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

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Abstract
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.

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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Methods: Monocular and binocular high- and low-contrast letter acuity and contrast sensitivity were assessed in a cross-sectional cohort of children (ages 5–17 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 ± 17 μm) trended lower when compared to corresponding measures in control eyes (109 ± 9 μm, $p=0.085$), we confirmed a highly significant reduction in mean RNFL thickness in MS eyes with a history of ON (86 ± 22 μm, $p<0.001$). RNFL thickness of MS ON− eyes in pediatric MS patients (109 ± 11 μm) 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.

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