Choroidal Changes in Anisometropic and Strabismic Children With Unilateral Amblyopia

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BACKGROUND AND OBJECTIVE: To detect changes in the choroidal layer at the macular area in amblyopic eyes.

PATIENTS AND METHODS: A cross-sectional study of 50 amblyopic patients (20 strabismic and 30 anisometropic) and 50 controls was done. Cross-sectional images using enhanced depth optical coherence tomography (OCT) were taken. Thicknesses were measured subfoveally and at 1,500 µm nasally, temporally, inferiorly, and superiorly. Submacular corresponding choroidal areas were also computed. Parameters were compared between amblyopic eyes, fellow eyes, and controls.

RESULTS: Significantly thicker choroid was detected in the subfoveal, temporal, and nasal locations (P = .007, .009, and .01, respectively) in amblyopic compared to fellow eyes; areas were also significantly greater temporally, nasally, and inferiorly. Significant differences in all choroidal measurements were found between amblyopic eyes and controls; these persisted only in the anisometropic subgroup.

CONCLUSION: Using enhanced depth OCT, the choroid of amblyopic eyes was observed to be thicker compared to normal fellow eyes and controls.

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INTRODUCTION

Advances in optical coherence tomography (OCT) have allowed more detailed assessment of the choroid and its role in retinal diseases.[1] Enhanced depth imaging using spectral-domain OCT (SD-OCT) and the longer-wavelength swept-source OCT (SS-OCT) have been particularly useful in the examination of choroidal anatomy. This increased the available knowledge about the pathophysiology of several ocular conditions, notably in adult chorioretinal pathologies.[2-6]

Recently, attention has turned to the pediatric age group. Some studies have looked at point thicknesses, whereas others have looked at choroidal volume using SD-OCT or SS-OCT. One study compared pediatric normal choroidal thicknesses with those of adults. The authors found that macular choroidal thickness was comparable to that in adults, with more difference seen on the temporal side of the fovea.[7] Another study concluded that the macular choroidal thickness and volume were significantly larger among children as compared to adults.[8] Mapelli et al. showed that choroidal thickness increased in early childhood before reaching a plateau in late childhood, and this agreed with Read et al.[9,10] Recently, studies have investigated choroidal thickness in children with amblyopia and found significantly thicker choroids in amblyopic eyes.[11-14]

The purpose of this study was to evaluate subfoveal choroidal changes in patients with amblyopia. We compared the subfoveal choroidal thicknesses and area in the amblyopic eye with the fellow eye and with eyes of normal age-matched and gender-

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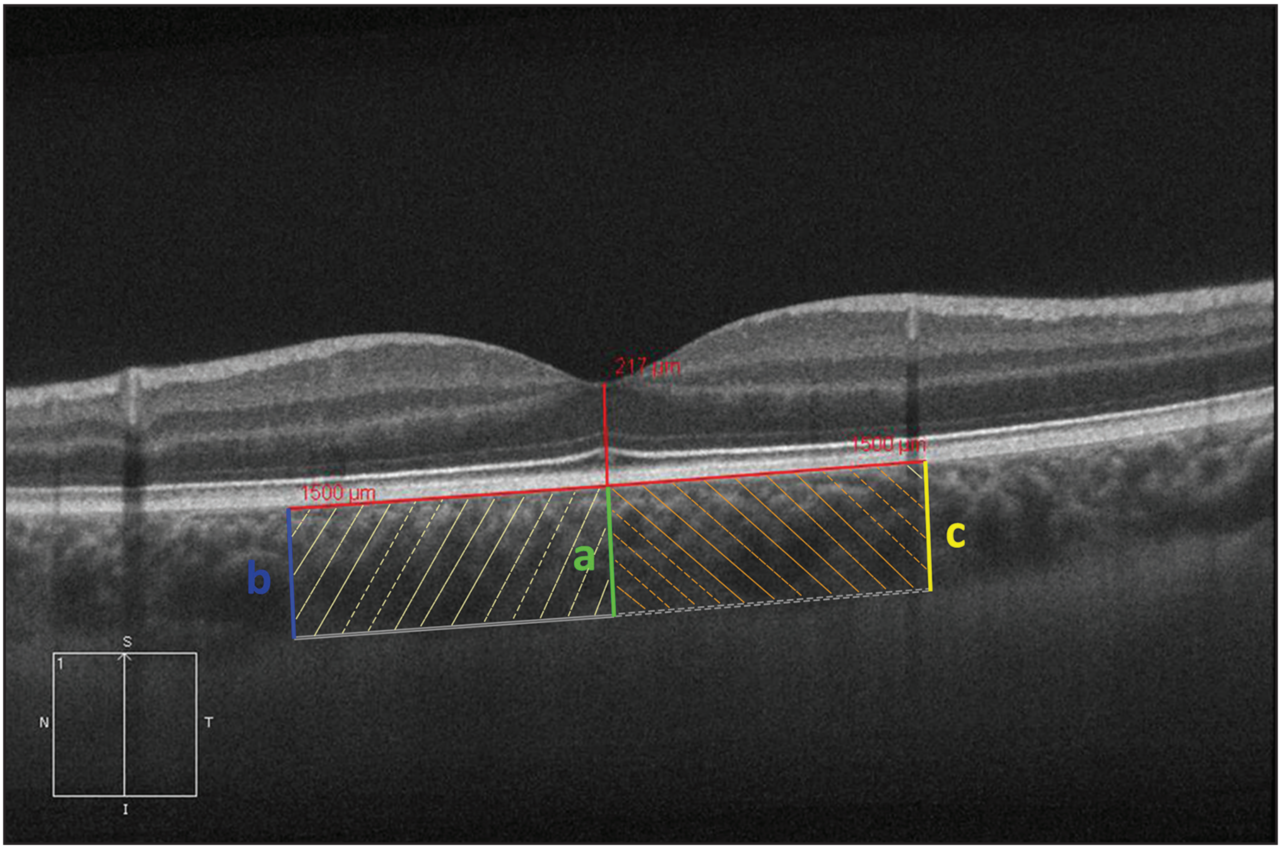

Figure. Illustrative figure showing how areas were computed. Images were magnified and areas were calculated from the center to 1,500 µm nasally and temporally as follows: nasal area (µm^2) = 1,500 * (a + b) / 2 and temporal area (µm^2) = 1,500 * (a + c) / 2, with "a" representing the subfoveal choroidal thickness, "b" representing the choroidal thickness taken at 1,500 µm nasally, and "c" representing the choroidal thickness taken at 1,500 µm temporally. Similar measurements were performed inferiorly and superiorly.

matched controls. Subjects were also subdivided into subgroups based on type of amblyopia (strabismic and anisometropic) and comparisons were performed among these groups.

PATIENTS AND METHODS

Study Population

This was a cross-sectional, observational study conducted at the American University of Beirut Ophthalmology Department from October 2012 to December 2015. The project was approved by the American University of Beirut Institutional Review Board. Written informed consents were obtained from all patients or from parents/guardians of minor subjects. Assent forms were provided to children and adolescents older than 7 years of age.

Fifty patients diagnosed with unilateral amblyopia (strabismic or anisometropic) were enrolled in the amblyopic group. Inclusion criteria included age of 6 years or older but younger than 18 years and a spherical equivalent (SE) refraction less than 7 diopters (D) of hyperopia or myopia. Patients with organic eye disease (history of intraocular surgery, laser treatment, cataract, glaucoma, or retinal disorders) and those not cooperative for OCT examination were excluded. Fifty age- and gender-matched individuals with 20/20 best-corrected vision in both eyes were recruited as a control group. Inclusion criteria for the latter group were subjects with normal ocular examinations, except for possible refractive errors, with SE ranging between –6.00 D and +6.00 D. The control subjects were selected from another study population (after matching for gender and age) and used to determine normative data for choroidal thickness in healthy eyes.

Ocular Examination

A comprehensive eye exam was performed, including best-corrected visual acuity (BCVA) with Snellen charts, slit-lamp examination, extraocular motility assessment, cycloplegic retinoscopy (30 minutes after instillation of 1% cyclopentolate and 2.5% phenylephrine), and dilated funduscopy. In

TABLE 1
Demographic Characteristics of the Study Population

Characteristics	All Amblyopic	Strabismic	Anisometropic	Controls (Right eyes)
Total	50	20	30	50
Female:Male Ratio	25:25	12:8	13:17	25:25
Mean Age (Years)	10.6 ± 3.9	9.5 ± 4.5	11.4 ± 3.4	11.5 ± 3.2
Mean Spherical Equivalence (D) ± SD				
- Amblyopic eyes	2.2 ± 3.8	2.6 ± 2.8	1.9 ± 4.3	
- Normal eyes	1.8 ± 2.5	2.5 ± 2.2	1.3 ± 2.6	0.3 ± 1.5
Mean Visual Acuity (logMar) ± SD				
- Amblyopic eyes	0.4 ± 0.2	0.4 ± 0.3	0.4 ± 0.2	
- Normal eyes	0.04 ± 0.10	0.06 ± 0.10	0.03 ± 0.09	−0.01 ± 0.01

SD = standard deviation

this study, amblyopia was defined as BCVA of 20/30 or worse and at least a two-line difference between the amblyopic and sound eye. Anisometropia was defined as a difference of 2 D or more between the two eyes.

SD-OCT Imaging

OCT images were obtained using high-definition SD-OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA). A depth enhanced, high-definition horizontal and vertical single-line scan through the fovea was obtained for each patient using an internal fixation target. If the patient had poor fixation, the image was centered on the fovea by the photographer according to the fundus image generated by the machine. All imaging was performed by an experienced ophthalmic photographer or one of the authors. The photographer was masked as to which eye was amblyopic and to whether the subject belonged to the control or amblyopic group. Signal strength of seven or more was considered acceptable. The right eye was scanned first, followed by the left eye. Multiple scans were taken and the best-centered scan was chosen for analysis. The images were converted and saved in grey scale for better visualization.

Analysis of the OCT images was then performed on 50 amblyopic patients (100 eyes) and 50 normal controls (50 eyes). Individual thicknesses were measured manually using the calipers available on the SD-OCT machine by two separate observers (to avoid interobserver bias) who were blinded as to whether an eye was amblyopic or not. Subfoveal choroidal thickness was measured from the outer aspect of the retinal pigment epithelium (RPE) to the inner aspect of the sclera. Choroidal thickness was also measured at 1,500 µm both nasally and temporally from the foveal center. For each of the studied thicknesses, an average of the two observers' measurements was computed, and that average was marked on the images using the calipers to delineate the borders of the choroidal area calculations. Snellen acuity was converted to logMAR scale to compute means. Right eyes of controls were selected for analysis.

Choroidal areas were computed in a manual fashion with Excel (Microsoft, Redmond, WA) using the area formula of a perpendicular trapezoid: nasal area (μm^2) = 1,500 * (a + b) / 2 and temporal area (μm^2) = 1,500 * (a + c) / 2, where "a" represented the subfoveal choroidal thickness, "b" represented the choroidal thickness taken at 1,500 µm nasally, and "c" represented the choroidal thickness taken at 1,500 µm temporally. Similarly, measurements were performed inferiorly and superiorly (Figure).

Statistical Analysis

Patient age, visual acuity in logMAR, SE of the refractive errors, and different choroidal measurements were summarized using means. Paired sample *t* test was used to compare subfoveal and parafoveal choroidal thicknesses and areas between amblyopic and normal fellow eyes, whereas the independent *t* test was used to do a similar analysis between amblyopic and control eyes. Subgroup analysis based on type of amblyopia (anisometropic vs. strabismic) was also performed. Pearson's correlation analysis was performed between the different thicknesses and the SE refraction. Intraclass correlation coefficient (ICC) was calculated using two-way mixed model to assess interobserver reliability of OCT measurements. All analyses were performed

TABLE 2

Choroidal Thicknesses and Areas: Amblyopic, Fellow, and Control Eyes

Variables	Amblyopic Eyes	Normal Fellow Eyes	Control Eyes	Amblyopic Versus Fellow Eyes, *P* Value	Amblyopic Versus Control Eyes, *P* Value	Normal Fellow Eyes Versus Control, *P* Value
Thicknesses, μm						
- Subfoveal	356.2 ± 53.5	338.4 ± 50.5	325.5 ± 55.9	.007	.006	.23
- Temporal	344.1 ± 63.4	322.2 ± 58.6	307.2 ± 55.6	.009	.003	.19
- Nasal	326.2 ± 65.6	305.4 ± 59.5	273.4 ± 61.6	.01	< .001	< .01
- Superior	338.2 ± 55.1	339.8 ± 56.4	305.1 ± 53.6	.84	.003	.002
- Inferior	347.9 ± 63.6	334.3 ± 52.8	319.3 ± 53.3	.09	.02	.16
Areas, μm^2						
- Temporal	52,520.6 ± 83,371.2	49,435.5 ± 75,386.0	47,455.5 ± 78,760.8	.002	.002	.20
- Nasal	51,179.6 ± 84,732.1	48,177.8 ± 77,778.0	44,920.5 ± 83,443.2	.005	< .001	< .05
Total (Temporal + Nasal)	10,370.0 ± 16,259.8	96,902.25 ± 14,162.5	92,376.0 ± 15,780.3	< .001	< .001	.13
- Superior	52,434.0 ± 76,502.2	50,754.8 ± 72,211.6	47.292.0 ± 74,759.0	.07	< .001	.02
- Inferior	53,164.5 ± 83,392.9	50,344.5 ± 70,753.6	48,358.5 ± 74,582.5	.004	.003	.17
Total (Superior + Inferior)	10,460.0 ± 15,379.3	10,109.9 ± 13,933.5	95,650.5 ± 14,675.1	.05	.004	.06

using IBM-SPSS program, version 22 (SPSS, Chicago, IL). Significance was set at a *P* value of 0.05.

RESULTS

Demographic Data

A total of 50 amblyopic children (20 strabismic and 30 anisometropic) were enrolled in this study in comparison with 50 control children. Mean ages of amblyopic and control children were 10.6 years ± 3.9 years and 11.5 years ± 3.2 years, respectively. Amblyopes and controls were matched for gender, and there was no difference between both groups with regard to age (*P* = .22). Mean age, gender, SE, and visual acuity (VA) of amblyopic and control children are listed in Table 1. There was no significant difference between the anisometropic and strabismic subgroups with regard to mean age (*P* = .06). The difference in mean VA and mean SE was significant between amblyopic and normal fellow eyes (*P* < .001 and *P* = .007, respectively), as well as between amblyopic and control eyes (*P* = .001 for both). VA and SE were also significantly different when comparing normal fellow eyes and controls (*P* = .002 and *P* = .001, respectively). Further analysis between strabismic and anisometropic subgroups showed no significant differences with regard to gender (*P* = .39), age (*P* = .06), VA (*P* = .81), or SE (*P* = .71). Excellent agreement was found between the two observer measurements at all time points, with ICC calculating greater than 0.931. Table 2 summarizes choroidal thicknesses changes among amblyopic, control, and fellow eyes.

Choroidal Changes Between Amblyopic and Fellow Eyes

Differences in average choroidal thicknesses between the amblyopic eyes and the normal fellow eyes were detected at the subfoveal, temporal, and nasal locations, with *P* values of .007, .009, and .014, respectively. Mean areas were also significantly larger temporally, nasally, and inferiorly in amblyopic compared to fellow eyes (*P* = .002, *P* = .005, and *P* = .004, respectively).

TABLE 3

Choroidal Thickness and Areas: Anisometropic Amblyopic Eyes Compared to Fellow Eyes and Controls

Variables	Anisometropic Eyes, µm	Normal Fellow Eyes, µm	Anisoemtropic Versus Normal, *P* Value	Controls	Anisometropic Versus Controls, *P* Value
Thicknesses					
- Subfoveal	367.8 ± 56.8	338.6 ± 51.6	.003	325.5 ± 55.9	.002
- 1,500 µm temporal	356.8 ± 64.2	328.9 ± 56.3	.016	307.2 ± 55.6	.001
- 1,500 µm nasal	332.3 ± 76.2	299.8 ± 59.9	.008	273.4 ± 61.6	.001
- 1,500 µm superior	342.6 ± 55.6	348.3 ± 55.2	.607	305.1 ± 53.6	.004
- 1,500 µm inferior	352.0 ± 68.0	331.8 ± 52.6	.066	319.3 ± 53.3	.029
Areas					
- 1,500 µm temporal	543,481.2 ± 85,914.1	499,318.7 ± 74,612.9	.003	47,455.5 ± 78,760.8	.001
- 1,500 µm nasal	525,131.2 ± 94,891.0	477,443.7 ± 79,166.6	.002	44,920.5 ± 83,443.2	.001
Total (temporal + nasal)	1,068,612.5 ± 174,084.6	973,425.0 ± 147,138.9	.001	92,376.0 ± 15,780.3	< .001
- 1,500 µm superior	537,825.0 ± 80,192.3	513,818.7 ± 71,634.1	.082	47,292.0 ± 74,759.0	.001
- 1,500 µm inferior	544,862.5 ± 88,967.9	501,431.2 ± 70,139.3	.002	48,358.5 ± 74,582.5	.003
Total (superior + inferior)	1,072,350.0 ± 167,401.1	1,015,250.0 ± 139,139.6	.018*	95,650.5 ± 14,675.1	.003*

Choroidal Changes Between Amblyopic and Control Eyes

Choroids were significantly thicker at all positions in amblyopic eyes, subfoveally, temporally, nasally, superiorly, and inferiorly compared to controls (*P* = .006, .003, < .001, .003, and .016, respectively). Moreover, all areas were significantly larger in amblyopic eyes with *P* value of less than .01.

Choroidal Changes Between Normal Fellow and Control Eyes

Significant differences in choroidal thicknesses were found between normal fellow eyes and controls, which was mostly noted in the nasal and superior locations (*P* < .01 and .002, respectively). In parallel, areas in the nasal and superior sections were also greater in normal fellow eyes (*P* = .046 and *P* = .02, respectively).

Choroidal Changes Among Anisometropic and Strabismic Subgroups Compared to Normal Fellow and Control Eyes

Point thicknesses and corresponding areas were similar, with no statistically significant differences noted when comparing amblyopic eyes in anisometropic and strabismic subgroups (Table 3). However, in the anisometropic subgroup, amblyopic eyes compared to the normal fellow eye had significantly thicker choroid at the subfoveal, temporal and nasal points (*P* = .003, .016 and .008, respectively). Furthermore, significantly larger areas were detected at the temporal, nasal and inferior locations (*P* = .003, *P* = .002 and *P* = .002; respectively). On the other hand, neither thicknesses nor areas were significantly different between amblyopic and fellow eyes in the strabismic subgroup.

Significant differences were found at all point thicknesses and areas comparing anisometropic subjects to controls (Table 3). However, this significance was only detected nasally in the strabismic group compared to controls (*P* = .002 [thickness] and *P* = .026 [area]).

Further analysis revealed no significant correlation between SE and all studied parameters, including thicknesses, areas, and BCVA (LogMar scale). Moreover, neither choroidal thickness nor areas were significantly affected by age or gender (*P* > .05).

TABLE 4

Literature on Choroidal Changes in Amblyopia

	Xu et al., 2014	Nishi et al., 2013	Aygit et al., 2015	Kara et al., 2015	Al-Haddad et al., 2016
Total Sample Size	59	45	120	57	100
Amblyopic (SE)	37 (+3.82 ± 2.17)	25 (+3.97 ± 1.86)	80	38	50 (+2.2 ± 3.8)
- Strabismic (SE)	16 (+3.21 ± 2.47)	0	40 (+2.61 ± 3.50)	17 (+2.47 ± 1.06)	20 (+2.6 ± 2.8)
- Anisometropic (SE)	21 (+4.29 ± 1.84)	25 (+3.97 ± 1.86)	40 (+2.63 ± 3.54)	21 (+3.97 ± 0.55)	30 (+1.9 ± 4.3)
Controls (SE)	22 (–0.02 ± 0.28)	20 (+2.75 ± 2.38)	40 (+1.58 ± 1.98)	19 (+2.83 ± 0.55)	50 (+0.3 ± 1.5)
Vision LogMar: Mean (±SD)	0.49 ± 0.22	0.29 ± 0.16			0.4 ± 0.2
Amblyopic	0.51 ± 0.25	n/a	0.69 ± 0.46	0.40 ± 0.17	0.4 ± 0.3
- Strabismic	0.47 ± 0.20	0.29 ± 0.16	0.57 ± 0.43	0.48 ± 0.18	0.4 ± 0.2
- Anisometropic Controls	–0.02 ± 0.39	–0.09 ± 0.06	0	1.00 ± 0.00	–0.01 ± 0.01
Age Groups (Years)	5-12	3-11	4-15	6-17	6-17
F:M Ratio	0.5	n/a	0.8	1.5	1
Mean Age Years of All Amblyopic (±SD)	8.5 ± 2.0	6.6 ± 2.2	n/a	11.31 ± 3.01	10.6 ± 3.9
Thickness Studied	SubF, T, N, S, I (1 mm, 2 mm)	SubF, S, I, T, N (1 mm, 3 mm).	SubF, N, T (500 µm; 1,000 µm; 1,500 µm; and 2,000 µm)	SubF, T, N (750 µm)	SubF, T, N, S, I (1,500 µm); Cross-sectional areas at T, N, S, I (1,500 µm)
Significant Findings					
Amblyopic Versus Control	SubF and S, I, N, T (1 mm), and S, N (2 mm)	SubF and N (1 mm).	Not performed	SubF, T, N (750 µm)	SubF and T, N, S, I (1,500 µm)
Amblyopic Versus Fellow	SubF, S (1 mm), I and N (1 mm, 2 mm)	SubF, N, T (1 mm).	Not performed	N (750 µm)	SubF and T, N (1,500 µm)
Strabismus Versus Fellow	SubF and S (1 mm)	n/a	SubF, N (500 µm) and N (1,000 µm)[a]	SubF and T, N (750 µm)[a]	None
Anisometropic Versus Fellow	SubF, S, I, and N (1 mm); I and N (2 mm)	SubF, N and T (1 mm)	SubF only[a]	SubF, T, N (750 µm)[a]	SubF, T, N (1,500 µm)
Fellow Eyes Versus Control	SubF, S, I, N, T (1 mm); S (2 mm)	None	Not performed	None	N and S (1,500 µm)

[a] *Analysis of variance between amblyopic, fellow, and control eyes..*

F = female; M = male; SubF = subfoveal; T = temporal; N = nasal; S = superior; I = inferior; SE = standard equivalent; SD = standard deviation

n/a = not applicable

DISCUSSION

Recent literature using high-definition OCT imaging has provided a closer look at the changes noted in retinal layers in amblyopia.[15-23] Using enhanced depth SD-OCT imaging, our study demonstrated significant choroidal thickness and area differences in amblyopic eyes compared to normal fellow eyes and age-matched controls. Interestingly, further analysis on subgroups found that these differences were observed in all of the choroidal locations in the anisometropic subgroup, whereas in the strabismic subgroup differences were detected only at the nasal area and section.

Many studies used optical coherence tomography to identify retinal changes associated with amblyopia.[15-20] These results were inconsistent.[21] Using SD-OCT, our group identified a significantly increased central macular thickness in amblyopic eyes compared to the fellow eyes, particularly in the anisometropic amblyopes with no significant interocular differences in peripapillary retinal nerve fiber layer.[22] Qualitative and quantitative differences in macular features were demonstrated, possibly representing signs of immaturity compared to the normal fellow eyes.[23] In this study, we wanted to investigate possible subfoveal choroidal changes in amblyopia.

With the introduction of new high-definition OCT software, the enhanced depth imaging feature provided a clearer view of the choroid. Although no automated measurements of choroidal thickness were provided by the software, the images allowed reproducible measurements of choroidal thickness. A number of authors have examined choroidal thickness in healthy pediatric patients; some concluded that choroidal thickness increased with age.[9] Others did not find any significant differences in choroidal thickness between adults and children.[7]

Few recent reports investigated choroidal changes in amblyopic patients summarized in Table 4.[11-14] Investigators performed measurements at different distances from the central fovea and interestingly most of them agreed, including our study, that amblyopic eyes especially of anisometropic origin had thicker subfoveal choroid compared to their fellow eyes.[11,12,14] Choroidal thicknesses in different locations from the fovea were however discrepant among studies. Only one study reported significant differences between normal fellow eyes and controls as observed in our work.[12] Others did not perform this comparison or they did not find any significant differences.[11,13,14] We elected to study areas to obtain a larger sample of the subfoveal choroid and maximize the probability of detecting differences. Whereas point thicknesses, as previously adopted, were measured manually, areas could be measured in a method that provides more objectivity. The significantly larger areas at the temporal, nasal, and inferior sections detected in our analysis were congruent with the increased choroidal thickness in amblyopic versus normal fellow eyes, as well as controls.

Our results were significant in the anisometropic but not the strabismic subgroup which seems to be in line with the fact that anisometropia and strabismus lead to amblyopia through different pathways. SE was not significantly different between strabismic and anisometropic amblyopic eyes in our cohort; this points to amblyopia, per se, being the underlying cause of the thicker choroid and not the refractive error. Animal studies have shown that changes in the refractive state lead to changes in choroidal thickness;[24] the increased thickness observed here, and that observed by Nishi et al.[11] could be related to the aberrant or halted emmetropization of the amblyopic eye. We may hypothesize that the expected choroidal compensation that normally follows refractive changes[26,27] does not occur in anisometropic amblyopes, which explains the thicker choroid observed in these eyes. This may not apply to strabismic amblyopia where suppression and consequent amblyopia follow a different pathophysiology. Another plausible explanation is that a thicker macula requires a larger vascular supply and, hence, a thicker choroid.[27] Interestingly, the choroid of normal fellow eyes was thicker than the controls. Therefore, the unilateral amblyopic process may affect the choroid in both eyes. This questions the cause-effect relationship between the pathophysiology of amblyopia and choroidal volume. Further studies are needed on amblyopic children under treatment for better understanding of choroidal changes especially in anisometropic eyes.

This study has two main limitations: a small sample size, although this was relatively larger than previous studies, and the manual delineation of the choroidal borders. Since there is no commercially available automated method to date, measurements were performed manually, which may lead to interobserver variability in recognizing choroidal borders. However, interobserver agreement in this study was high. On the other hand, studying choroidal areas that provide a larger choroidal sample was not previously investigated by others.

In conclusion, our study showed that in anisometropic amblyopia, the choroid was thicker than fellow eyes and normal controls. The mechanism for this phenomenon is still unclear and requires further investigation in larger studies.

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