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Assessment of Retinal Nerve Fiber Layer and Ganglion Cell Complex Thickness in Myopic versus Emmetropic Children attending Ophthalmology Outpatient Clinic in Suez Canal University Hospital

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Abstract

Background: **OCT is a useful tool for differentiating early stages of glaucoma in children as well as adults. Having a normative reference range for children helps in detecting such serious disease and treating it in earlier phases however, children's normative data are not provided by the OCT software. *Aim*: to share and establish reference values and data about retinal nerve fiber layer and ganglion cell complex thickness in the child age group, helping later earlier detection of disorders that possess damaging effects on such layers as glaucoma. *Patients and Methods*: one hundred thirty-five children were enrolled and divided into two groups, group including all emmetropic children with spherical equivalent between ≥ -1 and ≤ +1 diopter and group B including all myopic children with spherical equivalent between (≤ -1 and up to - 6 diopter) Measurement of retinal nerve fiber RNFL and ganglion cell complex GCC layer thickness using OCT scans were done using DRI OCT Triton plus. *Results*: Total retinal nerve fiber layers were thinner among the myopic group (106.2±5.65μm) than the emmetropic group (111.7±6.39μm) ($p<0.001$). The total ganglion cell complex layer was thinner among the myopic group (65.99±2.72μm) than the emmetropic group (70.22±2.84μm) ($p<0.001$). All RNFL and GCC thickness measurements showed significant indirect weak correlations with age. There is a significant correlation between axial length with (superior RNFL, average RNFL, superior GCC, inferior GCC, and total average GCC measurements). But no significant correlations were found between AL with Inferior RNFL thickness and age. *Conclusion*: Our study clearly demonstrates that myopic eyes have a thinner RNFL and GCC than emmetropic eyes. On one hand, this thinning may be a risk factor for glaucoma development, as variations in the arrangement of optic nerve head fibers have been postulated to render myopic eyes more susceptible to glaucomatous damage.**

Keywords: OCT, RNFL, GCC

Introduction

About 40% of all retinal nerve fiber layer (RNFL) axons are lost before any visual field defect could appear(1), so clinical assessment of RNFL is of high importance for the diagnosis and monitoring of all optic nerve diseases, particularly for glaucoma, which allows earlier initiation of treatment helping to prevent or control optic nerve damage as in glaucoma(2,3). The factors of age and axial length should

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be considered in the assessment of RNFL thickness. Certain studies have shown that the average RNFL thickness is inversely correlated with the axial length (AL), myopia as well as age[4,5]. By contrast, certain studies have reported a positive relationship between AL and RNFL thickness , so refractive errors caused by axial length variations are important factors affecting RNFL thickness [6], [7]. Refractive errors are common in childhood, with the World Health Organization estimating that 153 million people worldwide have visual impairment caused by uncorrected refractive errors[8]. In particular, myopia has become an important public health problem in Asia, with its prevalence and severity rising to epidemic levels[9]. In Egypt, Gawdat et al, in 1976, showed that myopia has a prevalence of 7.4%[10] while in 2015, Massoud and Nassr estimated that about 10.8% of university students are myopic[11] .indicating an increasingly higher prevalence of myopia among Egyptians over time. Many methods are now available to assess RNFL including classical RNFL photography[12,13] but such red-free photos of RNFL lacks quantification of changes in RNFL and can easily miss subtle RNFL loss early in glaucoma[14], also confocal scanner laser tomography[15], and lately the most sensitive optical coherence tomography (OCT) to detect early RNFL loss in adult patients with glaucoma[16,17].This would be particularly useful for children, in whom traditional tests such as stereoscopic optic disc photography and automated visual field (VF) testing are often impractical[18]. Literature has shown that OCT is a useful tool for differentiating early stages of glaucoma in children as well as adults. Having normative reference range for children helps in detecting such serious disease and treating it in earlier phases however, children normative data are not provided by the OCT software[19-21]. The normal range of RNFL and GCC thickness in adults has been measured by several investigators using OCT, but much less is known about normative RNFL and GCIL thickness values in children. The absence of normative RNFL values in children is an important gap in knowledge because evidence suggests that RNFL thickness in children and adults may differ[18].

Patients and Methods

From October 2019 to September 2020, a total of 135 children attending Ophthalmology clinic at Suez Canal University Hospital, Ismailia, Egypt. they were divided into two groups: myopic group and emmetropic group. Measurement of RNFL and GCC layer thickness using OCT scans Axial length measurement were done using DRI OCT Triton plus (Topcon Co., Tokyo, Japan) - Swept source with implemented SMART Track TM system©. Suez Canal University ethics and research committee approved this study. The exclusion criteria applied were; any type of glaucoma. Previous intraocular surgery, inherited fundus dystrophies, posterior segment diseases including uveitis, tumors, retinal detachment, ocular media opacities as cataract and corneal opacity, Children with strabismus or amblyopia, children with neurological, metabolic and vascular disorders. ,and patients who refuse to participate in this research. Before OCT and axial scan measurements, Complete medical history with emphasis on past history regarding ocular pathologies, surgeries, glaucoma, ocular diseases, and any intraocular surgeries and any systemic medical condition were obtained from all patients, the distant visual acuity measurement using Landolt C chart, subjective refraction, applanation tonometry and slit-lamp examination were carried out for all patients. Binocular indirect ophthalmoscopy fundus examination was also done to all patients, Axial length were measured by A-scan Sonomed E-Z Scan AB5500+ (Sonomed Escalon®, New York, USA) , contact technique , by one examiner. Children were divided into two comparison groups; group A including all emmetropic children with spherical equivalent between ≥ -1 and ≤ +1 diopter and group B including all myopic children with spherical equivalent between (≤ -1 and up to - 6 diopter)[22]. All children were dilated with cycloplegic eye drops (1% cyclopentolate eye drops) before examination, the child information was entered to the device and measurement of RNFL and GCC layer thickness using OCT scans were done using DRI OCT Triton plus (Topcon Co., Tokyo, Japan) - Swept source with implemented SMART Track TM system©. Two scans were acquired, 3D macular scan and 3D disc scan, the former includes a point to point tomographic analysis of a macular area over an area of 7mm x 7mm which yield multiple thickness maps of not only the macula, but also its RNFL, combined ganglion cell/inner plexiform layer thickness (GCIP expressed as GCL+), and combined macular RNFL /GCIP thickness expressed as (GCL++), the latter scan involves a optic nerve head 3D analysis over 6mm x 6mm area to assess RNFL where a 3.4 mm circular scan is placed around the optic disc. GCL+ (combined thickness of ganglion cell /inner plexiform layers) was measured at the macular region on SS-OCT images using a specific automatic segmentation algorithm. The overall average of macular GCIP in addition to detailed superior and inferior thickness of macular GCIP was measured. RNFL thickness parameters automatically calculated by the software and evaluated in this study included average/full circle thickness, temporal quadrant thickness, superior quadrant thickness, nasal quadrant thickness, and inferior quadrant thickness. The measured values among all participants were averaged, generating average RNFL and GCC thickness values in group A of the emmetropic children and group B of the myopic children in preparation for later-on statistical analysis.

Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). The significance of the obtained results was judged at the 5% level. The used tests were Chi-square test for categorical variables to compare between different groups, Monte Carlo correction to recheck chi-square results when more than 20% of the cells had expected count less than 5, Student t-test was used for normally distributed quantitative variables to compare between two studied groups, Mann Whitney U test was used to compare between two studied groups for abnormally distributed quantitative variables.

Ethical Considerations

Every participant's parent was informed about the aim of the study, its benefit to his child and to the community. Written consents were obtained from participants' parents and assent from children aged more than 12 years old before enrolling them in the study and they had the right to refuse participation. All data obtained from participants were used for scientific purposes only. No harmful maneuvers were performed. Researcher phone number was explained to the participants for any inquiry. Participants were announced by results of the study, and they had the right to refuse sharing their data, also they were free to withdraw from the study at any time.

Results

Two hundred and seventy eyes of one hundred and thirty-five children attending Ophthalmology outpatient clinic at Suez Canal University were enrolled in the study and assorted into two groups, the emmetropic group included 176 eyes and the myopic group 94 eyes. The mean age of patients was 13.2 ±22.3 years ranged from 10 to 16 years. Age, gender and side of affection were comparable between groups with statistical insignificant difference ($p<0.05$) (Table 1).

Table 1: Demographic data among study groups.

	Emmetropic group (n=176)	Myopic group (n=94)	Test value	P-value	Sig.
Age (yrs.) Mean±SD	13.4±2.1	13.3±2.2	0.196	0.845[1]	NS
Gender@ Male Female	94(53.4%) 82(46.5%)	46(48.9%) 48(51.1%)	0.127	0.722[2]	NS
Side of presentation@ • Right eye • Left eye	88(50%) 88(50%)	47(50%) 47(50%)	0.028	0.868[2]	NS

*@data are presented as (n, %); 1: Independent t test. 2: Chi-square test used. *Significant when p<0.05*

Mean intraocular pressure and vertical cup/disc ratio showed statistical insignificant difference between study groups as $p>0.05$. Axial length was higher among myopic group 24.15±0.625 than emmetropic group (22.92±0.455) with statistically significant difference ($p<0.001$) (Table 2). This study found that superior retinal nerve fiber layer was significantly thinner among myopic group (132.5±9.04μm) than emmetropic group (142.1±9.74μm) ($p<0.001$). Also, inferior retinal nerve fiber layer was significantly thinner among myopic group (139.3±8.11μm) than emmetropic group (142.9±9.99μm) ($p=0.002$). Total retinal nerve fiber layers were thinner among myopic group (106.2±5.65μm) than emmetropic group (111.7±6.39μm) with a statistically significant difference ($p<0.001$) (Figure 1).

Table 2: Comparison between study groups in IOP, Vertical cup/Disc ratio and Axial-scan results.

	Emmetropic group (n=176)	**Myopic group (n=94)**	**Test value**	**P-value**	**Sig.**
IOP (mmHg)	13.09±0.999	13.04±1.004	0.378	0.706[1]	NS
Vertical Cup/Disc ratio	0.471±0.087	0.458±0.089	0.556	0.226[1]	NS
Axial length	22.92±0.455	24.15±0.625	16.79	**<0.001*[1]**	S

*Data are presented as Mean±SD; 1: Independent t test. *Significant when p<0.05. IOP; intraocular pressure*

Also, superior ganglion cell complex layer was thinner among myopic group (65.91±2.61μm) than emmetropic group (69.91±2.73μm) with statistically significant difference ($p<0.001$). Inferior ganglion cell complex layer was thinner among myopic group (65.71±2.96μm) than emmetropic group (70.41±3.12μm) with statistically significant difference (p<0.001). Total ganglion cell complex layer was thinner among myopic group (65.99±2.72μm) than emmetropic group (70.22±2.84μm) with statistically significant difference (p<0.001) (Figure 1). All RNFL showed significant indirect weak. correlations with age. Also, GCC thickness measurements showed significant indirect weak correlations with age. There was a significant correlation between axial length with (superior RNFL, average RNFL, superior GCC, inferior GCC and total average GCC measurements). But no correlations were found between AL with Inferior RNFL thickness and age (Figures 2, 3).

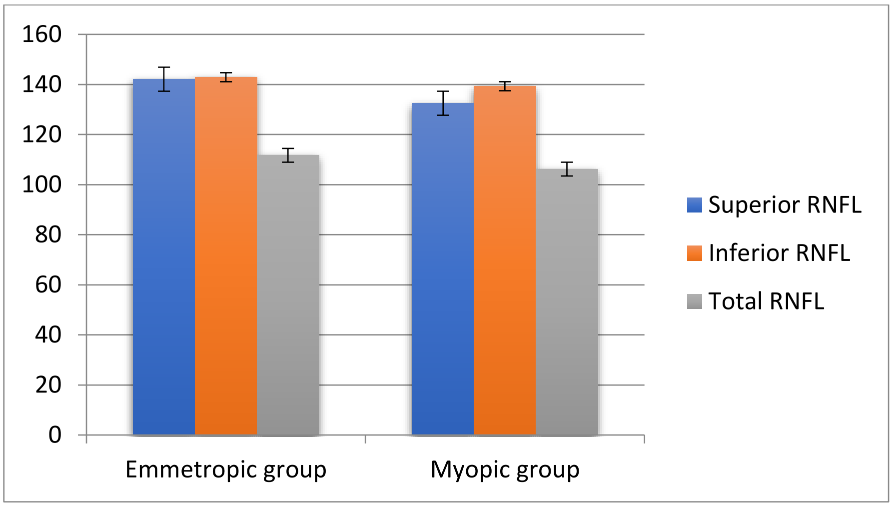

Figure 1: Mean retinal nerve fiber layers thickness distribution among the study groups.

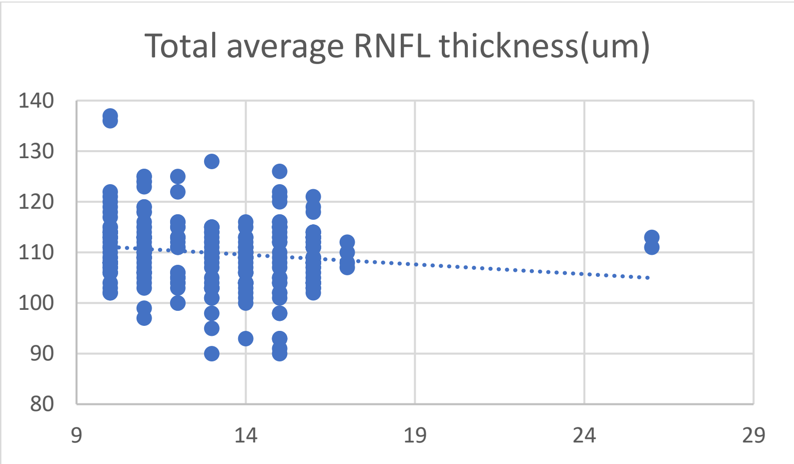

Figure 2: Correlation of total average RNFL with age.

Discussion

This prospective cross-sectional comparative study aimed at sharing and establishment of reference values and data about retinal nerve fiber layer and ganglion cell complex thickness in child age group attending the Ophthalmology Clinic in Suez Canal University Hospitals, by comparing group A including all emmetropic children with spherical equivalent between ≥ -1 and ≤ +1 diopter and group B including all myopic children with spherical equivalent between (≤ -1 and up to - 6 diopter), helping later-on earlier detection of disorders that possess damaging effects on such layers as glaucoma. In the present study, superior retinal nerve fiber layer was thinner among myopic group (132.5±9.04 µm) than emmetropic group (142.1±9.74 µm) with statistical significant difference (p<0.001). Total average retinal nerve fiber layers measurements were thinner among myopic group (106.2±5.65µm) than emmetropic group (111.7±6.39µm) with statistical significant difference (p<0.001).

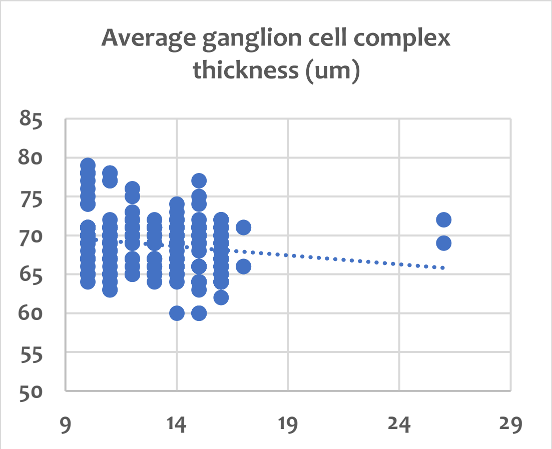

Figure 3: Correlation of total average GCC thickness with age.

Lee et al. conducted a study in China, from 2013 to 2014 about Retinal Nerve Fiber Layer Thickness in Myopic, Emmetropic, and Hyperopic Children aged 4 to 18 years using OCT. He found that the mean global RNFL thickness in myopic group was (101.9±11.0 µm) with significant difference. Also, found that the mean global RNFL in the myopic group was significantly thinner than the other group (P <0.0001). This suggested that the thinner RNFL in the myopic group was attributed to both an older age as well as refraction related factors[22]. This study is consistent with what reported in the Anyang Childhood Eye Study about the distribution of peripapillary retinal nerve fiber layer (RNFL) thickness in a population of 12-year-old children in central China using iVue-100 spectral-domain optical coherence tomography (version 2.5.0.100; Optovue). He found that the mean global RNFL thickness in myopic group was (103.1 µm)[23]. We have found a significant negative correlation between axial length with (superior RNFL, average RNFL, superior GCC, inferior GCC and total average GCC measurements). But no significant correlations were found between AL with neither Inferior RNFL thickness nor the age, in the age group of regard (10-16 years old). This comes in context with Lee et al. study who assessed the peripapillary retinal nerve fiber layer (RNFL) thickness in myopic, emmetropic, and hyperopic children using optical coherence tomography, they found that the axial length is negatively correlated with the global RNFL thickness (r= -0.4, P < 0.0001)[22], as well as the results of Leung et al study in 2010 in which the axial length measured by IOL master (Zeiss Humphrey System, Dublin, CA), and the peripapillary RNFL assessed by OCT in 104 children revealed a statistically significant negative correlation between these two variants[24]. In addition , Goh et al measured the distribution of macular ganglion cell-inner plexiform layer (GC-IPL) thickness and peripapillary RNFL thickness in children using a spectral domain Cirrus high definition optical coherence tomography system (Carl Zeiss Meditec Inc.). He found that multivariate analyses of average, superior, and inferior GCIPL thicknesses were significantly thinner with increasing AL[25]. Totan's et al study assessed the GC-IPL thickness, and peripapillary retinal nerve fiber layer (RNFL) thickness using OCT in 296 healthy Turkish children and found a significant negative correlation between them and AL[26]. Tong et al, on contrary, examined 316 Singaporean children aged 11 to 12 years using the Heidelberg Retinal Tomograph (Heidelberg Engineering, Heidelberg, Germany) and found no significant association between the RNFL with axial length, an important point in explaining such contradictory results is the fact that 142 participants comprising 44.9% of the study subjects had tilted disc which –in the author's words- affects all parameters of HRT imaging of optic disc except maximum cup depth(27). Another important aspect of regard is the different instruments and technologies used in both studies, In 2010, Leung et al found a much better sensitivity of OCT in assessment of RNFL versus the older technology of HRT (91.1% *vs.* 79.8 %)(28), also ethnicity has an effect on variation of the RNFL measurements that may share in such discrepancy(29,30). On the other hand, Lee et al found a moderate positive correlation between the axial length and age ($r=0.4$, $P< 0.0001$), contradicting our study results in such variant this may be attributed to the fact that Lee's study group included subjects aged between 4-18 years old (22), overlapping part of the critical time of ocular emmetropization during which the ongoing growth of the globe involves significant elongation of its axial length(31). In our study all RNFL showed significant indirect weak correlations with age as thinning in all quadrant of RNFL thickness will occur as the age advances. Also, GCC thickness measurements showed significant indirect weak correlations with age as thinning in all quadrants of GCC thickness will occur as the age advance. Similar results to our study were obtained from Salchow et al, who measured the peripapillary retinal nerve fiber layer (RNFL) thickness in 92 children aged 4 to 17 years using OCT. They found that age was correlated negatively with RNFL thickness(18). It was also reported in a large cohort study including 3000 Chinese children aged 6 to 19 years in which Cheng et al measured the GCIPL and outer retinal layer thicknesses using swept source-optical coherence tomography. They found a negative effect on GCIPL and outer retinal layer thicknesses when correlated with age and AL(32). In contrast, Lee et al in 2018 found no significant correlation between average GCIPL thickness and age in 127 children aged 3 to 17 years old using swept-source optical coherence tomography (SS-OCT)(33). Eslami et al study that included a total of 120 healthy Iranian children aged 8–17 years old also concluded that no significant correlation exists between age and RNFL global or individual quadrant thickness in such age group. The lack of significant correlation between RNFL thickness and age in the pediatric population can be explained from a statistical point of view: the narrow age range in pediatric population studies made it difficult for researchers to find a correlation between RNFL thickness and age, and extremely large sample sizes may be required to reveal such relationships(34). In our study, myopic group had significantly thinner total ganglion cell complex thickness (65.99±2.72μm) than emmetropic group (70.22±2.84μm) with $p<0.001$. This is in agreement with Jin et al study included two-hundred and seventy-six school children aged 7-13 years old in which he found that ganglion cell layer thickness of myopic participants was lower than in emmetropic participant using swept-source optical coherence tomography measurements(35). Similarly Jin et al. found that age was negatively associated with ganglion cell layer thickness ($r= -0.28$, $P < .01$)(35). Our results also suggest that although optic discs change as myopia progresses, RNFL thickness does not change during childhood regardless of whether the CDR is enlarged. Compared to the RNFL thickness, the macular GCC thickness was more greatly affected by CDR change, as the posterior pole region is more vulnerable to axial elongation than the peri-optic nerve region[36]. Strengths of our study include a relatively large sample size. Also, we utilized both eyes for the statistical analysis without consideration of eye dominance, as previous studies have found no difference in RNFL between the dominant versus nondominant eye. To our knowledge this is the first study to investigate peripapillary RNFL and GCC thickness in a large sample of Egyptian children as measured with DRI OCT Triton plus (Topcon Co., Tokyo, Japan) - Swept source with implemented SMART Track TM system©. Our study had its limitations. There was no longitudinal follow-up to investigate the rate of RNFL thinning between the 2 groups.

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