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Using OCT Fixation Shift to Assess Eccentric Fixation in Children With Residual Amblyopia

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Purpose: Eccentric fixation in amblyopia is often estimated grossly without precision. Although the usefulness of optical coherence tomography (OCT) fixation shift in the quantification of eccentric fixation in a small cohort of amblyopic children was recently reported, there is a lack of understanding of characteristics of OCT fixation shift. In a retrospective cohort study, we evaluated eccentric fixation with OCT in a large cohort of children with residual amblyopia.

Methods: Children, age 4 to 17 years, with residual amblyopia (amblyopic, $n = 56$) and without amblyopia (control, $n = 75$) were enrolled. Amblyopia was associated with anisometropia alone (anisometropia subtype, $n = 28$) and strabismus without or with anisometropia (strabismic subtype, $n = 28$). Spectral domain OCT was used to estimate fixation. The OCT fixation shift, defined as the distance between the fovea and the fixation point, was measured and adjusted with calculated axial length and converted into visual degrees. Fixation shift in amblyopic eyes, fellow nonamblyopic eyes, and right eyes of the control group were compared. Fixation shift between the anisometropic and strabismic amblyopia subtypes was also compared. Its correlation with visual acuity was estimated.

Results: The mean fixation shift was significantly different: 0.17° ± 0.29° for control right eyes, 0.94° ± 1.24° for amblyopic eyes, and 0.34° ± 0.57° for fellow eyes ($\chi^2 = 23.3$; $P < 0.001$). There was no significant difference between fellow eyes and control eyes ($P = 0.11$). Fixation shift in amblyopic eyes was significantly correlated with visual acuity ($R = 0.44$; $P < 0.001$), and it was significantly smaller in the anisometropic subtype than in the strabismic subtypes (0.34° ± 0.46° vs. 1.54° ± 1.48°, $W = 338$, $P < 0.001$).

Conclusions: OCT fixation shift can be used both in detection and quantification of eccentric fixation in children with residual amblyopia, especially in those with strabismus.

Translational Relevance: OCT fixation shift offers a convenient clinical approach in quantitative evaluation of eccentric fixation in children with strabismic amblyopia.

Introduction

Amblyopia is a leading cause of vision impairment in children, affecting 1.0% to 3.5% of the population in developed countries.[1,2] According to previous clinical trials by the Pediatric Eye Disease Investigator Group, even with great compliance and early treatments, approximately 25% to 40% of amblyopic children do not fully resolve and will be left with residual amblyopia.[3–7] Among potential causes of residual amblyopia, eccentric fixation may be a contributing factor, especially in strabismic amblyopia. Existing methods to measure eccentric fixation often offer a gross estimate with large variance. In the laboratory, Hess[8] described four tests to assess eccentric fixation: Maxwell's spot, Haidinger's brushes, visuoscopy, and fixation photography; he commented

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that none of these tests alone were satisfactory. Furthermore, some of these tests are difficult to carry out in pediatric clinical practice. Without a method for quantitative measurement of eccentric fixation, it is impractical to use eccentric fixation as a clinical marker during amblyopia treatment. Currently, eccentric fixation is not a part of routine amblyopia evaluation in most pediatric ophthalmology practices owing to limited availability, young children's inability to participate in the testing, and time constraints. As a result, most amblyopic patients are treated regardless of their fixation behavior, and visual acuity is often the only factor used to assess the therapeutic efficacy.

Optical coherence tomography (OCT) provides a quantitative method to examine the morphology of the retina in vivo with micrometer resolution. It is widely available in ophthalmology clinics and well tolerated by young children. In 2018, Nakamoto et al.[9] first report the use of OCT imaging to quantify eccentric fixation. They investigated 14 children with amblyopia, ages 3 to 16 years, and compared them with 10 normal young adults. Although this study has no age-matched control group and a small sample size without distinction of the types of amblyopia, they reported good repeatability of the OCT findings.[9] Also in 2018, Garcia-Garcia et al.[10] report measurement of eccentric fixation with OCT in 15 children with microtropia (most had amblyopia from 0.05 to 0.70 logarithm of the minimum angle of resolution [logMAR]) and compared them with 10 children without microtropia.

During OCT imaging, the patient fixates on an internal target, which is similar to fixation on the bullseye target of ophthalmoscopy. When the patient's fixation and the foveal center do not superimpose, eccentric fixation can be identified. Moreover, OCT-measured eccentric fixation is more accurate than that conventionally measured with ophthalmoscopy for two major reasons: (1) The dim and almost invisible illumination of OCT enables the patient to maintain fixation more comfortably than bright visible light in visuscope or ophthalmoscopy, and (2) with the aid of OCT three-dimensional scans, we are able to identify the fovea more accurately than estimating it by reflection with conventional ophthalmoscopy. In fact, Nakamoto et al.[9] failed to register eccentric fixation with ophthalmoscopy in three patients (21%), although they could measure all patients with OCT. Garcia-Garcia et al.[10] were not able to report eccentric fixation with visuscope for five patients (33%). We believe that OCT may provide a new objective tool to estimate eccentric fixation with more accuracy. To distinguish it from conventional eccentric fixation, this measurement is termed "OCT fixation shift."

In this retrospective study, we aim to (1) quantify the OCT fixation shift in children with both normal vision and amblyopia, (2) evaluate those children who have residual amblyopia and correlate visual function with OCT fixation shift, and (3) compare OCT fixation shift in anisometropic, strabismic, and combined types of amblyopia.

Methods

This study was approved by the Institutional Review Board of the Nemours Office of Human Subject Protection and conformed to the requirements of the United States Health Insurance Portability and Accountability Act. This research followed the tenets of the Declaration of Helsinki.

Medical records and OCT images of children, ages 5 to 17 years who visited the Ophthalmology Division at the Nemours/Alfred I. duPont Hospital for Children in Wilmington, Delaware from, January 2014 to March 2019, were reviewed. Children were classified into the amblyopia group or the age-matched control group with normal vision (called the control group hereafter). Data for the control group were from an earlier Institutional Review Board-approved study investigating foveal structure in children using OCT. These children visited our clinic for failed vision screen, blurred vision, family history of eye diseases (required glasses before 8 years of age), and headaches. Their eye examinations were normal.

Inclusion criteria for the amblyopia group were (a) children who had the first obtainable best-corrected visual acuity (BCVA) of 20/40 (equivalent to 0.3 logMAR) or worse in the amblyopic eye, and interocular difference of BCVA was at least two logMAR lines, (b) residual amblyopia was defined as worse or equal to 0.2 logMAR interocular difference of BCVA at their latest visit despite at least 12 weeks of amblyopia treatments (glasses, patching, and/or atropine), and (c) ocular causes of amblyopia that were identified as refractive (i.e., anisometropia), strabismus, or combined type. Anisometropia included an interocular difference of spherical equivalent (SEQ) 0.75 diopters (D) or more or an interocular difference of astigmatism cylinder magnitude of 0.75 D or more; strabismus included those with a deviation of 10 prism diopters or more on the day of OCT imaging or good alignment after prior strabismus surgery; and combined type included those who meet criteria of both anisometropia and strabismus.

Inclusion criteria for the age-matched control group were children who had BCVA of 20/40 or better in

both eyes, and interocular visual acuity difference was not more than one logMAR line. The refractive error SEQ ranged from –6 D to +9 D, and stereopsis (when obtainable) was equal to or better than 100 seconds of arc. Motility examinations showed no identifiable misalignment.

Exclusion criteria for all participants included children born before 32 weeks gestational age; those with neurologic, developmental, or systemic illnesses known to be associated with ocular pathologies; and those with congenital or acquired macular pathology.

Procedures

Demographics (including sex, ethnicity, age, gestational age at birth, and birth weight), cycloplegic refractive error, and treatment history were obtained from medical records. Each patient underwent a comprehensive ophthalmic examination. Patient information including BCVA, stereopsis, and ocular alignment was obtained on the day of OCT imaging.

OCT Imaging

All individuals were scanned with the Spectralis spectral-domain OCT (Heidelberg Engineering, Heidelberg, Germany) using the eye-tracking feature (automatic real time). All OCT images were taken by experienced ophthalmic technicians or one of the authors (AA). The subject was asked to focus on the internal fixation target. One to three volume scans of the macular region were obtained from both eyes for each subject. Only one volume scan with the best quality (by comparing Q-value in the software) was chosen to be analyzed for each eye. Only those with a clearly defined foveal pit on OCT images were included. Each image was constructed from a series of 25 parallel B scans in a 6 mm × 6 mm area.

OCT Fixation Shift Identification

Figure 1A shows the fixation point and foveal pit often coincide in normal eyes. The OCT software depicted three concentric circles of 1 mm, 3 mm, and 6 mm diameters. Figure 1B shows when the fixation point and foveal pit did not overlap, the distances between these two points were determined with a measuring function provided by the OCT program in micrometers and defined as an "OCT fixation shift," which reflects eccentric fixation of the eye at ex-fovea and also differentiates from conventional eccentric fixation measured with ophthalmoscopy. This procedure is very similar to that described by Nakamoto et al.[9] However, we used the volume scan function,

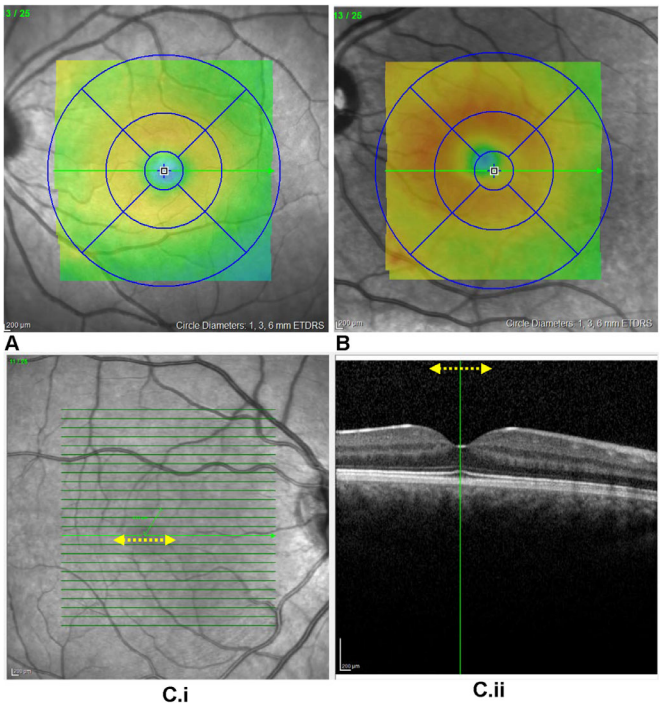

Figure 1. The fovea and fixation marker (*square*) coincide **(A)**. The fovea and marker do not coincide **(B)**. The OCT shift is measured using ruler feature in the "Display" window. Fovea is located by selecting the single B-scan through the foveal pit and aligning the vertical green line with the foveal center (**C i** and **C ii**). The *yellow dashed line* shows the refinement.

which allowed for easier identification of the foveal pit by comparing cross-sectional scans (Fig. 1C.i and ii). This approach further refines the measurement by Nakamoto et al., which used a single cross-sectional scan.

OCT Fixation Shift Adjusted with Calculated Axial Length

OCT devices assume a standard axial length; thus, individual differences in axial length (and, thus, ocular magnification) affect the absolute dimensions of the scan. It is suggested that the lateral scale of all OCT datasets must be corrected for individual differences in axial length.[11] Unfortunately, direct axial length measurement was not obtained from participants of this study. Therefore, we used axial length calculated from SEQ to adjust OCT fixation shift with the following steps.

1) Calculate axial length with SEQ. A recent study reported an inverse linear relationship between SEQ and axial length and the slope of regression line varies among different age groups.[12] Therefore, according to models for different age groups

Table 1. Demographic Characteristics of Subjects from the Amblyopia and Control Groups

	Amblyopia Group ($n = 56$)	Control Group ($n = 75$)	*P* Value
Sex			
Female	29 (52)	43 (57)	0.65*
Male	27 (48)	32 (43)	
Race/ethnicity			
African American	3 (5)	19 (25)	
Caucasian	47 (84)	40 (53)	
Hispanic	1 (2)	3 (4)	
Other	5 (9)	13 (17)	
Age (years)			
Mean ± SD	9.4 ± 3.3	10.5 ± 3.3	0.06
(min, max)	(3.9, 17.3)	(5.3, 17.9)	
Gestational age (weeks)			
Mean ± SD	39.4 ± 1.4	39.0 ± 1.8	0.23
(min, max)	(33, 42)	(33, 41)	
Amblyopic eye laterality			
Left	38 (68)		<0.001
Right	18 (32)		
Amblyopic types			
Anisometropic	28 (50)		
Strabismic	13 (23)		
Combined	15 (27)		

Values are number (%), mean ± standard deviation (SD), or (min, max).
*Comparison of proportion of females in two groups, $\chi^2 = 0.21$.

provided in this article, we estimated axial length = –0.28 × SEQ + 22.94 for a child less than 9 years of age; axial length = –0.32 × SEQ+23.48 for a child 9 to less than15 years of age; and axial length = –0.40 × SEQ + 23.41 for a child 15 to less than 18 years of age.[12]

2) Adjust fixation shift data with calculated axial length: fixation distance multiplies the ratio of the patient axial length estimated with SEQ to 24.385 mm (normal axial length assumed by the Spectralis system).
3) Convert OCT fixation shift from micrometers into degrees of visual angle. Typically, 288 µm corresponds with 1 visual degree in an eye with a normal axial length.[13]

OCT Fixation Shift Test and Retest

A small portion of subjects had more than one OCT measurement. Data from these children provided us an opportunity to estimate repeatability of the OCT fixation shift.

Statistical Analysis

We compared the right eyes in the control group with the amblyopic and nonamblyopic fellow eyes in the amblyopia group. Data analysis was performed and plotted using R 3.5.0 Statistics (R Core Team. URL http://www.R-project.org/). *P* values of less than 0.05 were considered significant. For normally distributed parameters like SEQ and visual acuity, we used the analysis of variance test. Because the OCT fixation shift was not normally distributed and skewed to zero, the Kruskal–Wallis test was used to compare fixation shift in the amblyopic eyes, the fellow eyes, and the right eyes of the control group. An independent two-group Mann–Whitney *U* test was used to compare the two subtypes of amblyopic eyes. For convenient comparison with existing OCT fixation shift literature, we reported means, standard deviations, and medians. Using Pearson correlation and linear regression tests, the associations between OCT fixation shift in the amblyopic eye and visual acuity, severity of amblyopia (i.e., interocular difference of BCVA), amblyopia types, as well as with stereopsis, were analyzed. Stereopsis was not normally distributed; we converted it on the log

Table 2. Summary Information of Eye Examination and OCT Fixation Shift Data at the Day of OCT Imaging

	Control Group	Amblyopia Group	
	Right Eyes	Fellow Eyes	Amblyopic Eyes
No.	75	56	56
SEQ (D) mean ± SD (min, max)	0.33 ± 2.5 (–5.5, 9.0)	2.00 ± 2.31 (–1.5, 8.25)	4.62 ± 2.32 (0.25, 10.25)
BCVA (logMAR) mean ± SD (min, max)	0.03 ± 0.07 (–0.12, 0.30)	0.07 ± 0.11 (–0.12, 0.40)	0.46 ± 0.19 (0.10, 1.00)
Stereopsis (arc sec) median (min, max)	40 (40, 100)	400 (40, >3000)	
Final severity of amblyopia (interocular difference of BCVA, logMAR)		0.41±0.17 (0.20, 0.82)	
Fixation shift (μm) mean ± SD (min, median, max)	50.8 ± 88 (0, 0, 300)	108 ± 182 (0, 0, 770)	303 ± 400 (0, 213.5, 1730)
Adjusted fixation shift with axial length (μm) mean ± SD (min, median, max)	48.6 ± 84 (0, 0, 275)	98 ± 164 (0, 0, 691)	272 ± 358 (0, 188.5, 1471)
Adjusted fixation shift (degree) mean ± SD (min, median, max)	0.17 ± 0.29 (0, 0, 0.95)	0.34 ± 0.57 (0, 0, 2.40)	0.94 ± 1.24 (0, 0.65, 5.11)
Shift frequency (%)	24 (32)	25 (45)	36 (64)

Note: Shift frequency is any visible fixation shift.
arc sec, seconds of arc; SD, standard deviation.

scale. Of note, we manually assigned 10,000 seconds of arc to nil stereopsis.[14]

Results

OCT images from a total of 56 children in the amblyopia group and 75 children in the control group were analyzed. Descriptive statistics of participants are summarized in Table 1. Most participants were Caucasian. There was no significant difference in sex for both amblyopia and control groups. Interestingly, two-thirds of the amblyopic eyes were the left eye. Of the amblyopic groups, one-half were anisometropic alone and one-half were either strabismic or combined anisometropic and strabismic. Strabismus and combined subtypes included 24 esotropia, one exotropia with dissociated vertical deviation, one esotropia with later consecutive exotropia, one with a history of esotropia surgery, and one with a history of exotropia surgery.

Table 2 shows a summary of ophthalmic examination findings of the control eyes, amblyopic, and fellow eyes. On average, the SEQ of the amblyopic eyes was significantly more hyperopic than the fellow eyes and the control eyes (analysis of variance test, $F = 49$; $P < 0.001$). Visual acuity in the amblyopic eyes was significantly lower than the fellow eyes and the control eyes (analysis of variance test, $F = 207$; $P < 0.001$). In addition, stereopsis on the log scale of the amblyopic group was worse than the control group ($T = 11$; $P < 0.001$).

OCT Fixation Shift

Table 2 summarizes OCT fixation shift results. We have listed absolute fixation shift in micrometers directly measured from OCT, adjusted fixation shift in micrometers with SEQ, and fixation shift in degrees.

The amblyopic eyes had significantly larger fixation shift than the fellow eyes and control eyes (Fig. 2A). In line with published literature, fixation shift mean and standard deviation were calculated. In the right eyes of the control group, the mean fixation shift was 0.17° ± 0.29°. In the amblyopic group, the mean fixation shift was 0.94° ± 1.24° in amblyopic eyes and 0.34° ± 0.57° in paired fellow eyes. Because OCT fixation shift was not normally distributed and skewed to zero, we

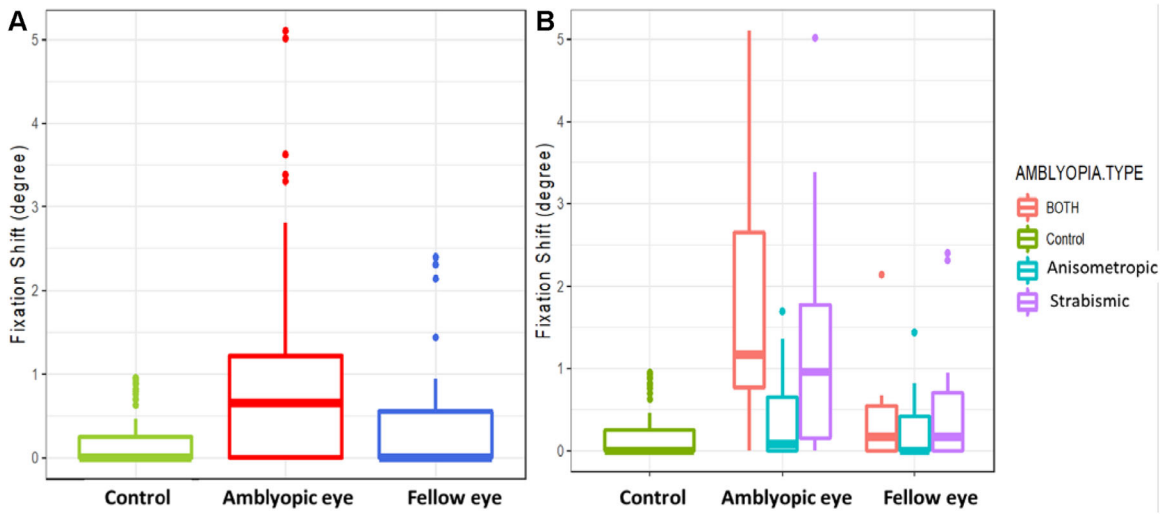

Figure 2. Fixation shift versus residual amblyopia and control group. Comparison of OCT fixation shift in degrees in three groups (the right eye of the control group, amblyopic eye, and fellow eye) **(A)**. Fixation shift versus subgroups in residual amblyopia. Comparison of OCT fixation shift in degrees in three amblyopic subgroups: anisometropic, strabismic, and BOTH (combination of both anisometropia and strabismus) **(B)**.

compared three groups with Kruskal–Wallis test, which showed a significant difference among the control eyes, the amblyopic eyes, and the fellow eyes ($\chi^2 = 23.3$; $P < 0.001$). A Mann–Whitney test showed a significant difference between the amblyopic eyes and the fellow eyes (W = 2085; $P < 0.01$), and no significant difference between the fellow eyes and the control eyes (W = 1800; $P = 0.11$); there were significant differences between the amblyopic eyes and control eyes (W = 1183; $P < 0.001$).

Both foveal fixation and OCT fixation shift were observed in amblyopic, fellow, and control eyes. In the amblyopic eyes, 36 of 56 (64%) had fixation shift, whereas 25 of 56 (45%) fellow eyes and 24 of 75 (32%) control eyes had fixation shift. A Z-score test found the fixation shift frequencies between the amblyopic eyes and the control eyes to be significantly different (Table 2; Z= –3.7; $P < 0.01$).

OCT Fixation Shift Versus Age and Sex

In the amblyopia group, the correlation between OCT fixation shift and age are not significant (R= –0.09; T = –0.66; $P = 0.5$). In the control group, comparison of fixation shift across sex was not significantly different (0.13° ± 0.27°, median = 0 for females versus 0.21° ± 0.32°, median = 0 for males; W = 1956.5; $P = 0.40$).

OCT Fixation Shift Versus Amblyopia Types

The fixation behavior in different types of amblyopia were compared in Figure 2B. The strabismic and combined types showed a larger fixation shift trend than the anisometropic type in both the amblyopic and fellow eyes. To increase sample size, we combined the strabismic and combined subtypes into one group for further analysis. In Table 3 and Figure 3, fixation shift in the anisometropic amblyopic eye ($n = 28$) is significantly smaller than that in the strabismic and/or the combined types ($n = 28$) (0.34° ± 0.46°, median = 0.08° vs. 1.54° ± 1.48°, median = 1.04°, Mann–Whitney test; W = 338; $P < 0.001$). These results indicate that strabismus plays an important role in OCT fixation shift.

OCT Fixation Shift Versus Visual Function

The OCT fixation shift in the amblyopic eye is also significantly correlated with patients' BCVA (R = 0.44; $P < 0.001$) on the day of OCT imaging. Note that an R of 0.44 has a relatively low intensity, although the P value is less than 0.001. The degree of fixation shift in the amblyopic eye is related to visual acuity in both the strabismic and combined types, but not in the anisometropic type (Fig. 3A). Replot of the data points from patients with strabismus alone and combined types showed the data fit with a linear regression line $Y = -0.78 + 4.73x$ (slope was significant, $P < 0.01$; Fig. 3B).

A similar correlation was revealed between amblyopia severity, that is, interocular difference, and the degree of OCT fixation shift (R = 0.33; $P < 0.05$; Fig. 4A). Note that an R of 0.33 has a relatively low intensity, although the P value is less than 0.05. Replot of the data points from patients with strabismus

Table 3. Summary of OCT Fixation Shift in the Amblyopic Subgroups

	Anisometropic Subgroup	Strabismic or Combined Subgroup
No. of eyes	28	28
Shift frequency, %	50	78.6
Measured fixation shift, µm, mean ± SD (min, max)	110 ± 148 (0, 25, 548)	496 ± 476 (0, 344, 1730)
Adjusted fixation shift with axial length, µm, mean ± SD (min, max)	99 ± 133 (0, 23, 488)	445 ± 426 (0, 299, 1471)
Adjusted fixation shift, degrees, mean ± SD (min, median, max)	0.34 ± 0.46 (0, 0.08, 1.69)	1.54 ± 1.48 (0, 1.04, 5.10)
Mann-Whitney test of adjusted fixation shift	W = 338; $P < 0.001$	

SD, standard deviation.

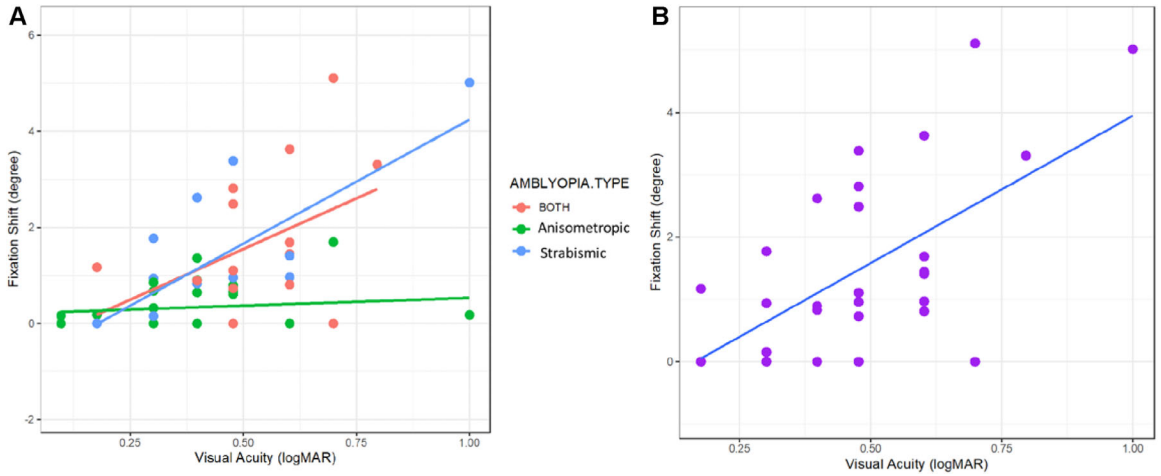

Figure 3. Fixation shift versus visual acuity. Correlation between OCT fixation shift and visual acuity in the amblyopia group **(A)**. Fixation shift versus visual acuity in the strabismic subgroup. Correlation between fixation shift and visual acuity in the strabismic and both subgroups **(B)**. BOTH, combination of both anisometropia and strabismus.

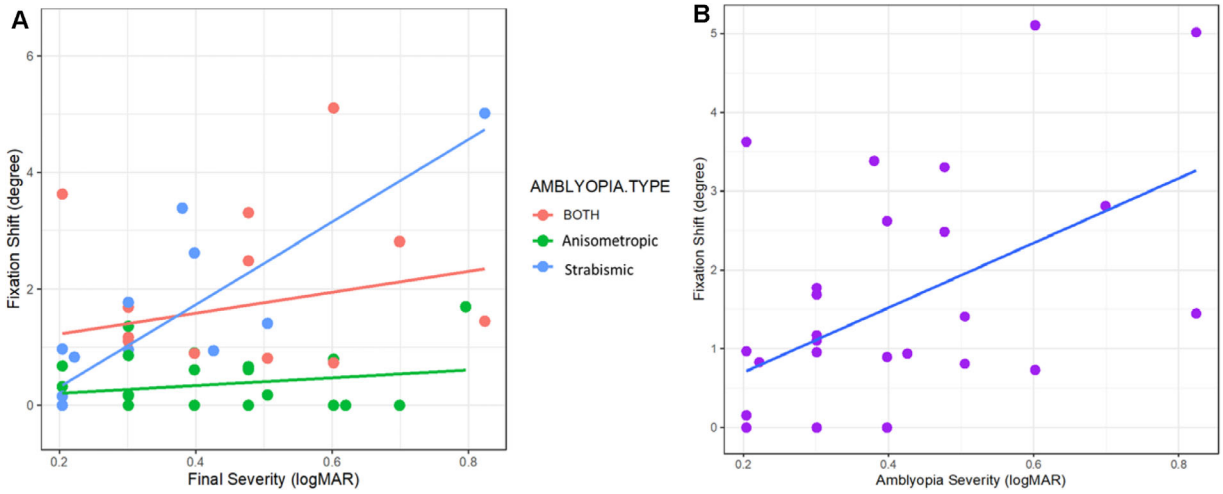

Figure 4. Distance versus final amblyopia severity. Correlation between OCT fixation shift and final amblyopia severity in the amblyopia group **(A)**. Fixation shift versus final amblyopia severity in the strabismus and both groups. Correlation between fixation shift and final amblyopia severity in the strabismic and both subgroups **(B)**. BOTH, combination of both anisometropia and strabismus.

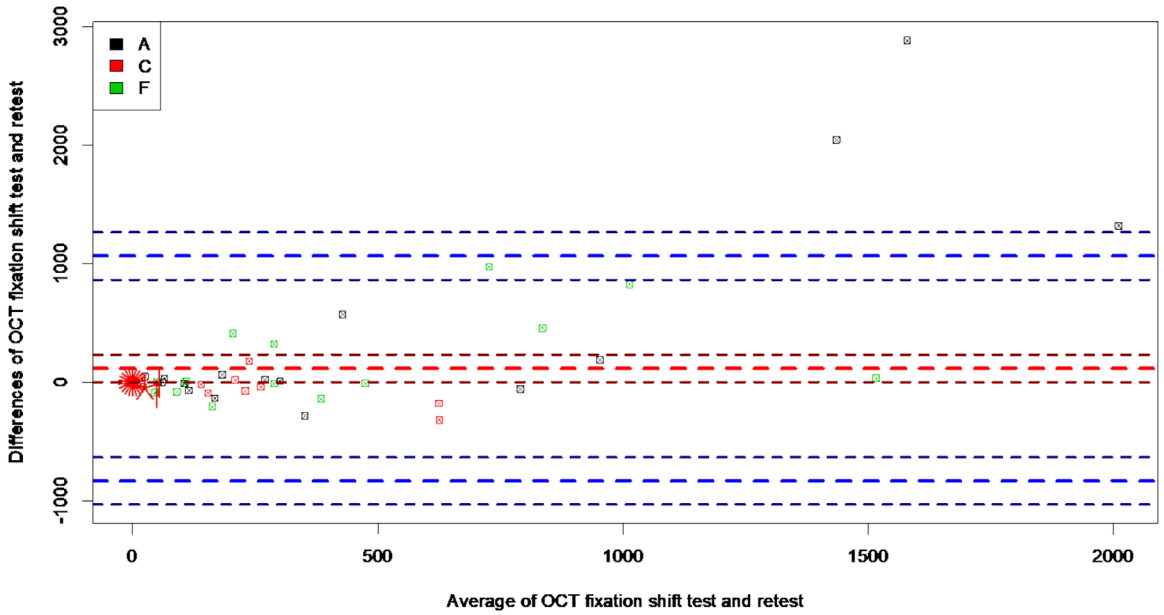

Figure 5. Repeatability of the OCT fixation shift in absolute value (micrometers) is shown in a Bland–Altman plot. The mean difference between the test and retest (second minus first, in *red*) of each individual is plotted against the mean of the two tests, and ±1.96 standard deviations were plotted in *blue*. The *black symbol* indicates "amblyopic eye" group individuals, and the green symbol indicates "fellow eye" group individuals, while the red symbol indicates "control" group individuals. The *fine dashed lines* show the 95% confidence interval for the mean and standard deviation, respectively. One symbol with "sunflower" pattern indicates repeated data from individuals, the more sunflower spikes indicate more individuals. For instance, at "zero," there were many spikes, and each spike indicates one individual.

alone and combined types produced a linear regression line $Y = -0.12 + 4.10x$ (slope was significant, $P < 0.05$; Fig. 4B).

OCT fixation shift in the amblyopic eye is not significantly correlated with stereopsis ($R = 0.25$, $P = 0.07$), although it shows a trend.

Directions of Fixation Shift

In the 28 amblyopic eyes associated with strabismus, 10 showed OCT fixation shift to nasal, 5 to supranasal, 4 to infranasal, and 6 to temporal. In the fellow eyes, nine showed fixation shift to nasal, two to infranasal, five to inferior, and five to superior. Although with much smaller magnitude, in the control eyes, 13 showed fixation shift to inferior, 6 to nasal, 7 to infranasal, and 3 to temporal. Thus, OCT fixation shift occurs in nasal, supranasal, and infranasal more often in amblyopic eyes and fellow eyes than other directions.

OCT Fixation Shift Repeatability

Some amblyopic eyes ($n = 26$), fellow eyes ($n = 26$), and control eyes ($n = 18$) had repeated OCT studies. The average duration between two tests was 2.5 years (range, 0 days to 6.03 years; only four subjects were retested on the same day). A Bland–Altman plot shows the repeatability of these tests (Fig. 5). OCT fixation shift generally within 1.96 standard deviations, which indicates a good precision when OCT fixation shift is lower than 1000 µm (3.47°). When the value is greater than 1500 µm (5.21°) in three amblyopic eyes, the repeatability was poor. This result suggests greater variability between tests when the patient has a large eccentric fixation.

Discussion

This study estimated OCT fixation shift study in a large cohort with residual amblyopia. Amblyopic eyes showed greater OCT fixation shift than normal control and fellow nonamblyopic eyes. Compared with anisometropic amblyopia, eyes with strabismic or combined amblyopia had significantly larger OCT fixation shift. In strabismic and combined-type amblyopic eyes, OCT fixation shift was significantly correlated with visual acuity and final amblyopia severity. Thus, OCT fixation shift might be used as an objective indicator of visual function for children with amblyopia, especially for those

Table 4. Comparison of Direct Measurement of OCT Fixation Shift in Micrometers with Literature

	Our Study	Nakamato et al.[9]	Garcia-Garcia et al.[10]
Number of eyes (amblyopic vs. control)	56 vs. 75	14 vs. 10	15 vs. 10
Types of amblyopia (*n*)	Anisometropic (28) Strabismic (13) Combined (15)	Anisometropic (3) Strabismic (2) Combined (9)	Microtropia with amblyopia
Age, years, mean ± SD (range)	8.7 ± 2.9 (3.9–17.3)	7.3 ± 4.2 (3–16)	8.9 ± 2.6 (5–14)
Brand of OCT	Spectralis spectral domain OCT, Heidelberg	Spectralis spectral domain OCT, Heidelberg	HD OCT, Cirrus
Measured fixation shift, μm [mean ± SD] (min, max)			
Control group	50.8 ± 88 (0, 300) in right eye	63.7 ± 36.4 in dominant eye 80.4 ± 37.7 in nondominant eye	<100
Residual amblyopia group			
Amblyopic eyes	303 ± 400 (0, 1730)	246.8 ± 199.1 (70.8, 726.9)	387 ± 199
Fellow eyes	108 ± 182 (0, 770)	83.5 ± 39.3 (0, 138)	

SD, standard deviation.

children with strabismic and combined types of amblyopia.

OCT Fixation Shift Versus Amblyopia Subtypes

We compared our results with the literature in Table 4. Our results agree with the findings of Nakamoto et al.[9] Compared with anisometropic amblyopia, we found that eyes with the strabismic or combined amblyopia have significantly larger OCT fixation shift. Our results on the strabismic or combined amblyopia were 496 ± 476 μm, which was higher than previous reports on microtropia associated with amblyopia (387 ± 199 μm).[10] This result was expected owing to the average larger angles of misalignment in our strabismic subgroup patients. We also found the fellow eyes of these patients have slightly higher OCT fixation shift than the control eyes, which confirms that fellow eyes have deficient fixation stability as well.[15,16]

Fixation shift is more frequent nasally, including supranasally and infranasally, than other directions in the amblyopic eye, correlating with most of our strabismic patients being esotropic. Garcia-Garcia et al.[10] report OCT fixation shift in 15 patients with microtropia, and found that 57% fixation shifts are superior nasal.

In addition, we found a significant correlation between visual acuity and OCT fixation shift in strabismic (without and with anisometropia) amblyopia. This finding is in agreement with Hess' conclusion that eccentric fixation correlates with optotype visual acuity and grating acuity in strabismic amblyopia.[8]

OCT Fixation Shift and Eye Movement

Interestingly, even in the control eyes, OCT fixation shifts were present. This offset in fixation for normal control adults was also reported by Nakamoto et al.[9] Our results in the control eyes were slightly lower than those reported by Nakamoto et al. (50.8 μm ± 88 μm vs. 63.7 μm ± 36.4 μm), which might be related to our refined measurements from volume scans. We agree with their three possible etiologies: (1) problems associated with the fixation target, (2) fixation instability or involuntary eye movement, and (3) anatomic factors. This offset may be the result of the fixation target being presented in a separate optical channel from the image acquisition optical channel. Although these channels are closely aligned, they are not precisely superimposed and the offset can vary slightly among individual units. Typically, it is about 0.25°,[9] which is similar to the fixation shift of the control eyes in our study (0.17° ± 0.29°). After correcting this offset, the OCT fixation shift will be close to zero in the control group.

Combining confocal scanning laser ophthalmoscope with OCT, Mallery et al.[17] were able to quantify both fixation eccentricity and instability in patients with optic neuropathy. They correlated fixation with the ganglion cell layer of the retina and found fixation eccentricity is significantly correlated with logMAR visual acuity, which agreed with our results.[17] They identified the preferred retinal locus and calculated fixation instability and fixation eccentricity to predict the presence of central scotoma. In this study, the exfoveal fixation identified using macular volume scan may emulate the preferred retinal locus. In future studies, it would be ideal to combine confocal scanning laser ophthalmoscope fixation instability measurement with OCT fixation shift.

In this retrospective study, the repeatability of OCT fixation shift measurements was assessed in a small

portion of patients. Repeatability was very good for small shifts but suboptimal for large shifts, likely owing to poor fixation stability in amblyopic eyes or changes in fixation shifts over time. Our results support the conclusion reached by Nakamoto et al.[9] that OCT fixation shift measurements are reliable.

Limitations

Our study has several limitations. First, we did not measure eccentric fixation in each patient with the traditional approach, namely, direct ophthalmoscopy. The OCT fixation shift is measured manually by moving the green line in the built-in software. The accuracy of the movement is limited by the ability of a human eye and certain increments of the movement determined by the OCT instrument. The true center may reside in between two incremental points. These errors would be small at most, and the same method was used consistently for all patients. Second, we corrected OCT fixation shift measurement with cycloplegic refractive error because of the strong relationship of SEQ and axial length as reported by previous studies.[12] However, it might be more accurate if we directly measure axial length in these subjects. Notably, all amblyopic eyes in this study were hyperopic, that is, having short axial lengths. Therefore, adjusted OCT fixation shifts were smaller than the direct measurements. With these adjustments, our data do not overestimate the difference between amblyopic eyes and control eyes. Last, residual amblyopia in this study was defined based on two visits, which might not fully meet criteria for the classic definition of residual amblyopia. A longer follow-up period, repeated amblyopia treatments, and follow-up OCT fixation shift measurement is preferable.

Clinical Implications

OCT fixation shift might be used as a new supporting measurement of amblyopia, especially in those with strabismus. OCT imaging is widely available and well-tolerated by children. Moreover, OCT fixation shift was highly correlated with visual acuity and severity of amblyopia. Traditionally, visual acuity has been the most important parameter to guide amblyopia treatment. Additionally, stereopsis and suppression[18–20] have been suggested as important factors for consideration. Although eccentric fixation has also been suggested, it has not been clinically considered as an indicator for amblyopia treatment owing to limitations of measurement technology and testing challenges in the target population. Using OCT, this study confirmed that amblyopia associated with strabismus has more eccentric fixation than those with anisometropia solely. Therefore, treatment protocols for amblyopia associated with strabismus might be combined with monitoring OCT fixation shift. Currently, we are investigating potential changes of OCT fixation shift during amblyopia treatments.

In conclusion, an analysis of OCT fixation shift found that amblyopic eyes exhibited suboptimal fixation behavior. Amblyopic eyes frequently use areas outside of the foveal center to fixate on a visual target. This is especially apparent in eyes with the strabismic or combined amblyopia. In the amblyopic eye, OCT fixation shift correlates with visual acuity and final amblyopia severity. Ultimately, OCT fixation shift can be used both in the detection and quantification of eccentric fixation in patients with residual amblyopia, especially in those with strabismus.

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