Retinal Nerve Fiber Layer Thickness in Myopic, Emmetropic, and Hyperopic Children

Jacky W.Y. Lee, FRCSEd, Gordon S.K. Yau, FRCSEd, Tiffany T.Y. Woo, MBBS, Doris W.F. Yick, FCOphthHK, Victor T.Y. Tam, FCOphthHK, and Jimmy S.M. Lai, MD

Abstract: The purpose of this study was to investigate the peripapillary retinal nerve fiber layer (RNFL) thickness in myopic, emmetropic, and hyperopic children using optical coherence tomography.

Two-hundred one right eyes of subjects aged 4 to 18 years were divided into 3 groups based on their postcycloplegic spherical equivalent: myopes ($<-1.0\,D$), emmetropes (≥-1.0 to $\leq+1.0\,D$), and hyperopes ($>+1.0\,D$). The RNFL was correlated with age, spherical equivalent, and axial length. The RNFL was compared between the 3 groups before and after age adjustment.

The RNFL was thickest in the hyperopic group ($107.2\pm10.13\,\mu$m, n = 73), followed by the emmetropic group ($102.5\pm9.2\,\mu$m, n = 61), and then the myopic group (95.7 ± 10.3, n = 67) (all $P<0.0001$). The myopic group (9.6 ± 3.9 years) was significantly older than the emmetropic (6.9 ± 2.7 years) and hyperopic (6.5 ± 1.9 years) groups (both $P<0.0001$). When adjusted for age, myopes had a thinner RNFL than the other 2 groups (all $P<0.0001$), but there was no RNFL thickness difference between the emmetropic and hyperopic groups ($P>0.05$). A thinner RNFL was associated with an older age ($r=-0.4$, $P<0.0001$), a more myopic spherical equivalent ($r=0.5$, $P<0.0001$), and a longer axial length ($r=-0.4$, $P<0.0001$) on Pearson correlation analysis.

The apparently thicker RNFL in hyperopic and emmetropic children was attributed to their younger age as compared with their myopic counterparts. When adjusted for age, only myopia was associated with a thinner RNFL, with emmetropic and hyperopic children having equal RNFL thicknesses. Advancing age, a more myopic spherical equivalent, and a longer axial length were associated with a thinner RNFL in children.

(*Medicine* 94(12):e699)

Abbreviation: RNFL = retinal nerve fiber layer.

INTRODUCTION

During optic nerve development, 2.85 million nerve fibers exist, but by the third trimester, we lose about 35%,[1] and the peripapillary retinal nerve fiber layer (RNFL) thickness will continue to decrease with advancing age.[2] Understanding the determinants that affect the RNFL reserve in childhood helps us in the diagnosis and monitoring of optic nerve diseases. Previous studies have found that white race,[3] lower birth weight,[4] longer axial length, and myopia have been associated with a thinner RNFL.[5] On the contrary, optic disc tilting[6] and Asian or Hispanic race have been associated with a thicker RNFL.[3] 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.[7] The prevalence of myopia ranges from 22.7% to 38.7% based on large population studies, with a higher prevalence in East Asian regions.[8–10] With age, the refractive status often changes from hyperopia to myopia; hence, the progressive RNFL thinning that comes with age can either be a result of age-related ganglion cell loss or due to the stretching of RNFL from the axial myopic shift in childhood.[5] The purpose of this study was to investigate the influence of refractive errors on RNFL thickness by comparing the differences in children with myopia, emmetropia, and hyperopia.

PATIENTS AND METHODS

The study was conducted in accordance with the Declaration of Helsinki and no patient's personal data was disclosed in the study. Study approval was obtained from the institutional review board of the Hospital Authority of Hong Kong. Informed consent was obtained from the parents or legal guardians of the subjects. The authors declare no financial or proprietary interests. This was a nonfunded study.

This cross-sectional study recruited consecutive cases of pediatric subjects aged 4 to 18 years, attending the ophthalmology specialist outpatient clinic of Caritas Medical Centre in Hong Kong Special Administrative Region, China, from 2013 to 2014. Subjects with only eye, ocular tumors, congenital glaucoma, congenital cataract, congenital nystagmus, microphthalmos, optic nerve or retinal disease, active cornea infections, corneal scars, and severe visual impairment of any cause (Snellen best corrected visual acuity ≤0.1) were excluded. To increase the generalizability of the study, there were no exclusions based on the refractive errors or axial length of subjects.

All subjects underwent a complete ophthalmological examination including ocular alignment and motility assessments as well as anterior and posterior segment examinations after pupil dilatation with a tropicamide 1% and phenylephrine hydrochloride 2.5% ophthalmic solution (Mydrin-P; Santen Pharmaceutical, Osaka, Japan).

Spherical Equivalent and Axial Length

All subjects received cycloplegic refraction with 3 drops of Cyclopentolate hydrochloride 1% (Bausch & Lomb, Rochester, NY) administered 5 minutes apart to relieve all accommodative component. After at least 30 minutes, postcycloplegic

autorefraction with a keratorefractometer (Topcon KR-8900; Topcon Europe Medical B.V., Capelle aan den IJssel, The Netherlands) was performed by an optometrist with at least 5 years of experience with pediatric assessment. The spherical equivalent was calculated in diopters. Axial length measurements in millimeters were obtained with the noncontact optical biometry (IOL Master; Carl Zeiss Meditec AG, Berlin, German).

Peripapillary RNFL Thickness Measurement

The protocol for RNFL measurement at our institution has been previously described in earlier publications by the authors[11–13] as "The Spectralis® Spectral Domain OCT (Heidelberg Engineering, 1808 Aston Ave., Suite 103, Carlsbad, CA 92008, United States of America) was performed after cycloplegia, by a single, imaging technician who was masked to subjects' clinical information. Scans were centred on the optic disc with a scanning diameter of 3.5 mm and 768 A-scans were obtained using the High Speed mode. To improve image quality, Automatic Real Time function was used to obtain multiple frames during scanning and to optimize images by noise reduction. Scans were repeated 3 times and assessed for signal strength and centration. Scans with signal strength quality ≤ 16 or poor centration were excluded. RNFL thickness was analysed with the RNFL Single Exam Report OU with fovea-to-disc technology. The RNFL thickness of each of the 4 quadrants and the global RNFL thickness were recorded in micrometers (μm)."

Statistics

Subjects were divided into 3 groups based on their postcycloplegic spherical equivalent: myopic (< -1.0 D), emmetropic (≥ -1.0 to $\leq +1.0$ D), and hyperopic ($> +1.0$ D). Only the right eye of each subject was used for statistical analysis. Statistical significance was considered when $P < 0.05$. Means were expressed with standard deviations.

The following were compared using one-way analysis of variance with Tukey multiple comparison test for the 3 groups:

- Age
- Spherical equivalent
- Axial length
- Global and quadrant RNFL thicknesses (before and after age adjustment)

Pearson correlation was used to analyze the association between the following parameters for the entire study population:

- RNFL (global and quadrant) thicknesses versus age
- RNFL (global and quadrant) thicknesses versus axial length
- RNFL (global and quadrant) thicknesses versus spherical equivalent
- Axial length versus age
- Axial length versus spherical equivalent

RESULTS

Of the 201 subjects eligible for the study, the mean age was 7.6 ± 3.3 years. There were 98 female and 103 male subjects; all were of Chinese ethnicity. There were 67 (33.1%) myopic eyes, 61 (30.1%) emmetropic eyes, and 73 (36.3%) hyperopic eyes. The mean RNFL thicknesses for the study population were interior (130.2 ± 21.1 μm), superior (125.9 ± 20.6 μm), nasal (63.6 ± 16.3 μm), temporal (87.4 ± 19.3 μm), and global (101.9 ± 11.0 μm).

The age distribution, spherical equivalent, axial length, RNFL, and age-adjusted RNFL of the myopic, emmetropic, and hyperopic groups were summarized in Table 1. The mean age in the myopic group was significantly older than the other 2 groups (all $P < 0.0001$). There was no significant age difference between the emmetropic and hyperopic group ($P > 0.05$). The mean spherical equivalents among the 3 groups were significantly different (all $P < 0.0001$). The axial length was the longest in the myopic group, followed by the emmetropic and hyperopic groups (all $P < 0.0001$). The mean global RNFL thickness in the 3 groups was significantly different (all $P < 0.0001$). When adjusted for age, the mean global RNFL was persistently thinner in the myopic group compared with the other 2 groups (both $P \leq 0.0001$). However, there was no significant difference in RNFL thickness between the emmetropic and hyperopic groups ($P > 0.05$) after age adjustment.

The correlations of RNFL thickness with age, spherical equivalent, and axial length were summarized in Table 2. There were significant correlations between the global RNFL with age ($r = -0.4$, $P < 0.0001$), spherical equivalent ($r = 0.5$, $P < 0.0001$), and axial length ($r = -0.4$, $P < 0.0001$) (Figures 1–3). There was a significant and negative correlation between the age and spherical equivalent ($r = -0.3$,

TABLE 1. Differences in Age, Spherical Equivalent, Axial Length, and RNFL in Myopic, Emmetropic, and Hyperopic Children

	Myopic Group (n = 67)	Emmetropic Group (n = 61)	Hyperopic Group (n = 73)	Statistical Significance
Age, y	9.6 ± 3.9	6.9 ± 2.7	6.5 ± 1.9	$P \leq 0.0001$ for myopia vs emmetropia or hyperopia; $P > 0.5$ for emmetropia vs hyperopia
Spherical equivalent, D	-3.9 ± 2.2	$+0.1 \pm 0.5$	$+3.0 \pm 1.6$	$P < 0.0001$ between all groups
Axial length, mm	24.2 ± 1.3	22.8 ± 0.8	21.7 ± 0.8	$P < 0.0001$ between all groups
RNFL, μm	96.7 ± 10.3	102.5 ± 9.2	107.2 ± 10.1	$P < 0.0001$ between all groups
RNFL, μm after age adjustment	94.1 ± 12.2 (n = 35)	102.5 ± 7.8 (n = 35)	107.8 ± 11.6 (n = 35)	$P \leq 0.0001$ for myopia vs emmetropia or hyperopia; $P > 0.5$ for emmetropia vs hyperopia

RNFL = retinal nerve fiber layer.

TABLE 2. Correlations of RFNL (Global and Quadrant) Thicknesses With Age, Spherical Equivalent, and Axial Length

	Inferior	Superior	Nasal	Temporal	Global
Age	$r = -0.2$	$r = -0.2$	$r = -0.2$	$r = 0.1$	$r = -0.3$
	$P = 0.0004$	$P = 0.0008$	$P = 0.0004$	$P = 0.06$ [*]	$P = 0.0001$
Spherical equivalent	R = 0.5	$r = 0.4$	$r = 0.3$	$r = -0.2$	$r = 0.5$
	$P < 0.0001$	$P = 0.0004$	$P = 0.0004$	$P = 0.009$	$P < 0.0001$
Axial length	$r = -0.4$	$r = -0.4$	$r = -0.2$	$r = 0.2$	$r = -0.4$
	$P < 0.0001$	$P < 0.0001$	$P = 0.0004$	$P = 0.02$	$P < 0.0001$

[*] Statistically insignificant.

$P < 0.0001$) and a positive correlation between age and axial length ($r = 0.5$, $P < 0.0001$). There was a significant and negative correlation between axial length and spherical equivalent ($r = -0.8$, $P < 0.0001$).

DISCUSSION

The mean global RNFL thickness reported in our study ($101.9 \pm 11.0 \,\mu m$) was consistent with that reported in the Anyang Childhood Eye Study ($103.1 \,\mu m$) and the Sydney Myopia Study ($103.2 \,\mu m$).[14,15] We have reconfirmed in our study that an advancing age in childhood was associated with a myopic shift ($r = -0.3$, $P < 0.0001$) and axial length elongation ($r = 0.5$, $P < 0.0001$), and that a longer axial length resulted in a greater degree of myopia ($r = -0.8$, $P < 0.0001$).

The association between myopia and a thinner RNFL has been well documented in both children and adults,[14,16,17] although there are others who have reported differently. Chen et al[18] did not find any association between the global RNFL with age nor spherical equivalent in a population aged 7 to 18 years. Likewise, Tong et al[6] examined 316 Singaporean children aged 11 to 12 years using the Heidelberg Retinal Tomograph (Heidelberg Engineering, Heidelberg, Germany) and did not find any significant association between the RNFL with axial lengths nor myopic status. In our study, the advancement in age ($r = -0.4$, $P < 0.0001$), a more negative (myopic) spherical equivalent ($r = 0.5$, $P < 0.0001$), and a longer axial length ($r = -0.4$, $P < 0.0001$) were correlated with a thinner global RNFL thickness. To determine whether thinner RNFL was predominantly due to the physiological ganglion cell loss that comes with aging or due to the stretching of the RNFL that comes from the axial myopic shift, we adjusted the data for age and recompared the differences in RNFL thickness among the 3 groups. We found that the mean global RNFL in the myopic group was still significantly thinner than the other 2 groups (both $P \leq 0.0001$), but there was no significant difference in RNFL thickness between the emmetropic and hyperopic groups ($P > 0.05$). This suggested that the thinner RNFL in the myopic group was attributed to both an older age as well as refraction-related factors. On the contrary, hyperopia did not confer a thicker RNFL as compared with those with emmetropia. The apparent RNFL difference in the hyperopic group prior to age adjustment was probably a result of the younger age of subjects in this group rather than associations with their refractive status. Our findings were consistent with that of Tas et al,[19] who reported similar RNFL thicknesses in those with high hyperopia ($+9.50 \,D \geq$ spherical equivalent $\geq +6.25 \,D$) versus low hyperopia ($+3.00 \,D \geq$ spherical equivalent $\geq +0.50 \,D$), but our result was in contrast to Zhu et al[14] who reported an association between hyperopia and a thicker RNFL in a population of 12-year-olds in China.

The correlation of the temporal RNFL quadrant with age, spherical equivalent, and axial length was different to that of the other quadrants or the global RNFL thickness. There was no correlation between the temporal quadrant with age ($r = 0.1$, $P = 0.06$) despite significant correlations in the other quadrants and global RNFL (all $P \leq 0.0004$). There was a negative correlation of the temporal quadrant with spherical equivalent
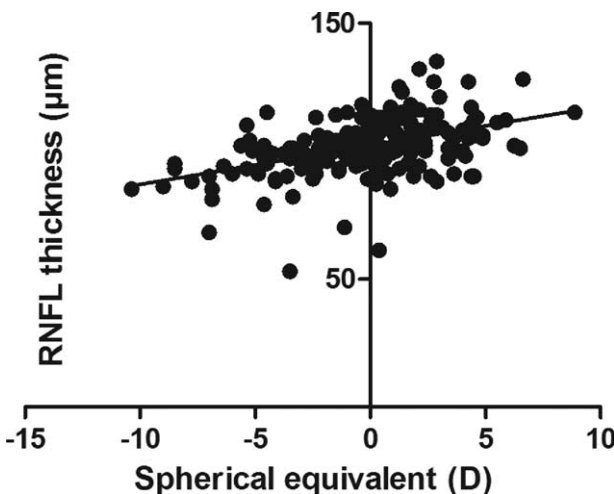

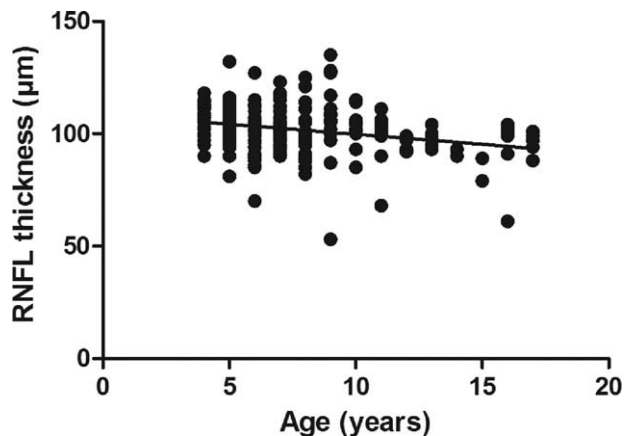**FIGURE 1.** Global RNFL thickness with spherical equivalent. RNFL = retinal nerve fiber layer.

FIGURE 2. Global RNFL thickness with age. RNFL = retinal nerve fiber layer.
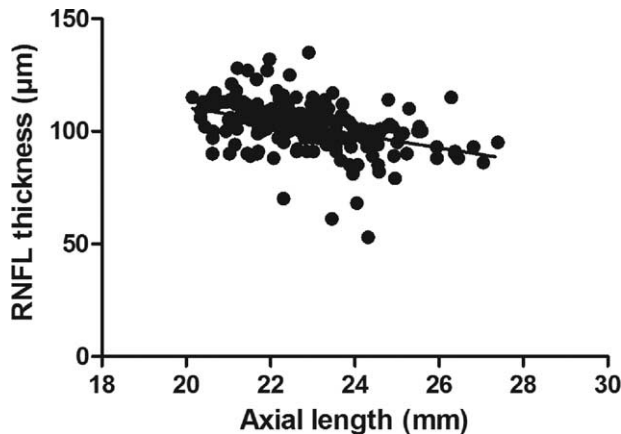
FIGURE 3. Global RNFL thickness with axial length. RNFL = retinal nerve fiber layer.

($r = -0.2$, $P = 0.009$) and a positive correlation with axial length ($r = 0.2$, $P = 0.02$) which was totally opposite to the results in the other quadrants and global RNFL thicknesses. Our findings were consistent with that of Xia et al[20] and Chen et al[18] who both reported a negative correlation between the temporal peripapillary RNFL thickness and spherical equivalent. Likewise, Kim et al[21] reported a negative association between the temporal RNFL thickness and myopia. Furthermore, Leung et al[22] and Tariq et al[23] also reported a positive correlation between a longer axial length and thicker temporal RNFL, which is in line with our findings.

Our study had its limitations. There was no longitudinal follow-up to investigate the rate of RNFL thinning between the 3 groups. We excluded eyes with poor visual acuity but not for those with amblyopia because previous studies did not find any difference between the RNFL in the amblyopic versus the fellow normal eye.[24] Likewise, we utilized all right 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.[25] To the best of our knowledge, this is one of the few studies investigating the peripapillary RNFL thickness in children along the refractive error spectrum (myopia, emmetropia, and hyperopia), with adjustments in age, as well as including children as young as 4 years old, although the findings of our results may not be generalizable to all populations. The majority of studies in the literature have reported on the RNFL thickness in myopic or hyperopic children separately or included children 6 years or older.[2,3,6,14,15,18,19,22–25]

The peripapillary RNFL thickness varied among children with different refractive status, with hyperopes having the thickest and myopes having the thinnest RNFL. When adjusted for age, only myopic children had a significantly thinner RNFL. Thus, the apparent RNFL differences in emmetropic and hyperopic children seem to be attributed to differences in age rather than refractive status. Advancing age, a more myopic spherical equivalent, and a longer axial length were associated with a thinner RNFL in a population of Chinese children.

ACKNOWLEDGEMENT

REFERENCES

1. Birch EE, O'Connor AR. Preterm birth and visual development. *Semin Neonatol.* 2001;6:487–497.

2. Ozdek SC, Onol M, Gurelik G, et al. Scanning laser polarimetry in normal subjects and patients with myopia. *Br J Ophthalmol.* 2000;84:264–267.

3. Alasil T, Wang K, Keane PA, et al. Analysis of normal retinal nerve fiber layer thickness by age, sex, and race using spectral domain optical coherence tomography. *J Glaucoma.* 2013;22:532–541.

4. Tariq YM, Pai A, Li H, et al. Association of birth parameters with OCT measured macular and retinal nerve fiber layer thickness. *Invest Ophthalmol Vis Sci.* 2011;52:1709–1715.

5. Leung CK, Mohamed S, Leung KS, et al. Retinal nerve fiber layer measurements in myopia: an optical coherence tomography study. *Invest Ophthalmol Vis Sci.* 2006;47:5171–5176.

6. Tong L, Chan YH, Gazzard G, et al. Heidelberg retinal tomography of optic disc and nerve fiber layer in Singapore children: variations with disc tilt and refractive error. *Invest Ophthalmol Vis Sci.* 2007;48:4939–4944.

7. World Health Organization. What is a refractive error? 2013. http://www.who.int/features/qa/45/en/. accessed May 3, 2014.

8. Katz J, Tielsch JM, Sommer A. Prevalence and risk factors for refractive errors in an adult inner city population. *Invest Ophthalmol Vis Sci.* 1997;38:334–340.

9. Wong TY, Foster PJ, Hee J, et al. Prevalence and risk factors for refractive errors in adult Chinese in Singapore. *Invest Ophthalmol Vis Sci.* 2000;41:2486–2494.

10. Wang Q, Klein BE, Klein R, et al. Refractive status in the Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci.* 1994;35:4344–4347.

11. Lee JW, Woo TT, Yau GS, et al. Cross-sectional study of the retinal nerve fiber layer thickness at 7 years after an acute episode of unilateral primary acute angle closure. *Medicine (Baltimore).* 2015;94:e391.

12. Lee JW, Yau GS, Woo TT, et al. The anterior chamber depth and retinal nerve fiber layer thickness in children. *ScientificWorldJournal.* 2014;2014:538283.

13. Lee JW, Yau GS, Woo TT, et al. The association between macular thickness and peripapillary retinal nerve fiber layer thickness in Chinese children. *Medicine (Baltimore).* 2015;94:e567.

14. Zhu BD, Li SM, Li H, et al. Retinal nerve fiber layer thickness in a population of 12-year-old children in central China measured by iVue-100 spectral-domain optical coherence tomography: the Anyang Childhood Eye Study. *Invest Ophthalmol Vis Sci.* 2013;54:8104–8111.

15. Tariq YM, Samarawickrama C, Li H, et al. Retinal thickness in the offspring of diabetic pregnancies. *Am J Ophthalmol.* 2010;150:883–887.

16. Szuminski M, Bakunowicz-Lazarczyk A. [Assessment of retinal ganglion cells thickness in high myopia]. *Klin Oczna.* 2012;114:180–183.

17. Jun JH, Lee SY. The effects of optic disc factors on retinal nerve fiber layer thickness measurement in children. *Korean J Ophthalmol.* 2008;22:115–122.

18. Chen W, Fu P, Yang Q, et al. [Evaluation of factors associated with variability in retinal nerve fiber layer thickness in myopic juveniles aged 7–18 years]. *Zhonghua Yan Ke Za Zhi.* 2010;46:1011–1015.

19. Tas M, Oner V, Turkcu FM, et al. Peripapillary retinal nerve fiber layer thickness in hyperopic children. *Optom Vis Sci.* 2012;89:1009–1013.

20. Xia ZR, Ying JL, Zhang J, et al. [Macular and retinal nerve fiber layer thickness in myopic children by three-dimensional OCT]. *Zhonghua Yi Xue Za Zhi.* 2013;93:3573–3576.

21. Kim MJ, Lee EJ, Kim TW. Peripapillary retinal nerve fibre layer thickness profile in subjects with myopia measured using the Stratus optical coherence tomography. *Br J Ophthalmol.* 2010;94:115–120.

22. Leung MM, Huang RY, Lam AK. Retinal nerve fiber layer thickness in normal Hong Kong Chinese children measured with optical coherence tomography. *J Glaucoma.* 2010;19:95–99.

23. Tariq YM, Samarawickrama C, Pai A, et al. Impact of ethnicity on the correlation of retinal parameters with axial length. *Invest Ophthalmol Vis Sci.* 2010;51:4977–4982.

24. Huynh SC, Samarawickrama C, Wang XY, et al. Macular and nerve fiber layer thickness in amblyopia: the Sydney Childhood Eye Study. *Ophthalmology.* 2009;116:1604–1609.

25. Samarawickrama C, Wang JJ, Huynh SC, et al. Macular thickness, retinal thickness, and optic disk parameters in dominant compared with nondominant eyes. *J AAPOS.* 2009;13:142–147.