Optical Coherence Tomography Angiography in Patients with Amblyopia

Zhale Rajavi

Shaheed Beheshti University of Medical Sciences

Hamideh Sabbaghi

Shahid Beheshti University of Medical Sciences School of Rehabilitation

Kiana Hassanpour

Shahid Beheshti University of Medical Sciences School of Medicine

Hamid Ahmadi

Shahid Beheshti University of Medical Sciences School of Medicine

Bahareh Kheiri

Shahid Beheshti University of Medical Sciences

Mojtaba Rajabpour

Shahid Beheshti University of Medical Sciences School of Rehabilitation

Ramin Nourinia (✉ ramin.retin@gmail.com)

ophthalmic research center

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Abstract

Purpose: To determine the OCTA parameters including foveal avascular zone (FAZ) and vessel density (VD) in the amblyopic eyes compared with the fellow sound eyes and the eyes of the non- amblyopic subjects.

Methods: In this case- control study, a total of 62 eyes from unilateral amblyopic children (n= 23) and the age- and sex- matched healthy children (n= 8) were included. The sound eye of the amblyopic children was considered as the internal control (n= 23) and the both eyes of the non- amblyopic children (n= 16) were considered as the external control. All participants underwent image recording with the optical coherence tomography angiography (OCTA)

Results: The average age of 23 cases and 8 controls were 9.86 ± 3.12 and 8.5 ± 2.35 years, respectively. Twelve patients (52.2 %) in the case group and 8 subjects (50%) in the control group were female. Macular VD in different regions of superficial and deep capillary plexuses (SCP, DCP) were comparable amongst the case group and both the internal and the external control groups. The average FAZ area was $0.26 \pm 0.06 \mu\text{m}^2$ in amblyopic eyes that was significantly larger than in the fellow eyes ($0.21 \pm 0.06 \mu\text{m}^2$; $P=0.007$) and was comparable to the healthy controls.

Conclusion: Lack of significant difference of the macular vessel density between the amblyopic and non- amblyopic eyes of the both internal and external controls may be attributed to this fact that the changes of the retinal vascular density cannot be considered as the pathogenesis of amblyopia.

Introduction

Amblyopia is a visual impairment demonstrating with decreased best corrected visual acuity (BCVA) as the hallmark and other visual disorders including reduced contrast sensitivity and the presence of relative afferent pupillary defect (RAPD).(1–3) Additionally, there are some studies reporting the involvement of choroidal and retinal layers (4, 5) such as significantly increased central macular thickness in eyes having moderate and severe amblyopia compared with the healthy eyes (6). A meta- analysis also showed a significant thickening of the peripapillary and foveal fiber layer of the amblyopic eyes compared with the non- amblyopic eyes.(6)

Recently, there have been advancements in image processing particularly application of the optical coherence tomography angiography (OCTA) in ophthalmology.(6–10) The OCTA is capable to illustrate blood flow and density of the superficial and deep capillary plexuses as well as the choriocapillaris and also the size of the foveal avascular zone (FAZ) (6–10). In the previous reports, a significant reduction of both SCP, DCP and a significant increase of the vessel density of the choriocapillaris was identified in the amblyopic eyes compared with the healthy eyes.(5, 7, 9, 10)

In this study, we aimed to evaluate the macular parameters including FAZ size and vessel density in the amblyopic eyes compared with the non- amblyopic eyes.

Methods

In this case-control study, 23 eyes of 23 unilaterally amblyopic children and both eyes of 8 age- and sex-matched healthy normal children were included. The sound eye of the amblyopic children was considered as the internal control (n=23) and both eyes of the non- amblyopic children (n= 16) were considered as the external control.

Amblyopia was considered if BCVA was less than 0.3 LogMAR without any organic reason or there was at least two lines of BCVA difference between the two eyes. All study procedures were explained to the study subjects and their parents before image recording or examination and a written informed consent was obtained from all participants' guardians. The study procedures were approved by the Ethics Committee of the Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences via the approval number of IR.SBMU.ORB.REC.1398.023.

Patients with nystagmus, no accurate fixation, unsteady fixation and low cooperation during image recording; amblyopic children with BCVA <20/200, deprivation amblyopia, strabismic amblyopia with a deviation angle of ≥ 10 prism diopters; eyes with an axial length of > 26mm and the spherical and cylindrical refractive errors of more than 5.00D; systemic disease and congenital ocular anomalies were excluded from the present study.

Visual and Ocular Examination

All ophthalmic examinations were performed including the measurement of BCVA, cycloplegic refraction 30 to 45 minutes following the installation of the ophthalmic eye drops of tropicamide 1% and cyclopentolate 1%, ocular motility function testing (+4 denoted as overaction and -4 denoted as underaction for the extraocular muscles), measurement of the ocular deviation using the alternative prism cover test, foveal fixation testing by visuoscopy and anterior and posterior ocular segments examination by using the biomicroscopy and indirect ophthalmoscopy, respectively. Finally, all participants underwent the image recording by OCTA (RTVue XR Avanti with Angio Vue; Optovue INC., Fremont, CA) by an experienced technician. In order to monitor the child's constant fixation, image recording was firstly performed on the amblyopic eye and secondly on the fellow non-amblyopic eye.

Optical Coherence Tomography Angiography

All OCTA scans were performed by a single experienced examiner using a spectral domain RTVue XR Avanti (Optovue, Inc, Fremont CA, USA) with split-spectrum amplitude decorrelation angiography (SSADA) algorithm. The device works with a central wavelength of 840 nm, an acquisition speed of 70,000 A-scans per second, and an axial and transverse resolution of 5microns in tissue. A good image quality is more than 4 according to the OCT manufacturer. The built-in software "AngioAnalytics" was used for analyzing vessel densities and the foveal avascular zone (FAZ).

Before imaging, pupils were dilated using tropicamide 1% eye drop. Study participants underwent SD-OCT imaging based on a protocol that contained AngioVue OCT 3D volume set of 6x6mm. An internal fixation

light was used for keeping the fixations central. Optimization of signal position and quality were performed through running the option of “Auto All”.

Based on the position of capillary plexuses in the retina and choroid, the boundaries of the superficial network extended from 3µm below the internal limiting membrane (ILM) to 15µm below the inner plexiform layer (IPL). The deep capillary network extended from 15 to 70µm below the IPL. The choriocapillaris extended from 30 to 60µm below the retinal pigment epithelium.

The centration of the fovea was checked for all images. All images were reviewed for the segmentation errors. Additional image artifacts including motion, banding and projection artifacts were evaluated, as well.

Vessel Density Analysis

Objective quantification of the vessel density was measured for each eye using the SSADA software. The OCTA en face images for each eye was used to perform quantitative analysis with the AngioVue software. The vessel density was defined as the percentage area occupied by vessels in a circular region of interest (ROI) centered on the center of the FAZ with a diameter of 3x3mm included inside the 6x6mm scan area. The AngioVue software automatically splits the ROI into two fields: the foveal area, a central circle with a diameter of 1 mm; and the parafoveal area that constitutes the remaining part inside the ROI. The three capillary systems were evaluated with quantitative analysis in the foveal and parafoveal areas and with qualitative analysis in the whole 6x6 mm scan area. The way that vessel density was calculated was previously described. For each patient, foveal and parafoveal vessel density (VD); and parafoveal VD in different quadrants (temporal, superior, nasal, inferior) of the SCP and DCP were calculated. OCTA images of the patients with quality score more than 6 were included in our study. A central 1 mm circle was considered as the foveal area. (11) A circle with an inner diameter of one millimeter and outer diameter of three millimeter was considered the parafoveal area. Accordingly, a circle with a diameter of 6 millimeter and inner diameter of 3 millimeters was considered as the perifoveal region. (12, 13) For each patient, foveal, parafoveal, and perifoveal VD of the SCP and DCP layers were calculated.

Two independent observer evaluated the all OCTA images regarding segmentation error and in cases with the possible segmentation error, it was manually corrected. Foveal macular thickness (MT), full parafoveal MT, and parafoveal MT in different retinal quadrants and ILM-IPL parafoveal MT were automatically calculated by the software on the OCTA 6x6 mm volume scan (XR Avanti1; Optovue, Inc., Fremont, CA, USA).

Statistical Analysis

To describe data, we used frequency (percent), mean $\pm$ SD, median and range. To evaluate the difference between three groups at baseline we used ANOVA for quantitative variables and Chi-Square and Fisher exact test for qualitative variables. To compare indexes of the OCTA between groups when considering the correlation of eyes, Generalized Estimating Equation (GEE) analysis was used.

A P-value less than 0.05 was considered as statistically significant. All statistical analysis was performed by SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

The average age of 23 cases and 8 controls were 9.86 ± 3.12 and 8.5 ± 2.35 years, respectively ($P=0.134$). Twelve patients (52.2%) in the case group and 8 (50%) in the control group were female.

Mean LogMAR BCVA was significantly worse in the amblyopic eyes (0.17 ± 0.13) compared with the fellow eyes (0.01 ± 0.03 , $P < 0.001$) and the eyes of healthy subjects (0.02 ± 0.04 , $P < 0.001$), respectively. Mean SE was $2.21 \pm 2.07D$, $1.80 \pm 1.9D$, and $0.75 \pm 1.43D$ in amblyopic eyes, fellow eyes and healthy controls, respectively ($P = 0.21$). Thirteen patients (56.5%) in cases versus seven subjects in healthy controls (87.5%) were orthophoric. Patients were comparable in terms of age, sex, SE and ocular alignment at far (Table 1).

OCTA parameters

Whole Image Vessel Density

In the amblyopic eyes, the whole VD was 49.19 ± 2.9 in SCP and 47.82 ± 4.0 in DCP. The corresponding values were 49.87 ± 4.14 and 46.84 ± 4.2 in the internal control as well as 48.12 ± 3.3 and 47.85 ± 7.1 in the external control. Amblyopic group was comparable to the internal and external control in terms of whole VD.

Foveal Vessel Density

The average foveal VD in SCP and DCP was 21.4 ± 10.51 and 40.16 ± 7.5 in the amblyopic eyes. These parameters were 21.47 ± 5.8 and 39.93 ± 7.2 in the fellow eyes and 20.53 ± 7.02 and 40.65 ± 9.96 in the healthy control.

Parafoveal Vessel Density

In SCP, three groups were comparable in terms of parafoveal VD (amblyopic eyes: 49.17 ± 5.6 , fellow eyes: 51.92 ± 4.9 and healthy eyes: 50.18 ± 4.34). In DCP, the average parafoveal VD was 53.16 ± 4.8 in amblyopic eyes, 52.78 ± 4.18 in fellow eyes and 52.78 ± 5.07 in the healthy controls.

Perifoveal Vessel Density

No significant difference was observed between the three study groups in terms of perifoveal VDs in both SCP and DCP.

FAZ

The average FAZ area was $0.26 \pm 0.06 \mu\text{m}^2$ in amblyopic eyes that was significantly larger than in the fellow eyes ($0.21 \pm 0.06 \mu\text{m}^2$; $P=0.007$) and was comparable to the healthy controls ($0.22 \pm 0.11 \mu\text{m}^2$; $P=0.209$). (Table 2)

Discussion

The present study demonstrates that macular vessel density in eyes with mild to moderate amblyopia is comparable to the both fellow and control eyes. Conversely, amblyopic eyes have significantly larger FAZ area compared with the control eyes.

Various studies used OCT-A as a noninvasive technique to investigate the changes of macular microvasculature of the retina in amblyopia.(5, 9, 10, 14–16) Regarding macular VD, mixing results have been reported. The studies performed by Sobral et al(10), Zhang et al (17), Yilmaz et al(5) and Lonngi et al(9) demonstrated lower macular VD in eyes with amblyopia. However, consistent with our results, Araki et al (14) and Demiyarak et al (18) found no differences regarding VD between amblyopic eyes and healthy controls.

There are several reasons to explain the different results noticed in several studies. First, the diversity of the results may be attributed to the different severities of amblyopia. For example, there is a wide range of refractive error in Lonngi et al's study (9) compared to the present study. Second, axial length and central subfield thickness (CST) affect the FAZ area and macular VD.(14, 19) Previous reports demonstrated different CST in amblyopic eyes, however not all amblyopic eyes show these differences. Macular thickness can affect the FAZ area through the hypothesis that higher macular thickness is associated with more compact inner retinal layer. Therefore, the continuity of INL results in a smaller FAZ area and vice versa.(20)

Third, amblyopia has different causes occurring in different ages. It has been proposed that neuronal development of GCL and NFL determine the vascularity of the macula in infancy and within the first years of life. However, amblyopic eyes with different severity and type could differently affect the neuronal development. The next reason could be attributed to the OCT-A device and its inherent differences. Araki and associates corrected the magnification error and found no changes in VD between amblyopic and healthy eyes. Considering these discrepancies and possible explanations, the vascular changes in amblyopia remain to be elucidated by further investigations.

Our results demonstrated larger FAZ area in amblyopic eyes compared with the fellow eyes and not with the healthy controls. The larger area achieved in the present study is in line with Sobral et al's study. while FAZ area did not show significant changes in studies by Wong(16), Zhang(17), Yilmaz(5), Lonngi(9), and Demiyarak(15). Additionally, Wong et al (16) reported decreased FAZ circularity and lower fractal dimension of retinal vessels while they found no change in FAZ area and vessel density. In contrast to our results, Araki and associates found smaller FAZ area compared with the fellow eyes of amblyopic eyes and the authors concluded that this finding seems to be clinically insignificant.(14)

Another possible mechanism explaining FAZ changes is the impact of AL on the area.(21) Sampson et al (19) reported longer axial length could cause apparent larger FAZ because of magnification. This effect is more prominent in hyperopia that causes overestimation of the FAZ area.

The strengths of the present study consist of inclusion of mild to moderate amblyopia, and comparison with the fellow eyes of patients with amblyopia. Our study is limited by not adjusting for AL, magnification error and age of the participants. However, the same method was applied in both patients and healthy controls.

In conclusion, this no significant difference of the macular vessel density between the amblyopic and non- amblyopic eyes of the both internal and external controls may be attributed to this fact that the changes of the retinal vascular density cannot be considered as the pathogenesis of amblyopia.

Declarations

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Competing Interest

The authors have no relevant financial or non-financial interests to disclose.

Authors' Contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Zhale Rajavi and Hamideh Sabbaghi. The first draft of the manuscript was written by Hamid Ahmadi and Ramin Nourinia and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristic of cases as well as the internal and external control groups.

Factors	Level	Total	Groups			P-value	Pairwise
			Case (n= 23)	Internal Control (n= 23)	External Control (n= 16)		
Sex (%)	Male	30 (48.4%)	11 (47.8%)	11 (47.8%)	8 (50.0%)	0.989*	
	Female	32 (51.6%)	12 (52.2%)	12 (52.2%)	8 (50.0%)		
Age (y)	Mean $\pm$ SD	8.28 $\pm$ 2.6	9.86 $\pm$ 3.12	7.5 $\pm$ 2.25	8.5 $\pm$ 2.35	0.134**	
	Median (Range)	8 (4 to 14)	9 (6.5 to 14)	7 (4 to 12)	9.5 (4 to 10)		
BCVA (LogMAR)	Mean $\pm$ SD	0.07 $\pm$ 0.11	0.17 $\pm$ 0.13	0.01 $\pm$ 0.03	0.02 $\pm$ 0.04	<0.001†	1,2 1,3††
	Median (Range)	0 (0 to 0.7)	0.15 (0.05 to 0.7)	0 (0 to 0.15)	0 (0 to 0.15)		
Ocular alignment at far (%)	XT	4 (6.5%)	2 (8.7%)	0 (0.0%)	2 (12.5%)	0.015#	
	ET	12 (19.4%)	8 (34.8%)	4 (17.4%)	0 (0.0%)		
	Ortho	46 (74.2%)	13 (56.5%)	19 (82.6%)	14 (87.5%)		
Angle of ocular alignment at far (pd)	Mean $\pm$ SD	1.05 $\pm$ 2.42	1.48 $\pm$ 2.71	0.83 $\pm$ 2.39	0.75 $\pm$ 2.05	0.569†	
	Median (Range)	0 (0 to 10)	0 (0 to 10)	0 (0 to 10)	0 (0 to 6)		

BCVA, best corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; XT, exotropia; ET, seotropia; pd, prism diopter; y, year; SD, standard deviation; P, probability

*Based on chi-square

**Based on ANOVA

†Based on GEE (bonferroni pairwise comparison)

Based on fisher exact test

†† The statistically significant difference was found in the separate comparisons of the BCVA between the case group (1) and each control groups (2 & 3).

Table 2. The mean indexes of the optical coherence tomography angiography (OCTA) in cases as well as the internal and external control groups.

Factors	Level	Total	Groups			P-value*	Pairwise
			Case (n= 23)	Internal Control (n= 23)	External Control (n= 16)		
Superficial							
	Whole Density (%)	49.15 ± 3.53	49.19 ± 2.99	49.87 ± 4.14	48.12 ± 3.27	0.315	
		49.1 (41 to 57.3)	49 (41.7 to 54.3)	49.45 (41 to 57.3)	49.1 (43.3 to 54.1)		
	Fovea Density (%)	21.19 ± 8.01	21.4 ± 10.51	21.47 ± 5.83	20.53 ± 7.02	0.899	
		21.25 (5.4 to 55.3)	19.4 (10.2 to 55.3)	22.55 (11.6 to 31.6)	20 (5.4 to 32.8)		
	ParaFovea Density	50.47 ± 5.13	49.17 ± 5.6	51.99 ± 4.99	50.18 ± 4.34	0.180	
	51.55 (37.8 to 58.8)	50.55 (37.8 to 56.6)	52.4 (38.8 to 58.8)	50.4 (40.9 to 57.8)			
	PeriFovea Density	50.06 ± 3.86	50.07 ± 3.5	50.52 ± 4.43	49.22 ± 3.55	0.623	
	50.05 (40.6 to 60.3)	50.05 (42 to 59.2)	50.05 (40.6,60.3)	50.45 (43 to 53.5)			
Deep							
	Whole Density	47.47 ± 4.99	47.82 ± 4	46.84 ± 4.16	47.85 ± 7.1	0.692	
		47.7 (37.5 to 60.3)	48.35 (37.5,54.9)	47.35 (40 to 57.7)	46.15 (38.2 to 60.3)		
	Fovea Density	40.21 ± 7.97	40.16 ± 7.5	39.93 ± 7.16	40.65 ± 9.96	0.968	
		39.95 (22.8 to 58.4)	37.85 (27.4 to 58.4)	40.35 (22.8 to 51)	40.9 (23.8 to 57.7)		
	ParaFovea Density	52.92 ± 4.59	53.16 ± 4.81	52.78 ± 4.18	52.78 ± 5.07	0.952	
	52.6 (39.5 to 62.8)	53.25 (39.5 to 60.8)	51.9 (46.9 to 62.8)	53 (46.4 to 62.4)			
	PeriFovea Density	47.22 ± 5.02	48.45 ± 4.68	47.42 ± 4.73	44.58 ± 5.57	0.034	1,3††
	48.45 (35.5 to 58.9)	49.1 (35.5 to 56.4)	48.1 (38.1 to 58.9)	43.95 (36.8 to 54.8)			
FAZ (mm ²)	-	0.2291 ± 0.0823	0.2598 ± 0.0619	0.207 ± 0.0691	0.2208 ± 0.1121	0.025	1,2††
		0.229 (0.036 to 0.484)	0.2605 (0.141 to 0.37)	0.1995 (0.065 to 0.348)	0.234 (0.036 to 0.484)		
PERIM (μm)	-	1.87 ± 0.418	1.977 ± 0.271	1.75 ± 0.312	1.902 ± 0.643	0.035	1,3††
		1.886 (0.731 to 3.413)	1.975 (1.503 to 2.559)	1.758 (0.927 to 2.278)	1.971 (0.731 to 3.413)		
Flow Area (mm ²)	-	1.254 ± 0.598	1.282 ± 0.646	1.181 ± 0.658	1.312 ± 0.479	0.772	
		1.199 (0 to 2.502)	1.212 (0 to 2.502)	1.212 (0 to 2.502)	1.287 (0.628 to 2.441)		

*Based on GEE

†† The statistically significant difference was found between the case group (1) and the external control group (3).