International Journal of Applied Research 2022; 8(6): 328-333

ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 8.4
IJAR 2022; 8(6): 328-333
www.allresearchjournal.com
Received: 03-03-2022
Accepted: 16-04-2022

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To establish a normative database of Retinal Nerve Fiber Layer (RNFL) thickness in children between 5-18 years of age

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Abstract

Background and Objectives: The diagnosis of ocular disease like glaucoma in children is more difficult because its difficult to obtain reliable and reproducible visual examinations. The study was conducted to compile a normative database of RNFL thickness in pediatric age of 5-18years.

Methods: This study presents 196 eyes of 200 children attending tertiary ophthalmic hospital, Davangere, Karnataka, South India, from November 2019-August 2021. The study included 65 males and 35 females. Complete ophthalmological examination was done in all children including cycloplegic refraction and fundus evaluation with 90D lens. Spectral domain OCT was performed using CIRRUS HD OCT-500. Axial length was obtained using ultrasound scanner-EPIDOT USO.

Results: 196 eyes of 200 children were analyzed with mean age of (13.3±2.4) years. Average spherical equivalent was -0.28±0.91 dioptre and average axial length was 23.1±0.7 mm. The mean global RNFL thickness was 97.0±8.8µm. It is marginally higher in female (97.8±8.6 µm) compared to males (96.6±8.9 µm). RNFL thickness was maximum in the inferior quadrant (126.0±13.7 µm) followed by superior quadrant (126.2±13.7 µm) and was least for temporal quadrant. RNFL thickness was thicker with shorter axial length ($p< 0.001$) and with higher hyperopia ($p< 0.001$).

Conclusion: Normative RNFL thickness in healthy children between 5-18 years were established in our demographic setup. RNFL thickness followed a normal distribution and varied marginally with gender. RNFL thinning was associated with increasing axial length and less positive refraction. The normative data from this study could serve as reference for further studies on pediatric glaucoma.

Keywords: Normative database, Retinal Nerve Fiber Layer (RNFL), thickness in children

Introduction

Optical coherence tomography (OCT) is an essential ancillary test for both macular and optic nerve diseases. It is a non-invasive technology that uses laser light to acquire *in vivo* high-resolution images and measurements of the central retina and the retinal nerve fibre layer (RNFL). Spectral domain-OCT significantly increases the amount of data acquired during each session; significantly reduces the motion artifacts; better repeatability and reproducibility and an increased signal-to-noise ratio are achieved compared with Time Domain-OCT. The data obtained with different OCT devices correlate with each other; however they are not exchangeable.

The diagnosis and follow-up of children with an ocular disease is more difficult than that of adults because of the challenge in obtaining reliable and reproducible visual examinations. Important diagnostic tools used in adults, such as visual fields, require their cooperation. However, OCT provides objective measurements of the affected structures. Generally, children older than 3 or 4 years of age can cooperate sufficiently. Macular measurements are even easier to obtain than those of the optic nerve, making OCT particularly suitable for use with uncooperative children or those with poor fixation.

Materials and Methods

Prospective observational study tertiary ophthalmic hospital, Davangere, Karnataka, South India, during the period November 2019 to August 2021 analyzing 100 patients (200 Eyes).

Inclusion Criteria: Any child of age 5-18 years but cooperative for OCT, no asymmetry in cup-disc ratio between fellow eyes greater than 0.2, no optic nerve head abnormalities and no optic disc margin hemorrhages were included.

Exclusion Criteria
Children with strabismus or amblyopia, any abnormalities of the disc or the retinal RNFL, family history of glaucoma, any other hereditary eye disease, history of intraocular surgery or any kind of laser therapy, mentally challenged children with neurological, metabolic or vascular disorders, other systemic disease possibly affecting the eye, presence of media opacity, best-corrected visual acuity of less than 20/30, hypermetropia more than +5D, myopia more than –5D or astigmatism more than 2D.

Method of collection of data
A total of 100 children age between 5- 18 years presenting to tertiary ophthalmic hospital, Davangere, Karnataka, South India, from November 2019 to August 2021 were included in the study. An informed consent was obtained from parents of all participants before participation. A detailed history and complete Ophthalmological examination was done in all children including visual acuity, slit lamp examination, fundus evaluation using Direct and Indirect ophthalmoscope. Spectral-domain OCT was performed with the Cirrus HD-OCT-500.

Images were reviewed and only images with a signal strength 46 with no movement artifact were included for the study. The parapapillary RNFL thickness parameters automatically calculated by the Cirrus software and evaluated in this study included average/full circle thickness – RNFL-FC (360ºmeasure), temporal quadrant thickness, RNFL-T, superior quadrant thickness, RNFL-S, nasal quadrant thickness, RNFL-N, inferior quadrant thickness, RNFL-I. Three such circular scans were performed successively. The average of the 3 scans was used in the analysis. All scans were performed by the same investigator. Mean RNFL thickness in micrometers along the whole circle circumference, four quadrants, 12'o clock hours were obtained.

Statistical Methods: SPSS (Version 16) software was used for all the analysis. Unpaired t-test was used to compare between two groups (male v/s female, right eye v/s left eye). Correlation and regression analysis was done to assess the relationship between RNFL and clinical parameters (age, sex and refractive error). A P-value of 0.05 or less was considered for statistical significance.

Results
200 eyes of 100 children were included in this study. Amongst these 200 participants 65 were male while 35 participants were females. Of the 200 eyes 4 were excluded from the study due to poor quality of scan due to corneal opacity.

The age of the patients in this study ranged from 5 to 17 years with the mean of 13.3±2.4SD years. There were 14 children in age group between 6-10 years, 56 children in age between 11-14years and 30 in the age group between 15-18 years. The study had 65 males and 35 females. 100 right eyes and 96 left eyes of 100 participants were analyzed.

The unaided visual acuity of all the eyes ranged from 6/6 to 6/36 with mean refractive error of -0.28 ± 0.91 diopters (range-4 to +2.5). The axial length varied from 21.7 mm to 25.7mm with the mean of 23.0±0.7 SD. The difference of mean axial length and the refractive error was not statistically significant between the right and the left eyes and the male and the female participants. (Table 1)

Table 1: Clinical parameters

Visual acuity	RE	LE	RE+LE (overall)
6/6-6/9	86	86	-
6/12-6/18	8	9	-
6/24-6/36	6	5	-
Refractive error (SE in Diopters)			
Mean ± SD	-0.25±0.89	-0.29±0.97	-0.28±0.91
Range	-4.0 to 2.5	-4.0 to 2.5	-4.0-2.5
Axial length (mm)			
Mean ± SD	23.0±0.7	23.1±0.7	23.1±0.7
Range	21.7 to 25.4	21.6 to 25.3	21.6 to 25.4

SD: standard deviation of the mean, SE: spherical equivalent, VA: visual acuity

The mean global RNFL thickness (RNFL-FC) was 97.0+/-8.8 µm(79.4 -114.6). The RNFL thickness was maximum in the inferior quadrant (RNFL-I) 126±13.7 µm, followed in order by superior(RNFL-S)126±16.3µm, nasal (RNFL-N) 70.5±12.3µm and temporal(RNFL-T)63.4±9.2µm, in both the sexes.

The mean RNFL thickness in the male participants were 96.6 +/- 8.9µm and 97.8+/- in the female participants. When comparing the mean RNFL between both sexes females had thicker RNFL than males which was not statistically significant ($p <$ 0.37). However when the nasal quadrant (RNFL-N) between both sexes were compared the mean difference was 4.40 with p value <0.03.

Table 2: Mean Global RNFL thickness and distribution of RNFL in Each Quadrant

Variable	Total	196
	Mean±SD(µ)	**Normal range (µ)**
RNFL-FC	97.0±8.8	79.4-114.6
RNFL-S	126.2±13.7	98.7-153.7
RNFL-I	127.7±16.3	95.2-160.2
RNFL-N	70.5±12.3	46.0-95.0
RNFL-T	63.4±9.2	45.0-81.9

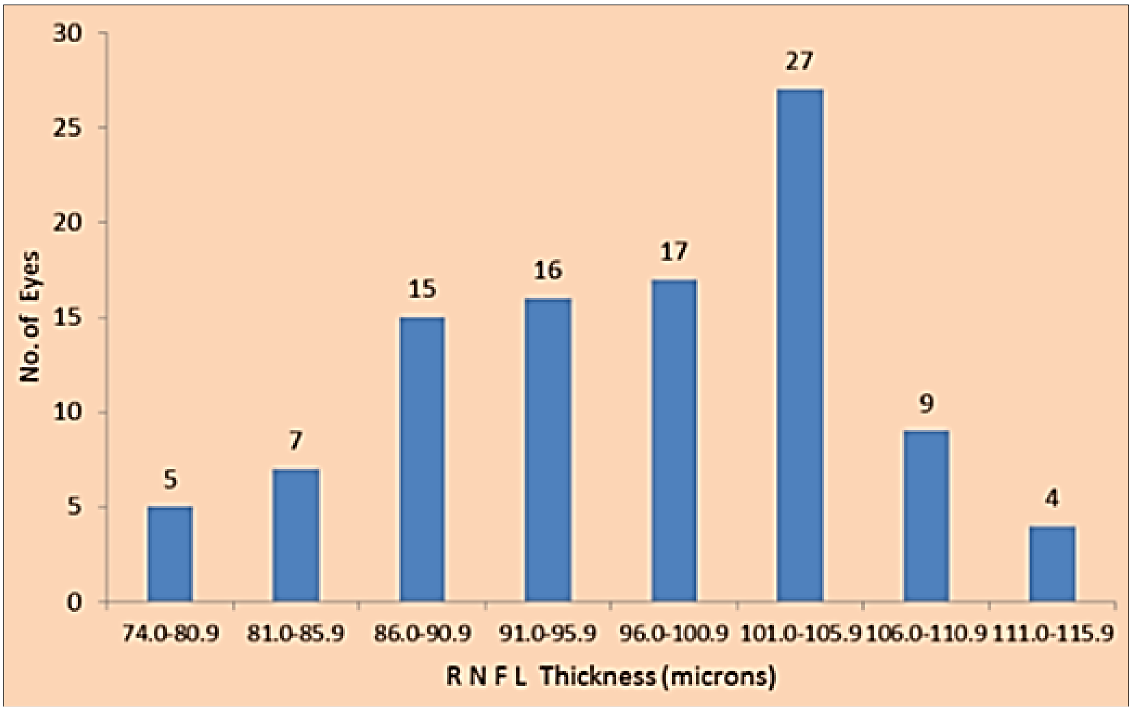
The above table shows, the inter-ocular variations in RNFL thickness in normal children measured by CIRRUS SPECTRAL DOMAIN OCT. The mean global RNFL thickness was 97.7±9.2SD in right eye (74.4-116 µm) and 96.3±8.4SDµ in left eye (79.5-113.1).The mean difference in global RNFL thickness between the two eyes was 1.38 with P value <0.27 which showed no statistical significance.

The mean RNFL thickness in the age group 6-10 years was 100.2 ± 6.4 µm it was 96.6 ± 8.9µm µm in the age group 14-18 years and 96.2 ± 9.4µm in the age group 5-18 years. The above table shows the mean global RNFL thickness and thickness of RNFL in each quadrant according to the age groups. From the above it can be seen that as age increases the mean RNFL thickness as well the thickness in each quadrant decreases. The RNFL thinning was found to be more in the superior quadrant (RNFL-S)

In order to assess the relationship between the age and the RNFL thickness correlation analysis was done. The analysis revealed that there is negative correlation between age and RNFL which shows that there is decrease in RNFL with increasing age(r=0.19).Though this relationship was weak, regression analysis was carried out to know the RNFL reduction for every 1yr increase in age. Analysis revealed that there was reduction of 0.70 micron in RNFL for average increase of one year. Explained variation was found to be (3.6%) R^2=0.036.

Table 3: Distribution of global RNFL (RNFL FC) thickness for all eyes

RNFL Thickness (µ)	No. of children
74.0-80.9	5
81.0-85.9	7
86.0-90.9	15
91.0-95.9	16
96.0-100.9	17
101.0-105.9	27
106.0-110.9	9
111.0-115.9	4
Total	100



Graph 1: Distribution of global RNFL (RNFL FC) thickness for all eyes

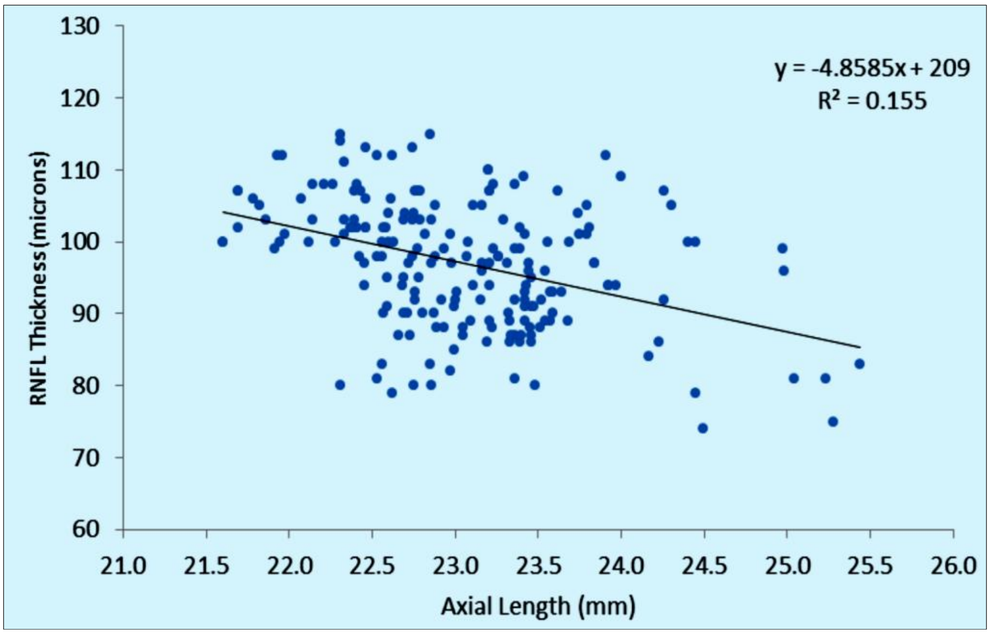
Table 4: Variation in the RNFL thickness between Male and Female in normal children < 18 yrs measured by Spectral Domain OCT

Variable	Males (128)		Females (68)		Males v/s Females		
	Mean ± SD (micron)	Normal Range(micron)	Mean ± SD	Normal Range	Mean Diff	t value	P value
RNFL-FC	96.6±8.9	78.7-114.4	97.8±8.6	80.6-114.9	1.19	0.91	0.37,ns
RNFL-S	126.7±13.5	99.6-153.7	125.3±14.2	96.9-153.7	1.36	0.65	0.52,ns
RNFL-I	126.7±16.7	93.4-160.1	129.6±15.4	98.9-160.3	2.85	1.20	0.23,ns
RNFL-N	69.0±10.7	47.2-90.7	73.4±14.1	45.1-101.7	4.40	2.24	0.03
RNFL-T	63.9+9.7	44.5-83.4	62.5±8.2	46.1-78.9	1.44 1	.10 0	.27,ns

Unpaired t test
**P*< 0.05, Significant

The mean RNFL thickness in the male participants were 96.6 + 8.9 and 97.8 + 8.6 in the female participants. When comparing the mean RNFL between both sexes females had thicker RNFL than males which was not statistically significant ($p <$ 0.37). However when the nasal quadrant (RNFL-N) between both sexes was compared the mean difference was 4.40 with P value<0.03).

The above graph shows significant positive correlation coefficient of 0.38 with refraction error in spherical equivalent (SE) with regression coefficient of 3.77. On analysis it was found that for every increase in one dipotre of spherical equivalent the mean RNFL increased by 3.77 microns. Explained variation was found to be 15.2% (R^2=0.036)



RNFL = 209.0-4.86 AXL, r = -0.39, R^2=0.155, *P*< 0.001

Graph 2: The correlation and regression analysis between axial length and RNFL thickness

The above scatter plot shows the correlation and regression analysis between axial length and RNFL thickness. The analysis revealed negative correlation between axial length and RNFL thickness, which shows there is reduction in mean RNFL thickness by 4.86 micron for every 1 mm increase in axial length (*p*< 0.001). The explained variation was found to be 15.2% (R^2=0.155).

Table 5: Correlation & Regression Analysis between RNFL thickness with age, refractive error and axial length

Relationship between	Corr. Coeff 'r '	Regn. Coeff 'ß'	Relation Equation	R²
Age & RNFL	-0.19	-0.70	RNFL = 106 - 0.70 Age	0.036 (3.6%)
Ref.Error & RNFL	0.38	3.77	RNFL = 98 +3.78 RefEr	0.152 (15.2%)
Axl and RNFL	-0.39	-4.86	RNFL = 209 - 4.86 Axl	0.155 (15.5%)

R^2 = Explained variation

The above table shows the correlation and regression analysis between RNFL thickness with age, refractive error and axial length. Positive correlation was seen with refractive error while inverse or negative correlation was seen with axial length and age.

Discussion

The study titled "To Establish A Normative Database Of Retinal Nerve Fiber Layer (RNFL) Thickness In Children Between 5-18 years Of Age" was done in the Department of Ophthalmology, J.J.M. Medical college, Davangere.100 children were included in the study which included 65 males and 35 females.

OCT has become widely used tool in clinical and scientific ophthalmology. Its uses in diagnosis of diseases is not restricted only to ophthalmology. Beside its use in identifying macular pathology and glaucoma, in recent year its application to diagnose various ocular conditions has widely been expanded such as multiple sclerosis, optic nerve gliomas, peudotumor cerebri, optic neuritis and papilloedema [1-4].

Normative data are provided automatically by OCT but the data base only include individuals 18years and above limiting its use in children. The application of OCT in children has been documented in several studies [5-8]. However no normative data base exist which would serve as a bench mark for reference and glaucoma scanning [9].

Average RNFL Thickness

The neuroretinal rim in normal eyes shows characteristic double hump configuration, which is usually the thickest in the inferior rim, followed by superior, nasal and the thinnest in the temporal rim, this is known as the Inferior Superior Nasal Temporal ISNT RULE. Several studies have confirmed this finding [10-12].

The average RNFL thickness in this study was 97.0± 8.8µm. When compared to other studies (Fig.14) in the past, the average RNFL of our study was lower to those studies done previously. The mean RNFL in the females were slightly higher than the male with *P*< 0.37 and was not statistically significant. The mean RNFL in RE was 97.7±9.2 µm and in the left eye 96.3±8.4 µm with *p*< 0.27. In a large study conducted by Huynh *et al.* [13] the average RNFL thickness was 103.7±11.4µm.The average RNFL in our study was lower to those of salchow *et al*. [14], Qian *et al*. [15], EL Dairi *et al*. [6] Leung *et al*. [16] and Ahn *et al*. [17].

Bourne *et al.* [18] compared the OCT 2000 with the Stratus OCT and found that the former model consistently yielded a higher RNFL thickness value. In comparison to the study conducted by Elai *et al.* [19], Barrio-Barrio *et al.* [20] Al-Haddad *et al.* [21] using cirrus OCT yielded results that were consistent with our finding.

The RNFL thickness varies significantly among types of OCT used and therefore direct comparison of RNFL thickness measurement among OCT instrument like Stratus and Cirrus may be misleading [9].

The distribution of RNFL thickness (thickest inferiorly and superiorly and thinner nasally and temporally) are in agreement with the normal distribution of RNFL. These variation are the result of the large number of nerve fibres converging to the optic nerve head from the superior and inferior arcuate bundles, relative to the number of fibres converging from the papillomacular bundles and nasal retina.

Studies vary as to whether the RNFL was thicker temporally or nasally or whether it was thicker superiorly or inferiorly. In our study it was seen that, in the age group between 5-10 years, superior RNFL was thicker compare to the inferior RNFL, with increasing age more thinning was seen in the superior RNFL compare to inferior RNFL, thinning was also seen in temporal RNFL while minimal changes were detected in the nasal RNFL [13].

RNFL Thickness with Age

Large number of studies have shown that RNFL thickness decreases as age increases [22-24]. It has been confirmed by several studies that the number of ganglion cells in human retina decreases with age which results in thinning of the RNFL. This has been confirmed by several investigation using OCT [25-26].

It has been estimated that normal individual loose ganglion cells at a rate of 4909 per year [27].

Bundez *et al.* [24] found that RNFL was thinner in older people with decline of appoximately 2 microns per decade. Qian *et al.* [15] and salchow *et al.* [14] reported that RNFL thickness tends to increase with age in a population younger than 18 years. B Alamouti *et al.* [26] studied 100 individual to establish changes in RNFL thickness with age in their study. They found highly significant correlation of both the retinal and the RNFL thickness with age. In these study the retinal thickness decreased by 0.53 μm per year. About 80% of the changes in retinal thickness over time are caused by a shrinkage of the RNFL. Poinooswamy *et al.* [28] examined 150 healthy volunteers of different ages using scanning laser polarimetry. They found a progressive reduction of the RNFL thickness with increasing age. The data presented in their study indicate a significant reduction of the RNFL thickness of 0.38 μm/year.

In this present study the mean age of the 100 participants were 13.3+2.4 years (6-18 years) we analyzed that there was mean global decrease in the RNFL, as well as decrease in RNFL in each quadrant with increasing age. the decrease in RNFL was more in superior quadrant compare to inferior quadrant, thinning was also seen in temporal quadrant while it was absent in nasal quadrant. Age was correlated negatively with RNFL thickness. In study conducted by Rajul S Parikh *et al.*, it was seen that RNFL tends to decrease with age. Average RNFL and RNFL by quadrant decreases especially after 50 years of age. Thinning of the RNFL is not uniform in all with maximum loss in the superior quadrant in comparison to inferior quadrant which is more resistant to loss. This finding were consistent in our studies also [29].

RNFL thickness with refraction

The effect of refractive error has been widely debated. Many studies have demonstrated positive correlation with spherical equivalent [13-15, 30]. Huynh *et al.* [13] studies on 1765 children less than 6 years reported significant trend for thicker RNFL with more positive refraction, however the changes were small. Qian *et al.* [15] reported a positive correlation of the average RNFL thickness with refractive error in healthy children. Merugacz *et al.* [5] compared RNFL thickness between 30 myopic and 15 controlled participants without myopia and reported no significant difference between the two groups. Vernon *et al.* [31] conducted similar study on 31 highly myopic eye of caucasian origin and observed no statistically significant correlation between the RNFL and spherical equivalent. A.Rao *et al.* [9] found that axial length and refractive status accounted for only 10% of the variation in RNFL thickness. In our study significant correlation was established between refractive error and global RNFL thickness, which showed regression coefficient of 3.77. Analysis revealed that there was increase in mean RNFL thickness by 3.77 microns for every unit diopter increase in refractive error.

RNFL Thickness with Axial Length

The relationship between RNFL with axial length has been established in many studies. Sony *et al.* [32] and Bayratkar *et al.* [33] reported no significant correlation between the RNFL average thickness and axial length, however these studies were limited by small sample size, While Huynh *et al.*[13] found significant trend toward thinner RNFL with longer axial length

Knight *et al.* [22] observed that axial length had a negative correlation with the mean RNFL thickness but had a positive correlation with the temporal quadrant in 63 chinese children.

Cheung *et al.* [34] reported that longer axial length was associated with thinner RNFL in a population based study of Chinese adults.

A. Rao *et al.* [9] in their study reported that the longer the axial length and greater the myopic shift early in life, the thinner will be the RNFL thickness.

In our study negative or inverse correlation is seen (R^2=0.155) with regression coefficient of -4.88, which shows that for every 1 mm increase in axial length, RNFL decreases by 4.88 microns.

Conclusion

Using Cirrus OCT, normative RNFL in healthy children between 5-18 yrs was established in our demographical set up. The retinal nerve fiber followed a normal distribution. RNFL varied minimally with gender, RNFL thinning was associated with increasing axial length and less positive refraction. The normative data from this study could serve as reference for further studies on pediatric glaucoma or other optic nerve head pathologies using nerve imaging modalities.

Limitation of the study

All the subjects included in our study population were hospital based and hence do not reflect the general population. Most childrens were between the age group of 11-15 years and therefore the result cannot be applied to the younger or older children accurately. The study did not consider the size of the optic disc which could be potential influencing factor for RNFL measurement. The study is also limited by exclusion of high refractive error and limited number of subjects.

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