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A Comparative Cross-sectional Study on Amblyopia and its Relationship with Retinal Nerve Fiber Layer Thickness

Muhammad Asad Saeed, BS Optom
Azka Sadat, MS HCM, BS Optom
Fareeha Ayyub, M Phil Optom
Amtul Aziz, DOMS, MBBS
Rida Fatima, BS Optom
Qurat ul Ain, BS Optom
Pakistan Institute of Ophthalmology, Al-Shifa Trust Eye Hospital • Rawalpindi, Pakistan

Muhammad Asad Saeed, BS Optom
Rawalpindi, Pakistan

Optometrist, Shifa International Hospital Islambad, Pakistan
BS Optometry and Orthoptics
PIO, ASTEH Rawalpindi, Pakistan, 2022
DHA-ELIGIBLE Optometrist
Worked on project "INSPIRE" in collaboration with KEMU Lahore, Pakistan and Sightsavers

ABSTRACT

Background: Amblyopia affects approximately 1.75% of the world's population. Atrophic alterations in the lateral geniculate nucleus have been observed in amblyopic eyes, leading to the hypothesis that retinal nerve fiber layer (RNFL) thickening is caused by a limitation of normal postnatal ganglionic cell reduction. This study was conducted to determine and compare the thickness of the RNFL in all types of amblyopic and non-amblyopic eyes.

Methods: A comparative cross-sectional study was conducted at Al-Shifa Trust Eye Hospital Rawalpindi over six months. Data were collected from 70 patients (140 eyes) using a clinical structured questionnaire. RNFL thickness was measured using optical coherence tomography. All amblyopic patients were included in this study. A one-way ANOVA and paired sample t-test were applied to compare the RNFL thickness between amblyopic and non-amblyopic eyes.

Results: The mean age of the patients was 10.20±2.811, ranging from 5 to 16 years. The mean thickness of RNFL globally in strabismic amblyopia was 108.1±14.1, whereas in anisometropic and bilateral refractive amblyopia, the RNFL thickness was 105.74±11.042 and 107.84±12.329, respectively. There was no statistical mean difference between thicknesses of strabismus, anisometropic, and bilateral amblyopia. There was no statistically significant difference found between the thicknesses among all quadrants of anisometropic amblyopia.

Conclusion: There was no significant difference in RNFL thickness between different types of amblyopia. Similarly, there was no significant difference in the thickness of RNFL in amblyopic and non-amblyopic eyes.

Keywords: amblyopia, optical coherence tomography, retinal nerve fiber thickness

Introduction

An estimated 285 million people around the world are visually impaired; nineteen million are children below the age of 14 years. Refractive errors, which are the most common cause of vision impairment in children, affect about 43% of this population.[1] In 2020, 16 million in Pakistan suffered distance vision loss, while over 10 million suffered from near-sightedness.[2] The prevalence of amblyopia is 1% to 5% globally, while Asians have a 3% prevalence.[3]

Refractive errors and amblyopia are the most common reasons for visual loss in children.[4] Amblyopia, which comes from the Greek phrase "dullness of vision," is the leading cause of vision loss in infants.[5] Amblyopia is a neurodevelopmental and neurophysiological ocular condition that causes poor vision but has no associated pathology. It can be treated most effectively if started at an early stage.[6]

However, recent research indicates that older patients may benefit from treatment since the visual system's plasticity persists into adulthood. Additionally, children and adults with amblyopia may benefit from treatment that focuses on the suppressive interactions within the visual cortex to enhance both binocular and monocular visual performance.[3]

Amblyopia is defined by diminished visual acuity in one or both eyes as a result of visual deprivation or aberrant interaction during vision development.[7] There are three main types: strabismic, anisometropic, and deprivation.[8,9] Atrophic alterations in the lateral geniculate nucleus have been observed in amblyopic eyes, leading to the hypothesis that retinal nerve fiber layer (RNFL) thickening is caused by a limitation of normal postnatal ganglionic cell reduction.[10] Between the inner limiting membrane and the retinal ganglion cell layer, the RNFL is densely packed. It is made up of ganglion cell axons, astrocytes, retinal arteries, and Müller cell processes, constituting the inner limiting membrane, which covers the nerve fiber layer's surface.[11] Between roughly 18 and 30 weeks of gestation, the total population of cells in the ganglion cell layer in humans reaches its peak (2.2-2.5 million cells). The cell number rapidly decreases to 1.5 to 1.7 million cells. In the adult human optic nerve, there are 1.1 million axons.[12] The RNFL thickness continues to diminish with advancing age.

The assessment of the RNFL is of high significance for the identification of glaucoma, optic nerve abnormalities, and other diseases. Optical coherence tomography (OCT) can be used to assess RNFL.[13] If amblyopia affects the process of postnatal reduction of ganglionic cells, RNFL thickness may be affected. Abnormal RNFL could lead to other diseases, such as glaucoma, optic neuropathies, and optic neuritis. Therefore, the purpose of this study was to find an association between amblyopia and RNFL thickness, as there are conflicting results in previous studies, and no such study has been conducted in Pakistan. This study will help us to determine the relationship between RNFL and amblyopia.

Methods

This study was conducted at the Orthoptics Department of Al-Shifa Trust Eye Hospital, Rawalpindi, a tertiary eye care facility. This comparative cross-sectional study included patients of both genders, ages 5 to 16 years, with amblyopia. This study included strabismic and refractive (anisometropic, isometropic, and meridional) amblyopia, as well as unilateral and bilateral amblyopia. Unilateral amblyopia was characterized as a ≥two-line difference in best VA, when <20/30 in the poorer seeing eye and with presence of past or current strabismus and/or anisometropia. Bilateral amblyopia was characterized as best-corrected visual acuity (BCVA) in the two eyes <20/40 within the sight of factors that aggravated the amblyopia.[14] All procedures and methods of data collection were conducted following the Declaration of Helsinki.

Sample size

The sample size of this study was calculated by using the WHO calculator at the confidence interval of 95%. The power of the test was 90%, and the population standard deviation was 16.2. The test value of the population mean was 107.2, and the anticipated population mean of the pilot study was 113.8. The sample size was 64. Seventy patients were included for this study.

Sample selection criteria

All types of amblyopia and both genders were included. Patients with any ocular pathology, such as glaucoma, optic nerve disease, cataract, or macular disease, as well as those not willing to participate, were excluded from the study.

Ethical consideration

Approval was given by the Ethical Review Committee at Al-Shifa Trust Eye Hospital (ERC-71/AST-21) and by the head of the department of the hospital before data collection. Moreover, verbal informed consent was also taken from every individual before they participated in this study. Face and content validity was checked by circulating it to experts in the field. Confidentiality of the patient's data was maintained, and ethical values of research were properly considered and followed at every step of the study.

Data collection procedure

Data collection for the study was done at the Paediatric and Diagnostic Department of Al-Shifa Trust Eye Hospital, Rawalpindi. By using the universal non-probability sampling technique, data was collected from the patients for six months, from October 2021 to March 2022. This was done to ensure the inclusion of all patients fulfilling the study criteria during the study duration, as it would allow a more accurate analysis of the variables. A clinical Performa was used, which was based on the previous studies and clinical findings. The first part of the Performa consisted of socio-demographic characteristics; the second part contained ocular parameters such as visual acuity and objective refraction. The last part consisted of RNFL thickness, including nasal, temporal, supra-nasal, supra-temporal, intranasal, and infra-temporal, which was measured by OCT.

The responses recorded in the Performa were recorded and analyzed using Statistical Package for social sciences (SPSS) version 21. The descriptive analysis was done on the categorical and continuous variables. Percentages and frequencies were reported for categorical variables, and mean and standard deviation were recorded for continuous variables. As the data were normally distributed, a parametric approach was used during inferential analysis. In inferential analysis, all statistical tests used a confidence interval of 95%, and a p-value of <0.05 was considered significant. Therefore, one-way ANOVA and paired sample t-test were used to compare the mean difference of RNFL thickness in different types of amblyopia and to compare the RNFL thickness of amblyopic and non-amblyopic eyes.

Results

A total of 140 eyes of 70 patients were included in the study. The mean age of participants included in the study was 10.20 (+/-2.811), ranging from 5 to 16 years. Both genders were included in the study, out of which males outnumbered females. Out of the total, 37 patients were from urban areas. Treatment included: 34 (48.6%) were using only glasses, while 36 (51.4%) were using both glasses and patching therapy (Table 1).

Table 1. Socio-Demographic Characteristics

Socio-Demographic Characteristics	Frequency	Percentage (%)
Gender		
Male	40	57.1
Female	30	42.9
Area of residence		
Urban	37	52.9
Rural	33	47.1
Other activities		
Outdoor activities	44	62.9
Indoor activities	26	37.9
Refractive error		
Myopia	14	20.0
Hyperopia	18	25.7
Astigmatism	38	54.3
Treatment		
Glasses only	34	48.6
Glasses with patching	36	51.4

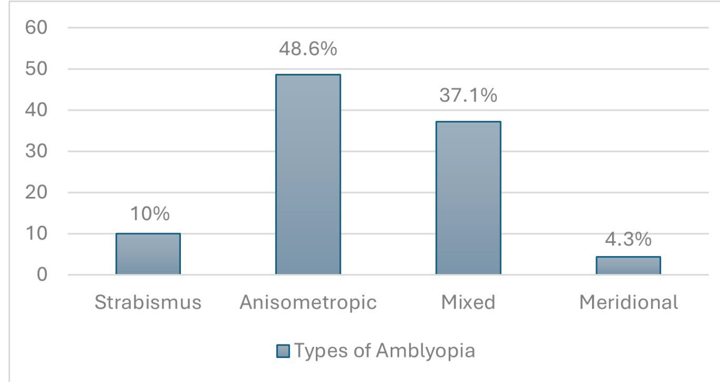

Figure 1. Types of amblyopia

Table 2. Ocular Parameters

Variables	N	Mean	Standard Deviation
BCVA in Amblyopic Eyes	95	0.81	0.570
BCVA in Non-Amblyopic Eyes	45	0.12	0.145

A majority of the patients (54; 77.1%) presented with a family history of amblyopia (Figure 1). The mean and standard deviation of best-corrected visual acuity were 0.81±0.570 logMAR in the amblyopic eyes, whereas the best-corrected visual acuity in the non-amblyopic eyes was 0.12±0.145 logMAR (Table 2). The most common presenting complaint was blurred vision (74.3%), as shown in Figure 2.

The one-way ANOVA was used to compare the mean difference in RNFL thickness among different types of amblyopia. There was no statistically significant difference between the various types of amblyopia (Table 3). The paired sample t-test was used to compare the RNFL thickness of the amblyopic and non-amblyopic eyes. Although the amblyopic RNFL was thicker than that of non-amblyopic eyes, no statistically significant difference was found (Table 4).

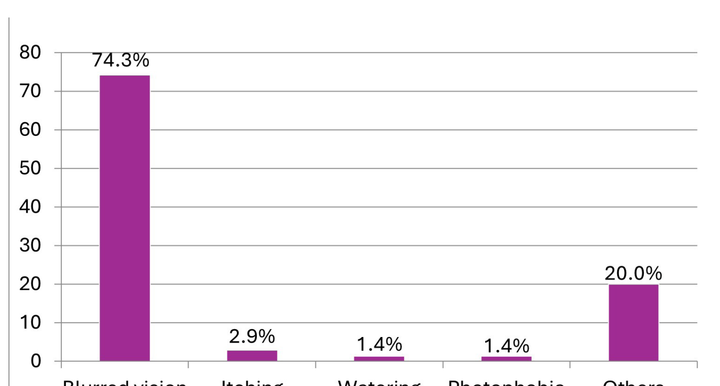

Figure 2. Chief complaints of amblyopic patients

Table 3. RNFL Thickness in Different Types of Amblyopia

RNFL Thickness	Strabismic Amblyopia		Anisometropic Amblyopia		Bilateral Amblyopia		Meridional Amblyopia		F	P-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Nasal Quadrant	80.82	12.17	85.82	20.77	94.65	24.46	81.20	20.42	1.792	0.15
Temporal Quadrant	69.88	9.84	75.67	14.53	68.09	13.61	75.20	9.83	2.266	0.86
Supra-Temporal Quadrant	132.63	20.56	135.38	16.47	133.84	21.84	133.60	11.78	0.071	0.97
Supra-Nasal Quadrant	142.38	25.66	121.05	30.23	122.23	27.53	125.80	23.67	1.313	0.27
Infero-Nasal Quadrant	150.13	27.28	126.18	28.52	136.37	25.44	148.00	50.79	2.343	0.078
Infero-Temporal Quadrant	139.75	23.87	143.92	17.16	145.07	26.05	140.60	10.04	0.173	0.915
Globally	108.13	14.11	105.74	11.04	107.84	12.32	105.80	12.65	0.251	0.860

Table 4. RNFL Thickness Between Amblyopic and Non-Amblyopic Eyes

RNFL Thickness	Amblyopic Eyes		Non-amblyopic Eyes		T	P-value
	Mean	SD	Mean	SD		
Nasal Quadrant	86.89	18.70	82.80	17.46	-1.275	0.209
Temporal Quadrant	75.87	14.17	74.27	10.54	-0.949	0.348
Supra-Temporal Quadrant	140.89	19.21	138.81	18.73	-0.791	0.433
Supra-Nasal Quadrant	132.57	27.07	129.47	27.85	-0.970	0.337
Infero-Nasal Quadrant	139.13	32.17	136.87	32.27	-0.750	0.457
Infero-Temporal Quadrant	147.18	22.15	146.11	20.74	-0.337	0.737
Globally	105.22	23.64	108.07	10.11	-0.877	0.385

The one-way ANOVA was used to compare the mean difference in RNFL thickness among different types of refractive errors. There was no statistically significant difference between various types of refractive error in all quadrants except supra-nasal. RNFL thickness for the supra-nasal quadrant in hyperopes was thicker amongst the refractive errors given (Table 5). The one-way ANOVA was also used to compare the mean difference in RNFL thickness among amblyopic patients with and without using patching therapy. No statistically significant difference was found in all quadrants, as shown in Table 6.

Discussion

The main objective of this study was to determine the RNFL thickness and compare it between different types of amblyopia and fellow non-amblyopic eyes. In the present study, the mean RNFL thickness was not statistically significantly different between amblyopic and non-amblyopic eyes, which is in accordance with the study conducted by Kee et al.,[15] in which the thicknesses of the superior, inferior, nasal, and temporal quadrants of the retinal nerve fiber layer between normal children and children with amblyopia were also not statistically significant. In a study by Yen et al.,[16] the difference in RNFL thickness between strabismic amblyopic eyes and fellow eyes did not reach statistical significance, so it was concluded that amblyopia is not linked with RNFL thickness.

In thirty individuals with aniso-hypermetropic amblyopia, Yoon et al.[17] used the OCT to evaluate both peripapillary and macular RNFL thickness. They found that anisometropic amblyopic eyes have thicker peripapillary RNFL than normal eyes. Because of the tiny size of the eye, those with high hypermetropia may have thicker RNFL, and the apparently increased thickness of RNFL may be attributable to this structural alteration in the eye rather than the effect of amblyopia.

Table 5. RNFL Thickness in Different Types of Amblyopia

RNFL Thickness	Myopic Amblyopia		Hypermetropic Amblyopia		Astigmatic Amblyopia		F	P-value
	Mean	SD	Mean	SD	Mean	SD		
Nasal Quadrant	91.07	30.78	94.11	22.202	89.08	18.720	0.305	0.738
Temporal Quadrant	72.67	11.98	70.39	18.449	69.32	13.973	0.274	0.761
Supra-Temporal Quadrant	140.60	23.874	132.89	18.739	130.47	15.305	1.662	0.197
Supra-Nasal Quadrant	103.93	22.864	134.50	29.159	122.03	25.251	5.756	**0.005**
Infero-Nasal Quadrant	127.80	26.138	137.17	26.320	136.74	30.674	0.591	0.556
Infero-Temporal Quadrant	146.80	13.241	138.72	22.533	143.18	25.628	0.524	0.595
Globally	106.07	12.157	108.17	14.738	103.13	18.425	0.613	0.545

Table 6. RNFL Thickness Between Amblyopic and Non-Amblyopic Eyes

RNFL Thickness	Glasses without patching		Glasses with patching		T	P-value
	Mean	SD	Mean	SD		
Nasal Quadrant	90.66	23.551	90.89	21.423	0.002	0.966
Temporal Quadrant	73.09	15.779	67.58	13.244	2.539	0.116
Supra-Temporal Quadrant	136.11	19.165	130.42	17.451	1.717	0.194
Supra-Nasal Quadrant	124.60	24.997	118.22	29.798	0.952	0.333
Infero-Nasal Quadrant	132.60	28.907	137.25	28.454	0.467	0.497
Infero-Temporal Quadrant	140.40	18.820	145.17	25.905	0.783	0.379
Globally	106.91	10.430	103.19	20.499	0.921	0.341

Another study conducted by Chen et al.[18] used Spectral Domain (SD)-OCT to compare the thickness of the macula and RNFL in children with anisometropic amblyopia. They discovered that the average thickness of the outer macular ring and RNFL was substantially thicker in anisometropic amblyopic eyes than in normal eyes. Furthermore, the macular thickness of both treated amblyopia and untreated amblyopia were the same. They observed that macular and RNFL thicknesses appeared to be more strongly linked with axial length and refraction variations than with amblyopic development.

Atsushi Miki and Motohiro Shirakashi[10] investigated 26 individuals with persistent unilateral amblyopia and 25 patients with treated unilateral amblyopia. The average RNFL thickness for the consistently amblyopic eyes was 105.5±14.0 µm. This value did not differ substantially from that of the normal eyes (105.2±13.0 µm) or the treated amblyopic eyes (107.1±11.7 µm). Hence, this study also proved that RNFL thickness is not associated with amblyopia.

Walker and Rubab[12] studied thirty patients older than 18 years. They did not find a significant difference in RNFL thickness between amblyopic and fellow eyes in adults. The average RNFL thickness was 90.6±9.6 µm in amblyopic eyes and 90.1±12.1 µm in fellow eyes. Another study was conducted to find choroidal and RNFL thickness in adults with anisometropic amblyopia by Aylin et al.[19] No significant difference in peripapillary RNFL thickness was found between amblyopic and fellow or control eyes. The results of the present study indicate that RNFL thickness does not differ between amblyopic and fellow eyes across all types of amblyopia.

Another study was conducted on 150 participants with myopia, hyperopia, or emmetropia using the OCT. The participants were 15-30 years old, were free from ocular disease, and had not undergone any surgery. The ANOVA revealed that the difference between the myopes vs. hyperopes and emmetropes was statistically significant ($p<0.05$) as compared to hyperopes vs. emmetropes ($p=0.152$). The mean values of RNFL thickness were thinner for myopes vs. hyperopes ($p<0.05$) in all quadrants. The mean value of RNFL thickness was greater in emmetropes than hyperopes in both the temporal and superior quadrants.[20] The findings of the present study indicate that RNFL thickness for the supra-nasal quadrant in hyperopic amblyopia was thicker amongst the refractive errors. There was no statistically significant difference between various types of refractive error in other quadrants.

Conclusion

This study offers a significant and surprising insight into the relationship between RNFL thickness and amblyopia. Our results contradict the widely held belief that identifiable structural alterations in the RNFL are a consequence of amblyopia, a disorder generally linked to aberrant visual development. The RNFL thickness of amblyopic eyes was found to be similar to that of their fellow (non-affected) eyes in all retinal quadrants. This held true regardless of the type of amblyopia. These findings directly contradict the conventional belief that amblyopia leads to thinning of the RNFL, which has been thought to reflect underlying retinal or optic nerve pathology. Our study suggests that the structural integrity of the RNFL may remain unaffected in amblyopia, even in the presence of significant visual deficits. This calls for assessing the existing theories of the pathophysiology of amblyopia, especially with regard to its assumed impact on retinal structure.

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Correspondence regarding this article should be emailed to Muhammad Asad Saeed, BS Optom at asadsaeed032@gmail.com.

Saeed MA, Sadat A, Ayyub F, Aziz A. Fatima R, ul Ain Q. A comparative cross-sectional study on amblyopia and its relationship with retinal nerve fiber layer thickness. Optom Vis Perf 2026;14(2):174-79.