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Retinal Nerve Fiber Layer Thickness in Amblyopic Eyes

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Abstract

Purpose—To compare the peripapillary retinal nerve fiber layer (RNFL) thickness of amblyopic and fellow eyes. We hypothesized that the RNFL of the amblyopic eye might be thinner.

Design—Prospective cross-sectional observational case series

Methods—Optical coherence tomography (OCT) of the peripapillary RNFL thickness of amblyopic and fellow eyes was performed in 37 patients age 7 to 12 years (mean 9.2 ± 1.5) with unilateral strabismic, anisometropic or combined mechanism amblyopia enrolled in a randomized treatment trial.

Results—Mean global RNFL thickness of the amblyopic and fellow eyes was 111.4 microns and 109.6 microns, respectively (mean difference = 1.8 microns thicker in the amblyopic eyes, 95% confidence interval -0.6 to +4.3 microns). The amblyopic eye was 8 or more microns thicker than the fellow eye in 9 patients (24%); the fellow eye was 8 or more microns thicker than the amblyopic eye in 2 patients (5%); and the difference was within test-retest variability (7 microns) in 26 patients (70%).

Conclusions—Our findings do not indicate that peripapillary RNFL thickness is thinner in eyes with moderate amblyopia compared with their fellow eyes.

Introduction

Amblyopia is reduced best-corrected visual acuity in one or both eyes caused by abnormal visual experience during visual development. Causes include strabismus, image blur from refractive error, form deprivation, or a combination of these factors. While most of the deficit is felt due to impairment of cortical development, changes have been seen in the lateral geniculate nucleus of non-human primates and humans following visual deprivation amblyopia during the neonatal period.[1], [2] A role for optic nerve abnormalities, termed

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* A list of the members of the Pediatric Eye Disease Investigator Group participating in the study appears in the acknowledgements. Participating coordinating center personnel and committee members have been published.[9]

"dysversion" or hypoplasia, in the genesis of visual loss diagnosed as amblyopia has been postulated by Lempert, who reported this optic nerve abnormality was present in optic nerve photographs in 45% of 205 amblyopic eyes.[3], [4] More recently Lempert has reported reduced optic disc rim areas for both amblyopic and fellow eyes with the reduction most prominent in the amblyopic eyes.[5]

Optical coherence tomography (OCT) of the peripapillary optic nerve is a non-invasive test in which the thickness of the retinal nerve fiber layer (RNFL) is measured. RNFL thickness correlates with disc area in children.[6] OCT has been used to compare the RNFL of amblyopic and fellow eyes of patients of varied ages.[7], [8] One study found a small statistically significant difference between eyes for anisometropic amblyopia (amblyopic eyes thicker) and no difference for strabismic amblyopia.[7] Another study found no difference but had insufficient numbers to evaluate subgroups by cause.[8]

The purpose of this study was to compare the peripapillary RNFL thickness of amblyopic and fellow eyes as measured with OCT in subjects 7 to 12 years old participating in a multicenter clinical trial of amblyopia treatment.

Methods

The study was performed at 12 clinical sites as an ancillary study of an amblyopia treatment trial conducted by the Pediatric Eye Disease Investigator Group. The respective institutional review boards approved the protocol and HIPAA-compliant informed consent forms. Separate written informed consent was obtained for the ancillary OCT study. Details of the randomized trial protocol have been published[9] and the protocol is available on the PEDIG website (http://www.pedig.net). Patients enrolled in the randomized trial had visual acuity of 20/40 to 20/400 with amblyopia due to strabismus, anisometropia, or both. To be eligible for the OCT study, patients had to have refractive error in each eye between -0.25 and +5.00D, inclusive (to avoid the need to adjust for refractive error since axial lengths were not obtained).

OCT images were obtained at either the baseline examination or one of the follow-up visits using the Humphrey-Zeiss Stratus (OCT3) (Carl Zeiss-Humphrey-Meditec, Dublin, CA), with software 4.0.1 or higher. The rapid RNFL scan was used. In this technique three circular samples of RNFL thickness were taken with a diameter of 3.44mm around the optic disc. The OCT software calculated the average thickness from the three samples for the entire 360 degree circumference (defined subsequently as global RNFL thickness) as well as average thickness values for each quadrant (superior, nasal, inferior, and temporal). The right eye was tested first, followed by the left eye. The test was repeated on each eye during the same visit to provide test-retest data.

Submitted scans were assessed for signal strength, image centration, and correct RNFL limits drawn in the color cross section. Scans with signal strength less than 5 (on a 10-point scale) were considered unacceptable and not included in the analyses. Scans were also excluded from the analyses if they were visibly de-centered or did not have normal

appearing color cross sections. If both the initial and retest scans were of good quality, the initial scan was used for analysis.

Statistical Methods

The primary outcome measure was global RNFL thickness, which was compared between amblyopic and fellow eyes using a paired t-test.

Test-retest data were analyzed to determine the difference in RNFL thickness to be considered within the variability of testing using a repeated measures analysis of variance to estimate the standard error of measurement (SEM) for each measure. The SEM was estimated separately for amblyopic and fellow eyes. Ninety-five percent limits of agreement were calculated for the amblyopic eye minus fellow eye differences in order to define a range to be considered as indicating “no difference”. It was assumed that the SEM of amblyopic and fellow eyes of the same patient were uncorrelated; this assumption was evaluated by calculating the Pearson correlation coefficient of the absolute value of the test-retest differences in amblyopic versus fellow eyes ($r=-0.20$, $p=0.29$).

Based upon the limits of agreement, for each patient a determination was made as to whether the RNFL was thicker in the amblyopic eye by 8 or more microns, thicker in the fellow eye by 8 or more microns, or similar in the two eyes (within 7 microns). Linear regression was used to evaluate the association between RNFL thickness and refractive error in the amblyopic and fellow eyes separately.

All analyses were repeated for each quadrant (superior, nasal, inferior, temporal). Analyses were performed using SAS (version 9.0., SAS Institute, Cary, NC).

Results

Forty-eight patients with amblyopia were enrolled in this ancillary study between December 2005 and June 2007. Eleven patients were excluded from the analysis because they did not have at least one acceptable image for each eye. The mean age of the 37 patients included in the analysis was 9.2 ± 1.5 years; 51% were female, and 38% were white. Additional baseline characteristics are listed in Table 1.

Test-retest data were obtained for 64 eyes (30 amblyopic eyes and 34 fellow eyes). The estimated standard error of measurement for a difference in global RNFL thickness was found to be 3.7 microns. The 95% limits of agreement for a difference in global RNFL thickness were calculated to be ±7 microns. Limits of agreement were also computed for the four quadrants.

The global RNFL thicknesses of the amblyopic and fellow eyes were 111.4 microns (range 93.4 to 136.0) and 109.6 microns (range 91.3 to 136.0), respectively (mean difference = 1.8 microns thicker in the amblyopic eyes, 95% confidence interval -0.6 to +4.3) (Table 2). The amblyopic eye was 8 or more microns thicker than the fellow eye in 9 patients (24%); the fellow eye was 8 or more microns thicker than the amblyopic eye in 2 patients (5%); and the difference was within 7 microns in 26 patients (70%). There were no significant differences

in RNFL thickness between amblyopic and fellow eyes in any of the four quadrants (Table 2).

There was no association between RNFL thickness itself and hypermetropic refractive error in the amblyopic eye (P=0.81) or sound eye (P=0.28).

Discussion

We measured peripapillary RNFL thickness in amblyopic and fellow eyes with OCT, employing a technique similar to that reported for glaucoma.[10], [11] We found the technique to have low variability among children 7 to < 12 years of age, with the 95% limits of agreement to be ± 7 microns. In the comparison of retinal thickness in the amblyopic and sound eyes, there was no meaningful difference in global RNFL thickness or in the thickness in any of the four quadrants (superior, inferior, temporal, or nasal). Therefore, the results do not suggest that an optic neuropathy is an important element of moderate anisometropic or strabismic amblyopia.

Normative peripapillary RNFL thickness data have been previously reported for children in our age group. In the largest study to date including 1309 normal 6-year old children, the global RNFL thickness in the right eye was 103.7 ± 11.4 microns.[12] In another study of 92 normal children, 4 to 17 years of age, the global RNFL thickness was reported to be 107.0 ± 11.1 microns.[13] A third study of 217 eyes found an average global RNFL thickness of 108 microns in children 3 to 17 years of age.[14] In our previous pilot study of 17 subjects with amblyopia (mean age 10.7 years), the global overall thickness in the fellow eye was reported to be 109.2 ± 17.3 microns[8], similar to what was found in the current study. The global fellow eye peripapillary RNFL thickness in the current study (109.6 microns) is similar to the normative data reported by Salchow[13] among similarly aged children, supporting our use of the fellow eye RNFL thickness as an appropriate comparison group.

Previous studies of OCT and amblyopia have reported differing results. Altintas and colleagues examined 14 patients with OCT and found the amblyopic RNFL to be 2.5 microns thicker on average than the fellow eye. They concluded there was no significant difference.[15] In our earlier pilot study of 17 amblyopic patients (who were not included in this study) we found a 5 micron difference (thicker in the fellow eyes), but this was not considered to be a clinically significant difference.[8] Rabbione and colleagues also found no difference between normal and amblyopic eyes (Rabbione MM, et al. IOVS 2004;45:ARVO E-Abstract 2574). Yen and colleague found the global RNFL thickness with OCT of 38 eyes of patients with unilateral amblyopia to be 7.7 microns thicker in amblyopic eyes compared to fellow eyes.[7] The difference was significant only for patients with anisometropic amblyopia.

There are several limitations to our study, the most important being the fact that 89% of our subjects had moderate amblyopia with 20/100 or better visual acuity in the amblyopic eye. Therefore, the results should not be generalized to those with severe amblyopia. In addition since patients enrolled in the present study had amblyopia due to anisometropia, strabismus,

or both, the results cannot be generalized to deprivational amblyopia. Sample size precluded subgroup analyses based on type of amblyopia.

Differences in magnification between the eyes has been a concern with optic nerve imaging including OCT.[16] When the amblyopic eye is more hypermetropic, magnification would increase the RNFL thickness measurement. A recent cross-sectional study in children found that the RNFL was 1.67 microns thicker per diopter of hypermetropia.[13] To reduce this potential concern, we performed intrapatient comparisons and did not enroll patients with myopia or hypermetropia >5.00D. The amblyopic eyes in this study were on average 1.02 D more hypermetropic than the fellow eyes, thus the effect of anisometropia would be negligible (about 2 microns). The current study did not find an association between RNFL thickness and increasing hypermetropia.

In summary, our findings do not indicate that peripapillary RNFL thickness is thinner in eyes with moderate amblyopia compared with their fellow eyes.

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C. Contributions to Authors in each of these areas: design and conduct of the study (MXR, RTK, RWB); collection, management, analysis, and interpretation of the data (MXR, RTK, SMT, DWS, NAS, RWB); and preparation, review, or approval of the manuscript (MXR, RTK, SMT, DWS, NAS, RWB).

D. This study was approved by the following IRBs: Joint Committee on Clinical Investigations, Johns Hopkins Medical Institutions, Baltimore, Maryland; Jaeb Center for Health Research Institutional Review Board, Tampa, Florida; University of Miami Human Subjects Research Office, Bascom Palmer Eye Institute, Miami, Florida.

E. not applicable

The Pediatric Eye Disease Investigator Group

Clinical Sites that Participated in this Protocol

Sites are listed in order by number of patients enrolled into the study. Personnel are listed as (I) for Investigator, and (C) for Coordinator.

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Table 1

Baseline Characteristics of Amblyopic Subjects Participating in this Study of Retinal Nerve Fiber Layer Thickness

	N=37 n (%)*
Gender: Female	19 (51)
Race / Ethnicity	
White	14 (38)
African-American	5 (14)
Hispanic or Latino	17 (46)
Asian	0
More than one race	0
Unknown/Not reported	1 (3)
Age at Enrollment	
Mean (SD) [range]	9.2 (1.5) [7.1 to 12.2]
Cause of Amblyopia	
Strabismus	10 (27)
Anisometropia	17 (46)
Strabismus and anisometropia	10 (27)
Distance Visual Acuity in Amblyopic Eye	
20/100-20/250	4 (11)
20/40-20/80	33 (89)
Mean (SD) Letter Score [Snellen approximation]	62 (8) [20/63]
Distance Visual Acuity in Fellow Eye	
20/25	7 (19)
20/20	16 (43)
20/16	14 (38)
Mean (SD) Letter Score[Snellen approximation]	86 (3) [20/20]
Intereye Acuity Difference	
Mean (SD) Difference in Lines	4.7 (1.8)
Refractive Error in Amblyopic Eye	
-0.25 to < 0 D	4 (11)
0 to <+1.00D	11 (30)
+1.00 to <+2.00D	4 (11)
+2.00 to <+3.00D	2 (5)
+3.00 to <+4.00D	11 (30)
+4.00 to +5.00D	5 (14)
Mean (SD) D	+2.03 (1.70)

	N=37 n (%)*
Refractive Error in Fellow Eye	
-0.25 to < 0 D	3 (8)
0 to <+1.00D	19 (51)
+1.00 to <+2.00D	7 (19)
+2.00 to <+3.00D	6 (16)
+3.00 to <+4.00D	1 (3)
+4.00 to +5.00D	1 (3)
Mean (SD) D	+1.03 (1.11)
Difference in Refractive Error (Amblyopic minus Fellow)	
< 0 D	7 (19)
0 to <+1.00D	16 (43)
+1.00 to <+2.00D	5 (14)
+2.00 to <+3.00D	4 (11)
+3.00 to <+4.00D	3 (8)
≥+4.00D	2 (5)
Mean (SD) D	+1.02 (1.47)

*n (%) unless otherwise stated

D = diopters, SD = standard deviation

Table 2

Retinal Nerve Fiber Layer Thickness by Optical Coherence Tomography of Amblyopic and Fellow Eyes (N=37 subjects)

	Global Thickness (microns)	Inferior Quadrant (microns)	Nasal Quadrant (microns)	Temporal Quadrant (microns)	Superior Quadrant (microns)
Amblyopic Eye					
Mean (SD)	111.4 (10.4)	147.3 (17.7)	92.0 (24.7)	69.8 (11.8)	135.1 (15.8)
Fellow Eye					
Mean (SD)	109.6 (11.4)	144.4 (16.5)	90.4 (21.7)	69.8 (11.0)	133.4 (17.9)
Difference (Amblyopic Eye - Fellow Eye)					
Mean (SD) Difference	+1.8 (7.2)	+2.9 (14.4)	+1.6 (21.2)	-0.1 (10.1)	+1.7 (12.8)
95% Confidence Interval	-0.6 to +4.3	-1.9 to +7.7	-5.5 to +8.7	-3.4 to +3.3	-2.6 to +6.0
P-value from paired samples t-test	0.13	0.23	0.65	0.97	0.43
Ho: mean difference = 0					
Amblyopic eye thicker than Fellow eye *	9 (24%)	3 (8%)	5 (14%)	2 (5%)	3 (8%)
Within variability of testing *	26 (70%)	32 (86%)	30 (81%)	32 (86%)	33 (89%)
Fellow eye thicker than Amblyopic eye *	2 (5%)	2 (5%)	2 (5%)	3 (8%)	1 (3%)

* Based on whether difference exceeded 95% limits of agreement for difference calculated using standard error of measurement from test/retest data (for global thickness ±7 microns; for inferior ±22 microns; for nasal ±26 microns; for temporal ±12 microns; for superior ±19 microns).