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Optic nerve head microvascular differences in ambliopic eyes- an observational case-control study

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Abstract

We aimed to assign optic nerve head microvascular variations in amblyopic eyes and compare them with healthy eyes. We designed this study as an observational case-control study. Seventeen strabismic, 20 anisometropic, 18 meridional, and 18 ametropic amblyopic eyes were enrolled as a study group. Seventy-two healthy eyes were selected as a control group. After full ophthalmic examination, optic nerve head-centered, 4.5 × 4.5 mm scan size images were taken from all groups. Retinal nerve fiber layer thickness, vessel density, and ganglion cell complex parameters were analyzed. For gender, age, and adjusted intraocular pressure, the groups were similar ($x^2(2, N=145)= 5.4$, p=0.34; p=0.49; p=0.61; respectively). In amblyopic eyes, the mean peripapillary, superior, inferior, nasal, and temporal vessel density was significantly higher (p=0.023; p=0.041; p=0.015; p=0.039; p=0.019; respectively), while the mean inside disk vessel density was lower compared to the control (p=0.038). Additionally, the mean total vessel density was similar in both groups (p=0.29). For retinal nerve fiber layer thickness and ganglion cell complex, no significant different data were obtained between the two groups and among amblyopic subgroups (p>0.05 for all). Optic nerve head vascularization may be altered in amblyopic eyes. Optical coherence tomography angiography can help us to understand the optic nerve head blood supply differentiations in amblyopic eyes. Prospective studies are required to assign the further outcomes of crowded optic nerve head in amblyopic eyes.

Keywords: Optical coherence tomography angiography, optic nerve head, amblyopia, peripapillary vessel density.

Introduction

Amblyopia is a visual impairment affected by several factors such as strabismus, refractive errors, and deprivation of vision in childhood [1]. It results in functional and structural changes in the brain, especially the lateral geniculate nucleus and retina [2]. In amblyopic eyes, some studies also showed differences in the optic nerve head (ONH), ganglion cell complex (GCC), retinal nerve fiber layer (RNFL) thickness, and retinal microvascularization [3-6]. However, there are few studies about the difference in amblyopic subgroups in the literature.

Optical coherence tomography angiography (OCT-A) is a nowel, non-invasive imaging technology. It provides both mechanical and functional details of the microvasculature of ONH, retina, and choroid.

This observational study aimed to determine microvascular changes in the ONH detected by OCT-A in amblyopic eyes and compare them within amblyopic subgroups and with healthy subjects.

Material and Methods

We included strabismic (manifest vertical, horizontal or both strabismus in one eye with correction of refractive error, no astigmatism more than 0.75 Diopter (D), no anisometropia or ametropia), ametropic (4.5 D or more hyperopia in both eyes, no anisohyperopia more than 1.5 D, no latent-manifest strabismus or astigmatism more than 0.75 D), anisometropic (1.5 D or more anisohyperopia in one eye, no astigmatism more than 0.75

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D, no ametropia), and meridional (1.5 D or more astigmatism in both eyes, no anisoastigmatism, anisometropia or ametropia) amblyopic eyes. In the control group, 72 health eye of 72 orthoforic patients whose spheric and cylindric power less than 0.75 D were included. The study eye was inconstantly chosen in the control group, ametropic, and meridional subgroups. After a full ophthalmological checkup (including visual acuity, anterior-posterior segment examination, adjusted intraocular pressure (IOP), ocular motility, and cycloplegic refraction), ONH was imaged automatically by a single person using an RTVue-XR Avanti (Optovue, Inc., Fremont, CA, USA) on a 4.5 × 4.5-mm scan size that was positioned on the papilla (Figure 1). Images with motion-originated artifacts (signal strength index less than 60) and patients with retinal vascular diseases; any kind of nystagmus; and previous ocular surgery, deprivation amblyopia, glaucoma, and neurological diseases were excluded. RNFL thickness (Figure 2: peripapillary, superior, inferior, nasal, temporal), vessel density (VD) (total, inside disc, peripapillary, superior, inferior, nasal, temporal), and GCC thickness (Figure 3: Average, superior, inferior) parameters were recorded. All patients and parents attained consent. Ethics approval was obtained from the Local Clinical Research Ethics Committee (Registration number: 04/VII- Date: 26/02/2020). After proving the normal distribution of RNFL thickness, VD, and GCC thickness with Shapiro-Wilk and Kolmogorov-Smirnov tests, and homogeneity with Levene's test ($p>0.05$ for all parameters with all tests), an independent samples t-test was performed. The one-way analysis of variance (One-Way ANOVA) with Dunnet posthoc test was used to compare amblyopic subgroups. Because IOP, age and best-corrected visual acuity (BCVA) were not distributed normally and homogeneously ($p<0.05$), the Kruskal-Wallis test was performed in the comparison of the groups. A Chi-square test was applied to compare all groups for gender. Statistical Package for the Social Sciences (SPSS) version 21.0.0.0 (IBM Corp., Armonk, NY, USA) was attained for data analysis, and we defined $p < 0.05$ as statistically significant.

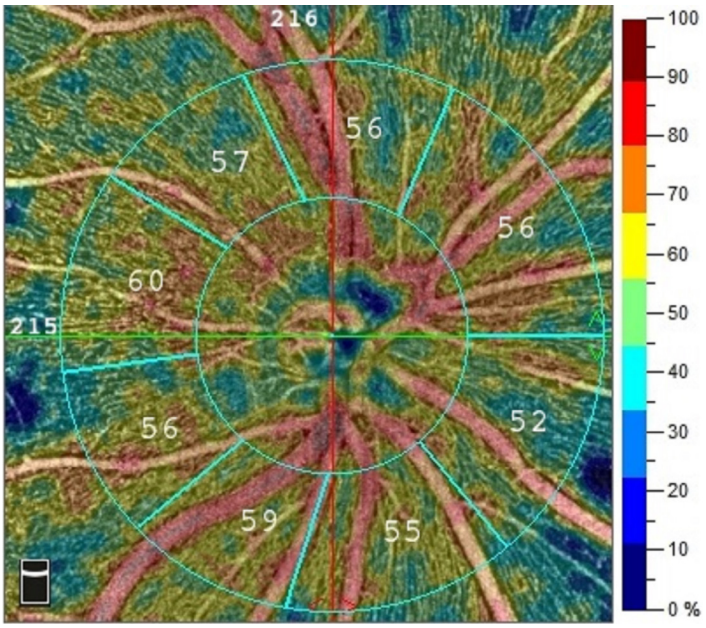

Figure 1. Optic nerve head angiography in a 4.5 × 4.5 mm scan size

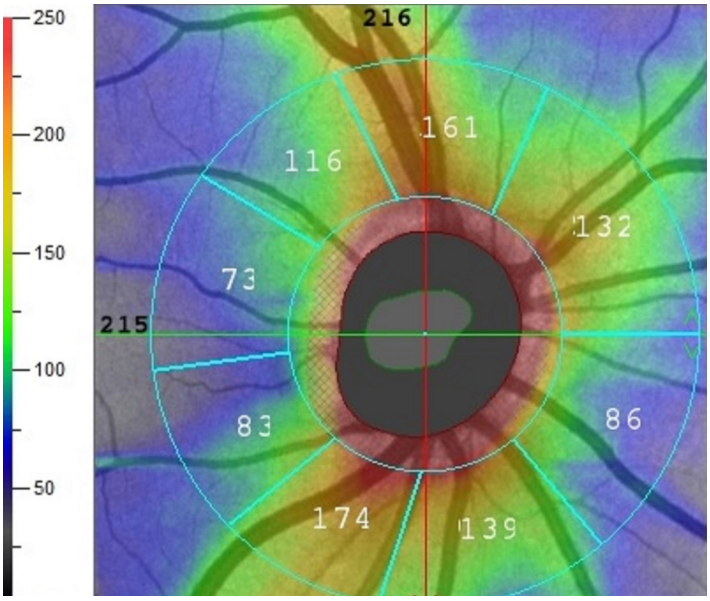

Figure 2. Retinal nerve fiber layer thickness and ganglion cell complex in a 4.5 × 4.5 mm scan size

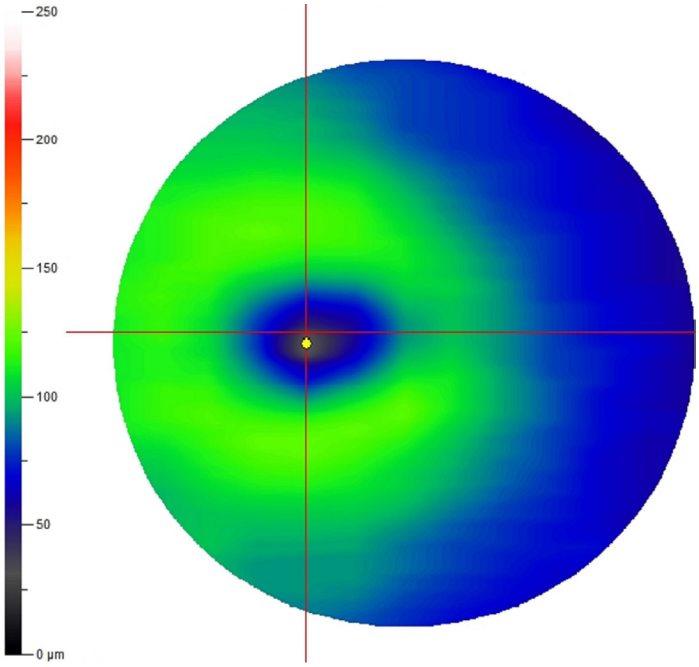

Figure 3. The thickness map of the ganglion cell complex

Seventeen manifest concomitant strabismic amblyopic eyes (The mean spherical, cylindrical power were 0.65 D (range 0.25 D to 0.75 D), 0.62 D (range 0.25 D to 0.75 D), respectively) of 17 patients with a correction of refractive error (8 constant exotropia, seven non-refractive esotropia, two hypertropia), 18 ametropic amblyopic eyes of 18 patients (The mean spherical, cylindrical power and anisohyperopia were 6.27 D (range 4.50 D to 7.50 D), 0.67 D (range 0.25 D to 0.75 D), 0.63 D (range 0 D to 0.75 D), respectively), 20 anisometropic eyes of 20 patients (The mean spherical, cylindrical power and anisohyperopia were 3.40 D (range 2.00 D to 4.25 D), 0.68 D (0 D to 0.75 D), 2.93 D (range 2.00 to 3.75 D), respectively), 18 meridional eyes of 18 patients (The mean spherical, cylindrical power were 0.61 D (range 0 D to 0.75 D), 3.68 D (range 1.75 D to 4.25 D), respectively), 72 healthy eyes

of 72 patients (The mean spherical, cylindrical power were 0.44 D (range 0 D to 0.75 D), 0.35 D (range 0 D to 0.75 D), respectively) were enrolled (Table 1). All the patients were orthoforic before and after the correction of refractive error in ametropic, anisometropic, meridional subgroups, and control groups. The mean age was 13.67 (range 10 to 15) years in the strabismic, 12.08 (range 11 to 15) years in the anisometropic, 13.15 (range 10 to 15) years in the meridional, 12.78 (range 11 to 14) years in the ametropic amblyopic subgroups, and 12.75 (range 12 to 14) years in the control group (Table 1). There was no difference in gender, age distribution, and adjusted IOP for central corneal thickness ($x^2(2, N=145)= 5.4$, p=0.34; p=0.49; p=0.61; respectively). The mean BCVA was 0.51 decimal in the study group, which was significantly lower from the control group (p=0.011); however, there was no difference among the amblyopic subgroups (p=0.74) (Table 1). The mean VD was significantly higher in all other quadrants (peripapillary, superior, inferior, nasal, temporal) (p=0.023; p=0.041; p=0.015; p=0.039; p=0.019; respectively) while the mean inside disc VD was lower in the study group (p=0.038). However, the total VD was similar in both groups (p=0.29) (Table 2). Although the mean RNFL thickness and GCC were more prominent in the study group in all quadrants, differences were not statistically significant compared with the control group (p>0.05 for all) (Table 3). Additionally, there were no significant differences in VD, RNFL thickness, and GCC among the amblyopic subgroups (p>0.05 for all) (Tables 4 and 5).

Table 1. Demographic characteristics and the mean best-corrected visual acuity of the study, control groups, and amblyopic subgroups.

	Strabismic (n=17)	Anisometropic (n=20)	Meridional (n=18)	Ametropic (n=18)	Total(n=73)	Control (n=72)	P-value
Mean age (year)	13.67	12.08	13.15	12.78	12.88	12.75	0.49
IOP (mmHg)	16.8	17.1	16.7	17.4	17.01	17.4	0.61
Gender							
Male	8	11	9	10	38	36	0.22
Female	9	9	9	8	35	36	0.34
Mean BCVA (Decimal)	0.51[a]	0.51[a]	0.51[a]	0.48[a]	0.51[a]	1.00[b]	0.011

BCVA: Best-corrected visual acuity. IOP: Intraocular pressure. The means in the same row that do not share the same letters differ at p<0.05.

Table 2. Comparison of the mean VD between study and control groups.

Density (%)	Study Group (n=73)	Control Group (n=72	P-value
	Mean±SD		
Total	56.7±2.4	56.2±2.3	0.29
Inside disc	61.6±3.7	63.9±3.2	0.038
Peripapillary	59.4±2.7	57.1±2.7	0.023
Superior	51.5±4.2	49.7±4.5	0.041
Inferior	53.9±4.1	51.3±3.8	0.015
Nasal	48.2±3.7	46.8±3.4	0.039
Temporal	53.3±4.5	51.7±3.6	0.019

VD: Vessel density. SD: Standard deviation

Table 3. Comparison of the mean RNFL Thickness and GCC between study and control groups.

	Study Group (n=73)	Control Group (n=72	P-value
	Mean±SD		
RNFL Thickness (µm)			
Peripapillary	111±15	110±13	0.77
Süperior	128±20	126±17	0.59
Inferior	143±20	142±18	0.41
Nasal	104±21	103±20	0.50
Temporal	75±15	73±13	0.28
GCC(µm)			
Average	97±8	95±5	0.34
Superior	96±7	94±5	0.25
Inferior	97±10	95±11	0.13

RNFL: Retinal nerve fiber layer, GCC: Ganglion cell complex, SD: Standard deviation.

Table 4. Comparison of the mean VD among amblyopic subgroups

	Strabismic (n=17)	Anisometropic (n=20)	Meridional (n=18)	Ametropic (n=18)	P-value
			Mean+-SD		
Density (%)					
Total	56.9±2.2	57.5±2.1	55.8±1.8	56.9±3.1	0.12
Inside disc	62.4±2.5	61.3±3.1	61.1±3.9	61.1±3.4	0.13
Peripapillary	59.5±2.4	59.6±2.3	58.9±1.9	58.1±2.4	0.41
Superior	51.9±4.2	51.8±4.9	50.4±3.7	52.5±4.1	0.43
Inferior	55.9±4.2	53.9±4.1	53.5±3.7	52.5±4.4	0.73
Nasal	47.3±4.1	48.5±3.1	48.5±3.8	48.2±4.4	0.82
Temporal	54.3±3.7	54.4±3.1	53.4±3.5	52.2±4.2	0.13

VD: Vessel density. SD: Standard deviation

Table 5. Comparison of the mean RNFL Thickness and GCC among amblyopic subgroups

	Strabismic (n=17)	Anisometropic (n=20)	Meridional (n=18)	Ametropic (n=18)	P-value
			Mean±SD		
RNFL Thickness(µm)					
Peripapillary	110±10	118±11	108±13	112±15	0.20
Superior	120±14	128±15	123±20	125±18	0.12
Inferior	136±14	150±17	140±35	140±25	0.25
Nasal	102±20	107±19	103±23	101±24	0.81
Temporal	74±12	79±14	72±24	77±17	0.52
GCC(µm)					
Average	95±4	97±6	95±10	98±14	0.86
Superior	94±6	97±6	96±11	99±13	0.80
Inferior	96±5	98±7	96±11	99±15	0.91

RNFL: Retinal nerve fiber layer, GCC: Ganglion cell complex, SD: Standard deviation

Discussion

Amblyopia develops during childhood and is defined as a difference in the BCVA of at least two acuity lines between the eyes. OCT-A is a new, non-invasive imaging technology that provides structural and functional details on ONH's microvasculature, retina, and choroid.

In this current study, on the ONH centered OCT-A images, we found that the mean peripapillary, superior, inferior, nasal, and temporal VD was significantly higher while the mean inside disc VD was lower in the study group compared to the controls. However, the mean total VD was not different in both groups. Although the mean RNFL and GCC were thicker in the study group in all quadrants, the differences were not statistically significant. In the subgroup analysis, there were no significant differences in the mean VD, RNFL thickness, or GCC.

Knowledge of the retinal and choroidal vascular networks is required to understand ONH microvascular differences in amblyopic eyes better. In the ganglion cell layer, the superficial capillary plexus (SCP) is supplied by the central retinal artery and comprises arteries, arterioles, capillaries, venules, and veins. Vertical anastomoses from the SCP forms the deep capillary plexuses (DCP) above and below the inner nuclear layer (Figure 4-B) [7-10].

The posterior ciliary arteries arising from the ophthalmic artery gives rise to the circle of Zinn–Haller and peripapillary choroidal vessels (Figure 4-A) [10,11]. Choriocapillaris is a layer of capillaries in the choroid that mainly originates from the posterior ciliary vessels (Figure 4-B) [10].

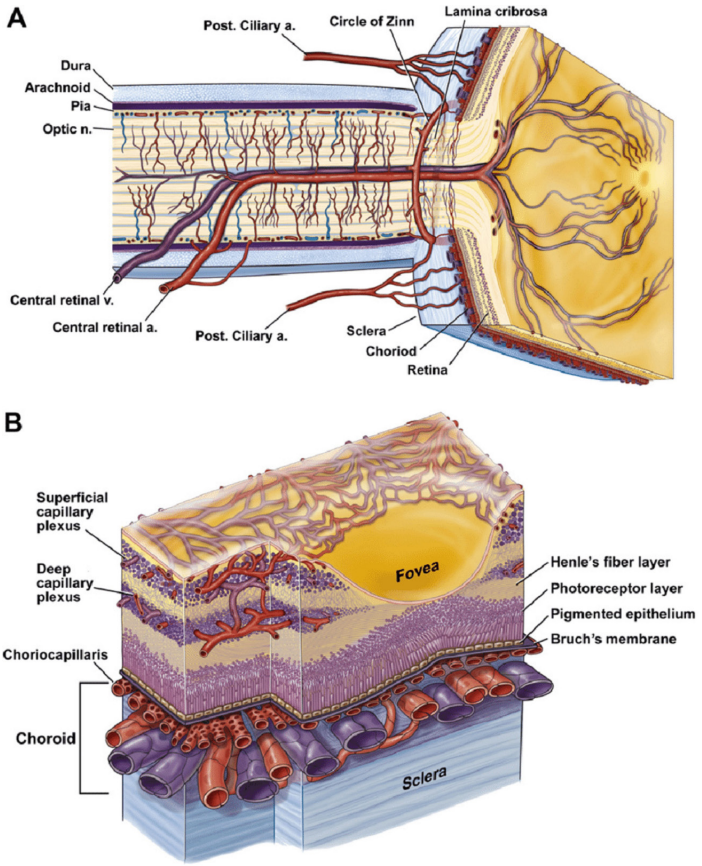

Figure 4. Vascular supply of optic nerve (A), retina (A-B), and choroid (A-B). a: Artery, v: Vein, n: Nerve. (with the permission of Progress in Retinal and Eye Research, Elsevier) [10].

The ONH is supplied mainly by the ciliary vascular system and not by the central retinal vessels (Figure 4-A) [10,12]. Additionally, the ONH's surface and retinal layer are supplied by a vascular network called the radial peripapillary capillary plexus (RPCP). The RPCP arises mainly from the central retinal artery, runs parallel to the RNFL axons, and supplies these dense bundles [13].

Using this novel, non-invasive imaging technology, the microvascular architecture of amblyopic eyes has been well defined. Most reports have shown retinal and choroidal changes. Like our previous study, Sobral et al. reported a significant decrease in SCP and DCP in amblyopic eyes [6,14]. Lonngi et al. also found subnormal SCP and DCP in the macula of amblyopic patients [15].

However, increased choriocapillaris VD has been shown in amblyopic eyes. Borrelli et al. reported that amblyopic eyes were found to have an increased choriocapillaris VD in their cohort study [16]. They thought this increase might be a compensatory response that supplies more blood to a thickened outer retina.

There have been limited reports that mention ONH microvascular differences in amblyopic eyes that were detected using OCT-A. In this current study, we found that the mean inside disc VD was lower while the mean peripapillary, superior, inferior, nasal, and temporal VD was significantly higher in amblyopic eyes than normal eyes. Consistent with our findings, Dereli et al. reported that the inside disk VD measurements were lower in the amblyopic eyes [17]. We can explain these results based on the ONH blood supply, as described above. The studies showed that capillary plexuses (SCP, DCP, inside disc) supplied by the central retinal vessels have a decreased VD while capillary plexuses (Choriocapillaris and peripapillary), which were supplied by posterior ciliary vessels, have an increased VD. These microvascular differences might be a functional compensatory response to structural changes in the retina, choroid, and RNFL layer in amblyopic eye§.

In this current study, we found that the mean inside disc VD in refractive amblyopic (anisometropic, ametropic, meridional) eyes was more different than strabismic amblyopic eyes compared to the control group. We do not know the exact mechanism. However, these differences may be originated from the mechanism of visual acuity loss. The primary visual acuity deprivation in refractive amblyopia is mainly due to grating visual acuity and contrast sensitivity losses restricted by features within the central visual system between the retina and the visual cortex [18]. On the other hand, strabismic amblyopia exhibits a significant loss in Vernier acuity than the grating acuity. In strabismus amblyopia, grating visual acuity and contrast sensitivity damages represent a moderately small portion of their complete visual loss [19,20] .Because the primary visual loss in refractive amblyopia includes contrast sensitivity and grating resolution decrease because of low info transmission between the retina and visual cortex, refractive amblyopic eyes may be more likely to have the retinal and optic disc microvascular changes.

The GCC is formed by three layers: the inner plexiform layer, the ganglion cell layer (ganglion cell dendrites and bodies), and RNFL (ganglion cell axons). Macular GCC and peripapillary RNFL become thinner in glaucoma, diabetes mellitus, and ischemic optic neuropathy patients while their changes are controversial in amblyopia [21-24]. In this current study, we found that the mean RNFL thickness and GCC were more prominent in the study group in all quadrants, although the differences were not statistically significant. There were also no significant differences in the amblyopic subgroup. The RNFL and GCC thickness in amblyopic eyes are controversial. Some studies demonstrated thicker peripapillary RNFL and GCC, while others reported thinner peripapillary RNFL and GCC in amblyopic eyes [25-27]. Moreover, Celik et al. reported that the RNFL and GCC thickness were not statistically significant in amblyopic eyes compared to controls [28].

Our observational case-control study is the first to analyze the peripapillary RNFL, GCC, and the ONH microvascular changes in amblyopic eyes and amblyopic subgroups using OCT-A.

This study has some limitations. Although the groups showed similar age, gender, and IOP, we did not consider the effects of some confounding factors such as refractive error and axial length. Future studies will be useful to demonstrate the efficacy of these factors on ONH microvascularity in amblyopic eyes.

Thus, the central retinal vessels and posterior ciliary vessels' blood supply variation might be a compensatory response to the architectural changes in the choroid, retinal layers, and ONH in amblyopic eyes. OCT-A results will provide a better understanding of amblyopia, and it will confirm the potential involvement of microvascular ONH structures in amblyopia.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Ethics approval was obtained from the Local Clinical Research Ethics Committee (Registration number: 04/VII- Date: 26/02/2020).

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