Peripapillary Retinal Nerve Fiber Layer Thickness by Optical Coherence Tomography in Patients with Unilateral Amblyopia

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ABSTRACT:

BACKGROUND:

Amblyopia is a common cause of unilateral visual defect, affecting patients with history of strabismus, refractive errors, and those who had visual deprivation in the critical period of visual development. Amblyopia may have an effect on various levels of the visual pathway. Cells atrophy in the lateral geniculate nucleus that receives information from the affected eye, and a shift in the dominance pattern in the visual cortex have been reported. Retinal involvement in amblyopia is controversial.

SUBJECTS AND METHODS:

This is a cross sectional study carried out in Al-Shaheed Ghazi al-Hareery Teaching Hospital in Medical City at Baghdad, Iraq .Forty-two patients with unilateral amblyopia were selected, 23 males and 19 females with age range of 12-40(mean age of 25.33 years) all of these patients had one amblyopic eye and the other eye normal. OCT scan was done for both eyes of each patient and the RNFLT measured after complete ophthalmological examination (VA, refraction, slit lamp, and funduscopic examination

RESULTS:

It has been noticed that the mean of NFLT in normal eyes was higher than that of amblyopic eyes (108.88 versus 105.05) but this difference was statistically not significant (P=0.074).

CONCLUSION:

OCT is a sensitive way to estimate RNFLT, we concluded that there is no statistically significant difference in NFLT between the amblyopic, compared to the normal eyes. Also NFLT seems not affected by: type of amblyopia, age of patients and also the severity of amblyopia as all these factors didn't reach statistical significant.

KEY WORDS: amblyopia, retinal nerve fiber layer thickness, Optical coherence tomography

INTRODUCTION:

Anatomy of visual pathway

The visual pathway [fig.1] consists of the groups of cells and synapses that carry visual input from the eye to the brain and then process the information. It includes the retina, optic nerve, optic chiasm, optic tract, lateral geniculate nucleus, optic radiations, and striate cortex. The first receptive cell type in this pathway, highly specialized sensory cell, the photoreceptor, converts the light energy into a neural signal that is passed to bipolar and amacrine cells and then reaches the ganglion cell. These mentioned cells and synapses all lie in the retina. [1]The nasal fibers from each eye cross in the optic chiasm and end in the opposite side of the visual cortex, while the temporal fibers do not cross at the chiasm. The optic tract carries nerve fibers from the chiasm to the lateral geniculate nucleus which is topographically organized and the fibers synapse there. The fibers leave the lateral geniculate nucleus as the optic radiations that end in the visual cortex of the occipital lobe (the striate cortex area 17 and V1) then fibers terminate in the calcarine fissure. In the cortex information about the visual environment is processed and conveyed to the related neurologic centers and to visual association areas in the brain [2].

Definition: Amblyopia is the decrement in the best corrected visual acuity in one or, less commonly, both eyes that cannot be caused by any structural defect of the eye. Amblyopia is also considered as a developmental disorder of spatial vision, amblyopic primates show reduced contrast sensitivity that is restricted to

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mid to high spatial frequency ranges of stimuli also exhibit lower optotype acuity for the affected eye. [4]. Amblyopia is associated with the presence of strabismus, anisometropia, or form deprivation early in life. If the same disorders occur later in life, amblyopia does not occur. It is also the most common cause of decreased vision in a single eye among children and young adults. [5]

The term "amblyopia" is sometimes incorrectly used interchangeably with a term called “lazy eye”. "Amblyopia" is made up of ambly- from the Greek "amblys" meaning blunt, faint, dull, or dim and –opia came from a Greek word "ops" meaning eye, referring to vision, so amblyopia literally means dim vision. [6]

Epidemiology, prevalence and screening: Amblyopia affects about 2%-5% of population, the prevalence have been found to increase in children with history of prematurity, those with positive family history of amblyopia, and children with developmental delay. Some authors suggested that strabismic amblyopia found in 3.3% of white children, but lower at 2.1% among African American children [7].

Amblyopia is a preventable and reversible with early detection and management. Thus, it is very important to identify the children in risk at younger age, so the prognosis is better than later detection.

There are many screening techniques for amblyopia which vary according to the age of the child, these include directly testing visual acuity, and risk factors detection. The first category include: visual acuity testing which has a subjective component and therefore should be chosen with respect of child’s age, and level of cooperation; for example a 3 year old child would name or matches letters and shapes, while an infant or toddler is better tested by assessing fixation preference or using forced preferential fixation test like teller cards. With a wide variety of methods for vision testing, it has been shown that vision screening identified about 92% of patients with visual defects. [4]

Pathophysiolog: Amblyopia is in general, a defect of central vision; and the peripheral vision is usually normal.

Although there are many types of amblyopia, it is believed that their basic mechanisms are the same even though each factor may contribute different amounts to a specific type of amblyopia. In general, it is believed to result from inadequate foveal or peripheral retinal stimulation and/or abnormal binocular interaction that cause different visual input from the foveae. [9]

Three critical periods of human visual acuity development have been identified. Vision can be affected by the various mechanisms to cause amblyopia during these periods. These are as follows:

The development of visual acuity from the 20/200 to 20/20; which occurs from birth to age 3-5 years.

The period of the highest risk of development of deprivation amblyopia, from a few months of life to 7 or 8 years.

The period to obtain recovery from amblyopia, suggested that it starts from the time of deprivation up to the teenage years or even sometimes the adult years. These above time frames when determined, they might help in planning treatment for each age group [10].

The most prominent effect of early monocular amblyopia is anomalous changes in the ocular dominance distribution of V1 neurons (ocular dominance plasticity), also the afferent fibers from LGB compete for consolidation of functional connections in V1 also termed(ocular competition) ,which occurs in the critical period of development, this competition is activity dependent; therefore depriving normal signals from one eye makes the other eye in a challenge of competitive disadvantage and leads to severe loss of functional connections in V1 from the affected eye. Electrophysiological studies consistently report severe loss of binocularity driven cells and a clear shift in the ocular dominance of cortical neurons from the deprived eye, in subcortical structures there is mild shrinkage of cell bodies of LGB neurons of the affected eye. Regarding the retina there is no significant structural or functional defects due to early monocular amblyopia. [4]

Amblyopia may have an effect on various levels of the visual pathway. Cells atrophy in the lateral geniculate nucleus that receives information from the affected eye [11], and a shift in the dominance pattern in the visual cortex [12,13] have been reported . Retinal involvement in amblyopia is controversial [14-18].

A role for optic nerve involvement, termed dysversion or hypoplasia, in amblyopia has been suggested by Lempert, who reported this optic nerve abnormality was present in optic nerve photographs in 45% of 205 amblyopic eyes [19-20].

More recently Lempert had reported reduced optic disc rim areas for both amblyopic and the fellow eyes with the reduction more pronounced in the amblyopic eyes [21].

Classification

Strabismic amblyopia: one of the most common etiological cause of amblyopia which develops in the deviating eye of a child with strabismus , which is thought to be a result of inhibitory interaction between neurons carrying no fusible information from the two eyes. This will result in the domination of visual centers in the cortex by the input from the fixating eye, at the same time the deviating eye will suffer from reduced cortical responsiveness. Therefore suppression develops as an adaptive way to prevent diplopia and confusion.[22]

Refractive: the cause of this common type of amblyopia is constant defocus of retinal images in one or both eyes. Two types which are: anisometropic and isometropic. Anisometropic levels that cause amblyopia are: greater than 1.50 D of anisohypermetropia, 2.00 D of anisoastigmatism, and 3.00 D of anisomyopia. Higher degrees of anisometropia are associated with greater risk of amblyopia. Isometropic amblyopia develops when there is bilateral decrease in the visual acuity due to large, approximately equal, uncorrected refractive errors in both eyes, hyperopia greater than 4.00-5.00D, myopia greater than 5.00-6.00 D have a risk of developing isometropic amblyopia.[22]

Deprivative: this type is the least common, most severe, and most difficult to treat. Visual deprivation occurs due to obstruction of visual axis of any cause, causes are; congenital or early- onset cataract, blepharoptosis, periocular lesions, corneal opacities, and posterior segment disease as vitreous hemorrhage.[22]

Reverse amblyopia is a subtype of deprivation amblyopia that develops in the fellow eye as a result of prolonged patching or penalization.

Another classification of amblyopia as mild, moderate, and severe; according to best corrected visual acuity [23]

Evaluation Diagnosis of amblyopia can be made when the patient has decreased visual acuity that cannot be attributed to a physical abnormality and there is a factor which is known to cause amblyopia, as strabismus, cataract, etc. There is no pathognomonic feature of amblyopic vision but, for example, crowding phenomenon is typical although not uniformly demonstrated. Peripapillary nerve fiber layer thickness (RNFLT) has been studied before to know if there is any correlation between it and amblyopia in unilateral cases. [24]. Several techniques are available to evaluate RNFLT such as, Red free ophthalmoscopy, Scanning laser polarimetry (SLP), and Ocular coherence tomography (OCT). SLP estimates the RNFLT based on the birefringence of nerve fiber layer that retards the laser beam, but errors can be made attributed to anterior segment decompensation. OCT measures RNFLT more accurately and results corresponds to the RNFLT measured histologically. [24]. OCT is based on near-infrared interferometry, and this is why its measurements are not affected by the refractive state of the patient, axial length, or mild cataracts. RNFLT measured with OCT is also not affected by LASIK (laser-assisted in situ keratomileusis). [25]

However, secondary cataract, dense nuclear sclerosis, and replacement of vitreous with silicon; all these can reduce accuracy of OCT measurements. Excluding these above mentioned conditions, OCT is considered a reliable imaging technology. [Fig. 2]

OCT was first described in 1991 by Huang et a and is widely used in the evaluation of retinal and also of optic nerve diseases, especially glaucoma. OCT imaging had many technological advances, the most important of these was the development of spectral domain OCT (SD-OCT) technology (also known as Fourier domain OCT. Image speed is 60 times faster and image resolution is five times higher than in conventional time-domain OCT.[24]

RNFL thickness measured by SD-OCT machines are interpreted as normal or abnormal with the aid of normative databases of RNFL thickness values for age-matched individuals, each machine has its own database. For a commonly used SD-OCT (Cirrus, Carl Zeiss, USA) this database constitutes of 284 healthy individuals with an age range of 18-84 years. Normal RNFL values are not interchangeable between different SD-OCT machines. [26]

Aim of the study: The target is to find out if there is any change in thickness of retinal nerve fiber layer by OCT in patients with amblyopia.

SUBJECTS AND METHODS:

Study design, setting and data collection time: This is a cross sectional study carried out in Al-Shaheed Ghazi al-Hareery Teaching Hospital in Medical City at Baghdad, Iraq.

Subjects: Forty-two patients with unilateral amblyopia were selected, 23 males and 19 females with age range of 12-40(mean age of

25.33 years) all of these patients had one amblyopic eye and the other eye normal.
Socioeconomic status was not put in consideration when data collected.
Source of data: Patients attended outpatient department, all of them were thoroughly examined and sent to be examined at OCT department al- Shaheed ghazi hospital.
Inclusion criteria: Patients with amblyopia, either strabismic or refractive.
Exclusion criteria:
1-patients with high refractive errors; myopia more than 5 D, hyperopia more than 4 D .
2-patients with optic disc anomalies
3-patients with suspicion of glaucoma
4-patients with any retinal, optic disc disease or history or evidence of intraocular surgery.
5-patients older than 40 and younger than 10 years
Methods: Patients with unilateral amblyopia were enrolled. After proper history taking both medical and ophthalmological, Clinical examinations done for each one of them including best corrected visual acuity, refractive error, extraocular muscles motility, intraocular pressure measured, slit lamp examination, fundoscopy, and A-scan for axial length.
After dilating the pupils with one drop of 1% tropicamide, OCT scan taken using one device (OPTOVUE RTvue, a form of F-D/S-D OCT) for all patients with the same setting for measurement of peripapillary retinal nerve fiber layer thickness for both eyes of each patient and results obtained by the same operator(to decrease chance of inter individual variation of results), limits drawn in the color cross section. Scans with signal strength less than 5 were considered unacceptable and not included. Scans were also excluded from the analyses if they were visibly de-centered or did not have normal appearing color cross sections average, RNFLT was measured three times for each eye, the mean of normal eyes and that of the amblyopic eyes were measured and comparison done between them.
Putting in consideration that for each normal individual, mean RNFL thickness between the two eyes should not differ by more than 9 to 12 µm. [28].
Statistical analyses: The data analyzed using Statistical Package for Social Sciences (SPSS) version 23. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Student t-test was used to compare the continuous variables among study groups. P – value less than 0.05 was considered significant.

RESULTS:

Distribution of study patients according to the difference in NFLT between the normal and amblyopic eyes

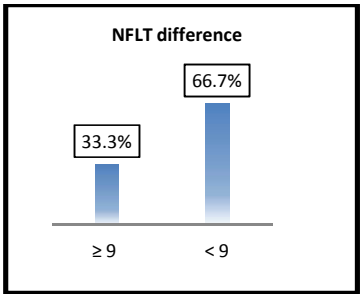

Table 3.1: Difference in means of NFLT between normal and amblyopic eyes (with strabismus and refractive).

Eye	NFLT		P- Value
	Mean	Std. Dev	
Normal	108.88	10.15	0.074
Amblyopia	105.05	9.21	

Table 3.2: Difference in mean of NFLT between normal and amblyopia with strabismus.

Eye	NFLT		P- Value
	Mean	Std. Dev	
Normal	109.94	8.99	0.148
Amblyopia with strabismus	106.49	8.91	

Table 3.3: Difference in mean of NFLT between normal and eye with refractive amblyopia.

Eye	NFLT		P- Value
	Mean	Std. Dev	
Normal	106.5	12.43	0.239
Refractive amblyopia	101.8	9.40	

Table 3.4: Difference in mean of NFLT between normal and eye with mild amblyopia.

Eye	NFLT		P- Value
	Mean	Std. Dev	
Normal	107.63	8.15	0.95
Mild amblyopia	107.85	9.13	

Table 3.5: Difference in mean of NFLT between normal and eye with severe amblyopia.

Eye	NFLT		P- Value
	Mean	Std. Dev	
Normal	109.32	10.79	0.059
Severe amblyopia	104.33	9.57	

Table 3.6: Difference in mean of NFLT between normal and amblyopic eye in study patients aged < 25 years.

Eye	NFLT		P- Value
	Mean	Std. Dev	
Normal	112.78	9.78	0.093
Amblyopia	108.04	8.92	

Table 3.7: Difference in mean of NFLT between normal and amblyopic eye in study patients aged ≥ 25 years.

Eye	NFLT		P- Value
	Mean	Std. Dev	
Normal	104.15	8.64	0.333
Amblyopia	101.44	8.41	

DISCUSSION:

Amblyopia is defined as unilateral- or bilateral-reduced best-corrected visual acuity in response to abnormal visual stimulus during a critical period of development of the visual areas in the brain. Yet, some studies found a strong association between the amblyopic eye and cellular atrophy in the lateral geniculate nucleus (LGB). [29]

Early strabismus and refractive errors are risk factors for unilateral amblyopia, whereas bilateral
astigmatism and hyperopia are risk factors for bilateral amblyopia. [30]The sensitive period during which acuity of an amblyopic eye can be improved is usually up to 7-8 years in strabismic amblyopia, and may be longer (into teens) in anisometropic amblyopia. [22]

Treatment of amblyopia is effective in reducing the overall prevalence and severity of visual loss. Correction of refractive error alone has been shown to significantly reduce amblyopia and less frequent occlusion can be just as effective as more extensive occlusion. Putting in mind that occlusion or penalisation in amblyopia treatment can give negative changes in behavior in children and impact on family life, and these factors should be considered in prescribing treatment, particularly because of their influence on compliance. [31]

In several studies which were investigating the relationship between amblyopia and retinal anatomy, retinal nerve fibers layer thickness (RNFLT) was found thicker comparing control patients. [32]

In this study, the total number of study patients was 42. All of them were diagnosed with unilateral amblyopia.

Amblyopia:about 57.1% of the study population with strabismic type of amblyopia was more than two thirds of study patients (69%).This result was approaching to a result observed in Turkish study in 2015 conducted on 61 patients with amblyopia, in which the strabismus type of amblyopia observed in 30 patients (50%) of the remaining amblyopic patients. [33] Lower results obtained by different studies included the following;

In Taiwan (2004), Among 38 patients with unilateral amblyopia included in a study, amblyopia distributed evenly in both eye 50% for each (19 patients with right eye and 19 for left), in the same study, twenty had strabismus amblyopia (52.7 %) while the other 18 without strabismus (47.3%) had a diagnosis of refractive amblyopia. [26]

An Egyptian study conducted in 2014 on 64 patients with unilateral amblyopia, divided the patients into three groups, where the strabismic subtype found in 22 patients (34%) of the total amblyopic patients. [34]

Korean study (2006) conducted on 26 children (52 eyes total) with unilateral amblyopia, with regard the type of amblyopia they observed that strabismus amblyopia found in six cases (23%) of other types. [35]

Nerve fibers layers' thickness (NFLT) in normal and amblyopic eye

In the current study, difference in NFLT between the normal and amblyopic eye less than 9µm had the highest proportion which represented 66.7% of the patients in this study, while mean of NFLT in normal eyes was higher than that of amblyopic eyes (with strabismus and refractive) which was 109.94 versus 106.49, but this difference was statistically not significant (P=0.148). Mean of NFLT in normal eye was higher than that of eye with refractive amblyopia (106.5 versus 101.8), which also was statistically not significant (P=0.239).

In comparison, a result observed in 37 patients with unilateral amblyopia enrolled in a study conducted in 2009 from 12 different clinical sites, in which they found that the global RNFL thicknesses of the amblyopic and normal eyes were 111.4 µm (range 93.4 µm to 136.0 µm) and 109.6 µm (range 91.3 µm to 136.0 µm), respectively (mean difference = 1.8 µm thicker in the amblyopic eyes). There were no significant differences in RNFL thickness between amblyopic and normal eyes in any quadrants (P =0.482). [36]

Another comparison with the current study was found in an Australian study conducted in Sydney Childhood Eye Study center (2009), in which they found that peripapillary RNFL thickness was not significantly different between amblyopic and normal fellow eyes or normal eyes of non-amblyopic children. [37]

Korean study (2006) conducted on 26 children was also compared with the current study in that no statistically significant difference between the retinal NFLT of the normal fellow eyes and that of the amblyopic eyes in the children with amblyopia (P= 0.810), in which the mean of retinal NFLT of the amblyopic and normal fellow eyes was 107.2±16.2 and 106.7±16.5 respectively. [35]

Amblyopic eyes were compared with their fellow eyes with regard retinal NFLT in a Turkish study conducted on 61 patients with amblyopia in 2015 and noticed that strabismic group had slightly thicker RNFL (106 µm) comparing to control group (104 µm), in which no significantly different found between strabismic and normal fellow eyes (P 0.650).[33]

In contrary to the current study, Taiwanian study (2004) observed that the difference in RNFLT between the amblyopic with strabismus and the normal fellow eyes was statistically significant (P=0.003) and the mean of NFLT in amblyopic eyes with strabismus was higher than that of normal eyes (129.15 µm versus 128.2µm) with mean difference = 11.55 µm thicker in the amblyopic eyes, while the mean of NFLT of eye with refractive amblyopia was higher in comparison to NFLT of normal eye (136.6 µm versus 129.7 µm), statistical significance (P <0.001) difference in RNFLT between the

amblyopic with refractive type and the normal fellow eyes. [26]

Also in contrast with an Egyptian study in 2014, in which (regarding the strabismus group) they showed, the mean of parapapillary RNFLT in strabismic amblyopic eyes and normal eye was 105±9.22 versus 104±8.23 respectively, with a significant difference in the global RNFLT values between the amblyopic with strabismus and the normal fellow eyes (P= 0.021). [34] This puts in mind that there might be a correlation between amblyopia and retinal changes, which didn't approved by our study.

In general many studies support our results and proved the fact that there is little if any retinal changes in amblyopic eyes, and this is a disorder of higher center rather than retina; nevertheless, this fact need to be supported by more studies.

CONCLUSION:

OCT is a sensitive way to estimate RNFLT, we concluded that there is no statistically significant difference in NFLT between the amblyopic, compared to the normal eyes.

Also NFLT seems not affected by: type of amblyopia, age of patients and also the severity of amblyopia as all these factors didn't reach statistical significant.

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