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Evaluation of retinal nerve fiber layer thickness with optical coherence tomography in various amblyopia types

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Abstract

To investigate of the thickness of the retinal nerve fiber layer (RNFL) in pediatric patients who have unilateral amblyopia that was caused by anisometropia or strabismus via the use of optical coherence tomography (OCT). Enrolled in this study were 111 eyes of 111 pediatric patients. The patients were separated into 3 groups, comprising the strabismic amblyopia group, which consisted of 35 eyes of pediatric patients who had strabismic amblyopia; anisometric amblyopia group, which consisted of 36 eyes of pediatric patients who had anisometric amblyopia; and the control group, which consisted of 40 eyes belonging to age- and gender-matched healthy pediatric individuals. The thickness of the RNFL was measured in the inferior, superior, nasal, and temporal quadrants via the use of OCT. The groups were similar regarding the age and the gender ($P > 0.05$) of the participants. No statistically significant differences were observed between the anisometropic amblyopia and control groups ($P > 0.05$). The inferior RNFL was thinner in strabismic amblyopia group compared to the control group participants ($P = 0.013$). The thickness of the RNFL of superior, nasal, and temporal quadrant did not differ statistically significantly. The thickness of the RNFL was similar in the anisometric amblyopia, strabismic amblyopia, and control groups. In the amblyopic patients, it is believed that there may be some damage caused to the higher visual pathways, such as the lateral geniculate nucleus and visual cortex, rather than structural damage to the retina.

Keywords: Amblyopia, anisometropia, optical coherence tomography, retinal nerve fiber layer, strabismus

Introduction

Amblyopia involves a decrease in vision due to abnormal visual development in one or both eyes without any organic pathology [1]. A difference of 2 lines or more in the visual acuity (VA) between 2 eyes as assessed by visual charts is considered as amblyopia. Amblyopia is the most seen cause of unilateral loss of vision in childhood, which is seen in approximately 2% to 5% of society [2]. The most seen causes of amblyopia are strabismus, anisometropia, deprivation, and uncorrected high refractive errors [3].

Amblyopia is not only caused by an ocular pathology but can also be considered as a brain injury that happens during visual development, which is a critical period. Previous studies haveshown abnormal neurophysiological activity in stimuli from the amblyopic eye to the cerebral cortex [4]. A decrease in the number and size of lateral geniculate nucleus (LGN) cells was found in autopsy studies performed in people with amblyopia [4].

Although it has been reported that visual cortex changes are prominent in patients who have been diagnosed with amblyopia, there is no consensus on whether the retinal nerve fiber layer (RNFL) is affected or not. In these cases, the RNFL can easily be evaluated with optical coherence tomography (OCT) due to its non-invasive nature.

In the current research, it was aimed to investigate of the thickness of the RNFL in pediatric patients who have unilateral amblyopia that was caused by anisometropia or strabismus via the use of OCT, and to compare these results with the healthy eyes.

Materials and Methods

Ethical Considerations

This study adhered to the Declaration of Helsinki and was granted approval by the local ethics. All the parents or guardians of the participants were informed before the procedures were conducted and signed consent forms were obtained from all the participants.

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Participants

Enrolled in this study were 111 eyes of 111 Caucasian pediatric patients who applied to the Department of Ophthalmology of Gaziantep University. The patients were separated into 3 groups, which comprised group 1, consisting of 35 eyes of pediatric patients who had strabismic amblyopia; group 2, consisting of 36 eyes of pediatric patients who had anisometric amblyopia; and group 3, consisting of 40 eyes belonging to the age- and gender-matched control group. All the participants underwent complete ophthalmic examinations. The gender and age of the subjects were noted. The best corrected VA (BCVA) was obtained via the use of a Snellen chart, which was then converted to as logarithm of minimum angle of resolution (LogMAR) for use in the statistical analyses. Cover tests were performed for all the patients to determine whether strabismus was present. In patients with strabismus, the amount of far and near deviation was measured via the use of the prism cover test. Anterior segment examination was performed via slit lamp bio microscopy, and the intraocular pressure was measured via pneumotonometry. Cyclopentolate hydrochloride (1%) drops were applied to both eyes of the patients, 3 times, with an interval of 5 min, and refraction was measured 40 min later via retinoscopy. Subjects with significant refractive errors were recalled after the cycloplegic effect had passed, and their BCVAs were recorded. A fundus examination was performed using a slit lamp while the pupil was dilated. The fundus was examined in detail for organic pathologies.

The criteria for amblyopia included 2 or more lines of difference between the BCVAs on the Snellen chart between both eyes, provided that 1 eye had full vision and no organic pathology was observed during the examination. Patients with hyperopic refraction of 1 diopter or more and myopic refraction of 2 diopters or more between both eyes were included in anisometric amblyopia group. The manifested minimum angle of deviation in the cover test was 10 prism diopters in the strabismic amblyopia group. The right eyes of patients with spherical and cylindrical refraction less than 1 diopter, no movement in their eyes in the cover test, and a visual level of 10/10 according to the Snellen chart were included as participants in the control group.

Patients who had a history of previous ocular surgery, nystagmus, glaucoma, opacity of cornea and lens, fundus pathologies, peripapillary atrophy, a cylindrical refractive error of 2 diopters or more, a history of neurological disease, the inability to maintain fixation steadily behind the OCT were not included in the study.

Measurement Protocol

Measurement of the thickness of the RNFL was performed via the use of OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany). The fast RNFL protocol, which was performed via the use of a circular scan, which was placed around the optic disc after pupil dilation, was used for measurement. With this protocol, 3 consecutive circles with 256 A-scans each were scanned in approximately 1.92s. A scan diameter of 3.46 mm was used for the measurement, which is recommended in the circular tomograms of the peripapillary region and for which the normal database of OCT-3 was created. Also performed were ocular measurements and tests between 10 am and 12 pm, on the same day. All the measurements were made prospectively by the same physician (B.Ö.). At least 3 measurements were taken for each eye. Circular scanning was performed while the optic disc was centered. Internal fixation light, which has been reported to have higher reproducibility in previous studies, was used for all the measurements. For all the eyes, both the nerve fiber thickness (NFT) and the mean NFT of the 4 quadrants, which comprised nasal, superior, temporal, and inferior, were calculated in microns. The values of the NFT and mean thickness of the RNFL of the nasal, superior, temporal, and inferior quadrants that were measured in both the right eye and in the amblyopia eye of the control group were used for the analyses (Figure 1).

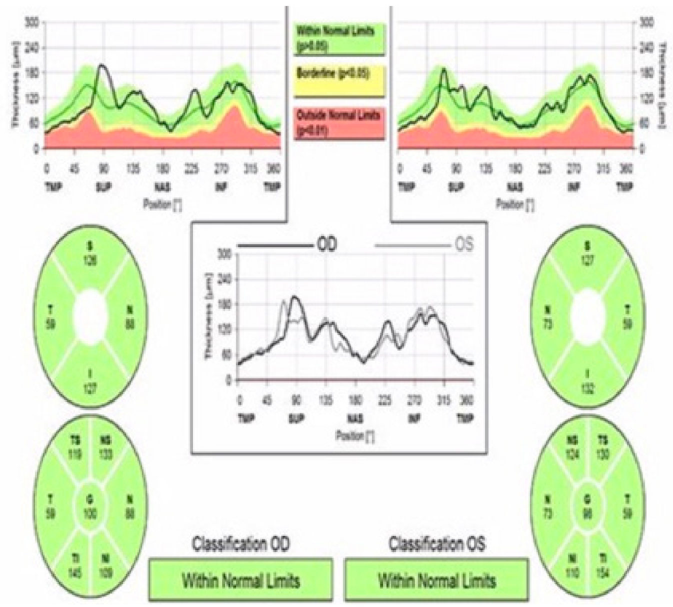

Figure 1. Spectral domain optical coherence tomography analysis data showing peripapillary retinal nerve fiber layer thickness

Statistical Analysis

IBM SPSS Statistics for Windows 22.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analyses. The parametric or non-parametric test was selected by looking at the normal distribution of the data with the single-sample Kolmogorov-Smirnov test and considering the number of eyes examined. As a parametric test, the independent sample t-test was utilized of to conduct a comparison of the data between the groups and Pearson test was utilized of in the correlation analysis. As a non-parametric test, Mann-Whitney U test was made utilized in the comparison of the data between the groups and Spearman test was utilized in the correlation analysis. The chi square test was utilized of to conduct a comparison of the categorical variables. $P<0.05$ was accepted as statistically significant.

Results

The study population comprised 35 pediatric patients in the strabismic amblyopia group, 36 pediatric patients in the anisometric amblyopia group, and 40 eyes in the control group. The groups were all similar regarding gender ($P=0.782$) and age ($P=0.209$). The characteristics of the participants at baseline were tabulated and summarized and are given in Table 1.

The right eyes of all the control group participants were evaluated. The strabismic amblyopia group consisted of 18 patients who had amblyopia of the right eye as well as 17 patients who had amblyopia of the left eye. The anisometropic amblyopia group consisted of 19 patients who had amblyopia of the right eye as well as 17 patients of the left eye. The anisometropic amblyopia group consisted of 29 hyperopic and 7 myopic amblyopia eyes. Strabismic amblyopia group consisted of amblyopic eyes with 27 esotropia and 8 exotropia. The mean refraction was +2.82±4.42 diopters (between –6.75 and +9.50) in the anisometropic amblyopia group,+1.16±0.69 diopters in the strabismic amblyopia group (between 0.00 and+2.75), and –0.05±0.42 diopters (between –0.75 and +0.75) in the control group. The mean BCVA was 0.61±0.37 (1.52–0.15) LogMAR in the strabismic amblyopia group, and 0.58±0.33 (1.30–0.15) LogMAR in anisometropic amblyopia group.

When a comparison of the thickness of the RNFL of the participants in the control and amblyopia groups was conducted, there were no statistically significant differences were observed regarding the mean thickness of the RNFL in any of the quadrants (P>0.05) (Table 2). When the thickness of the RNFL of the participants in the control, anisometropic amblyopia, and strabismic amblyopia groups were compared, it was observed that it was statistically significant thinner in the inferior quadrant in the strabismic amblyopia group (P = 0.013). No statistically significant differences were observed between any of the groups in the other quadrants regarding the mean thickness of the RNFL (Table 3). When the strabismic amblyopia and anisometropic amblyopia groups were compared, a statistically significant difference was observed in the thickness of the RNFL in the inferior quadrant (P=0.007), while no statistically significant differences were observed in the other quadrants.

Table 1. The baseline characteristics of the patients

	Anisometric amblyopia group (n=36)	Strabismic amblyopia group (n=35)	Control group (n=40)	p value
Female/male	16/20	17/18	21/19	0.782
Mean age	11.58 ± 3.69	10.1±3.12	10.85±3.36	0.209
Refractive value	+2.82±4.42	+1.16±0.69	-0.05±0.42	
BCVA*(LogMAR)	0.58±0.33	0.61±0.37		

* Best corrected visual acuity

Table 2. Retinal nerve fiber layer thickness of the patients

		Temporal RNFL* (µm)	Nasal RNFL (µm)	Superior RNFL (µm)	Inferior RNFL (µm)	Mean RNFL (µm)
Control group	**Mean**	**76.4**	**76.87**	**129**	**130.45**	**103.14**
	N	40	40	40	40	40
	Std. Deviation	8.32	11.87	17.13	17.13	9.72
	Minimum	63	54	99	93	79
	Maximum	106	107	166	190	126
Amblyopia group	Mean	77.09	81.61	127.47	130.07	103.54
	N	71	71	71	71	71
	Std. Deviation	19.14	21.29	20.32	23.34	13.78
	Minimum	49	20	65.00	81	74
	Maximum	163	150	171.00	213	148
P value		0.833	0.197	0.680	0.938	0.872

* Retinal nerve fiber layer

Table 3. Subgroup analysis of amblyopia cases

		Temporal RNFL* (µm)	Nasal RNFL (µm)	Superior RNFL (µm)	Inferior RNFL (µm)	Mean RNFL (µm)
Control group	**Mean**	**76.42**	**76.87**	**129.05**	**130.40**	**103.15**
	N	40	40	40	40	40
	Std. Deviation	8.32	11.87	17.13	17.13	9.72
	Minimum	63	54	99	93	79
	Maximum	106	107	166	190	126
Anisometropic amblyopia group	Mean	76.02	82.38	130.05	137.30	106.66
	N	36	36	36	36	36
	Std. Deviation	18.38	24.75	22.43	27.01	16.43
	Minimum	52	20	86	88	79
	Maximum	163	150	171	213	148
Strabismic amblyopia group	Mean	78.2	80.82	124.82	122.62*	100.34
	N	35	35	35	35	35
	Std. Deviation	20.09	17.35	17.84	16.06	9.61
	Minimum	49	43	65	81	74
	Maximum	150	129	152	147	135
P value		0.834	0.410	0.479	0.013*	0.099

* Retinal nerve fiber layer

Discussion

Amblyopia is defined as decreased VA and abnormal binocularity despite the absence of any organic pathology upon examination of the eye [5]. Amblyopia is defined as there being a difference of a minimum of 2 lines between the VA of two eyes. The RNFL consists of ganglion cell axons and extends to the lateral geniculate with the optic nerve, and in the case of amblyopia, it is thought that the retinal ganglion cells develop abnormally in the postnatal period, and accordingly, the macula as well as the RNFL may be affected [6]. Whether or not retinal involvement occurs in strabismic or anisometropic amblyopia is one of the most debated issues. The visual systems of humans and apes are similar. In the retina, the Ganglion cells are divided into 2 groups, as X and Y cells. The X, or sustained, cells in the central region of the retina are believed to provide high VA. In 1977, von Noorden demonstrated a reduction in the size and density of the parafoveal retinal ganglion cells because of eyelid suturing over a period of 24 months (equivalent to 8 human years) in monkeys [4]. Ikeda and Tremani, in 1979, showed that these cells decreased in the central retina of the deviated eye in cats after experimental esotropia [7]. Even though the visual cortex is the main site where amblyopia occurs, it is controversial as to whether the retinal and thickness of the RNFL change with it. With the development of technology, NFA-GDx (nerve fiber analyzer) and OCT devices have made RNFL measurable in vivo, and many studies have been carried out on this subject. There are many studies in the literature showing whether a difference occurs in the retinal NFT in amblyopia. In the current research, it was aimed to conduct a comparison of the retinal NFT of unilateral anisometropic and strabismic patients and healthy controls.

Repka et al., in their study with 4 anisometropic amblyopia, 6 strabismic amblyopia, and 8 combined amblyopia patients determined that, regardless of the type of amblyopia, no statistically significant difference could be determined between the eyes of the patients regarding the mean thickness of the RNFL [8]. Altintas et al., used OCT to examine 14 patients with strabismic amblyopia. The temporal, upper, nasal, lower quadrant RNFL values and the mean RNFL values of the patients were examined, and no statistically significant difference could be determined between the healthy eyes and those with amblyopia [9]. Firat et al. did not find any statistically significant differences in mean inferior, superior, nasal, and temporal thickness of the RNFL between the amblyopic eye, healthy eye, and eyes of the healthy controls in their study on 36 anisometropic and strabismic amblyopia patients and 32 emmetropic healthy subjects [10]. Ersan et al. performed OCT on 40 healthy patients and 35 strabismic amblyopia and 30 anisometropic amblyopia patients [11]. They did not find any significant differences in the thickness of the RNFL in any of the quadrants between the amblyopic eyes and the healthy eyes in the strabismic group. The temporal thickness of the RNFL in the patients who had hyperopic anisometropic amblyopia was found to be statistically significantly thinner when compared to the healthy eye. No statistically significant differences were observed between the control group and amblyopic eyes. Yalcin et al. studied 30 unilateral hyperopic anisometropic amblyopia and 30 emmetropic patients and found no statistically significant differences regarding the mean thickness of the RNFL between the amblyopic eyes, healthy eyes, and emmetropic eyes [12]. Andalib et al. found no statistically significant differences in mean thickness of the RNFL between the amblyopic eyes and the other eye in their study of 25 anisometropic amblyopia and 25 strabismic amblyopia patients [1]. When a comparison was conducted of the thickness of the RNFL of the anisometropic and strabismic groups, they did not find a statistically significant difference. Kee et al. conducted a study using OCT on 42 healthy children and anisometropic (5 hyperopic and 10 myopic patients), strabismic (6 patients), and combined amblyopia (5 patients), and regardless of the type of amblyopia, they did not find any statistically significant differences between the amblyopic eyes and the normal eyes of the patients in terms of the thickness of the RNFL in any of the quadrants and mean thickness of the RNFL [13]. In terms of the same parameters, no statistically significant differences were determined to exist between the amblyopic eyes of the amblyopic patients and the healthy eyes of healthy subjects. It was determined that the mean thickness of the RNFL was significantly thicker in the anisometropic amblyopia group, which included patients with hyperopia and myopic anisometropia, when compared to that in the strabismic amblyopia group. Yoon et al. conducted a study on 31 anisohypermetropic amblyopic patients, and the thickness of the RNFL was observed to be statistically significantly thicker in the amblyopic eyes of the patients than in their normal eyes [14]. Yen et al. did not find any statistically significant difference in the thickness of the RNFL in strabismic amblyopia in their study using OCT, whereas the retinal NFT in anisometropic amblyopia was found to be significantly thicker [15]. In the study performed by Ekici et al., on 35 unilateral anisometropic amblyopia patients, they did not find any statistically significant differences in the thickness of the RNFL between the healthy eyes and the amblyopic eyes [16]. Uçak et al. in their study of 89 anisometropic amblyopia patients, they did not find any statistically significant differences between the thickness of the RNFL in the amblyopic patients and the control group [17]. Şahin et al. in their study of 74 anisometropic amblyopia patients and 78 healthy controls, it was found that the temporal thickness of the RNFL was statistically significantly thinner in the eyes of the patients in the amblyopia group, and it was found that the thickness of the nasal RNFL was statistically significantly thicker in the patients in the amblyopia group [18]. Yakar et al., in their study with 30 unilateral anisometropic amblyopia patients, did not find any statistically significant differences in the thickness of the RNFL between the amblyopia eyes and the healthy eyes [19].

When the literature was examined, anisometropic amblyopia was mostly evaluated alone, or where anisometropic and strabismic amblyopia were evaluated together, they a comparison was conducted with healthy eyes. Herein, the eyes in the anisometropic and strabismic amblyopia groups were compared with those in the control group. In the current research, no statistically significant differences were found between the mean thickness of the RNFL in the eyes in the control group and amblyopia patients. When the thicknesses of the RNFL of the eyes in the control, anisometropic, and strabismic groups were compared, no significant differences were observed to occur between the groups regarding the mean thickness of the RNFL; however, it was observed that statistically significant thinning occurred in the inferior quadrant in the strabismic group ($P=0.013$). This thinning in the patients in the strabismic amblyopia group may have resulted from the difficulty of fixation due to strabismus in the pediatric age group during the measurement, as well as the low number of patients.

Conclusion

In conclusion, the thickness of the RNFL can be evaluated non-contact, non-invasively, and in vivo via the use of OCT. At the same time, it should be kept in mind that OCT can function like an optical biopsy. In the current literature, there is no consensus on whether the thickness of the RNFL changes in amblyopic patients. The current study was found to be close to studies in which no significant changes were observed in the thickness of the RNFL in amblyopia patients. In amblyopia patients, it is believed that there may be damage caused to higher visual pathways, like the LGN or visual cortex, rather than structural damage to the retina. This study did have some limitations, such as the small number of patients, as the major limitation. Additionally, this study did not have a histological design. More histological and case studies should be conducted to determine whether there is retinal damage in amblyopia.

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

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Ethical approval
Ethics Consest was obtained from Gaziantep University(research protocol code: 45/2013).

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