes) given the high rate of asymptomatic abnormalities seen in the fellow eyes of adults enrolled in the Optic Neuritis Treatment Trial (Beck et al., 1993). Participants were excluded if they had ON within the month prior to examination as swelling may transiently affect RNFL thickness (Kupersmith et al., 2011).

The study was approved by the Institutional Review Board at each institution. Written informed consent was provided by all participants, and child assent was obtained.

2.2. Visual Function Testing

Visual function testing was performed beginning with a standard protocol for refraction and visual acuity testing (CAPT, 1999; Ferris and Bailey, 1996). Retroilluminated Early Treatment of Diabetic Retinopathy Study (ETDRS) charts (Lighthouse Low Vision Products, Long Island, NY) were used for the determination of high-contrast visual acuity. Using the same retroilluminated cabinet, low-contrast Sloan letter charts were used to measure low-contrast letter acuity. These charts have the same format as the ETDRS charts with respect to number and spacing of letters and logarithmic scaling and consist of 12 letter sizes. Low-contrast letter acuity measurements were obtained at two meters for each of two contrast levels (2.5% and 1.25%). First monocular and then binocular measurements were obtained for all vision testing parameters. Charts were scored letter-by-letter, and the number of correct letters (range 0-70) was recorded.

Whereas low-contrast Sloan letter charts consist of progressively smaller letters of uniform contrast on a white background, Pelli-Robson contrast sensitivity charts present the same size letters of progressively lower contrast (Pelli et al., 1988). Letters are presented in triplets; 16 groups are presented for a total of 48 letters, and log contrast sensitivity scores were recorded (maximum log score of 2.25).

2.3. Optical Coherence Tomography

OCT was performed in each eye using Stratus OCT (OCT-3 with OCT 4.0 software, Carl Zeiss Meditec, Inc., Dublin, CA) at all three study sites on the same day as the visual function tests described above. The fast RNFL, macular, and optic disc protocols were used under optimal conditions (including an eye patch placed over the opposite eye to aid in fixation and limiting external light to maximize scan signal strength). Only scans with signal strength of seven or higher were included in the analysis. Scans were performed without pharmacologic pupillary dilation.

2.4. Statistical Analysis

The demographics and clinical characteristics were summarized using descriptive statistics. Visual function tests (high- and low-contrast letter acuity and Pelli-Robson) were compared between subjects and controls using generalized estimating equation (GEE) regression models, accounting for within-patient, inter-eye correlations (Katz et al., 1994). Pelli-Robson testing was performed in the subset of patients from CHOP only; the number of patients who completed each test is reported.

Evaluation of the relative abilities of binocular visual function tests to differentiate MS patients with a history of ON in either eye from MS patients without a history of ON in either eye (MS ON–eyes) and healthy eyes was performed using logistic regression models, with clustering for within-patient, inter-eye correlations, followed by areas under the receiver operating characteristic (ROC) curve. The area under the ROC curve represents the probability that a test or model will correctly rank any randomly selected pair of individuals as being diseased (in this case has MS) or non-diseased (healthy control) (i.e. analyzing for the relationship between sensitivity and specificity). The vision measure with the greatest area under the ROC curve was considered the test that best distinguishes MS participants from controls on the basis of binocular visual function. The high- and low-contrast letter acuity scores were further assessed for binocular summation and binocular inhibition in each participant by comparing the number of letters correctly identified using both eyes together (binocular score) to the monocular score for the better eye (see Table 1 for definitions). Descriptive statistics were used to assess the frequency of binocular summation and inhibition in pediatric MS for each visual function. The magnitudes of binocular summation and inhibition were compared between controls and pediatric MS patients, with and without ON, using a two-sided t-test.

RNFL thickness was compared first between all MS and control eyes using GEE models, accounting for age, history of ON, and within-subject, inter-eye correlations. Similar models were used to determine the relation between a decrease in visual function score and RNFL thickness.

All data analyses were performed using Stata statistical software (version 12.0, StataCorp, College Station, TX). A *p*-value of less than or equal to 0.05 was used to determine significance.

3. Results

3.1. Demographics

Table 2 summarizes the group characteristics. of the 22 MS and 29 control participants. The clinical characteristics of each of the MS patients are summarized in the Supplementary Table.

3.2. Visual Function Testing

3.2.1. Monocular scores—Monocular visual function scores are presented in Table 3. Visual acuity scores were decreased in MS ON+ eyes only compared to control eyes, a difference that was only detected using low-contrast visual acuity testing. MS ON+ eyes were also decreased compared to MS ON– eyes. MS ON+ eyes identified 10 fewer letters correctly using the 2.5% contrast charts compared to MS ON– eyes ($p=0.027$, GEE models) and 9 fewer letters using the 1.25% contrast charts vs. MS ON– eyes ($p=0.006$, GEE models). The log score for Pelli-Robson charts were also decreased among MS ON+ eyes compared to MS ON– eyes ($p=0.001$, GEE models).

The MS ON– eyes of patients with unilateral ON (MS ON+/MS ON–) were compared to the eyes of patients without ON in either eye (MS ON–/MS ON–). There were no differences in high- or low-contrast scores, contrast sensitivity, or Pelli-Robson scores between the MS fellow and MS ON– eyes.

3.2.2. Binocular scores—Using binocular scores, low-contrast letter acuity (1.25% charts) had the greatest capacity to distinguish all MS patients from controls using logistic regression and ROC areas (ROC area 0.6721, $p=0.006$). In comparison, ROC areas were decreased and did not distinguish between healthy controls and MS participants using binocular high-contrast acuity, 2.5% low-contrast, and Pelli-Robson scores. High-contrast binocular visual acuity did not differ between controls and MS participants ($p=0.994$, Table 4). The binocular low-contrast letter acuity score (1.25%) was significantly decreased in all MS subjects compared to controls; however, this decrease was driven by lower binocular scores among patients with a history of ON. MS ON+ subjects correctly identified 8 fewer letters using binocular vision compared to healthy controls ($p=0.007$). For MS subjects without a history of ON in either eye, the binocular score only differed by 2 letters compared to controls ($p=0.108$). Binocular Pelli-Robson scores were significantly decreased only in subjects with a history of ON compared to controls ($p=0.025$).

3.2.3. Binocular summation and inhibition—Using high-contrast letter acuity, binocular summation occurred in 54% of the controls and 50% of children with MS. The binocular scores increased over the better eye score by a mean of 3 letters in the control group and 4 letters in the MS group without ON (Table 4). Binocular inhibition occurred in 18% of MS participants and 7% of controls using high-contrast visual acuity; however, on average, the mean magnitude of binocular inhibition in MS participants was 1 letter. The remainder of the participants (39% of controls and 32% of children with MS) demonstrated no change between their binocular and better eye scores (the magnitude of binocular summation was 0).

Binocular summation occurred in 93% of healthy controls using 2.5% low-contrast letter charts; the remaining 7% of controls demonstrated no change between their binocular and better eye scores. Similarly, 95% of MS participants demonstrated binocular summation using 1.25% low-contrast letter charts, and 5% (one child with MS and a history of bilateral ON) demonstrated no change between the binocular and better eye score. The magnitude of binocular summation did not differ between healthy controls and MS participants using low-contrast letter acuity.

The mean scores for the visual function tests and magnitude of binocular summation are presented in Table 4. While the binocular scores (or number of letters read correctly using both eyes) differed between controls and MS participants, the magnitude of binocular summation was preserved, even in the setting of ON. Both controls and MS participants demonstrated a mean improvement of 8 letters in their binocular 2.5% low-contrast score compared to their better eye score ($p=0.602$, t -test) (Table 4). Improvements in the binocular score were also seen in children with MS and ON compared to controls ($p=0.460$). Using the 1.25% low-contrast charts, the mean magnitude of binocular summation for controls was 10 letters, which represents a 2-line improvement in low-contrast visual acuity. Children with MS and ON had similar improvements (12 letters) in their binocular scores. Binocular inhibition did not occur in any subject using low-contrast Sloan 2.5% or 1.25% charts.

3.2.4. Floor effects of low-contrast letter acuity—In the entire cohort of 102 eyes, only 5 eyes (4 subjects) had difficulty reading the low-contrast letter charts (defined as a low-contrast score of 0, Table 5). Two eyes in the MS group (representing 2 different subjects) were unable to read any letters using the low-contrast 2.5% and 1.25% charts.

Three additional eyes (2 controls, 1 MS patient with bilateral ON) were unable to read the 1.25% charts. However, all patients had non-zero scores using the binocular 2.5% charts. Only the 1 patient mentioned above with MS and ON in both eyes had a binocular score of zero using the 1.25% chart.

3.3. Optical coherence tomography

Mean RNFL thickness was 109 ± 9 μm for control eyes which did not differ from the 103 ± 17 μm for all MS eyes, accounting for age and inter-eye correlations ($p=0.089$, Table 3). Average RNFL thickness in MS ON- eyes was similar to controls (109 ± 11 μm , $p=0.960$). The decrease in RNFL thickness in MS participants vs. controls was driven by ON eyes (RNFL thickness was 86 ± 22 μm , $p<0.001$). Fellow eyes had a slightly reduced RNFL thickness (103 ± 12 μm) compared to MS ON- eyes although the difference was not significant ($p=0.375$). RNFL thickness for MS ON+ eyes was significantly reduced compared to MS ON- eyes ($p=0.002$). Comparing all MS eyes and controls, RNFL thinning was not associated with a decreased low-contrast letter acuity score using the Sloan 1.25% contrast charts ($p=0.103$ accounting for age and inter-eye correlations). The small sample size of MS ON+ eyes precluded further statistical analysis comparing the relationship between low-contrast letter acuity and RNFL thickness for MS ON+ eyes and controls. Of note, age was included in the models examining RNFL thickness but was not a significant factor in our cohort.

4. Discussion

Low-contrast Sloan letter charts detect visual dysfunction not captured by high-contrast visual acuity (ETDRS charts) in pediatric MS eyes. The 1.25% low-contrast Sloan charts had the greatest capacity to distinguish binocular and monocular visual acuities between pediatric MS participants and healthy controls, specifically the ON-affected eyes of MS patients. RNFL thinning occurs in MS ON+ eyes, but not in the eyes of pediatric MS patients unaffected by ON. Together, these findings indicate that while visual recovery from an episode of ON in children with MS is associated with normal acuity as measured by conventional acuity charts, persistent optic nerve injury can be detected by low-contrast acuity and RNFL thickness measures.

We did not demonstrate impaired visual acuity using high- or low-contrast letter acuity, contrast sensitivity, or RNFL thinning in pediatric MS subjects without a history of optic neuritis in either eye. Our findings differ from those in adult MS where decreased RNFL thickness decreased irrespective of a history of ON (Fisher et al., 2006). Larger studies are needed to confirm this observation. If confirmed, the biological explanation for preserved RNFL in young MS patients compared to the clinically silent retinal axonal loss in adult-onset MS would require further study.

Abnormalities in contrast sensitivity have been documented in up to 33% of fellow eyes of adults with unilateral ON (Beck et al., 1993). We distinguished fellow eyes from the eyes of children without a history of ON in either eye to determine whether asymptomatic optic nerve dysfunction was present in the “healthy” eyes of patients with unilateral ON. No differences were detected between fellow eyes and MS ON- eyes in any of monocular visual function tests or RNFL thickness; therefore, we conclude that subclinical demyelination resulting in optic nerve dysfunction was not present in the unaffected eyes of children with MS and unilateral ON.

Our work compares to a single center study in which 17 children with MS (7 of whom also had ON) correctly identified a decreased number of letters using low-contrast letter acuity (Sloan 2.5%) charts compared to 20 controls in a subanalysis (Yeh et al., 2009). Both our

study and Yeh et al. report similar low-contrast letter acuity scores using 2.5% contrast for healthy control eyes and MS ON+ eyes. However, Yeh et al. concluded that 2.5% contrast charts did not demonstrate a benefit over standard Snellen visual acuity when the low-contrast letter acuity scores of children with all demyelinating diseases (including ON as a clinically isolated syndrome, transverse myelitis, acute disseminated encephalomyelitis, and chronic relapsing inflammatory optic neuropathy) were compared to controls. Of note, low-contrast letter acuity using 1.25% contrast charts was not utilized in that study. Our data would support 1.25% contrast charts as a more sensitive metric in pediatric cohorts, which differs from adult cohorts in which there appears to be a floor effect and loss of sensitivity (Balcer et al., 2012). Approximately 23% of adult MS eyes were unable to read any letters using the 1.25% Sloan chart in a multi-center study (Talman et al., 2010; Balcer et al., 2013). While 5% of monocular eyes in our cohort scored a zero using these low-contrast (1.25%) charts, only 1 subject had a binocular score of zero.

In contrast to the present study, Yeh et al. reported a trend towards decreased RNFL thickness in the MS ON- eyes (101 μ m, standard deviation of approximately 13 among 20 eyes) compared to controls (107 μ m, standard deviation of approximately 8 μ m among 40 eyes) (Yeh et al., 2009). RNFL thickness moderately correlated with 2.5% low-contrast letter acuity scores in their cohort when the scores of all demyelinating disease eyes were compared to controls ($R=0.42$, $p=0.002$); data comparing only the MS group to controls was not provided due to small sample sizes.

We then examined the relationship between monocular and binocular visual function and demonstrated improved binocular scores over the better eye score for all patients, including healthy controls, MS patients without ON in either eye, and MS patients one or both eyes affected by ON. This phenomenon, called binocular summation, has been demonstrated in adult normal, healthy eyes (Blake et al., 1981). Adults with MS and ON demonstrate reductions in the ability to summate and have even demonstrated binocular inhibition (Pineles et al., 2011). However, in our pediatric MS patients, binocular summation appeared robust and similar to that of healthy children. Moreover, children with MS and ON did not demonstrate binocular inhibition using low-contrast letter acuity in our study.

The significance of the preserved binocular summation in pediatric MS provides insight into the interplay between the afferent visual pathway and cortical interpretation. While the exact mechanism is unclear, binocular summation likely represents a post-geniculate phenomenon, perhaps occurring at the cortical level (Blake et al., 1981). In adults with MS, increasing age was associated with a decrease in the magnitude of binocular summation (Pineles et al., 2011). Children with MS may not yet have acquired cortical injury to impair this process or may simply have more robust compensatory mechanisms.

While monocular scores are useful in determining the extent of visual dysfunction in each eye, the binocular score represents a patient's function in "everyday" life. Given the robust binocular summation in pediatric MS, it is possible that subtle monocular visual acuity deficits do not influence visual quality of life in these children. Further studies are needed to determine the impact of visual function on patient-reported quality of life in pediatric MS.

In adult MS trials, binocular low-contrast letter acuity has been used as a secondary outcome metric and successfully captured not only visual dysfunction but also treatment effects (Balcer et al., 2005; Balcer et al., 2007). Clinical trials of new therapeutic agents in pediatric MS populations will soon occur (Chitnis et al., 2013). Results of these investigations support the inclusion of low-contrast acuity metrics in clinical practice and pediatric trials as a more sensitive diagnostic tool to detect optic neuritis. As such, it is important to fully understand the process of binocular summation and the impact of subtle unilateral deficits on binocular

vision in children with MS. In addition, OCT has been identified as a promising outcome measure for neuroprotection trials in adults with MS (Barkhof et al., 2009). Longitudinal OCT studies in pediatric MS are needed to determine whether RNFL thinning occurs as a function of disease duration or whether age at disease onset impacts the trajectory of axonal loss.

We acknowledge our limited sample size in the current investigation: an ongoing challenge in studies of rare pediatric diseases. The three center collaboration has provided important insight for future multicenter trial methodology, partly related to consistency of testing parameters and selection of a single OCT device. Newer OCT devices, namely spectral-domain OCT, provide greater image resolution and further retinal segmentation, and will likely be selected for upcoming trials. Finally, this study captured children early in the disease course which may account for the preservation of axons as measured by OCT and greater magnitude of binocular summation compared to adults. However, RNFL thinning has been reported in adults with clinically isolated syndromes (excluding ON) and disease duration less than 1 year (Gelfand et al., 2012) suggesting that the short disease duration in our study may not account for the loss of axonal integrity.

5. Conclusion

Our study highlights important considerations in the assessment of monocular and binocular visual function in children and potential differences between adult and pediatric MS with regard to vision. Preserved binocular summation suggests a functional compensatory mechanism in pediatric MS patients that is not evident in adults with MS. Whether loss of binocular summation and RNFL thickness occurs with disease duration or with increasing MS disease activity will require prospective serial analysis of pediatric MS patients. Additional data is also needed to determine whether visual impairment and RNFL thinning impact visual processing and a child's school performance and quality of life. Such studies are currently underway to elucidate the mechanisms leading to visual disability in children with MS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ETDRS	early treatment of diabetic retinopathy study
MS	multiple sclerosis
OCT	optical coherence tomography

ON	optic neuritis
RNFL	retinal nerve fiber layer
SD	standard deviation

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Highlights

- We examined low-contrast letter acuity in pediatric multiple sclerosis (MS).
- Low-contrast letter scores are decreased in pediatric MS-optic neuritis (MS ON +) eyes.
- Binocular summation is preserved in pediatric MS.
- Subclinical RNFL thinning does not appear to occur in early MS in children.
- We identified differences in visual outcomes between pediatric and adult MS.

Table 1

Definitions

Group or term	Definition
MS ON- eyes	Eyes of patients with multiple sclerosis but no clinical symptoms or radiographic evidence of optic neuritis in either eye
MS ON+ eyes	Eyes of patients with multiple sclerosis and clinical symptoms of optic neuritis in that eye
MS fellow eyes	The MS ON- eyes of children with multiple sclerosis and unilateral optic neuritis in the opposite eye
Monocular score	The number of letters read correctly on an eye chart using one eye
Binocular score	The number of letters read correctly on an eye chart using both eyes simultaneously
Better eye score	The number of letters read correctly by the better eye for an individual patient
Worse eye score	The number of letters read correctly by the worse eye for an individual patient
Binocular summation	The ability to identify a greater number of letters correctly when both eyes are used compared to the better eye alone
Binocular inhibition	A decreased number of letters are correctly identified when both eyes are used compared to the better eye alone
Magnitude of binocular summation	The difference between the binocular score and the better eye score
Magnitude of binocular inhibition	The difference between the better eye score and the binocular score

Table 2

Demographics and clinical characteristics of the pediatric cohort

	Controls	Patients with Multiple Sclerosis	<i>p</i> -value [*]
Number of patients	29	22	
Number of eyes	58	44	
Age, mean (SD)	12.8 (3.7)	14.3 (3.6)	0.153
Sex, number of female (%)	15 (52)	12 (55)	0.777
Race, number of patients (%)			
Caucasian	25 (86)	17 (77)	0.122
African American	3 (10)	5 (23)	
Asian/Pacific Islander	1 (3)	0 (0)	
Number of patients with a history of optic neuritis (%)	N/A	8 (36)	
Unilateral ON (MS ON+/MS ON-)		6 (27)	
Bilateral ON (MS ON+/MS ON+)		2 (9)	

MS = multiple sclerosis, ON = optic neuritis, SD = standard deviation

* The *p*-value was calculated using a t-test or chi-square test depending on the type of variable (categorical vs continuous).

Table 3

Results of Monocular Visual Function Tests and OCT in Children

	Healthy Controls	All MS patients		MS ON– eyes		MS ON+ eyes	
	N=58 eyes	N=44 eyes	<i>p</i> -value vs control	N=28 eyes	<i>p</i> -value vs control	N=10 eyes	<i>p</i> -value vs control
High-contrast letter acuity (ETDRS), number of letters correct (SD)	64 (4)	62 (9)	0.135	62 (6)	0.174	59 (16)	0.059
Low-contrast letter acuity (2.5%), number of letters correct (SD)	33 (8)	29 (10)	0.067	31 (8)	0.352	21 (12)	0.001
Low-contrast letter acuity (1.25%), number of letters correct (SD)	22 (8)	16 (9)	0.004	18 (8)	0.124	9 (9)	<0.001
Pelli-Robson, log score (SD)	1.64 (0.06) (N=22 eyes)	1.61 (0.15) (N=36 eyes)	0.583	1.66 (0.09) (N=22 eyes)	0.417	1.48 (0.22) (N=9 eyes)	0.039
RNFL Thickness, μm (SD)	109 (9) (N=56 eyes)	103 (17)	0.085	109 (11)	0.994	86 (22)	<0.001

ETDRS = early treatment of diabetic retinopathy study, MS = multiple sclerosis, OCT = optical coherence tomography, ON = optic neuritis, RNFL = retinal nerve fiber layer, SD = standard deviation. The *p*-values were determined using generalized estimating equation models.

Table 4

Results of binocular visual function tests in children

	Healthy controls		All MS patients		MS, no history of ON in either eye (MS ON-/-)		MS, history of ON in one or both eyes (MS ON +/- MS ON- or MS ON +/- MS ON+)	
	N=29 patients		N=22 patients	p-value vs. control	N=14 patients	p-value vs. control	N=8 patients	p-value vs. control
High-contrast letter acuity (ETDRS), number of letters correct, (SD)	66 (4)		66 (4)	0.994	67 (4)	0.661	65 (4)	0.541
Magnitude of binocular summation	3 (2)		4 (2)	0.115	4 (2)	0.056	1	-
Low contrast letter acuity (2.5%), number of letters correct, (SD)	42 (6) (N=28)		39 (8)	0.186	41 (4)	0.653	36 (12)	0.061
Magnitude of binocular summation	8 (4)		8 (4)	0.602	8 (4)	0.850	7 (4)	0.460
Low contrast letter acuity (1.25%), number of letters correct, (SD)	35 (6) (N=28)		30 (8)	0.016	32 (5)	0.108	26 (12)	0.007
Magnitude of binocular summation	10 (5)		12 (6)	0.192	11 (6)	0.328	12 (5)	0.234
Pelli-Robson, (SD)	1.77 (0.13) (N=11)		1.71 (0.14) (N=18)	0.230	1.77 (0.11) (N=13)	0.931	1.61 (0.15) (N=5)	0.025

ETDRS = early treatment of diabetic retinopathy study, MS = multiple sclerosis, OCT = optical coherence tomography, ON = optic neuritis, RNFL = retinal nerve fiber layer, SD = standard deviation. The *p*-values were determined using generalized estimating equation models.