Original Article

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Evaluation of Peripapillary and Macular Nerve Fiber Layer Thickness in Paediatric Glaucoma Suspects

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Abstract

Introduction: Glaucoma patients are known to have optic disc cupping, leading to loss of retinal ganglion cell axons. This peripapillary nerve thinness is known to be associated with glaucoma in adult patients. Hence, we intended to evaluate the peripapillary and macular nerve fiber thickness in eyes of pediatric glaucoma suspects using spectral domain optical coherence tomography (OCT).

Methods: This cross-sectional analytical study included 44 eyes of 22 paediatric glaucoma suspects, who were compared with 40 eyes of 20 normal paediatric eyes. Pearson correlation coefficients were calculated to assess the relations between the peripapillary retinal nerve fiber layer (RNFL) thickness and ganglion cell complex (GCC). Receiver Operating Characteristics (ROC) curve was plotted for OCT parameters in both the groups along with area under the curve (AUC) calculation. P values < 0.05 were considered as statistically significant.

Results: We found the RNFL to be thickest in the superior, inferior, nasal and temporal quadrants in both glaucoma suspects and normal group. When compared among quadrants in RNFL, all the values in different quadrants were statistically significant from each other and in between groups with p < 0.01. The RNFL thickness was statistically different in glaucoma when compared with normal in superior, temporal, and nasal quadrants however, no statistically significant difference was found in inferior quadrant RNFL. The largest AUC for discrimination of glaucoma suspect eyes from normal in peripapillary RNFL in was nasal quadrant in right eye, followed by temporal quadrant whereas it was largest in superior followed by nasal quadrants then average in left eye. However, AUC for discrimination of glaucoma suspects from normal in GCC was poor.

Conclusions: Glaucoma suspect paediatric eyes showed significant thinning in peripapillary nerve fiber layer thickness compared to normal subjects.

Introduction

Glaucomatous optic disc cupping is associated with the loss of retinal ganglion cell axons.[1] Normal optic disc usually has the inferior neuroretinal rim as the thickest portion of the rim, followed by the superior rim, and then the nasal rim, with the temporal rim being the thinnest portion.[2] Violation of this ISNT rule has shown to have predictive value in diagnosing glaucoma in adults.[3,4]

The faster image acquisition with spectral-domain OCT (SD - OCT) like RTVue has made OCT even more feasible in children.[5-9] OCT has been used in eyes of normal children but published reports of the use of OCT in paediatric glaucoma suspects are sparse.

This study tries to explore and correlate the measurements of peripapillary RNFL thickness and macular thickness in paediatric glaucoma suspects with that of normal using SD - OCT. To the best of our knowledge, this is one of the first studies using the OCT machine to investigate the correlation between the macular thickness and the peripapillary RNFL thickness in pediatric glaucoma and suspects.

Methods

This was a hospital-based cross-sectional comparative study. Written informed consent was obtained from all parents or guardians. Approval from the Institutional Review Committee of Institute of Medicine was taken. The study duration was from 15th June 2021 to 15th December 2021. From a prevalence of childhood glaucoma from previous study done in Nepal,[9] a sample size of 22 was calculated for glaucoma suspects and 20 cases were taken in for control. The non-probability purposive sampling method was applied. Children aged between five to 17 years with glaucoma suspect were included in study. Children less than five years, those with hypermetropia more than + 3D, myopia more than – 5D, or astigmatism more than 2D, pseudophakia and prematurity at birth, corneal lesions, chronic uveitis, secondary glaucoma, optic neuropathy other than glaucoma, retinal pathology, maculopathy and previous ocular trauma history were excluded from this study. The peripapillary retinal nerve fiber layer (RNFL) and macular thickness mainly ganglion cell complex (GCC) was compared amongst two groups: normal eyes, eyes with glaucoma suspects. Glaucoma suspects were defined as eyes with (cup disc ratio > 0.4 and < 0.7, IOP < 21), with or without family history of glaucoma, vertical cup-to-disc ratio asymmetry > 0.2 between the two eyes without focal notching or generalized loss of the neuroretinal rim, excavation of the optic disc was taken as glaucoma suspects. The normal subjects were from patients coming for routine ophthalmic examination, with no clinical suspicion of glaucoma, who also had optic nerves and retinas that were considered clinically normal. Family history in these individuals was negative for glaucoma. All subjects underwent a complete ophthalmological examination. The intraocular pressure (IOP) was measured with Keeler, UK pulse air desktop non-contact applanation tonometry and any high reading > = 21 were be reconfirmed with Goldman applanation tonometry. For peripapillary RNFL and Ganglion cell complex in macular thickness measurements the RTVue -100 software was used. Peripapillary RNFL thickness measurements were performed by the same investigator using RTVue OCT (Optovue, Fremont, CA). The RNFL thickness was measured by averaging the results of three sequential circular scans. Images with signal strength index ≥ 50 were included in the study. Both eyes from each individual were included in the analyses. The statistical package for social sciences (SPSS) version 22.0 was used in the analysis. Pearson correlation coefficients were calculated to assess the relations between the peripapillary RNFL thickness and GCC. Interocular OCT parameters difference among gender was calculate with paired t test. Interocular OCT parameters difference was calculated with paired t test among glaucoma suspects and control. The OCT parameters were compared among the two groups by one-way ANOVA test. Receiver Operating Characteristics (ROC) curve was plotted for OCT parameters in both control and glaucoma suspect along with area under the curve (AUC) calculation. The diagnostic specificity and sensitivity of the main parameters (AUC > 0.7) for distinguishing fellow eyes from normal eyes were evaluated, and cut-off points were presented. A probability value (P value) less than 0.05 was considered as significant at 95% confidence level.

Results

The mean age of the subjects in the study was 14.59 ± 1.89 years (11 years - 17 years). Of the total 22 subjects in the study, 54.5% (n = 12) were males and 45.5% (n = 10) were females. The mean cup disc ratio was 0.56 ± 0.078 in right eyes and 0.55 ± 0.071 in left eyes. Twenty age and gender matched normal children were also included in the study. The mean age of normal group was 13.80 ± 2.14 years (11 - 17 years). Male to female ratio was 1:1 in control group. All subjects had best corrected visual acuities of 0.0 logMAR or better. None of subjects had glaucoma, ocular hypertension. There was no effect of age on RNFL thickness in glaucoma suspects and normal as presented in Table 1. Average OCT parameters were not statistically significant in relation to gender (RE, p = 0.630, LE p = 0.178, independent t - test) in glaucoma suspect group.

Table 1. OCT parameters in relation to gender

OCT Parameters (µm)		Male	Female	P value (Independent t-test)
Right Eye	Superior	22.77 ± 130	16.15 ± 129.60	0.876
	Inferior	24.05 ± 127.83	14.54 ± 121.00	0.422
	Temporal	12.39 ± 75.75	7.43 ± 72.70	0.485
	Nasal	12.50 ± 74.66	12.77 ± 82.10	0.186
	Average	17.48 ± 104.37	11.26 ± 101.35	0.630
Left Eye	Superior	13.36 ± 133.33	12.73 ± 124.10	0.114
	Inferior	18.77 ± 128.91	15.74 ± 120.00	0.240
	Temporal	8.14 ± 77.50	8.52 ± 71.30	0.099
	Nasal	8.80 ± 76.66	11.00 ± 79.20	0.564
	Average	9.24 ± 104.10	9.02 ± 98.65	0.178

In this study, we found RNFL to be thickest in the superior, inferior, nasal and temporal quadrants, in that order in both glaucoma suspects and control group. When compared among quadrants in RNFL, all the values in different quadrant were statistically significant from each other and in between groups with $p < 0.01$ when tested with ANOVA test. This means, there was statistically significant difference in RNFL thickness quadrant wise and in between groups. RNFL thickness was statistically different in glaucoma suspects when compared with control in superior, temporal, and nasal quadrants as presented in Table 2.

Table 2. Intraocular differences in peri papillary nerve fiber thickness along different quadrant

OCT characteristics (µm)	Right Eye		P value (ANOVA)	Left Eye		P value (ANOVA)
	Glaucoma Suspects	Normal		Glaucoma Suspects	Normal	
Superior	19.59 ± 130.31	142.31±7.10	0.005	13.60 ± 129.13	6.22 ± 144.60	0.000
Inferior	20.14 ± 124.72	9.73 ± 124.72	0.680	17.65 ± 124.86	8.60 ± 126.10	0.744
Temporal	22.79 ± 78.90	4.75 ± 82.80	0.002	8.70 ± 74.68	5.77 ± 82.40	0.005
Nasal	12.89 ± 78.04	9.73 ± 93.20	0.000	9.70 ± 77.81	10.22 ± 90.30	0.000
Average	14.72 ± 103.00	6.14 ± 110.85	0.019	9.34 ± 101.62	6.44 ± 110.85	0.001

The macular ganglion cell complex thickness was similar in both groups with no statically significant difference quadrant wise in both right eye and left eye respectively. (Table 3)

Table 3. Distribution of macular ganglion cell thickness

Ganglion cell thickness (µm)	Right Eye		P value (ANOVA)	Left Eye		P value (ANOVA)
	Glaucoma Suspects	Normal		Glaucoma Suspects	Normal	
Superior quadrant	12.20 ± 94.50	2.68 ± 95.10	0.648	7.08 ± 94.59	3.78 ± 93.10	0.458
Inferior quadrant	10.45 ± 93.68	3.22 ± 95.20	0.296	6.83 ± 94.90	3.52 ± 92.70	0.291
Average	10.98 ± 94.09	2.92 ± 95.15	0.460	6.69 ± 94.75	3.58 ± 92.9	0.349

However, there was no statistically significant interocular difference quadrant wise in right eye and left eye respectively. (Table 4)

Table 4. Comparison between mean peri-papillary nerve fiber thickness between right eye and left eye in glaucoma suspect group

Quadrant	Right Eye	Left Eye	P value (t-test)
Superior	19.59 ± 130.31	13.60 ± 129.13	0.765
Inferior	20.14 ± 124.72	17.65 ± 124.86	0.972
Temporal	22.79 ± 78.90	8.70 ± 74.68	0.887
Nasal	12.89 ± 78.04	9.70 ± 77.81	0.926
Average	14.72 ± 103.00	9.34 ± 101.62	0.584

The peri-papillary RNFL in all quadrants showed a positive correlation with GCC in right eyes whereas no such correlation was found in left eyes and in both eyes of control group. Pearson correlation coefficients among the different quadrants to that of GCC displayed significant correlation with that of all quadrants and average parameters in right eye and only superior quadrant in left eye in glaucoma suspect group. (Table 5)

Table 5. Correlation between peri papillary nerve fiber thickness and average macular ganglion cell thickness (Pearson Correlation)

	Glaucoma Suspect		Control	
Quadrant	(GCC (RE	(GCC (LE	(GCC (RE	(GCC (LE
Superior	(r = 0.755, p = 0.000)	(r = 0.410, p = 0.058)	(r = 0.343, p = 0.331)	(r = 0.371, p = 0.291)
Inferior	(r = 0.587, p = 0.004)	(r = 0.077, p = 0.734)	(r = -0.177, p=0.625)	(r = -0.066, p = 0.856)
Temporal	(r = 0.785, p = 0.000)	(r = 0.252, p = 0.257)	(r = 0.314, p = 0.377)	(r = -0.100, p = 0.784)
Nasal	(r = 551, p = 0.008)	(r = 0.392, p = 0.071)	(r = -0.256, p = 0.475)	(r = -0.228, p = 0.527)
Average	(r = 0.658, p = 0.001)	(r = 0.346, p = 0.115)	(r = -0.007, p = 0.984)	(r = -0.045, p = 0.901)

ROC curves were plotted and AUC calculated for right eye and left eye for RNFL thickness and GCC thickness respectively. The largest AUC for discrimination of glaucoma suspect eyes from normal in peripapillary RNFL in was nasal quadrant (0.84) in right eye, followed by temporal quadrant (0.78) whereas it was largest in superior (0.85) followed by nasal quadrants (0.83) then average (0.80) in left eye. This was statistically significant to diagnose glaucoma suspects from normal eye. However, AUC for discrimination of glaucoma suspects from normal in GCC was poor in right eye (0.54) and had no discrimination in left eye (0.38).

Discussion

The present study showed that average peripapillary RNFL and peripapillary RNFL of all sectors except for inferior was significantly thinner in glaucoma suspects compared to normal children. Since glaucomatous optic neuropathy has been documented to develop locally rather than globally[3]

The normal group of participants had thicker RNFL using SD-OCT as compared to earlier studies,[3,4] with maximum thickness in the superior quadrant, contradicting the ISNT rule. Some researchers have reported the thinning of average RNFL thickness in all sectors between paediatric glaucoma and controls. However, other researchers have found that children with glaucoma and normal participants have comparable RNFL thickness in some regions such as the temporal, nasal, and inferior nasal quadrants.

The average peripaillary thickness was 110.85 ± 6.14 in right eyes and 110.85 ± 6.44 in left eyes in normal group which is slightly higher than reported in various studies[11-14] but almost similar to reported in others.[15-17] This may be attributed to ethnic differences and differences in the OCT version used in earlier studies.

Studies of the sensitivity and specificity of OCT for the diagnosis of glaucoma have primarily focused on glaucoma patients who already have visual field defects.[18,19] However, in our study, the largest AUC for discrimination of glaucoma suspect eyes from normal in peripapillary RNFL in was nasal quadrant in right eye, followed by temporal quadrant whereas it was largest in superior followed by nasal quadrants then average in left eye. Budenz and associates found higher AUC values for mean RNFL thickness, superior quadrant and inferior quadrant.[8] Similarly, in a study comparing SD-OCT to stratus OCT, the RNFL parameters with the highest AUCs were in similar locations as those in the Stratus OCT.[20] The ability to discriminate normal from glaucomatous results is directly proportional to the magnitude of disease severity as suggested in previous studies.[19,21,22] The changes of pRNFL thickness are meaningful in these children with less severe glaucomatous optic nerve damage, where the damage of visual function may be difficult to measure. Age-related decrease in RNFL has been reported in adults[11,23] using OCT however it was not found in our study of paediatric age group. Similar to our finding, Rao et al also showed that peripapillary RNFL thickness was independent of age in children.[24] Alamouti and Funk have suggested that the rate of decrease in RNFL thickness is slower in the younger age.[23] However, it is still unclear as to the exact age at which the thinning starts. More so, it is possible that such an age-related process starts in adult life, which may explain the lack

of correlation of age with RNFL thickness in the paediatric group.[24]

Gender also did not contribute to the variability in RNFL thickness in our study. Similarly, such gender related difference in the pediatric age group was not found in other studies too.[25,26] In our study, we did not find significant differences between the two eyes with symmetric RNFL and macular parameters. Similarly, no significant difference in mean RNFL thickness of the four quadrants was seen between the two eye in other studies.[7,24] However, eye side had significant influence on RNFL thickness in some studies.[8,10,13] The mechanism underlying interocular differences is unclear in normal children, it may be physiological however in children with glaucoma suspects or glaucoma it could be attributed to the asymmetrical nature of the disease itself.

In addition to peripapillary RNFL thickness, macular thickness especially GCC has been shown as an important parameter for the early detection of glaucoma in adults, with significant differences reported by some between glaucomatous and normal eyes. In the study by Hess et al, significant differences were found in the OCT scans obtained from glaucoma patients compared with those of normal children, using both the RNFL map protocol and the fast macular map.[27] However, another study has showed that macular thickness had lower diagnostic capability compared with peripapillary RNFL thickness in early glaucoma.[19] Similarly, no much difference was found in our study too. Since diagnostic accuracy of GCC is significantly influenced by disease severity. Moreso, this difference may not be pronounced in early disease state. Our group of glaucoma suspect eyes based on optic nerve cupping. Even though we did not correlate RNFL and cupping, a study had correlated RNFL and cupping and found that the degree of optic nerve cupping does not correlate with the RNFL thickness.[10] The glaucoma suspects patients may represent a mild or early stage of glaucomatous damage. This provides us with a standard comparison for glaucoma screening since any deviation from the normative database would be definite along with other factors. Inclusion of eyes with glaucoma in the group would probably have made the differences between the glaucoma and normal groups even larger. The axial length was not taken into account in our study and our measurements were obtained in children without ocular disease and significant refractive error as previous studies showed that they did not affect the RNFL and GCC parameters significantly.[13,15]

The strength of the study is that it included a heterogeneous mixture of Nepalese ethnic group visiting a tertiary eye care center in Kathmandu, Nepal. The major limitation of the present study is related to the characteristics of the subjects enrolled ranging mainly in age group 11 - 17 years, so results may not be applicable to younger age groups. More so, a larger sample size will help to differentiate better predictive value of each parameter. Longitudinal follow-up of eyes with paediatric glaucoma suspects, and serial OCT measurements in these same eyes, will assess the use of this technology in monitoring glaucoma progression and evaluate outcomes in more detail along with identification of additional risk factors in the development of glaucoma in paediatric glaucoma suspects.

Conclusions

This study demonstrated that spectral domain OCT of RNFL can quantitatively measure structural changes that are known to occur with glaucoma, in glaucoma suspects. In our study, paediatric glaucoma suspects had significantly reduced average quadrants RNFL thickness compared with healthy controls along with largest AUC for discrimination of glaucoma suspect eyes from normal in nasal quadrant and temporal quadrant in right eye, and superior, nasal quadrants and average RNFL in left eye. We would like to highlight SD-OCT has potential clinical value in early diagnosis in pediatric glaucoma suspects.

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