Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol. (7) Issue (6) (2022), (125-130) **online: ISSN 2356–976x**
http://bjas.journals.ekb.eg

Macular Optical Coherence Tomographic Angiography Changes in Amblyopia Running title: Macular OCTA Changes in Amblyopia

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Abstract:

Background: Amblyopia is reduced vision that is caused by disruption of the normal development of vision during childhood. Aim and objectives: the main aim of this study was to detect macular vascular changes in amblyopic eye by optical coherence tomographic angiography. Subjects and methods: This cross-sectional comparative observational study was conducted on 59 patients with amblyopia. this study enrolled patients from May 1,2021, through December 1,2021. All participants in this study signed their written consent to participate.This study was approved by ethical committee on May 1,2021. Results: The foveal and parafoveal macular vessel density was lower in amblyopic eye than control eye . Severe OCTA changes were found to be significantly related to patients with high error of refraction and degree of amblyopia. As regarding UCVA and BCVA, it was found that they were both significantly lower among patients with severe changes compared to those with mild and moderate changes (0.04, 0.10 versus 0.25, 0.10, 0.25 and 0.25 respectively). Conclusion: Young patients with amblyopia have reduced superficial and deep retinal capillary density on OCTA. These vascular changes may be associated with decreased visual acuity. Our findings indicate a possible association between retinal microcirculation and amblyopia. The clinical relevance of this finding remains to be determined.

Keywords: Amblyopia; Optical Coherence Tomography Angiography; Retinal Capillary Density.

1. Introduction

Amblyopia is reduced vision that is caused by disruption of the normal development of vision during childhood.

Amblyopia is the unilateral, or rarely bilateral, decrease in the best corrected visual acuity caused by vision deprivation and/or abnormal binocular interaction, for which there is no identifiable pathology of the eye or visual pathway **[1]**.

Amblyopia may be classified as strabismic, refractive (anisometropic and isometropic), deprivational, idiopathic, and mixed types. If the same disorders occur later in life, amblyopia does not develop.

Strabismic amblyopia results from abnormal binocular interaction where there is continued monocular suppression of the deviating eye.

Anisometropia has been defined as a condition in which there is a difference of 0.5–2 diopters in refractive error between the two eyes. **[2]**

Optical coherence tomographic angiography (OCTA) is a new non-invasive imaging technique that employs motion contrast imaging to high-resolution volumetric blood flow information generating angiographic images in a matter of seconds. OCTA compares the decorrelation signal (differences in the backscattered OCT signal intensity or amplitude) between sequential OCT b-scans taken at precisely the same cross-section in order to construct a map of blood flow. Axial bulk motion from patient movement is eliminated so sites of motion between repeated OCT b-scans represent strictly erythrocyte movement in retinal blood vessels. **[3]**

The vascular system of the retina is vital for visual function, and its assessment is valuable in the evaluation of macular diseases. Optical coherence tomographic angiography (OCTA) provides depth resolved visualization of the microvasculature of the retina, allowing the identification of the superficial retinal capillary plexus (SCP), the deep retinal capillary plexus (DCP), and the choroid and assess the density of the retinal capillary and radial peripapillary plexuses as well as the area of the foveal avascular zone (FAZ) in amblyopic eyes. **[4]**

Aim of the work was to detect macular vascular changes in amblyopic eye by optical coherence tomographic angiography.

2.Subjects And Methods

This a cross-sectional observational comparative study that was conducted on (59) patients chosen from outpatient clinic.

Inclusion criteria

Age above 5years, no apparent ocular abnormality, no systemic diseases, best-corrected VA in the amblyopic eye less than 6/12, 5-Best corrected VA in the sound eye 6/12 or better, inter-eye acuity difference ± 2 Snellen lines and no ocular pathology causing reduced visual acuity, nor prior ocular surgery.

Exclusion criteria

History of neonatal seizures, prematurity (birth weight < 1500 g or gestational age <34 weeks) and incubation, mental retardation, ocular anomalies, macular and disc lesions, nystagmus, glaucoma and history of intraocular surgery.

Methods:

All subjects underwent a comprehensive ophthalmological examination as following**:** UCVA and BCVA with Snellen chart including crowding phenomenon and neutral denisty filter. Cycloplegic refraction 45 min after using cyclopentolate eye drops. Full anterior segment examination by slit lamp biomicroscopy. Indirect ophthalmoscopical examination of the posterior segment (with detailed optic nerve head and macular examination) and ocular motility tests.

OCTA ,which was performed using a-spectral-domain optical coherence tomographic angiography (Optovue version 2018, RTVue XR Avavnti Scanner

,Made in U.S.A).Macular 6 × 6-mm scans were performed in amblyopic eye and control eye. Each scan was automatically segmented by the software to visualize the SCP,DCP and Foveal avascular zone (FAZ).

Statistical analysis:

All data were collected, tabulated and statistically analyzed using SPSS version 19. Continuous Quantitative variables were expressed as the mean ± SD & median (range), and categorical qualitative variables were expressed as absolute frequencies (number) & relative frequencies (percentage). Continuous data were checked for normality by using kolmogorov-smirnov test. Mann-Whitney test was used to compare quantitative not-normally distributed data of each 2 groups separately. All tests were two sided. P-value< 0.05 was considered statistically significant (S), p-value < 0.001 was considered highly statistically significant (HS), and p-value ≥ 0.05 was considered statistically insignificant (NS).

3.Results

The age of the studied participants ranged between 7 and 29 years with mean of 15 years. More than half of them were males (57.6%). **(Table 1)**

Table (1) Demographic data among the studied group.

Variable	Studied group (n=59)	
Age: (years)		
Mean ± SD	15.1 ± 4.9	
Range	7 - 29	
	No	**%**
Sex:		
Female	25	42.4
Male	34	57.6

More than half of the studied patients had right amblyopia and the remaining 45.8% had left amblyopia. **(Table 2)**

Table (2) Detected pathologies among the studied group.

Variable	Studied group (n=59)	
	No	**%**
Pathology:		
Left amblyopia:	27	45.8
Right amblyopia:	32	54.2

This table shows that the majority of patients showed moderate OCTA changes (69.5%), 16.9% showed mild changes and the lowest frequency showed severe changes. **(Table 3)**

Table (3): Detected OCTA Macular Vascular changes among the studied group.

Variable	Studied group (n=59)	
	No	**%**
OCTA changes:		
Mild:	10	16.9
Moderate:	41	69.5
Severe:	8	13.6

This table shows that there was non-significant relation between type of pathology and the detected OCTA changes. Table (4)

Table (4) Relationship between type of pathology and detected OCTA changes among the studied groups.

Variable	Left amblyopia (N=27)		Right amblyopia (N=32)		χ^2	P value
	No	**%**	**No**	**%**		
OCTA changes:						
Mild:	8	29.6	2	6.3		
Moderate:	16	59.3	25	78.1	5.693	0.058
Severe:	3	11.1	5	15.6		(NS)

NS: non-significant (p≥0.05).

This table shows that there was significant relation between the detected OCTA changes and age. Small ages were found to be significantly related to severe changes. However, there was non-significant relation between OCTA changes and sex. Table (5)

Table (5) Comparison of demographic data among the studied groups.

Variable	Mild OCTA changes (N=10)		Moderate OCTA changes (N=41)		Severe OCTA changes (N=8)		KW test	P value
Age: (years)								
Median	17		15		10.5		**7.993**	**0.01**
Range	12 - 22		9 - 29		7 - 23			**(S)**
	No	**%**	**No**	**%**	**No**	**%**	χ^2	**P**
Sex:								
Female	3	30	17	41.5	5	62.5	1.698	0.374
Male	7	70	24	58.5	3	37.5		(NS)

KW: Kruskaal-wallis test. S: significant difference (p<0.05).
NS: non-significant difference (p>0.05).

This table shows that there was significant difference between the detected OCTA changes and sphere. Severe OCTA changes were found to be significantly related to patients with high error of refraction. As regarding UCVA and BCVA, it was found that they were both significantly lower among patients with severe changes compared to those with mild and moderate changes (0.04, 0.10 versus 0.25, 0.10, 0.25 and 0.25 respectively). **(Table 6)**

Table (6) Comparison of clinical data among the studied groups.

Variable	Mild OCTA changes (N=10)	Moderate OCTA changes (N=41)	Severe OCTA changes (N=8)	KW test	P value	MW test
Sphere:						>0.05 [1]
Median	0	-5	-9.5	**11.39**	**0.003**	**<0.05** [2]
Range	(-4) - 2	(-8) – 5.5	(-11) - 6		**(S)**	**<0.05** [3]
Refraction errors:						****
						<0.05 [1]
Myopia:	3 (30%)	25 (61%)	7 (87.5%)	**35.14**	**<0.001***	**<0.05** [2]
Astigmatism:	6 (60%)	0 (0%)	0 (0%)			>0.05 [3]
Hypermetropia:	1 (10%)	16 (39%)	1 (12.5%)			
Cylinder:						
Median	-2	--	--	--	--	---
Range	(-5) - 2					
UCVA:						**<0.05** [1]
Median	0.25	0.10	0.04	**33.80**	**<0.001**	**<0.05** [2]
Range	0.10 – 0.33	0.08 – 0.25	0.02 – 0.07		**(HS)**	**<0.05** [3]
BCVA:						**<0.05** [1]
Median	0.25	0.25	0.10	**22.84**	**<0.001**	**<0.05** [2]
Range	0.25 – 0.33	0.08- - 0.33	0.08 – 0.10		**(HS)**	**<0.05** [3]

KW: Kruskal-wallis test. S: significant difference (p<0.05). *: Chi-square test.
**: Chi-square for trend. HS: High-significant difference (p<0.001).MW:Mann-whitney test.
1: mild versus moderate changes groups. 2: mild versus severe changes groups.
3: moderate versus severe changes groups.
This table shows that there was a significant difference between SCP, DCP, and FAZ. **(Table 7)**

Table (7) Macular vessel density OCTA among the studied groups.

	Amblyopic eye	Fellow eye	t	P value
SCP: Mean ± SD	44.03±4.57	48.55 ± 3.87	**5.8**	**<0.001**
Temporal Mean ± SD	41.73 ± 9.28	47.76 ± 6.85	**4.02**	**.0001**
Nasal Mean ± SD	40.98±5.17	49.03 ± 8.56	**6.18**	**<0.001**
Superior Mean ± SD	44.05±9.39	50.26 ± 8.97	**3.67**	**.0004**
Inferior Mean ± SD	45.78±7.38	49.81 ± 7.72	**2.9**	**.004**

DCP: Mean ± SD	38 ±7.57	52.39 ± 4.23	**12**	**<0.001**
Temporal Mean ± SD	46.6 ±9.58	55.35 ± 6.17	**5.9**	**<0.001**
Nasal Mean ± SD	44.65 ± 10.22	57.27 ± 5.54	**8.51**	**<0.001**
Superior Mean ± SD	49.5 ± 7.32	54.99 ± 4.23	**4.99**	**<0.001**
Inferior Mean ± SD	46.45 ± 9.19	55.18 ± 4.84	**6.46**	**<0.001**
FAZ: Mean ± SD	0.525 ±0.283	0.222 ± 0.087	**7.86**	**<0.001**

4. Discussion

Amblyopia is the reduction of visual acuity in mostly one eye or both eyes despite normal structural findings. It is a common cause of visual impairment in children, with a worldwide prevalence of 1–4%. **Lonngi et al., [5]**

Optical coherence tomographic angiography (OCTA) is a noninvasive modality that provides depth-resolved visualization of the microvasculature of the retina, allowing the identification of the superficial retinal capillary plexus (SCP), the deep retinal capillary plexus (DCP), and the choroid. To our knowledge, macular OCTA findings in children with amblyopia have been very limited investigated. So, the main aim of this study was to detect macular vascular changes in amblyopic eye by optical coherence tomographic angiography.

Regarding the demographic data of the studied group, we found that the age of the studied participants ranged between 7 and 29 years with mean of 15 years. More than half of them were males (57.6%).

The current study was supported by the observational case-control study by **Lonngi et al., [5]** aimed to evaluate the retinal and microvascular features using OCTA in children (<18 years) with amblyopia. The study enrolled a total of 63 eyes of 59 patients were included in the study, 13 (21%) of which were amblyopic eyes and 50 (79%) were control eyes. Of the 50 control eyes, 46 (92%) were eyes of normal patients and 4 (8%) were normal fellow eyes of patients with amblyopia. The sample included 33 female children (56%), and the mean (SD) age was 8.0 (4.0) years (range, 4-17 years) for patients with amblyopia and 10.3(3.3) years (range, 4-17 years) for the controls. No difference in age or sex was observed between groups.

Also, in line with the current study **Hamurcu et al., [6]** aimed to investigate the structural and functional changes of the retina and optic nerve in amblyopia by OCTA, the study a total of 45 (24 female, 21 male) patients were included in the study (18 in the amblyopic and 27 in the control group). The mean age was 22.75 ± 10 years [range 18–57] and 22.90 ± 11.2 years [range 18–57] in amblyopic and control groups, respectively. No difference in age and sex was detected between the groups. The mean visual acuity of the amblyopic eyes was 0.25 (± 0.16). The mean spheric equivalent is 3.08 ± 1.10 [range 1.0–5.25] in amblyopic eyes.

Furthermore, the study by **Doğuizi et al., [7]** aimed to evaluate optical coherence tomographic angiography (OCTA) findings on retinal microcirculation in hyperopic anisometropic amblyopia compared with fellow eyes and nonamblyopic control eyes. A total of 40 pediatric patients with hyperopic anisometropic amblyopia and 57 control subjects were recruited, and 137 eyes (40 amblyopic, 40 fellow, and 57 control eyes) were evaluated. No significant difference was noted between patients with amblyopic eye and healthy controls in terms of age (P = 0.15), sex (P = 0.13), and laterality of the eye (left in 26 [65%] patients vs 27 [47%] controls; P= 0.09.(

The current study showed that there was non-significant relation between type of pathology and the detected OCTA changes.

To the best of our knowledge the current study was the first study assessed relation between type of pathology and the detected OCTA changes.

The current work revealed that there was significant relation between the detected OCTA changes and age. Younger ages were found to be significantly related to severe changes. However, there was non-significant relation between OCTA changes and sex.

The current study showed that that there was significant difference between the detected OCTA changes and sphere. Severe OCTA changes were found to be significantly related to patients with high error of refraction.

As regarding UCVA and BCVA, it was found that they were both significantly lower among patients with severe changes compared to those with mild and moderate changes (0.04, 0.10 versus 0.25, 0.10, 0.25 and 0.25 respectively).

To our knowledge this is the first study compared groups with Mild, Moderate, and Severe OCTA changes in eyes of children with amblyopia .

Our results were supported by **Lonngi et al., [5]** as they found that OCTA illustrates a significantly lower vessel density of the DCP, with a mean of a 5.7% reduction in the 6 × 6-mm scan in children with amblyopia. This reduction was a mean of 1.8% in the SCP. They did not find any statistically significant difference in the FAZ or foveal thickness between groups. This was in disagreement with the study by **Li et al., [8]** who performed a meta-analysis to clarify the retinal changes in unilateral amblyopia and found a thicker foveola in the amblyopic eyes than in visually normal control eyes; however, inner macular thickness

was not considerably different from outer macular thickness. The results by Lonngi are not consistent with the findings of Li because Lonngi found no differences between amblyopic and control eyes.

However, the study by **Doğuizi et al., [7]** reported that there was significant refractive difference in the sphere and spherical equivalent between the three studied groups as it was significantly higher in Amblyopic eyes while no significant refractive difference in cylinder was found between the studied groups. As well they reported that there was significant difference in BCVA between the three studied groups.

Pineles and Demer, [9] using magnetic resonance imaging, concluded that unilateral amblyopia is associated with subclinical bilateral hypoplastic optic nerves.

On the other hand, **Repka et al., [4]** used OCT and reported no difference in global or quadrantic retinal nerve fiber layer thickness compared with the fellow nonamblyopic eyes. These results indicate that optic atrophy is not the cause of moderate anisometropic or strabismic amblyopia. **Lonngi et al., [5]** found no abnormality in papillary and peripapillary vessel density, which is consistent with the findings of **Repka et al., [4]**.

Regarding the Macular vessel density OCTA among the studied groups, our results showed that there was a significant difference between Amblyopic eye and Fellow eye as regard SCP, DCP, and FAZ.

In agreement with our results, the study by **Rajavi et al., [10]** reported that Macular VD in different regions of super¦cial 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±0.06 µm2 in amblyopic eyes that was significantly larger than in the fellow eyes (0.21±0.06 µm2; P=0.007) and was comparable to the healthy controls.

In addition, **Doğuizi et al., [7]** reported that compared with fellow and control eyes, amblyopic eyes were associated with significantly lower foveal vessel density values within 300 mm around the foveal avascular zone (P<0.01) and lower vascular density in certain areas of superficial and deep retinal capillary plexus in axial length- and refraction-adjusted analysis (P < 0.05 for all), along with significantly higher full thickness of the central macula (P = 0.04). In amblyopic eyes, best-corrected visual acuity values were negatively correlated with foveal density (r = - 0.57; P 5 0.02) and deep capillary retinal plexus vascular density in foveal (r = - 0.51; P 5 0.03) parafovea temporal (r = - 0.52; P 5 0.03), and parafovea superior (r = - 0.51; P 5 0.04) areas .

Furthermore, the Systemic Review and Meta-Analysis by **Gao et al., [11]** enrolled 12 studies to examine the quantitative measurements of OCTA in children with amblyopia using the meta-analysis methodology and concluded that According to OCTA, amblyopic eyes had lower vessel density in parafoveal SCP and DCP compared with healthy control eyes, but not compared with fellow eyes. There were no significant differences regarding the foveal avascular zone area and foveal thickness between amblyopic and non-amblyopic eyes.

In the earliest observation by **Guo et al., [12]** on OCTA in amblyopic patients (anisometropic (n=13) and strabismic (n=9) total n= 22), they discovered no significant changes in SCP and DCP vessel density values as compared to fellow eyes. Even though they tested a heterogeneous group of patients (up to ~6 D refractive errors), they did not encounter any differences in retinal vasculature.

This study has several limitations, including a small sample size and lack of additional tests at the time of OCTA imaging. The importance of the small sample size cannot be understated, and it is unclear whether our findings would be generalizable to a larger group of patients .

5. Conclusion

Young patients with amblyopia have reduced superficial and deep retinal capillary density on OCTA. These vascular changes may be associated with decreased visual acuity. Our findings indicate a possible association between retinal microcirculation and amblyopia. The clinical relevance of this finding remains to be determined. Further studies with larger sample size are needed to confirm the current results.

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