ORIGINAL RESEARCH PAPER

FAMILY HISTORY OF GLAUCOMA: A PREDICTIVE FACTOR??

ABSTRACT:

Aim: To provide the data differences in normal eyes with positive and negative family history of glaucoma.

Methodology: 300 eyes from 150 healthy subjects aged 40 years and above with no ocular pathologies were examined using standard protocols by a single examiner. Two groups were made based on the positive and negative family history of glaucoma. There were 224 eyes in negative family history group and 76 eyes in positive family history group. Subjects with history of diabetic or hypertensive retinopathy, raised intraocular pressure (> 21mmHg) and previous intraocular or laser surgery were excluded from the study. The mean retinal nerve fiber layer thickness was calculated in each quadrant separately.

Results: The mean global retinal nerve fiber layer thickness was found to be 101.93 ± 7.77 µm in those having negative family history of glaucoma. It was 90.46 ± 7.06 µm in those having positive family history of glaucoma ($p = < 0.001$).

Conclusions: Keeping in mind the variations in RNFL thickness with positive family history of glaucoma, this study provides the normal values of RNFL thickness according positive and negative family history of glaucoma. It is concluded that RNFL thickness is found to be significantly decreased in those having positive family history of glaucoma.

KEY WORDS:

Retinal nerve fiber layer (RNFL), optical coherence tomography (OCT), family history, glaucoma

INTRODUCTION:

Retina is the sensory neural layer of the eyeball lining its inner posterior surface. It lies between the choroid externally and the vitreous body internally. The retina consists of ten layers one of which is the retinal nerve fiber layer (RNFL). These layers are usually apparent in histological sections but now it has become possible to observe them in vivo by OCT which is a non invasive imaging technique providing

high resolution dimensions of retinal nerve fiber layer (RNFL) thickness, macular thickness and optic nerve head measurements.(1-5) Several studies suggest that the RNFL and macular thickness is affected by a variety of factors like age, gender, race, positive family history of glaucoma, smoking, error of refraction etc. (6-15) Therefore, these factors have to be given importance while assessing the RNFL thickness.(9, 10) (16)

Glaucoma is one of the leading causes of blindness worldwide, and its insidious onset is often associated with diagnostic delay. The progression of disease can be slowed down by giving appropriate treatment but this cannot reverse the damage which had already taken place. Therefore, identifying those at risk for glaucoma could potentially lead to early detection and prevention of associated vision loss.

Positive family history of glaucoma is a well recognised risk factor for the development of the disease. It is an established fact in that people having first-degree affected relatives either develop the disease in future or they are highly suspected of having the disorder. (17) Genetic factors have been thought to play an important role in the development of glaucoma. Recently, genome-wide association (GWA) studies identified multiple loci associated with the susceptibility to glaucoma, including the *SIX1–SIX6* locus (18, 19) This needs another platform of research to further strengthen the involvement of these particular genes or some other suspected genetic involvements.

The objective of this study was to provide normal values of RNFL thickness in those having positive family history of glaucoma and to find the difference with those having negative family history of glaucoma. This will help the clinicians in making valid decisions regarding ophthalmic problems in future. It is the purpose of this paper to estimate the risk of developing glaucoma if one has a family member with the disease.

It is stated that aging is accompanied by a reduction of retinal sensitivity and a deterioration of the visual function. (9-14) This is the reason why subjects who were 40 years and above were recruited in this study because usually the ophthalmic problems are followed by aging. Therefore, by relating the normal data obtained through this study, it will get easier for the clinicians to screen the high risk individuals prior to the onset of diseases involving the retina.

METHODOLOGY:

This was a cross sectional study recruiting 300 eyes from 150 subjects visiting an ophthalmic OPD in Karachi. Informed consent was obtained from all the subjects. All subjects aged 40 years were included in this study. All had normotensive eyes with IOP of $\leq$ 21mmHg and normal cup disc ratio (CDR) i.e. $\leq$ 0.4. Subjects with retinal pathologies, history of intraocular surgery or laser therapy and diabetic or hypertensive retinopathy were excluded from the study.

Initially a proforma was filled based on the demographic profile that included age, gender, ethnicity, history of smoking, past medical illness, past eye illnesses and family history of glaucoma. Detailed comprehensive ophthalmic examination was done including testing for refractive error and visual acuity, slit-lamp biomicroscopy, CDR measurement by using 90 diopters lens and then IOP was measured by Goldmans applanation tonometer.

OCT Examination:

Single experienced technician did all OCT testing by using Spectralis Heidelberg's OCT after dilating the eyes with 1% tropicamide eye drops. Cross sectional retinal images were produced on the computer screen during OCT scanning. Each subject had to fix their gaze at the light source seen through the lens of OCT apparatus in order to ensure proper positioning of the RNFL with respect to the optic nerve head. After capturing few sequential OCT images, scanning was stopped and the RNFL position was tracked on OCT scan with respect to optic nerve.

The RNFL examination was under predefined OCT software algorithm which identified the entire width of RNFL and calculated the thickness in different sectors to give an average measurement of RNFL globally and in each quadrant (nasal, temporal, superior and inferior). [Fig. 1]

Statistical analysis:

SPSS version 20 was used for statistical analysis. All quantitative variables are presented as mean and standard deviation. Normality of data was first checked by applying Kolmogorov-Smirnov Test before application of any test of significance. Difference between quantitative variables was tested by applying independent (Pooled) t- test. P value $\leq$0.05 was taken as significant.

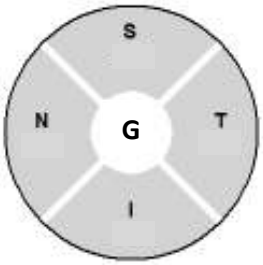

Figure 1: Quadrants of optic disc. G: Globalaverage, I: Inferior Quadrant, S: Superior Quadrant, N: Nasal Quadrant, T: Temporal Quadrant

RESULTS:

Three hundred eyes from 150 healthy subjects were clinically examined and were subjected to OCT testing. Subjects were divided into 2 groups: 1st group included subjects (n = 224 eyes) with negative family history of glaucoma, 2nd group included subjects with positive family history of glaucoma (n = 76 eyes). Their baseline characteristics according to their distribution on the basis of family history is shown in Table 1. [Table 1]

In subjects having negative family history of glaucoma, the mean global retinal nerve fiber layer thickness was found to be 101.93 ± 7.77 µm. The superior quadrant showed mean thickness of 124.58 ± 13.81 µm; for inferior quadrant the mean thickness was 130.22 ± 15.43 µm. The nasal quadrant showed mean thickness of 81.33 ± 14.05 µm and the mean thickness for temporal quadrant was found to be 71.12 ± 13.14 µm. [Table 2]

In subjects with positive family history of glaucoma, the mean global retinal nerve fiber layer thickness was found to be 90.46 ± 7.06 µm. The superior quadrant showed mean thickness of 112.43 ± 14.91 µm; for inferior quadrant the mean thickness was 115.33± 13.24 µm. The nasal quadrant showed mean thickness of 72.11 ± 11.39 µm and the mean thickness for temporal quadrant was found to be 62.34 ± 10.64 µm. [Table 2] The RNFL thickness showed significant decrease in thickness in those who had positive family history of glaucoma with P= 0.001

Table 1 : Baseline characteristics of the participants

Family h/o glaucoma	**Total n= 300**	**Mean ± S.D.**		
		Age (years)	**IOP (mm Hg)**	**CDR**
Yes	76	68.87 ± 8.28	15.46 ±1.19	0.34 ± 0.06
No	224	53.87 ±9.73	13.79 ± 0.98	0.24 ± 0.06

n= no. of eyes
S.D. Standard deviation

Table 2: RNFL measurements in each quadrant of optic nerve head

	Optic Nerve Head Quadrants Mean ± S.D. (µm)				
Family h/o Glaucoma	**Global**	**Superior**	**Inferior**	**Nasal**	**Temporal**
Yes	90.46 ±7.06	112.43±14.91	115.33±13.24	72.11±11.39	62.34±10.64
No	101.93±7.77	124.58±13.81	130.22±15.43	81.33±14.05	71.12±13.14
P value	0.001*	0.001*	0.001*	0.001*	0.001*

*very highly significant

n= no. of eyes

S.D. Standard deviation

DISCUSSION:

In the present study we determined the normal values of RNFL thickness according to our set of population. By relating this normal data, it will be easier for the clinicians to screen the high risk individuals prior to the onset of various diseases involving the retina especially glaucoma as it is one of the leading causes of irreversible blindness in the world. Our data can be used as screening tool for subjects having positive family history of glaucoma

Treatment of glaucoma cannot correct the damage but it can prevent the disease to progress, so the sooner the patient is kept on treatment the quicker it can be prevented from causing more harm. Thus, differentiating between healthy eyes and glaucomatous eyes by measuring RNFL thickness may aid in early detection of glaucoma suspects preventing future progression of the disease.

In glaucoma there is a gradual loss of retinal ganglion cells (RGCs) leading to reduced retinal thickness (20). It has been found that before the visual field defect is clinically symptomatic, 30% or more of RCGs are already lost. Significant loss in thickness may lead to visual field defects and optic disc cupping. It has been reported that thinning of retina starts even in the initial stages of glaucoma, therefore, RNFL thickness can be used as a predictive indicator for glaucomatous damage. (14, 21)

We found reduced RNFL thickness in those who had positive family history of glaucoma. [Table 1] This has been reported by other studies done in California. (22, 23) They proposed that positive family history of glaucoma increases the risk of developing glaucoma as it has a genetic link. Genetic link means that there may be a variation in one or more genes that may cause certain individuals to be more susceptible to the disease. Many studies have stated few of these proteins and gene which can be one of the reasons. These include myocilin, optineurin, and CYP1B1 ,GLC3A (2p21) (24), SRBD1, ELOVL5, CDKN2B/CDKN2B-AS1, SIX1/SIX6 and ATOH7 genes(25), COL5A1 (rs1536478 and rs7044529) (26). The identification of exact gene locus involvement in such cases and to access that to how much extent the disease can progress based on the involvement of particular protein is another outlook of research. Many studies have been done and still a large scale researches are on the go. Future studies are required to look for the gene involvement or any protein defect that is actually causing the reduction in RNFL thickness even if glaucoma is not present but family history of glaucoma is positive.

We noticed maximum RNFL thickness in inferior quadrant followed by superior, nasal and temporal quadrants in this study. This pattern of RNFL thickness is in accordance with ISNT rule established by Jonas et al in their study conducted in Germany in 1999. (27) The ISNT rule is an easy way to remember how the optic nerve is supposed to look in a normal eye. In general, the neuro-retinal rim is thickest inferiorly and thinnest temporally. Any deviation from ISNT rule will help the clinicians to detect the optic nerve pathologies at an early stage.

This data can be applied in routine clinics by ophthalmologists in diagnosing the subjects long before they become symptomatic. It can also be used as a screening tool for subjects having positive family history of diseases such as glaucoma that affects RNFL thickness and the symptoms appear after >40% of ganglion cells have been destroyed.

CONCLUSION:

The results of our study have established normal data of RNFL thickness for each quadrant particular to our set of population. This may be used in future by clinicians to screen the high risk individuals prior to the onset of various ophthalmic diseases that involve retina particularly glaucoma in this article.

The RNFL thickness is significantly decreased in those with positive family history of glaucoma when compared to those with negative family history. Assessment of RNFL thickness in various ophthalmic conditions should be interpreted keeping these findings in context.

REFERENCES:

1. Rao H, Babu J, Addepalli U, Senthil S, Garudadri C. Retinal nerve fiber layer and macular inner retina measurements by spectral domain optical coherence tomograph in Indian eyes with early glaucoma. Eye. 2012;26(1):133-9.
2. Medeiros FA, Zangwill LM, Bowd C, Vessani RM, Susanna R, Weinreb RN. Evaluation of retinal nerve fiber layer, optic nerve head, and macular thickness measurements for glaucoma detection using optical coherence tomography. American journal of ophthalmology. 2005;139(1):44-55.
3. Wollstein G, Ishikawa H, Wang J, Beaton SA, Schuman JS. Comparison of three optical coherence tomography scanning areas for detection of glaucomatous damage. American journal of ophthalmology. 2005;139(1):39-43.
4. Seong M, Sung KR, Choi EH, Kang SY, Cho JW, Um TW, et al. Macular and peripapillary retinal nerve fiber layer measurements by spectral domain optical coherence tomography in normal-tension glaucoma. Investigative ophthalmology & visual science. 2010;51(3):1446-52.
5. Mukhtar S, Hassan N, Dawood Z. OCT–A WINDOW TO RETINA.

6. Grover S, Murthy RK, Brar VS, Chalam KV. Comparison of retinal thickness in normal eyes using Stratus and Spectralis optical coherence tomography. Investigative ophthalmology & visual science. 2010;51(5):2644-7.
7. Appukuttan B, Giridhar A, Gopalakrishnan M, Sivaprasad S. Normative spectral domain optical coherence tomography data on macular and retinal nerve fiber layer thickness in Indians. Indian journal of ophthalmology. 2014;62(3):316.
8. O'Rese JK, Girkin CA, Budenz DL, Durbin MK, Feuer WJ, Group CONDS. Effect of race, age, and axial length on optic nerve head parameters and retinal nerve fiber layer thickness measured by Cirrus HD-OCT. Archives of ophthalmology. 2012;130(3):312-8.
9. Katz J, Sommer A. Asymmetry and variation in the normal hill of vision. Archives of ophthalmology. 1986;104(1):65-8.
10. Heijl A, Lindgren G, Olsson J. Normal variability of static perimetric threshold values across the central visual field. Archives of ophthalmology. 1987;105(11):1544-9.
11. Ooto S, Hangai M, Sakamoto A, Tomidokoro A, Araie M, Otani T, et al. Three-dimensional profile of macular retinal thickness in normal Japanese eyes. Investigative ophthalmology & visual science. 2010;51(1):465-73.
12. Alamouti B, Funk J. Retinal thickness decreases with age: an OCT study. British Journal of Ophthalmology. 2003;87(7):899-901.
13. Song WK, Lee SC, Lee ES, Kim CY, Kim SS. Macular thickness variations with sex, age, and axial length in healthy subjects: a spectral domain-optical coherence tomography study. Invest Ophthalmol Vis Sci. 2010;51(8):3913-8.
14. Mukhtar S, Hassan N, Dawood Z, Zehra N. Retinal Nerve Fiber Layer Thickness in a Subset of Karachi (Pakistan) Population. British Journal of Medicine and Medical Research. 2015;10(9).
15. Kashani AH, Zimmer-Galler IE, Shah SM, Dustin L, Do DV, Eliott D, et al. Retinal thickness analysis by race, gender, and age using Stratus OCT. American journal of ophthalmology. 2010;149(3):496-502. e1.
16. Celebi ARC, Mirza GE. Age-related change in retinal nerve fiber layer thickness measured with spectral domain optical coherence tomography. Investigative ophthalmology & visual science. 2013;54(13):8095-103.
17. Cheng C-Y, Allingham RR, Aung T, Tham Y-C, Hauser MA, Vithana EN, et al. Association of Common SIX6 Polymorphisms With Peripapillary Retinal Nerve Fiber Layer Thickness: The Singapore Chinese Eye StudyAssociation of SIX6 Variant With RNFL Thickness. Investigative ophthalmology & visual science. 2015;56(1):478-83.
18. Osman W, Low S-K, Takahashi A, Kubo M, Nakamura Y. A genome-wide association study in the Japanese population confirms 9p21 and 14q23 as susceptibility loci for primary open angle glaucoma. Human molecular genetics. 2012:dds103.
19. Wiggs JL, Yaspan BL, Hauser MA, Kang JH, Allingham RR, Olson LM, et al. Common variants at 9p21 and 8q22 are associated with increased susceptibility to optic nerve degeneration in glaucoma. PLoS Genet. 2012;8(4):e1002654.
20. Na JH, Sung KR, Baek S, Kim YJ, Durbin MK, Lee HJ, et al. Detection of glaucoma progression by assessment of segmented macular thickness data obtained using spectral domain optical coherence tomography. Investigative ophthalmology & visual science. 2012;53(7):3817-26.
21. Leung CK-s, Cheung CYL, Weinreb RN, Qiu K, Liu S, Li H, et al. Evaluation of retinal nerve fiber layer progression in glaucoma: a study on optical coherence tomography guided progression analysis. Investigative ophthalmology & visual science. 2010;51(1):217-22.
22. Kuzin AA, Varma R, Reddy HS, Torres M, Azen SP, Group LALES. Ocular biometry and open-angle glaucoma: the Los Angeles Latino Eye Study. Ophthalmology. 2010;117(9):1713-9.

23. Pan Y, Varma R. Natural history of glaucoma. Indian journal of ophthalmology. 2011;59(Suppl1):S19.
24. Sarfarazi M, Akarsu NA, Hossain A, Turacli EM, Aktan GS, Barsoum-Homsy M, et al. Assignment of a locus (GLC3A) for primary congenital glaucoma (Buphthalmos) to 2p21 and evidence for genetic heterogeneity. Genomics. 1995;30(2):171-7.
25. Mabuchi F, Sakurada Y, Kashiwagi K, Yamagata Z, Iijima H, Tsukahara S. Involvement of genetic variants associated with primary open-angle glaucoma in pathogenic mechanisms and family history of glaucoma. American journal of ophthalmology. 2015;159(3):437-44. e2.
26. Sundaresan P, Prasanthi N, Gowthaman G, Krishnadas SR, Das M, Willoughby CE. Involvement of collagen-related genes and its influence on keratoconus and primary open angle glaucoma patients in India. Investigative Ophthalmology & Visual Science. 2014;55(13):3822-.
27. Jonas JB, Budde WM, Panda-Jonas S. Ophthalmoscopic evaluation of the optic nerve head. Survey of ophthalmology. 1999;43(4):293-320.