Analysis of Optic Nerve Head Parameters in Different Refractive States Pediatrics Using Spectral Domain Optical Coherence Tomography

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Short title: Optic disc cup size in pediatric population

ABSTRACT

Purpose: to analyze normative values of optic nerve head in pediatric age group using spectral domain optical coherence tomography (OCT) in different refractive states.

Methods: An observational cross-sectional study recruiting 174 healthy children from Nile Delta region aged 6 to 16 years with no ocular comorbidity except a refractive error. A thorough examination of the eyes was conducted, measuring axial length using IOL Master machine, and the Cirrus OCT device was used to quantify retinal nerve fiber layer (RNFL), and macular thickness. Main outcome parameters were macular volume, macular thickness and RNFL thickness values as well as their correlations with age, refractive error and axial length.

Results: the study included 74 females and 100 males. They were divided into 3 groups according to their refractive error. Group 1 (80) emmetropes, group 2 (62) myopes and group 3 (32) hypermetropes. Average spherical equivalent refraction (SE) was -0.20 ±0.77diopters in group 1, -3.17±1.27 in group 2 and 1.77±0.57 diopters in group 3. The average axial length was 22.97±.738 mm in group 1, 23.86±0.925in group 2 and 22.97±0.67mm in group 3. There was a statistically significant difference among the studied groups as regards the mean values of disc area, and Horizontal disc diameter ($p<0.05$), but no statistically significant differences were found regarding the mean rim area ($p=0.064$). As for the disc area, statistically significant differences were found when comparing group (1) with group (2), and group (2) with group (3).

Conclusions: SD-OCT could be of an important value in assessment of optic nerve head in pediatric age group despite the absence of normative database in the software. It shows values and trends similar to that in adults.

Keywords: Optic disc, Pediatric Population, Nile Delta**,** spectral domain OCT.

INTRODUCTION

Imaging of the retinal tissue by OCT machines has revolutionized the field of chorioretinal imaging, providing a non-invasive, non-contact method to provide high resolution scans. The spectral domain optical coherence tomography (SD-OCT), in particular can provide macular and retinal nerve fiber layer (RNFL) structure with up to 5 microns accuracy in resolution[1].

The optic disc morphology is known to play a major role in the diagnosis of glaucoma. Increased cup disc ratio (CDR) is one of the most important clinical signs in early diagnosis[2]. There is a wide variability in CDR in normal discs according to their size, where small discs tend to have smaller cup compared to normal or large discs (which tend to show larger cups and may be mistaken for early glaucomatous changes)[3].

The use of RNFL OCT imaging in children is controversial, mainly due to the lack of a normative database for this population, which makes the differentiation between normal and abnormal optic nerves difficult. On the other hand, several studies showed that these modalities can show excessive information. The ISNT rule has been verified in children[4-5]. It was also shown that ametropia plays a role in RNFL thickness, where wide rims in hypermetropic eyes and narrower rims in myopic ones[6]. Another study showed that the thickness of the RNFL and macular volume significantly differ between normal and glaucomatous children[7].

An incorporated normal database is present in all OCT devices for the population older than 18 years, in contrary to younger age group but clinical studies have demonstrated the viability of OCT in the pediatric population[8-15]. Earlier studies adopting time domain OCT (TD-OCT) machines showed readings typical to adults in the under 18 age group[9-17]; but equivalent findings using SD-OCT are very rare. Although RNFL measures from both machines are equivocal, there are substantial variations and the data cannot be employed interchangeably[18,19]. Measurement technique varies even within different SD-OCT devices[20-21]. A few studies in the literature reported normative reference ranges by SD-OCT[22-27]. Normative measures in children using Cirrus are seldom published, particularly for macular parameters. The clinical uses of SD-OCT are rising and appropriate reference values for RNFL and macular thickness are required in the juvenile population[28].

The aim of this study was to evaluate macular thickness and optic disc parameter in healthy, normal children population from the Nile Delta region in correlation with age, gender, axial length, and refractive error using SD-OCT

METHODS

This was a cross-sectional study of healthy Egyptian children aged 6 to 17 who visited the Pediatric Ophthalmology Clinic at Kafrelsheikh University Hospital in Kafrelsheikh governorate between September 2017 and October 2021.

These children were referred as a result of either a positive school visual impairment screening, visual behavior anomalies noticed by parents, a confirmed family history of refractive errors, or a physician referral.

The Kafrelsheikh University Institutional Review Board approved the research. A written informed consent was signed by the parents or the legal guardians. The study adhered to the research ethics stated by the declaration of Helsinki.

A total of 174 children and adolescents were enrolled prospectively. Inclusion criteria: children below 18 years, emmetropia or refractive error less than 7.00 diopters (of hyperopic or myopic spherical equivalent), normal best corrected Snellen visual acuity of 20/20, and an intraocular pressure less than 21 mmHg. Exclusion criteria were history of intraocular or strabismus surgery , Any ocular pathology (other than refractive error), anisometropia greater than 1.50 diopters, and amblyopia. Children with history of prematurity, neurologic, metabolic, or other systemic diseases were also excluded.

After obtaining full history and recording the essential demographic data, a detailed ophthalmic examination was performed including; Uncorrected visual acuity and best corrected visual acuity (BCVA) using Snellen chart, intraocular pressure using Goldmann's applanation tonometer (Keeler ltd., Windsor, UK) or Tono-Pen® (Reichert Inc., USA), ocular motility, slit lamp examination, dry and cycloplegic refraction by Nidek ARK-510A auto-refractometer (Nidek, Gamagori, Japan), and dilated fundus examination using 90 diopter lens. Cyclopentolate 1% eye drops instilled 3 times 10 minutes apart was used before cycloplegic refraction and fundus examination.

The children were divided into 3 groups according to their refraction. Group 1 included 80 emmetropic, group 2 included 62 myopic and finally group 3 included 32 hyperopic children.

The IOL master (Nidek Co. Ltd, Gamagori, Japan) was used to measure axial length (AL-scan). Multiple AL measurements (at least three) were taken, and an average value was recorded. Spectral domain OCT imaging (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) device was used to obtain high-definition images. Macular cube 512x128 and optic disc cube 200 x 200 were used to measure macular and peripapillary RNFL thickness, respectively. Measurements included volume, RNFL thickness (average, superior, nasal, inferior, and temporal quadrants), and macular thickness (average, central, and all subfields). Other disc parameters measured included: disc area, rim area, horizontal and vertical disc diameter, cup area, cup disc ratio (including linear and vertical), cup volume and rim volume. Signals with a strength of 6 or more were deemed acceptable. Internal fixation was employed to guarantee correct eye alignment.

Statistical analysis and data interpretation:

The data was collected and statistically analyzed using the Statistical package for Social Science (Version 22.0 of IBM SPSS Statistics for Windows, IBM Corp., Armonk, New York, USA). Number and percentage were used to describe qualitative data. After determining the normality of the data using the Kolmogorov-Smirnov test, quantitative data were presented using the median (interquartile range) for non-parametric data and the mean and standard deviation for parametric data. Significance of the obtained results was judged at the (0.05) level. Chi-Square test was used to compare qualitative data. One Way ANOVA and Kruskal Wallis test were used to compare more than 2 independent groups with Post Hoc Tukey test to detect pair-wise comparison after One Way ANOVA test and Mann Whitney U test after Kruskal Wallis test (For normally and non-normally distributed data, respectively). Correlation analysis was carried out using the Pearson correlation equation for variables with linear relations and the Spearman correlation equation for variables with nonlinear correlation.

RESULTS

The study included 174 eyes of 174 patients. The majority of subjects in all groups were males (57.5% of group 1, 58.1% of group 2, and 56.3% of group 3). The mean age of the studied subjects in group (1) was 11.60±3.07 years, while it was 11.55±3.78 years in group (2), and 11.38±3.17 years in group (3). No statistically significant differences were found among the studied groups regarding age, sex, or ocular distribution. The demographic data are illustrated in table 1.

Table (1): Demographic characters of the studied groups.

	Group 1 n=80	Group 2 n=62	Group 3 n=32	Test of significance	Within group significance
Age/years mean±SD	11.60±3.07	11.55±3.78	11.38±3.17	F=0.052 p=0.950	p1=0.928 p2=0.749 p3=0.813
Sex n(%)					
Female	34(42.5)	26(41.9)	14(43.7)	χ^2=0.028	p1=0.946
Male	46(57.5)	36(58.1)	18(56.3)	p=0.986	p2=0904 p3=0.866
Eye n(%)					
Right	42(52.5)	30(48.4)	14(43.8)	χ^2=0.742	p1=0.627
Left	38(47.5)	32(51.6)	18(56.3)	p=0.690	p2=0.403 p3=0.669

n= number, SD= standard deviation F: One Way ANOVA test

p1: between group 1&2, p2: between groups 1&3, p3: between groups 2&3

All the included subjects had a BCVA of 20/20. Table (2) demonstrates the spherical equivalent (SE), average keratometry readings (K average), axial length, and IOP among the studied groups. The results showed that there were statistically significant differences among the studied groups as regards the mean values **of** SE and axial length (p<0.001), while no statistically significant differences as regards the mean values of K. average, and IOP (p= 0.611 and 0.484 respectively).

Table (2): The spherical equivalent, average keratometry readings, axial length, and IOP among the studied groups.

	Group 1 n=80	Group 2 n=62	Group 3 n=32	Test of significance	Within group significance
SE mean±SD	-0.205±0.771	-3.17±1.27	1.77±0.57	F=323.89 p<0.001*	p1<0.001* p2<0.001* p3<0.001*
K. average mean±SD	43.46±0.85	4330±0.90	43.37±1.26	F=0.493 p=0.611	p1=0.324 p2=0.662 p3=0.729
Axial length mean±SD	22.97±.738	23.86±0.925	22.97±0.67	F=25.19 p<0.001*	p1<0.001* p2=0.975 p3<0.001*
IOP mean±SD	13.40±3.01	13.79±3.08	13.06±1.93	F=0.729 p=0.484	p1=0.423 p2=0.575 p3=0.246

n= number, SD= standard deviation, SE= spherical equivalent, K. average= average keratometry readings, IOP= intra-ocular pressure

F: One Way ANOVA test, *statistically significant. p1: between group 1&2, p2: between groups 1&3, p3: between groups 2&3

Table (3) demonstrates the average RNFL, superior, inferior, nasal, and temporal thickness differences across the groups. According to the current results, there were statistically significant differences among the studied groups as regards the mean values of RNFL, superior, inferior, and temporal (p<0.05), while no statistically significant differences were found among the studied groups as regards the mean nasal (p=0.154

Table (3): GRNFL, superior, inferior, nasal, and temporal among the studied groups.

	Group 1 n=80	Group 2 n=62	Group 3 n=32	Test of significance	Within group significance
RNFL mean±SD	105.88±6.35	100.05±8.49	105.78±6.09	F=13.13 p<0.001*	p1=0.001* p2=0.950 p3=0.001*
Superior mean±SD	128.61±14.62	117±11.93	128.56±17.07	F=13.26 p<0.001*	p1=0.001* p2=0.987 p3=0.001*
inferior mean±SD	134.35±11.18	130.24±18.22	138.28±7.89	F=3.86 p=0.023*	p1=0.078 p2=0.172 p3=0.008*
Nasal mean±SD	82.16±11.36	78.19±12.68	82.69±18.75	F=1.89 p=0.154	p1=0.083 p2=0.852 p3=0.126
Temporal mean±SD	79.16±9.78	72.81±10.04	74.59±9.27	F=7.81 p=0.001*	p1=0.001* p2=0.027* p3=0.402

n= number, SD= standard deviation, RNFL= retinal nerve fiber layer. F: One Way ANOVA test, *statistically significant

p1: between group 1&2, p2: between groups 1&3, p3: between groups 2&3

Table (4) illustrates disc area, rim area, and horizontal disc diameter among the studied groups. There were statistically significant differences among the studied groups as regards the mean values of disc area, and horizontal disc diameter (p=0.001 and 0.019 respectively), while no statistically significant differences were found as regards the mean rim area (p= 0.064).

Table (4): Disc area, rim area, and horizontal disc diameter among the studied groups.

	Group 1 n=80	**Group 2 n=62**	**Group 3 n=32**	**Test of significance**	**Within group significance**
Disc area mean±SD	2.69±0.45	2.36±0.54	2.72±0.37	F=10.18 p=0.001*	p1=0.001* p2=0.782 p3=0.001*
Rim area mean±SD	1.97±0.75	1.66±0.84	1.84±0.75	F=2.80 p=0.064	p1=0.019* p2=0.449 p3=0.269
Horizontal disc diameter mean±SD	1.73±0.25	1.64±0.187	1.75±0.126	F=4.07 p=0.019*	p1=0.012* p2=0.723 p3=0.02*

n= number, SD= standard deviation F: One Way ANOVA test, *statistically significant

p1: between group 1&2, p2: between groups 1&3, p3: between groups 2&3

As for cup area, cup area ratio, linear CDR, vertical CDR, cup volume, rim volume, and vertical disc diameter among the studied groups they are illustrated in table (5). There were statistically significant differences among the studied groups as regards the median values of cup volume, and vertical disc diameter (p= 0.009 and 0.001 respectively). The rest of the previously mentioned parameters didn't show a statistically significant difference.

Table (5): The cup area, cup area ratio, linear cup disc ratio, vertical cup disc ratio, cup volume, rim volume, and vertical disc diameter among the studied groups.

	Group 1 n=80	**Group 2 n=62**	**Group 3 n=32**	**Test of significance**	**within group significance**
Cuparea median (IQR)	0.39 (0.185-0.660)	0.3 (0.1075-0.50)	0.40 (0.30-0.69)	KWχ^2=5.14 p=0.077	p1=0.200 p2=0.182 p3=0.027*
CD area ratio median (IQR)	0.15 (0.083-0.24)	0.135 (.05-0.22)	0.17 (0.11-0.275)	KWχ^2=4.42 p=0.110	p1=0.379 p2=0.111 p3=0.04*
Linear CDR median (IQR)	0.375 (0.265-0.50)	0.365 (0.200-0.465)	0.400 (.343-.518)	KWχ^2=3.81 p=0.149	p1=0.410 p2=0.153 p3=0.058
Vertical CDR median (IQR)	0.350 (0.240-0.480)	0.385 (0.225-0.503)	0.345 (0.270-0.443)	KWχ^2=0.162 p=0.922	p1=0.827 p2=0.716 p3=0.789
Cup Volume median (IQR)	0.055 (0.022-0.100)	0.05 (0-0.10)	0.09 (0.04-0.188)	KWχ^2=9.38 p=0.009*	p1=0.210 p2=0.019* p3=0.004*
Rim volume median (IQR)	0.775 (0.608-0.938)	0.705 (0.50-0.80)	0.75 (0.535-0.887)	KWχ^2=3.77 p=0.152	p1=0.068 p2=0.476 p3=0.229
Vertical disc diameter median (IQR)	1.98 (1.81-2.09)	1.83 (1.6-1.99)	2 (1.81-2.11)	KWχ^2=14.42 p=0.001*	p1=0.001* p2=0.500 p3=0.002*

n= number, CD= cup disc, CDR= cup disc ratio. IQR: Interquartile range, KWχ^2: Kruskal Wallis test, *statistically significant

p1: between group 1&2, p2: between groups 1&3, p3: between groups 2&3

The correlations between axial length and spherical equivalent, and average RNFL and disc area were performed. There was a significant moderate correlation between axial length and average RNFL with the Spearman correlation coefficient (95% confidence interval) of -0.433 (-0.547 to -0.304) (Figure 1). There was a significant weak to moderate correlation between SE and average RNFL (95% confidence interval) of 0.359 (0.222 to 0.482). There was no significant correlation between disc area and both axial length and SE.

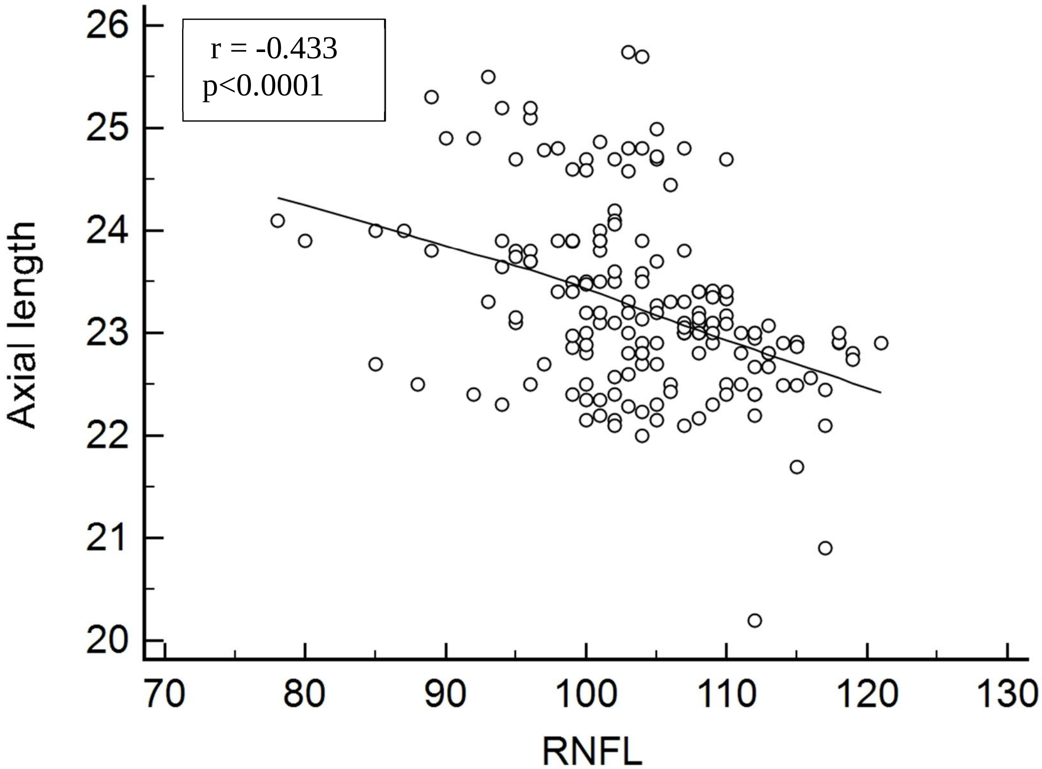

Figure (1): Relation between axial length and RNFL

DISCUSSION

Glaucoma assessment is crucial as it causes permanent visual loss in the form of gradual visual field decay. Assessment can be accomplished by IOP measurement, optic head morphology, visual field testing and RNFL analysis[29].

Meticulous clinical examination is mandatory to reveal early glaucoma disease in pediatrics together with imaging modalities including RNFL, visual field tests, and disc photography; but unfortunately visual field tests are extremely difficult to be obtained in young people. So, cupping and cup to disc ratio assessment are golden tools for early discovery of glaucoma in pediatrics[30]. The study of the optic disc morphology using OCT is a sensitive diagnostic tool for early detection of glaucoma in children[31].

There are certain factors that affect optic disc head morphology including axial length, vertical disc diameter, race, and age. Axial length affects disc head morphology noticeably; as axial length increases, rim becomes thin and cup becomes larger. Age affects size of cupping but with little extent[32-33].

Previous study by old generation (TD-OCT) in Australian children concluded that axial length has a great rule to determine disc and rim size than refraction, and disc area increased noticeably with axial length but, the assessments of optic nerve head parameters supplied by TD- OCT and SD-OCT show significant variation and cannot be regarded comparable[34,35].

The current study was conducted to investigate normative optic disc biometrics using SD- OCT in normal Nile delta region children. There were statistically significant differences in the mean values of SE, and axial length among the analyzed groups, but no statistically significant changes in the mean K values, and IOP. Furthermore, RNFL thickness were measured, and statistically significant differences in the mean values of RNFL, superior, inferior, and temporal sections were observed but not nasal one among the studied groups.

RTVue OCT machine was used before to assess the effect of axial length on RNFL thickness in myopic, hyperopic and emmetropic eyes in children. That study found that, axial length has an impact on peripapillary RNFL thickness but authors of this study thought that thickness variation arise from ocular magnification effects in relation to axial length and those effects could be amended by Littman formula[36].

Comparably a study on RNFL in Chinese children revealed myopic eyes had thinner peri-papillary RNFL, larger cup, smaller rim and optic nerve head volume but the regression line for those correlations was trivial and the absolute differences were minor in comparison with emmetropic and hyperopic eyes[37]. The results of our study are in agreement with the findings of those two studies, in particularly regarding what we get in the myopic group as they had the least optic nerve head volume.

The cupping can be greatly affected by axial length and this fact was proven in adult population[35], as axial length increased, optic disc area as well as rim area reduced.

However, another study by confocal scanning laser ophthalmoscopy confirmed that disc area increased with increasing axial length and negative (SE) on OCT measurement but this study included adults rather than pediatric age group and was conducted on Chinese ethnic group[38].

Therefore, the most important factor in determining cup size especially with extensive cupping founded to be axial length as well as SE. These correlations demonstrate the adult population's commonality[39]. SE is a strong determinant of RNFL thickness as well[40].

Additionally, disc size is a major predictor of other disc parameters, and the size of both the rim and cup parameters is much dependent on disc size[41].

Jung et al. in their study which included children with large cupping[29] found that cup size had a positive correlation between disc area and an inverse relationship with rim area, which supports the idea. As a consequence, children with significant cupping may have a big disc region and a tiny rim area. Furthermore, there was a substantial positive link between disc area and horizontal cup disc ratio, vertical cup disc ratio, and cup disc area ratio[42]. As a result, as the disc area grows, so does the cup to disc ratio. Our findings show a similar pattern, with a positive association between cup to disc ratio and disc area although we included children within normal cup to disc ratio by fundus examination.

In accordance, Jun and Lee[43] investigated the effect of variation in the optic disc area induced by axial length and refractive error by older generation OCT in children during 2003 to 2004, as well as the resulting changes in the distance from the optic disc margin to the circular scan (OD-CS) of OCT on the assessment of RNFL thickness. They concluded that the optic disc area of children differed significantly based on age, refractive error, and axial length, and that the OD-CS of OCT could be significantly adjusted depending on the disc area. When a result, as the axial length increases and a myopic refractive state develops, the RNFLT produced by performing circular scanning on a given diameter tends to decrease in a particular optic disc area.

The RNFL should be measured accurately to diagnose juvenile glaucoma based on the previously mentioned criteria. Their study also showed ethnic but not gender differences were demonstrated for most parameters. Significant differences in disc, cup, and neural rim parameters were also found between East Asian and European white children.

To the best of our knowledge this study is the first study which enrolls the normative data of pediatric peri-papillary RNFL parameters in Nile delta region. The limitation of this study is the sample size which may be considered relatively small. Patients in this age group are rarely referred for investigative purposes especially that they have no complaints, their parents may neglect complaints even if they are there.

Finally, when it comes to SD-OCT optic disc characteristics, axial length is a significant factor defining RNFL thickness. Correlation of axial length and disc size needs to be explored more to eliminate any possible magnification effect

DATA AVAILABILITY

All data are included in this article.

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None

Conflict of Interest

Authors declare no conflicts of interest.

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Ethics declarations

Conflict of interest

Mohammed Elashri, Maiada A. Youssif, Ahmed O. Hashem, Mo'mena A. Awad-Allah, all authors have no conflicts of interest that are directly relevant to the content of this review.

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