RESEARCH ARTICLE

Differences in optic nerve parameters and retinal nerve fiber layer thickness in the eyes of normal and amblyopic Filipino children

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ABSTRACT

Background: Optical coherence tomography (OCT) can accurately assess the optic nerve and retinal fiber layer (RNFL) to closely look at the anatomical ocular pathology of amblyopia.

Objectives: This study aimed to determine and compare optic nerve parameters and RNFL in amblyopic and normal Filipino children using OCT.

Methodology: Forty-two eyes of 21 normal participants and 40 eyes of 20 amblyopic participants underwent complete eye examinations and OCT scanning of optic nerve and RNFL. The following data were collected: age, refraction, intraocular pressure, optic nerve parameters (including rim area-vertical cross-section, average nerve width, disc diameter, cup diameter, rim length, vertical integrated rim area, horizontal integrated rim width, disc area, rim area, cup area, cup to disk area ratio, cup-to-disk horizontal ratio, cup to disc vertical ratio), and peripapillary RNFL.

Results: There was a statistically significant difference between normal and amblyopic groups with regard to the following parameters: cup area, rim area, cup-disc area ratio, cup-disc horizontal ratio, cup-disc vertical ratio, superior RNFL, and inferior RNFL. The rim area was significantly smaller in amblyopic eyes compared to normal whereas the cup-disc area ratio, cup area, cup-disc vertical and horizontal ratios were significantly larger in amblyopic eyes. The RNFL inferiorly and superiorly were also thinner in amblyopic eyes.

Conclusion: As measured by OCT, some optic nerve parameters and RNFL thickness in Filipino children were significantly different in amblyopic eyes compared to normal.

Keywords: *optic nerve, retinal nerve fiber layer, OCT in children, optic nerve parameters in children, amblyopia*

Introduction

Amblyopia is the decrease in best-corrected visual acuity with no clinical evidence of organic eye pathology. It can be caused by abnormal visual experience during the period of visual development by uncorrected strabismus, refractive errors, or visual deprivation such as cataract [1]. This description of amblyopia was made when quantitative methods of disc and retinal nerve fiber layer measurement were not available and were mainly based on subjective eye examination. Previous studies on amblyopia identified the lateral geniculate nucleus as the primarily affected part [2]. The introduction of new ophthalmic technology which can accurately assess the optic nerve and retinal fiber layer (RNFL) such as the optical coherence tomography (OCT) resulted in current studies to closely look at the anatomical ocular pathology of amblyopia. OCT allows detailed noninvasive, noncontact examination of the posterior segment. It is almost similar to a histologic examination of the retina and optic nerve and gives a more accurate and reproducible measurement [3]. Lempert *et al.* found that eyes that were presumed to be amblyopic actually had a subclinical optic nerve pathology [4,5]. Studies on the RNFL also found a significant difference in its thickness between amblyopic, especially those from refractive causes, and non-amblyopic eyes [6,7].

This study aimed to determine optic nerve parameters and RNFL thickness in normal and amblyopic eyes of Filipino children using an OCT and determine if there are significant differences. These may help ophthalmologists in distinguishing normal from amblyopic eyes using an OCT especially in cases where it is challenging to diagnose with just a standard ophthalmic examination.

Methodology

An analytic cross-sectional study was conducted in the Department of Ophthalmology and Visual Sciences of the Philippine General Hospital. This study was approved by the University of the Philippines Manila Review Ethics Board and was conducted in accordance with the guidelines set by the Declaration of Helsinki. Assent and informed consent were obtained from all the participants and their parents or caregivers. A minimum number of 20 children for each group were recruited and enrolled to detect differences of 0.77 millimeter between the rim area of normal eyes and amblyopic eyes at 80% statistical power and 5% level of significance.

Twenty-one participants aged 6 to 10 years from a nearby school with a best-corrected visual acuity (BCVA) of 20/20 or better, both eyes and with normal findings based on standardized ophthalmologic eye examination, were randomly recruited and assigned in the normal group. The participants had no ocular problems such as congenital cataracts, corneal opacities, and retinal lesions other than refractive errors between -3.00 to +3.00 diopters (D) and astigmatism less than -1.50 D. Twenty participants aged 6 to 10 years who were patients of the Section of Pediatric Ophthalmology and Strabismus diagnosed with amblyopia in one or both eyes from refractive error or/and strabismus were purposely selected due to low number of patients to allow random selection. Amblyopia was defined in this study as BCVA of less than 20/20 despite correction of refractive error and strabismus and with no current clinical evidence of any ocular pathology based on standardized ophthalmologic eye examination. All participants were normal on neurological examination.

An ophthalmic examination including BCVA testing using the linear Snellen chart was done to detect amblyopia, cover and uncover testing with prisms to assess strabismus, slit lamp examination, fundus examination, air puff tonometry to rule out glaucoma, and cycloplegic automated refraction to measure refractive errors. These were all done by a single examiner. Although only the Snellen chart was used to measure visual acuity for standardization purposes, the visual acuity determination was only conducted by the Pediatric Ophthalmology fellow who was trained to determine if the inability to further read the letters was due to illiteracy. Biometry was also done to measure axial length. The presence of glaucoma had to ruled out since it can significantly affect the optic nerve parameters. Similarly, myopia, a refractive error, is associated with a long axial length which can also significantly affect RNFL thickness. Data on age at consult, refraction for both eyes, intraocular pressure, and axial length were recorded.

The optical coherence tomographer (Stratus OCT, software v.4.0; Carl Zeiss Meditec, Inc., Dublin, CA) was used to measure optic nerve parameters and retinal nerve fiber layer thickness through dilated pupils. A built-in refraction correction was used for focusing on patients with significant errors of refraction. A total of 17 parameters (13 optic nerve parameters and 4 RNFL thickness) were taken. Three fast optic disc scans were performed and the measurements were averaged before analysis. All scans were performed by a single experienced operator. Only scans that were free of artifacts, complete, and have signal strengths of at least five were accepted. The optic nerve head scan used six radially oriented four-millimeter linear scans centered on the optic nerve head. The disc reference points were placed at the termination of the retinal pigment epithelium at the optic nerve head (ONH).The measurements were based on this anatomical marker.

Parameters that were examined in all eyes included the:
1. rim area
2. average nerve width
3. disc diameter
4. cup diameter
5. rim length

The following optic nerve head measurements were derived from a summary of the six individual radial scans:
1. vertical integrated rim area
2. horizontal integrated rim width
3. disc area
4. cup area
5. rim area
6. the cup/disc area ratio
7. cup/disc horizontal ratio
8. cup/disc vertical ratio

The superior, nasal, inferior, and temporal peripapillary RNFL thickness were also measured. The fast RNFL thickness acquisition protocol was used. The RNFL was differentiated from other retinal layers by using a thresholding algorithm and was measured in an automated fashion.

Student's t-test was used to compare the baseline characteristics of the left to right eyes of the normal participants and the eyes of the normal participants to the amblyopic participants. The distribution of the data from the groups being compared was parametric. The optic nerve parameters and RNFL thickness between the left and right eyes of normal subjects, more amblyopic and fellow eyes of amblyopic subjects, more amblyopic eyes and right eye of normal subjects and fellow eyes of amblyopic eyes and right eye of normal subjects were compared. Analysis of Variance (ANOVA) was utilized to test for variability of the three types of amblyopia. Data were tabulated using Microsoft Excel version 2016 (Microsoft Corporation, Redmond, WA, USA) and were subjected to statistical analysis using Stata 14 (StataCorp, College Station, TX: StataCorp LP).

Results

A total of 42 eyes of 21 normal participants and 40 eyes of 20 amblyopic participants were included in the study. The mean age for the ophthalmologically normal group was 7.52±1.76 years, not significantly different from the amblyopic group which was 7.25±1.76 years (p=0.63). Significant differences with refraction in spherical equivalent [+0.75 diopter (-0.12, +1.09) vs. -1.75 (-7.15, +3.03), p<0.01] and axial length [22.63±0.70 millimeters vs. 23.75±1.89, p<0.001] were noted.

Ophthalmologically Normal Group

There was no significant difference in the baseline characteristics, optic nerve parameters, and RNFL between the left and the right eye of the normal group where all had p>0.05. As such, values from the right eye were used for succeeding analysis.

Amblyopic Group

The amblyopic group was composed of patients with 3 types of amblyopia: (a) strabismic alone, (b) refractive alone, and (c) strabismic + refractive. Each patient's eyes were further grouped into the more amblyopic eye and the fellow eye. An Analysis of Variance showed no significant differences among the three types in their more amblyopic eyes and fellow eyes since all had p>0.05. As such, values from the patients' eyes were grouped together.

The baseline characteristics, optic nerve parameters, and RNFL were also compared between the more amblyopic eyes to the fellow eyes. There were no significant differences found between them as all had p>0.05.

Ophthalmologically Normal versus Amblyopic group

A comparison was made between the eyes of the normal participants and the more amblyopic eyes of the amblyopic participants (Table 1).

Aside from the refraction and axial length, there were other statistically significant differences between normal and amblyopic groups on the following parameters: rim area, cup-disc area ratio, cup-disc horizontal ratio, and superior RNFL. The rim area was significantly smaller in amblyopic eyes compared to normal while cup-disc area ratio and cup-disc horizontal ration were significantly larger in amblyopic eyes. The superior RNFL is also thinner in amblyopic eyes.

A comparison was also made between the eyes of the normal participants and the fellow eyes of the amblyopic participants considering that there was no significant difference between the more amblyopic eyes and fellow eyes.

There were also statistically significant differences between normal eyes and the fellow eyes of the amblyopic groups on the following parameters: cup area (0.50±0.26 millimeter^2 vs. 0.51±0.83, p<0.03), rim area (2.03±0.36 millimeter^2 vs. 1.69±0.65, p<0.05), cup-disc area ratio (0.19±0.08 millimeter^2 vs. 0.33±0.26, p<0.03), cup-disc horizontal ratio (0.46±0.11 vs. 0.58±0.20, p<0.02), cup-disc vertical ratio (0.40±0.10 vs. 0.51±0.20, p<0.05), superior RNFL (147.76±15.37 μ vs. 134.45±18.43, p<0.02) and inferior RNFL (139.52±14.48 μ vs. 129.30±15.27, p<0.04). The rim area was significantly smaller in amblyopic eyes compared to normal while the cup-disc area ratio, cup area, and cup-disc vertical and horizontal ratios were significantly larger in amblyopic eyes. The RNFL inferiorly and superiorly were also thinner in amblyopic eyes.

Discussion

This study found that there exist significant differences in optic nerve parameters and RNFL in both eyes of amblyopic Filipino children compared to ophthalmologically normal ones. These changes were identified using optic nerve parameters and RNFL thickness measured by an optical coherence tomographer. Similar results were found by Lempert *et al.* and Yoon *et al*. [4-6]. The results of these studies are contrary to those that found no evidence of ocular pathology in amblyopic patients based on standard ophthalmologic examination and can also complement studies that identify the lateral geniculate nucleus as the affected part in amblyopia [2].

Table 1. *Characteristics of eyes of normal right eyes and more amblyopic eyes.*

	Normal eye N=21	More Amblyopic eye N=20	p-value
Age (years)	7.52±1.76	7.25±1.76	0.63
Refraction in SE in diopters (quartile)	0.75 (-0.12,+1.12)	-2.93 (-8.53,+3.60)	0.04
Intraocular pressure in mmHg	12±4	12±3	0.55
Axial Length	22.6±0.7	23.9±2.2	0.02
Rim area (vertical cross section) in millimeter^2	0.28±0.13	0.24±0.12	0.30
Average nerve width in millimeter	0.38±0.06	0.36±0.07	0.26
Disc diameter in millimeter	1.90±0.50	1.69±0.51	0.21
Cup diameter in millimeter	0.51±0.36	0.52±0.36	0.98
Rim length in millimeter	1.38±0.51	1.18±0.45	0.18
Vertical internal rim area in millimeter^3	0.58±0.20	0.52±0.29	0.43
Horizontal internal rim width in millimeter^2	1.92±0.20	1.77±0.28	0.07
Disc area in millimeter^2	2.52±0.45	2.36±0.47	0.26
Cup area in millimeter^2	0.50±0.26	0.77±0.57	0.07
Rim area in millimeter^2	2.03±0.36	1.51±0.61	0.01
Cup Disk (CD) area ratio	0.19±0.08	0.33±0.26	0.04
CD horizontal ratio	0.46±0.11	0.57±0.20	0.04
CD vertical ratio	0.40±0.10	0.50±0.22	0.10
Retinal Nerve Fiber Layer (RNFL) superior in micrometer (µm)	147.76±15.37	128.55±20.88	0.002
RNFL nasal (µm)	84.48±14.12	79.85±30.45	0.55
RNFL inferior (µm)	139.52±14.48	131.25±18.05	0.12
RNFL temporal (µm)	76.90±10.45	79.20±19.93	0.66

Ophthalmologically Normal Eyes

This study also provided baseline information on optic disc parameters and RNFL thickness in normal Filipino children. Mean disc diameter, disc area, rim area, horizontal integrated rim width, and average nerve width were larger while cup diameter was smaller in Filipinos compared to the European Caucasian, East Asian, and Middle Eastern participants of Huyn *et al*. (Table 2) [8]. Girkin *et al*. also found smaller optic disc parameters among European Caucasians compared to African-Americans [9]. Huynh *et al*. suggested that these differences have genetic etiology rather than developmental since they were seen in children and adults [8].

The RNFL thickness in this study was consistent with several studies showing the superior and the inferior RNFL being thicker than the nasal and the temporal [10-15]. Compared with other studies, though the RNFL values in this study were relatively higher for the superior and temporal quadrants (Table 3). Similar to variations in optic disc size, RNFL thickness may also vary interracially [16]. Samarawickrama found larger mean cup-to-disc ratios and thicker RNFL in East Asian children compared to European Caucasian children [17].

Amblyopic Eyes

This study found that the rim area was significantly smaller in amblyopic eyes compared to normal ones while cup-disc area ratio, cup area, cup-disc vertical and horizontal ratios were significantly larger in amblyopic eyes. The bigger cup-disc area can be associated with more myopic refraction of the amblyopic group [18]. However, based on the same article, the rim area was larger in the presence of myopia which was not the case in this study. The RNFL, inferior and

Table 2. *Comparison of Optic Disc Parameters with Selected Studies*

	Huynh *et al*[9]			Present study
Eyes	866	53	199	42
Age range	6			6-10
Measuring equipment	OCT			OCT
Mean Refraction (diopter)	+1.28±0.02			+ 0.75 (-0.12, +1.09)
Race	European Caucasian	Middle Eastern	East Asian	Filipino
Average nerve width in millimeter Horizontal Vertical Overall	 0.24 (0.234–0.246) 0.34 (0.332–0.347) 0.292 (0.287–0.298)	 0.29 (0.27–0.30) 0.37 (0.35–0.38) 0.33 (0.31–0.34)	 0.287 (0.284–0.290) 0.364 (0.360–0.368) 0.328 (0.326–0.331)	0.38 ±0.06 (H)
Disc diameter in millimeter^2	2.28 (2.24–2.32)	2.12 (2.01–2.22)	2.19 (2.16–2.22)	2.52±0.45 (H)
Disc Diameter in millimeter Horizontal Vertical	 1.56 (1.53–1.59) 1.81 (1.78–1.84)	 1.52 (1.48–1.56) 1.74 (1.67–1.82)	 1.52 (1.51–1.54) 1.80 (1.78–1.81)	1.91±0.43 (H)
Cup area in millimeter^2	0.68 (0.64–0.73)	0.41 (0.33–0.48)	0.42 (0.40–0.44)	0.50±0.26
Cup diameter in millimeter Horizontal Vertical	 0.88 (0.84–0.91) 0.88 (0.85–0.92)	 0.67 (0.60–0.73) 0.69 (0.63–0.75)	 0.66 (0.64–0.68) 0.63 (0.67–0.71)	0.51±0.36 (L)
Cup volume in millimeter^3	0.10 (0.09–0.12)	0.04 (0.03–0.06)	0.05 (0.045–0.053)	
Cup-to-disc ratio Horizontal Vertical	 0.56 (0.54–0.58) 0.49 (0.47–0.51)	 0.44 (0.40–0.48) 0.40 (0.36–0.44)	 0.43 (0.42–0.44) 0.39 (0.38–0.41)	 0.46±0.11 0.40±0.10
Cup-to-disc area ratio	0.30 (0.28–0.32)	0.19 (0.16–0.23)	0.19 (0.185–0.20)	0.19±0.08
Rim area in millimeter^2	1.62 (1.56–1.68)	1.74 (1.62–1.86)	1.80 (1.76–1.83)	2.03±0.36 (H)
Integrated rim area (vertical) in millimeter^3	0.48 (0.44–0.52)	0.74 (0.63–0.86)	0.74 (0.71–0.77)	0.58±0.20
Rim area (vertical cross-section) in millimeter^2 Horizontal Vertical	 0.13 (0.11–0.14) 0.24 (0.22–0.26)	 0.22 (0.19–0.25) 0.36 (0.30–0.41)	 0.21 (0.20–0.22) 0.35 (0.34–0.37)	0.28±0.13
Integrated rim width (horizontal) in millimeter^2	1.58 (1.55–1.62)	1.72 (1.62–1.83)	1.74 (1.72–1.76)	1.92±0.20 (H)

*refraction in diopter sphere

Table 3. *Comparison of Retinal Nerve Fiber Layer Thickness with Selected Studies.*

RNFL	Chua *et al*[11]	Gupta *et al*[12]	EL Dairi *et al*[13]	Savini *et al*[14]	Salchow *et al*[15]	Present study
Eye	181	25	36	54	92	42
Age range	16-55	6-13	5-14	15-54	4-17	6-10
Measuring equipment	OCT	OCT	OCT	OCT	OCT	OCT
Mean Refraction (diopter)	Not specified	Not specified	-	Not specified	-0.57 2.43	+ 0.75 (-0.12, +1.09)
Location or Race	Philippines	Rhode Island, USA	North Carolina, USA	Bologna, Italy	Hispanic (91%) African American (8%) Caucasian (1%)	Philippines
RNFL superior um RNFL nasal um RNFL inferior um RNFL temporal um	139.56±16.09 84.66±16.06 142.08±18.73 76.10±11.46	122±4.5 76.4±3.3 132±3.9 73.5±4.3	139.5±18.9 87.9±23.3 120.5±29.5 75.3±16	124.29±16.59 81.24±17.9 129.83±19.26 69.94±13.17	135.4±19.3 83±18 136.9±16.9 72.5±13.4	143.67±27.27 (H) 80.31±17.74 137.40±27.97 76.57±20.02 (H)

*refraction in diopter sphere

superior, were also thinner in amblyopic eyes. Refraction can significantly affect RNFL thickness with the more myopic refraction or larger axial length leading to thinner RNFL in all quadrants [19]. However, only the superior RNFL thickness was significantly different between the two groups.

Although the rim areas in the more amblyopic and fellow eyes were significantly smaller than the normal eyes, the other optic nerve parameters were significantly larger. This is contrary to the results of Lempert *et al.*'s where optic disc areas were found to be significantly smaller in amblyopic subjects compared with normal subjects [5]. This is also contrary to the findings of Huynh *et al.* where there was no significant difference between amblyopic and normal eyes [20].

The superior and inferior RNFL were also thinner in amblyopic eyes in this study. This may be from amblyopia being shown to reduce retinal ganglion cells and alter retinal receptive fields and causes a decrease in nucleolar volume in ganglion cell cytoplasm and thinning of internal plexiform layer in rats and cats [21-22]. However, changes in optic nerve parameters and RNFL thickness were also found to be significantly correlated to intraocular pressure, refraction, and axial length making it difficult to specify if the changes were from amblyopia or from the factors that caused the amblyopia itself.

The significant differences in refraction and axial length between the eyes of the normal group and amblyopic group was expected since 18 out of 20 (90%) of the more amblyopic eyes have refractive component. Despite the difference in the optic nerve parameters and RNFL between amblyopic and normal eyes, this study found no significant difference between the more amblyopic and the fellow eyes of the amblyopic group. These may suggest that despite the eye being less affected, the changes noted in optic nerve parameters and RNFL can be seen in both eyes of amblyopic individuals. This finding is similar to those of Altintas *et al.* with subjects having strabismic amblyopia and Repka *et al.* with subjects having strabismic, anisometropic, and combined amblyopia [23-24]. Repka *et al.* suggested that the non-difference removes optic neuropathy as a component in moderate amblyopia from anisometropia or strabismus [24]. However, our findings were in contrast to that of Yoon *et al.* which revealed a significantly thicker RNFL in eyes with refractive amblyopia [6]. Yen *et al.* also showed a significant difference between amblyopic eyes from refractive causes and the fellow less amblyopic eyes [7].

It is important to determine the presence or absence of amblyopia so that better management can be administered or to discontinue amblyopia treatment for those who are non-responsive to the treatment [25]. OCT can be used as an adjunct when it is difficult to diagnose amblyopia based on standard eye examination alone. Although only a few eyes were measured, the provided values by this study can be used as references to determine normal and significant differences in the optic nerve and RNFL parameters which can better establish if the eye in consideration is amblyopic or not.

This study was limited by the number of participants recruited especially in the amblyopic group. Recruiting participants with just one type of amblyopia proved challenging despite conducting the study in a high-volume patient eye center. The refractive error of the amblyopic group was also significantly different from the normal group and was on the myopic side which can explain the significant difference in the cup-to-disc area. However, it did not explain the larger rim area and thinner superior RNFL thickness only in the amblyopic group. Since the study had limited participants, the findings cannot be directly attributed to amblyopia alone. As such, the authors recommend that a multicenter study be conducted to be able to recruit the needed number of participants and determine if a larger rim area and thinner superior RNFL can be used as indicators to assist in the diagnosis of amblyopia despite the refractive state.

Conclusion

Some optic nerve parameters and RNFL thickness in Filipino children were significantly different in amblyopic eyes and even their fellow eyes compared to normal eyes. The differences cannot just be attributed to the refractive state of the amblyopic group.

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