Macular ganglion cell and retinal nerve fiber layer thickness in normal Vietnamese children measured with optical coherence tomography.

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Purpose: *To obtain the macular ganglion cell–inner plexiform layer (GC–IPL) and the retinal nerve fiber layer (RNFL) thickness normative values of Vietnamese children.*

Methods: *A cross–sectional study was conducted on 152 healthy eyes from 76 children aged between 6 and 16 years. The macular ganglion cell–inner plexiform layer and the retinal nerve fiber layer thickness were measured by a spectral domain Cirrus high definition optical coherence tomography (version 10.5). Only scans with signal strength > 6/10 were included.*

Results: *The mean age was 10.13±2.47 years and the mean spherical equivalent refraction was –1.05 ± 1.27D. The average and minimum GC–IPL thickness were 84.74±5.17µm and 80.18±7.84µm, respectively. The average RNFL thickness was 103.18 ± 9.50µm. The mean central macular thickness was 240.51±15.47µm. The rim area was correlated with the average RNFL (ß=13.742, p<0,001). Age, spherical equivalent refraction and gender were correlated with the central macular thickness (ß= –1.437, p<0.01, ß= –5.204, p<0.001 and ß =5.660, p<0.02). The minimum GC–IPL thickness was not effected by gender, age and spherical equivalent refraction.*

Conclusion: *This study provides normative GC–IPL and RNFL thickness values for Vietnamese children. It may assist in identifying changes in GC–IPL and RNFL thickness in children. The rim area had correlated with RNFL thickness while the spherical equivalent refraction and gender had related with the central macular thickness. The minimum GC–IPL can be used in managing pediatric glaucoma patients.*

Conflict of interest: *none.*

Keywords: *children, optical coherence tomography, macular ganglion cell–inner plexiform layer thickness, retinal nerve fiber layer thickness.*

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Introduction

Optical Coherence Tomography (OCT) is a non-invasive, non-contact, transpupillary imaging method that performs objective high-resolution cross-sectional images of retinal tissue. It has proven to be valuable in the detection of glaucomatous damage. With its high resolution and proven measurement reproducibility, OCT has the potential to become an important tool for glaucoma progression detection. The recently introduced spectral domain OCT (SD-OCT) provides measurements of the optic nerve head, retinal nerve fiber layer (RNFL) and macula ganglion cell layer (GCL) with greatly improved image acquisition speed and image resolution.This is particularly helpful when applying this technology in uncooperative children.[2]

Several studies in literature have reported values of optic nerve head, RNFL thickness and macular ganglion cell for normal children in some countries such as Sweden, Hong Kong,[6] India,[7] America,[8] as well as abnormal children with refractive errors,[4] obesityand diabetes. Nevertheless, all OCT devices have an integrated normative database only for adult subjects 18 years of age and older.

Thus far, there is no literature to evaluate the normative values of optic nerve head, RNFL and macula GCL thickness for Vietnamese children. The purposes of the study were to collect normative values of macular thickness and volume and RNFL thickness in healthy eyes of normal children from 6 to 16 years old by using the most recent commercially available Zeiss HD-OCT Model 5000 and to research the effects of age, gender, and refractive errors on these values.

Methods

A prospective cross-sectional study of 152 healthy eyes of 76 children who were children of employees in the hospital and some of them visited the Refraction Section, was done at Diagnostic Imaging Department, HCMC Eye Hospital, Vietnam. Inclusion criteria included subjects with (1) age from 6 to 16 years old, (2) full-term infant or weight at birth >2,500g, (3) best-corrected visual acuity of > 6/10 or better on both eyes, (4) refractive errors in spherical equivalent within ±3.00 D and/ or astigmatism under than 2.00D, (5) OCT results have signal strength > 6/10. Exclusion criteria were strabismus, amblyopia, family history of glaucoma with optic nerve photographs which documented an optic disc hemorrhage, a localized notch or thinning of the rim, a diffuse or localized area of pallor or other detected optic nerve abnormalities, any hereditary eye diseases or autoimmune diseases.

All subjects received a full ophthalmic examination including cycloplegic refraction and slit-lamp evaluation. Pupils were dilated with Mydrin P (tropicamide 0.5% and phenylephrine 0.5%) for fundus examination. Age, gender, weight at birth, best corrected visual acuity (BCVA) and refractive errors for each eye were recorded. Informed written consent was obtained from the parents of the children before all experimental measurements. This study was approved by Science and Technology Committee of our hospital.

Oct Measurement

The ZEISS HD-OCT Model 5000 instrument with AngioplexTM optical coherence tomography (OCT) angiography capability is an upgrade of the existing CIRRUSTM Model 5000 instrument (version 10.5) which generates high-resolution three-dimensional maps of the retinal and choroidal microvasculature at a rate of 68,000 A scans per second, with an A-scan depth of 2.0mm in tissue (1,024 pixels), an axial resolution of 5 microns in tissue and a transverse resolution of 15 microns. The mean of the 3 scans was used to compute measurements.[12]

The Cirrus HD-OCT produces an RNFL thickness map by acquiring a 6 × 6 mm cube of signal data in the peripapillary region. Each cube of data obtained with the Cirrus HD-OCT consists of 40,000 data points (200x200 A-scans). For each eye, RNFL thickness was measured in 12 segments represented by clock hours; the 1-o'clock value represents the segment between 0° and 30°, with 0° being superior) and displayed for 4 quadrants (superior, nasal, inferior, temporal). The average of the entire 360° (global RNFL thickness) was also calculated.

Cirrus HD-OCT software then extracts a 3.46-mm peripapillary circle of data points centered on the optic disc from the cube of acquired data to construct a peripapillary RNFL map. OCT has allowed for optic nerve head analysis using spectral-domain technology; including the specific parameters: optic disc area (mm2), optic rim area (mm2), optic cup volume (mm3), average cup–disc ratio and vertical cup–disc ratio.

The higher resolution capability of SD-OCT allows for segmentation and thickness measurement of the perimacular ganglion cell complex (GCC), defined as the ganglion cell layer (GCL) and inner plexiform layer (IPL). SD-OCT computes GCC thickness data from 6mm square area scan centered over the fovea. An elipse with 2x2.4mm diameter is automatically drawn to analyze including parameters: average GC–IPL (mm), minimum GC– IPL (mm) and internal limiting membrane-retinal pigment epithelium (ILM-RPE) thickness (μm) for 6 sectors (superior, superonasal, superotemporal, inferior, inferonasal, inferotemporal).

Statistical Analysis

Data were coded and entered using the statistical package SPSS version 20. Data were summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. The Kolmogorov-Smirnov test was used to assess for normality of the distribution. If the Kolmogorov-Smirnov test has $p > 0.05$, the data is normal distribution. Multivariable regression analyses were used to analyze the effect of age, gender, and refraction on RNFL and GCL thickness. *P* values less than 0.05 were considered as statistically significant.

Results

A hundred fifty-two healthy eyes of 76 children which qualified the inclusion criteria were enrolled in the study. Demographic data of sample was summarized in table 1.

1.1 Demographics

Table 1: Characteristics of participants (n = 76)

	Mean ± SD	Max – Min
Age (years)	10.13 ± 2.47	6 – 16
Spherical equivalent (D)	–1.05 ± 1.27	–4.50 – 0
Gender		
+ Male	40 (52.6%)	
+ Female	36 (47.4%)	

The average age of children was 10.13 ± 2.47 years and 52.6% of them were male. The mean spherical equivalent was –1.05 ± 1.27 D in which 47.4% of the children had no refractive error.

1.2 Characteristics of optic disc and retinal nerve fiber layer thickness

1.2.1 Optic disc

Table 2: Characteristics of optic disc

	Mean ± SD	Max – Min
Disc area (mm^2)	2.15 ± 0.40	1.42 – 3.83
Rim area (mm^2)	1.54 ± 0.26	0.36 – 2.11
Cup volume (mm^3)	0.17 ± 0.16	0 – 0.78
Cup/Disc area ratio	0.47 ± 0.50	0.06 – 0.77
Vertical Cup/Disc ratio	0.44 ± 0.17	0.05 – 0.72

The parameters of optic disc were showed in table 2 with the mean disc area 2.15±0.40 mm2, mean rim area 1.54±0.26 mm2. The cup volume was 0.17±0.16 mm3 with 10 eyes (6.58%) having no cup.

1.2.2 The retinal nerve fiber layer thickness

The total average RNFL thickness was 103.18±9.50µm (range, 79–127µm) in which eyes having the average RNFL thickness > 90µm took 93.4%.

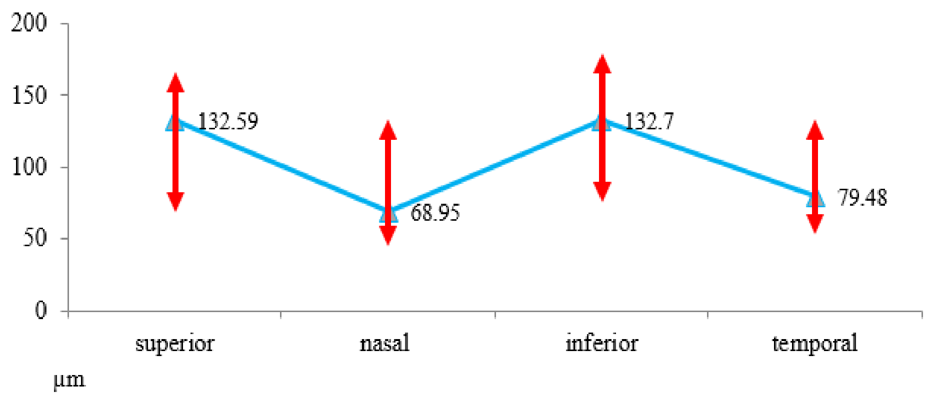

Figure 1: The mean RNFL thickness (µm) in 4 quadrants.

The average of RNFL quadrant thickness was 132.59±18.30 µm, 68.95±13.39µm, 132.59±18.30µm and 79.48±15.29µm at superior, nasal, inferior and temporal quadrant, respectively (figure 1).

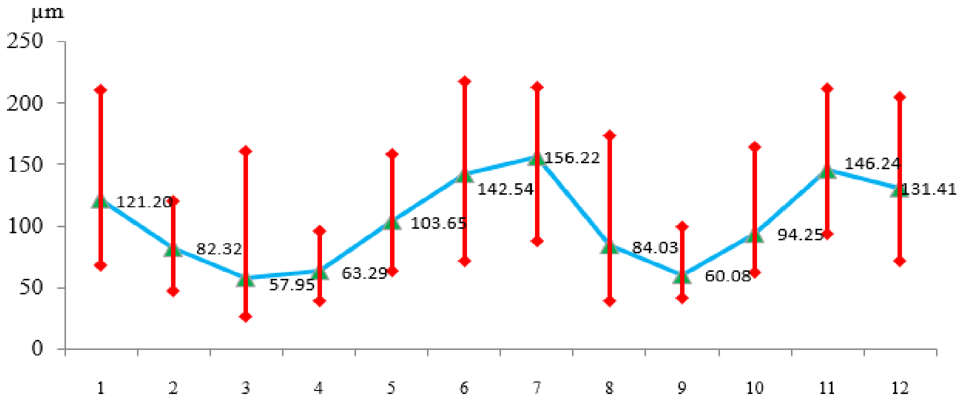

Figure 2: The mean RNFL thickness in clock hours (µm) (3= nasal, 6= inferior, 9 = temporal and 12= superior).

The thickest clock hour segments of the RNFL were at inferior temporal (156.22±23.92µm) and superior temporal (146.24±22.88µm). The thinnest clock hour segments were at temporal (60.08±9.90µm) and nasal (57.95±17.01µm) (figure 2).

1.3 The central ILM–RPE thickness

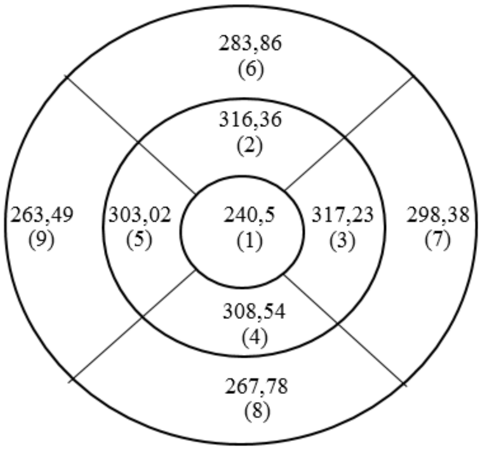

Figure 3: The mean central macular thickness (µm) (1= central, 2= superior inner, 3= nasal inner, 4= inferior inner, 5= temporal inner, 6= superior outer, 7= nasal outer, 8= inferior outer and 9= temporal outer).

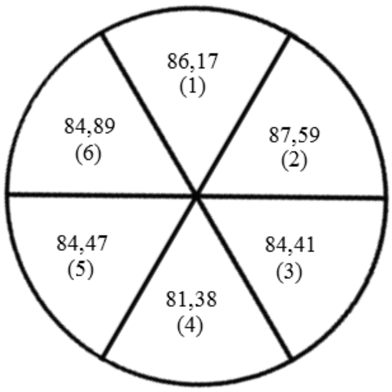

Figure 4: The GC–IPL thickness in six sectors (µm) (1 = superior, 2 = superonasal, 3 = inferonasal, 4 = inferior, 5 = inferotemporal, 6 = superotemporal).

The mean macular volume was 10.04±0.42mm3 and the average macular thickness value presented 279.06±11.60µm. The mean central macular thickness at 4 segments were also divided into central, inner and outer macula ring showed in figure 3. The thickest mean thickness of segments was 317.23µm at nasal inner and 316.36µm at superior inner sector while the thinnest ones were 263.49µm and 240.51µm at temporal outer and central macular sectors, respectively.

1.4 The GC–IPL thickness

The average GC-IPL and the minimum GC-IPL thickness were 84.74±5.17µm and 80.18±7.84µm, respectively. Figure 4 showed the GC-IPL thickness in six sectors in which the thickest one was 87.59µm at superonasal and the thinnest one 81.38µm at inferior sector.

	Mean RNFL thickness	Mean central ILM–RPE thickness	Mean GC–IPL thickness	Minimum GC–IPL thickness
Age				
• β	-0.288	-1.437	-0.126	-0.031
• P	0.844	0.006	0.501	0.981
Gender				
• β	-0.146	5.660	-0.555	-0.035
• P	0.671	0.016	0.502	0.904
Spherical equivalent refraction				
• β	0.361	-5.204	0.701	0.522
• P	0.567	< 0.001	0.050	0.350
Disc area				
• β	1.733			
• P	0.385			
Rim area				
• β	0.406			
• P	< 0.001			

β: Estimate of fixed effect

The result of multivariable regression analysis indicated that only the rim area was powerfully correlated with the mean RNFL thickness ($\beta = 13.692$, $p<0.001$). Therefore, the larger rim area was, the higher RNFL thickness existed.

The mean central ILM-RPE thickness was found to be significantly and negatively correlated with age and spherical equivalent refraction ($\beta=-1.437$, $p=0.006$ and $\beta=-5.204$, $p<0.001$, respectively). Also, gender was positively correlated with the central ILM-RPE thickness ($\beta=5.660$, $p=0.016$), male had thicker central ILM-RPE thickness than female.

Spherical equivalent refraction was the only factor positively correlated with the mean GC–IPL thickness ($\beta=0.701$, $p=0.05$). Consequently, more hyperopia was correlated with higher mean GC-IPL thickness. There was no correlation of the minimum GC-IPL thickness with age, gender and spherical equivalent refraction (table 3).

Dicussion

The Optical Coherence Topography has become a widely utilized tool in scientific and clinical practice. However, the result of OCT measurements has been limited in children because of the lack of a normative database. Our study provides the first normative database of the parameters measured by the AngioplexTM OCT in Vietnamese children between 6 and 16 years old.

Optic disc and retinal nerve fiber layer thickness

Table 4: Comparison of optic disc parameters with the study of Tariq et al.

	Disc area (mm^2)	Rim area (mm^2)	Cup volume (mm^3)	Cup/ Disc area ratio	Vertical cup/ disc ratio
Tariq (2012) [9]	1.98 ± 1.94	1.50 ± 1.47	0.13 ± 0.09	0.44 ± 0.47	0.42 ± 0.45
Pham Tien (2017)	2.15 ± 0.40	1.54 ± 0.26	0.17 ± 0.16	0.47 ± 0.50	0.44 ± 0.17

The result of disc area, rim area and vertical cup/ disc ratio in a study of Tariq et al. had larger standard deviation than these parameters in our study (table 4). This can be explained by Tariq et al, who reported the results of children from different ethnicity as White, East Asian, South Asian, Middle Eastern.[9]

The RNFL thickness

In comparison to researches of Salchow, Tariq and Goh, our study gave the same mean RNFL thickness.[4,8,9] The result of RNFL thickness in clock hours in adult population usually follows the "inferior superior nasal temporal" pattern (ISNT rule), in which the RNFL thickness is thicker in the inferior and superior quadrants than in nasal and temporal ones.

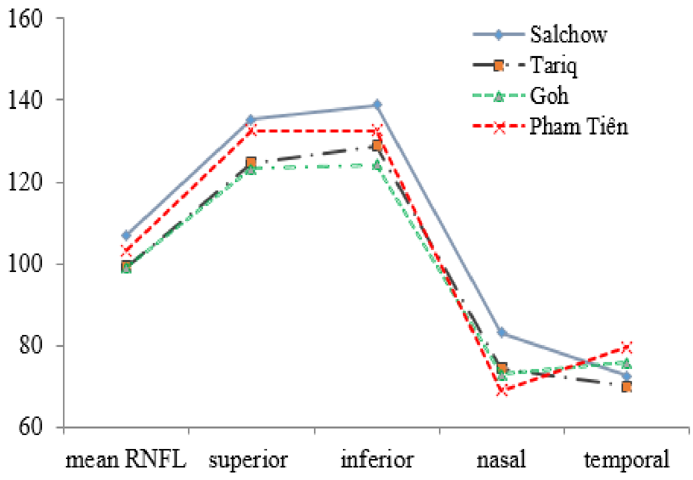

Figure 5: Comparison of studies reporting OCT RNFL thickness (µm) in normal pediatric subjects

However, the mean RNFL thickness of our study did not obey this rule, the temporal quadrant was thicker than nasal one. The results of Goh study for Singapore children subjects and Leung research for Hong Kong pediatric population were similar to the distribution of RNFL thickness of our study.[4,6] In contrast, the RFNL thickness of normal children in study of Salchow and Tariq followed the pattern of adult population. Tariq concluded that the thinner nasal RNFL in East Asians could be explained by the greater prevalence of myopia in his population, which may be associated with a temporal shift in the arcuate nerve fiber bundles.[9] However, more researches about the anatomy of the RNFL of children from different ethnicities should be performed to explain for abnormal distribution of RNFL thickness.

The central ILM–RPE thickness

Table 5: Comparison of the central ILM-RPE thickness with study of Al-Haddad

	Central ILM–RPE thickness (µm)	Macular volume (mm^3)
Al-Haddad (2014).[1]	249.10 ± 12.50	10.10 ± 0.50
Pham Tien (2017)	240.51 ± 15.47	10.04 ± 0.42

There was the similarity of the central ILM–RPE thickness and the macular volume between our study and Al-Hadded one (table 5).

Al-Haddad and Zhang indicated that central macular segment was thinnest, followed by the outer ring, then inner ring .[1,13] It was also found that the thickness in the nasal sector in the outer ring was much greater than that of the other three sectors, whereas there were no large differences between the inner ring sectors. Ooto et al. speculated that greater asymmetry of the macula thickness of the outer ring compared with that of the inner ring may be due to the vertically symmetric, but horizontally asymmetric anatomic nature of the RNFL, in which converging retinal nerve fibers form the superior and inferior arcuate bundles of nerve fibers within the optic disc. In contrast, the inner ring corresponds to regions with the thickest total retina and ganglion cell layer and a relatively thin RNFL.[11]

The GC–IPL thickness

Table 6: Comparison of studies reporting OCT GC-IPL thickness (µm) in normal pediatric subjects

	Average GC-IPL thickness (µm)	Minimum GC-IPL thickness (µm)
Totan et al.[10]	83.36 ± 5.40	78.69 ± 9.31
Goh et al.[4]	82.59 ± 6.29	77.17 ± 9.65
Pham Tien	84.74 ± 5.17	80.18 ± 7.84

The average GC-IPL thickness and the minimum GC–IPL thickness was similar to the results of Totan et al and Goh et al.[4,10]

There was also the similarity between the GC-IPL sectors thickness of our study and the results of Lee et al and Totan et al.[5] The thickest and thinnest sectors were superonasal and inferior sectors, respectively. This result is supported by Curcio and Allen in a histologic study that shows greater ganglion cell density in the nasal and superior retinal regions. However, this conclusion should be made clear by studies about the anatomy of ganglion cell layer between different ethnicities.[3]

The correlation between the RNFL thickness, the central ILM–RPE thickness, the GC–IPL thickness and other risk factors

By using multivariate regression analysis, it was found that only the rim area strongly correlated with the mean RNFL thickness and the RNFL thickness was not dependent on age as adult population. This finding was similar to the conclusion of Leung and Pawar.[6,7] They suggested that the rate of decrease in RNFL thickness is slower in younger age group. However, further study with larger sample size was needed to confirm whether the effect of age on RNFL thickness in children was.

Both of Zhang and current study displayed that there was differences between gender in central macular thickness, with boys having thicker retina than girls.[1 3] Therefore, it was necessary to consider sex factor when reading the results of ILM-RPE on OCT printout.

The study of Goh and Pham Tien indicated that the spherical equivalent refraction was correlated with the central macular thickness. However, in contrast to our findings, Goh concluded that hyperopic children have thicker central macular thickness than myopic ones.

The result of multivariate regression analyses shows that only spherical equivalent refraction was correlated with the mean GC–IPL thickness. This finding was similar to the result of Goh et al,[4] the hyperopic groups had thicker mean GC-IPL thickness than the myopic and emetropic groups.

The minimum GC-IPL thickness did not have any correlation with age, gender and spherical equivalent refraction. The progressive thinning of the choroid, retina, and sclera with axial elongation is likely diffuse and is thus reflected in thinner average GC-IPL values. This is in contrast to minimum GC-IPL which is defined as the lowest GC-IPL thickness over a single meridian crossing the annulus. The minimum GC-IPL was the best diagnostic performance among GC-IPL parameters in early glaucoma, especially in children.[4]

Conclusions

This study provides normative GC–IPL and RNFL thickness values for Vietnamese children. It may assist in identifying changes in GC–IPL and RNFL thickness in children. The rim area correlated with RNFL thickness while the spherical equivalent refraction and gender related with the central macular thickness. The minimum GC-IPL thickness was not affected by age, gender and spherical equivalent refraction, therefore, it can help to diagnose and follow-up pediatric glaucoma patients.

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