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Original Article

Evaluation of Choroidal Vascular Structure in Hyperopic Anisometropic Amblyopia

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Abstract

Objectives: The aim of the study was to investigate the choroidal structure of patients with anisohypermetropic amblyopia compared to that of healthy eyes in controls of the same age.

Methods: The study comprises three groups: One group was the amblyopic eyes of patients with anisometropic hypermetropia (AE group), another group was the fellow eyes of patients with anisometropic hypermetropia (FE group), and a final group of healthy controls. Both the choroidal thickness (CT) and choroidal vascularity index (CVI) values were obtained using the spectral-domain optical coherence tomography (OCT) method of improved depth imaging (EDI-OCT; Heidelberg Engineering GmbH, Spectralis, Germany, Heidelberg).

Results: This study included 28 anisometropic amblyopic patients (AE and FE groups) and 35 healthy controls. Regarding the distribution of ages and sexes (p=0.813 and p=0.745), the groups were the same. The mean best-corrected visual acuity in AE, FE, and the control group was 0.58±0.76, 0.008±1.30, and 0.004±1.20 logMAR units, respectively. There was a significant difference in terms of CVI, luminal area (LA), and all the CT values between groups. Post hoc univariate analyses indicated that CVI and LA were significantly higher in AE compared to FE and the control group (p<0.05, for each). The temporal, nasal, and subfoveal CT values were considerably higher in AE compared to FE and the control groups (p<0.05, for each). However, there was no difference between FE and the control group (p>0.05, for each).

Conclusion: The AE group had larger LA, CVI, and CT values compared to the FE and control groups. These results show that choroidal changes in amblyopic eyes in children are permanent in adulthood if untreated and are involved in the pathogenesis of amblyopia.

Keywords: Amblyopia, Choroidal vascularity index, EDI OCT, Hyperopia

Introduction

Amblyopia is a condition that occurs when the processing of visual information is hindered, leading to either nonuse due to a lack of clarity in the retina or aberrant binocular interactions (1). Anisohypermetropic amblyopia is experienced along with a decrease in visual acuity in one eye due to having more hyperopic refraction than in the other eye (2). Anisohypermetropic amblyopia can be treated by appropriate re-

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fraction and patching until the ages of 11–12 (2). After these ages, due to the completion of cortical maturation, desired vision levels cannot be reached.

Conventionally, there have been no morphological abnormalities in the structure of amblyopic eyes (3-5). However, thanks to the technological developments in optical coherence tomography (OCT), contrary to what was thought, it has been observed that there may be some ocular changes. Recent studies reported choroidal and retinal changes that occurred in amblyopic eyes (6-9).

The choroid is a crucial structure for improving the eye's refractive error and function, and in addition to the refractive error, it can also influence the eye's development (10,11). Many studies have shown subfoveal choroidal thickness (CT) to increase in amblyopic anisohypermetropic eyes compared to their age-matched control eyes and fellow eyes. A novel approach has recently been developed that focuses on choroidal vasculature employing binarization studies for evaluating choroidal structures apart from the thickness (12,13). Nishi et al. (6) reported a difference in the choroidal structure of amblyopic eyes in comparison to hyperopic controls and fellow eyes in children. Moreover, they observed improvement of the choroidal structure following appropriate treatment of amblyopia (2). However, the choroidal structure of amblyopic eyes following a period of patching treatment has not been demonstrated.

In this regard, we sought to quantify the choroidal architecture of individuals with anisohypermetropic amblyopia to those of age-matched controls.

Methods

This cross-sectional, retrospective, and experimental investigation was conducted at the tertiary clinic's ophthalmology department. The local ethics commission gave its approval to the study protocol, which followed the guidelines of the Helsinki Declaration. After notifying all of the cases and their parents about the study's goal, informed consent was attained in writing from the participants or their legal guardians.

The study was composed of three groups: One group was the amblyopic eyes of patients with anisometropic hypermetropia, another group was the fellow eyes of patients with anisometropic hypermetropia, and a final group of healthy controls. When the best-corrected visual acuity of the amblyopic eye was poorer than 20/30 and was at least two Snellen lines inferior to that of the other eye, the participant was identified as amblyopic (14). Anisohypermetropia is a condition in which one eye's refractive error (spherical equivalent) is ≥1.5 diopters higher than the other (14).

Participants who visited the ophthalmology clinic for a routine checkup and had best-corrected vision of 20/20 and no other ocular or systemic diseases except modest refractive errors (between−1.00 and +1.00 diopters) were selected for the control sample. For data analysis, just the observations regarding the control group's right eye were utilized. Cases with any of the following conditions were excluded: Age lower than 11, strabismus, eccentric fixation, previous ocular surgery, not suitably cooperative enough for OCT tests, ocular diseases (retinal diseases, glaucoma, cataract, etc.), and any systemic conditions.

Complete ophthalmological tests were performed on all cases, such as best-corrected visual acuity screening using a basic Snellen chart, which was later adapted to the logarithm of the minimal angle of resolution (logMAR) for the statistical studies, and cycloplegic refraction using a keratometer/autorefractor (KR-8100, RM8900, Topcon, Tokyo, Japan), EDI-OCT examination, extraocular movements, cover-uncover and cover test, fundus examination, and slit-lamp biomicroscopy. All ocular tests were performed between the hours of 10 a.m. and 12 a.m. to avoid affecting the diurnal deviations in CT.

Spectral-domain OCT's (EDI-OCT; Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany) increased depth imaging mode was used to measure the choroidal vascularity index (CVI). The images were viewed and measured using the Heidelberg Eye Explorer software (Version1.8.61.0; Heidelberg Engineering). Only scans with a high quality (> 25Q) were considered. Manual CT values were taken in three areas: 500 μm temporal, 500 μm nasal, and subfoveal CT. The CT was determined as the vertical distance between the inner surface of the choroidal-scleral junction and the outside edge of the hyperreflective retinal pigment epithelium. Finally, the OCT scans produced were analyzed using an image processing tool in order to determine CVI.

Image processing was conducted using free and open-source software (http://fiji.sc/). The OCT scans were viewed using the ImageJ version 1.53 platform as part of a system previously reported by Agrawal et al., (15) which was used to evaluate the images (National Institutes of Health, Bethesda, MD, USA). First, the software's default scale was used to indicate the length unit (as μm) and pixel distance (as 200 μm). To identify the choroid-scleral junction, the pictures were transformed to 8-bit format and binarized utilizing Niblack autolocal criterion. The polygon tool was then used to calculate the total choroidal area between the choroid-scleral junction and the retinal pigment epithelium. This section was saved for the manager of the region of interest (ROI). The photos were then transformed to the Red-Green-Blue color model, and then the ROI manager picked the dark pixels that represented the luminal region using the color threshold tool. Finally, both areas within the ROI manager's region were chosen and combined using the "AND" command to

determine the region of vascularity inside the selected polygon. The CVI was calculated as the proportion of luminal area (LA) to total choroidal area. By deducting the LA from the overall choroidal area, the pixels of light color indicated the stromal region (Fig. 1). Two researchers (HK and DK), who were given the participants' blind data, measured the CT and CVI values one at a time. In the statistical analysis, the means of the two researchers' measurements were used.

Statistical Analysis

SPSS ver.22.0 (SPSS Inc., Chi., IL) was used to conduct the statistical analysis. The data are presented as the means±standard deviations. One-way Analysis of variance (ANOVA) was used to compare the data of the control, fellow, and amblyopic eye groups. If ANOVA revealed a significant difference, a pair-wise comparison using the Bonferroni test was performed. P values smaller than 0.05 were deemed significant.

Results

This research included 28 anisometropic amblyopic individuals (an amblyopic eye group and a fellow eye group) and 35 healthy individuals for control. Table 1 demonstrates the demographic and clinical features of the samples. The groups were similar with regard to the distribution of gender and ages (p=0.813 and p=0.745). The mean best-corrected visual acuity in amblyopic eyes, fellow eyes, and the control group was 0.58±0.76, 0.008±1.30, and 0.004±1.20 logMAR units, respectively. The mean best-corrected visual acuity of amblyopic eyes was substantially lower than that of the control and fellow eyes (p<0.001). Compared to the fellow eye group and the control group, the mean refractive error was substantially higher (p<0.001). The amblyopic eye group's mean axial length was considerably shorter than those of the fellow eye and control groups (p<0.001).

Choroidal structural and CT values of the samples are

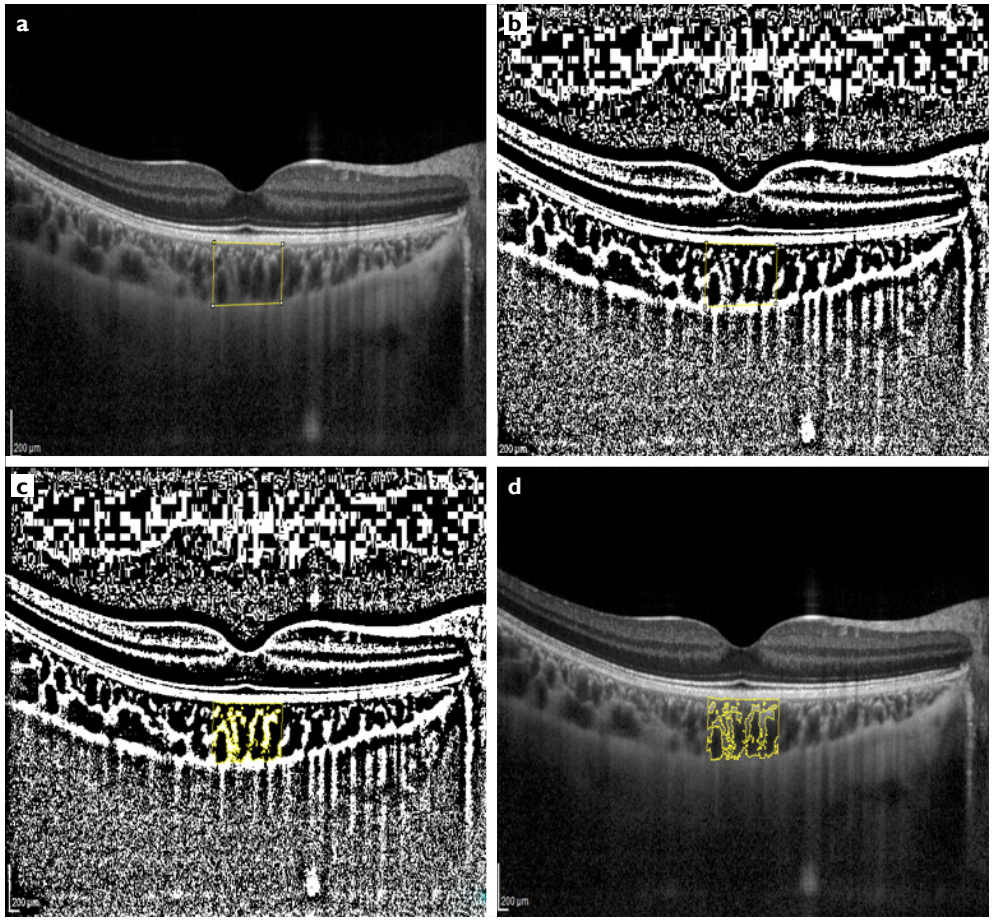

Figure 1. Choroidal vascularity index (CVI) with binarization of EDI-OCT image. **(a)** 1.5 mm segmentation part of the subfoveal choroidal area and yellow lines identify the total choroidal vascular area. **(b)** The segmented OCT image was binarized using Niblack's auto-local threshold, **(c)** The color threshold was used to demontrate the luminal area. **(d)** Overlay of the region created with binarization was performed on EDI-OCT image. The CVI was calculated by dividing luminal area by total choroidal area.

Table 1. Demographic information of the amblyopic patients and controls

	Amblyopic eyes (n: 28)	Fellow eyes (n: 28)	Control eyes (n: 35)	p*
Age (year)	25.50±14.89	25.50±14.89	27.65±12.45	0.813
Male/Female	12/16	12/16	17/18	0.745
Visual acuity (logMAR)	0.58±0.76	0.008±1.30	0.004±1.20	<0.001
Spherical equivalent (D)	4.85±1.40	1.25±1.60±	0.80±0.65	<0.001
Axial length (mm)	20.8±1.2	21.9±0.7	22.1±0.9	<0.001

D: Diopters, *ANOVA, Data are expressed as means±standard deviations.

shown in Table 2. With respect to all the CT, LA, and CVI, there was a substantial difference among samples. Post hoc univariate analyses indicated that CVI and LA were substantially bigger in amblyopic eyes with respect to fellow eyes and the control sample ($p<0.05$, for each). The subfoveal, nasal, and temporal CT values were substantially higher in amblyopic eyes when compared with the fellow eye and control groups ($p<0.05$, for each). However, between fellow eyes and the control samples, no change was observed ($p>0.05$, for each).

Discussion

Numerous eye illnesses have been linked to the pathophysiology of the choroid. The index of choroidal vascularity is a new and rigorous indicator for studying the pathophysiology of choroidal diseases as it is less variable than CT and is unrelated to most physiological parameters (16). From this context, we compared the choroidal architecture of patients with anisohypermetropic amblyopia with those of age-matched controls. Our analyses showed that LA, CVI, and CT change substantially within the samples of normal control, fellow, and amblyopic eyes.

Many studies have investigated choroidal structure in anisohypermetropic amblyopia. Araki et al., (4) showed no changes in choroidal vascular density within the eye samples of normal control, fellow, and amblyopic eyes. However, Terada et al. (17) reported that both amblyopic and fellow eyes have a greater outer choroidal vascular area with respect to healthy ones. The research of Nishi et al. (1) demonstrated a significantly larger total choroidal region and luminal region in amblyopic eyes when compared to both control eyes and fellow eyes. The stromal region that they detected was slightly smaller in amblyopic eyes, but this result was not calculated to be significant. Moreover, they assessed the effect of wearing optical correction on these choroidal values and they observed that the choroidal values in the amblyopic eyes approached the fellow eyes with optical correction (2). They reported that as the LA narrowed, there was an enlargement in the stromal area, which was proportional to the best-corrected visual acuity (2).

In our study, we investigated anisohypermetropic patients older than the age where one would benefit from optical correction treatment. We found enlargement in LA and CVI. The stromal area was slightly narrower in amblyopic eyes when compared to fellow and control eyes. These results show that the choroidal values shown by Nishi et al., (1,2) in children with anisohypermetropic amblyopia do not improve and remain at the same level when they do not receive appropriate treatment.

Table 2. Comparison of the choroidal thicknesses in three locations and choroidal vascularity index between the groups

Parameters, mean±SD	Amblyopic eyes (n: 28)	Fellow eyes (n: 28)	Control eyes (n: 35)	p*
Subfoveal central CT	345.51±70.28	299.13±35.11	305.50±37.43	0.004, 0.008[a], 0.027[b], 0.960[c]
Temporal 500 µm CT	329.86±1.53	272.36±37.29	272.22±32.86	<0.001, 0.003[a], 0.002[b], 0.870[c]
Nasal 500 µm CT	310.44±68.61	268.81±39.45	270.00±35.58	0.007, 0.019[a], 0.023[b], 0.890[c]
LA	0.54±0.09	0.48±0.07	0.46±0.06	0.001, 0.024[a], 0.002[b], 0.899[c]
SA	0.21±0.04	0.23±0.05	0.25±0.08	0.092
TCA	0.76±0.10	0.71±0.08	0.72±0.10	0.146
CVI	0.71±0.05	0.65±0.06	0.64±0.09	0.007, 0.042[a], 0.006[b], 0.607[c]

TCA: Total choroidal area; LA: Luminal area; SA: Stromal area; CVI: Choroidal vascularity index; CT: Choroidal thickness; ST: Standard deviations; *One-way ANOVA; Bonferroni correction: [a]Group 1 vs group 2, [b]Group 1 vs group 3, [c]Group 2 vs group 3.

The stromal area has nonvascular smooth muscle that modulates CT to maintain a stable foveal position throughout the accommodation (18-21). CT decreases as a result of the action of non-vascular smooth muscles in eyes that have an appropriate accommodation response. As commonly understood, accommodation responses do not work normally in amblyopic eyes (20). This causes the nonvascular smooth muscle to malfunction, resulting in an increase in CT and a narrowing in the stromal area. This will cause an indirect enlargement in LA. Therefore, the larger LA and CVI in amblyopic eyes may be an indirect sign of immaturity in these eyes. As the appropriate treatment was applied, the stromal area enlarged and the LA narrowed (2). Taking all these together, our study confirmed the results of Nishi et al., (1,2) We think that choroidal changes in amblyopic eyes are permanent for life in cases where the accommodation response cannot be adequately increased with appropriate treatment. In elderly patients who receive amblyopia treatment and whose cortical maturation has begun to be completed, it may be predicted whether amblyopia treatment can be of further benefit by monitoring the CVI and LA changes.

In adults with anisohypermetropic amblyopia, there was no notable change in subfoveal CT between amblyopic eyes, fellow eyes, and control groups (5,22). Conversely, Nishi et al. (6) reported larger CT in amblyopic eyes. Similarly, we also found larger subfoveal, temporal, and nasal CT in the amblyopic eye group compared to the fellow eye and control groups. Thicker choroid in amblyopic eyes can be attributed to the lack of function in nonvascular smooth muscle cells that do not receive the appropriate accommodation response. Thicker choroid can potentially delay eye development by acting as a barrier to growth factor diffusion or even as a mechanical buffer to restrict the eye's elongation (10). Therefore, amblyopia may cause a thicker choroid, and a thicker choroid may result in more hyperopia and induced amblyopia.

The strength of our study is that we examine choroidal changes in patients with anisometropic amblyopia who lost the chance to improve with treatment. Other studies in the literature were performed on patients whose choroidal structure was still open to change with amblyopia treatment. Our study has limitations. A modest number of anisohypermetropic amblyopic eyes in Turkish children were studied. More research with a greater number and different ethnicity of subjects will be required.

Conclusion

Amblyopic eyes have larger LA, CVI, and CT values compared to the fellow eye and control groups. These results show that children's choroidal changes in amblyopic eyes are permanent in adulthood if untreated. These choroidal parameters, which can be improved with appropriate treatment, are involved in the pathogenesis of amblyopia.

Disclosures

Ethics Committee Approval: The study was approved by the Adiyaman University Ethics Committee (date: 14.12.2021, no: 2021/10-15).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Conception – B.O., H.K.; Design – B.O.; Supervision – A.B.; Materials – F.O.; Data Collection and/or Processing – F.O., D.O.K.; Analysis and/or Interpretation – D.O.K.; Literature Search – H.K.; Writing – B.O., H.K.; Critical Reviews – A.B., E.Y.

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