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Family History of Glaucoma: A Predictive Factor?

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Authors' contributions

This work was carried out in collaboration between all authors. Author SM designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors MK and IR managed the literature searches and author NZ carried out statistical analysis. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To provide the data differences in normal eyes with positive and negative family history of glaucoma.
Methodology: 152 eyes from 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 76 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 (> 21 mmHg), any neurological diseases e.g. Parkinson's disease 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 102.57 ± 7.27 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

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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.

Keywords: Retinal nerve fiber layer (RNFL); optical coherence tomography (OCT); family history; glaucoma.

1. 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.

2. METHODOLOGY

This was a case control study recruiting 152 eyes from 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 $\leq$ 21 mmHg and normal cup disc ratio (CDR) i.e. $\leq$ 0.4. Subjects with retinal pathologies, any neurological diseases e.g. Parkinson's disease, 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 after applying flourescent dye strip in order to highlight the tear film.

2.1 Sample Size

Sample size is calculated by using OpenEpi sample size calculator for case control study. For

sample size estimation a thorough literature search was adopted. Sample size was calculated at 95% confidence interval with power = 80% using a 1:1 ratio of cases to controls while looking for 3.6 odds ratio for positive family history of glaucoma [20]. Total size will be calculated as 135 with 64 cases and 64 controls. However to avoid data wastage sample size is inflated to 152 with 76 eyes in each group of cases and controls.

2.2 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].

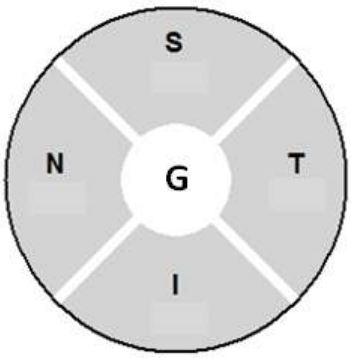

Fig. 1. Quadrants of optic disc
G: Globalaverage, I: Inferior Quadrant, S: Superior Quadrant, N: Nasal Quadrant, T: Temporal Quadrant

2.3 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.

3. RESULTS

152 eyes from healthy subjects were clinically examined and were subjected to OCT testing. Subjects were divided into 2 groups: 1st group included subjects (n = 76 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.

In subjects having negative family history of glaucoma, the mean global retinal nerve fiber layer thickness was found to be 102.57 ± 7.27 µm. The superior quadrant showed mean thickness of 122.83 ± 13.20 µm; for inferior quadrant the mean thickness was 131.09 ± 12.68 µm. The nasal quadrant showed mean thickness of 79.59 ± 13.30 µm and the mean thickness for temporal quadrant was found to be 76.95 ± 12.99 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.

4. 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.

Table 1. Comparison of IOP and CDR on the basis of family history of glaucoma among study participants

Family h/o glaucoma	Total n= 152	Mean ± S.D.	
		IOP (mm Hg)	CDR
Yes	76	15.46 ±1.19	0.34 ± 0.06
No	76	13.68 ± 0.91	0.24 ±0.05
P- value		0.001***	0.001***
95% CI of mean		1.43-2.12	0.09-0.12

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

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

Family h/o glaucoma	Optic nerve head quadrants Mean ± S.D. (µm)				
	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	102.57±7.27	122.83±13.20	131.09±12.68	79.59±13.30	76.95±12.99
P value	0.001***	0.001***	0.001***	0.001***	0.001***

****very highly significant*
n= no. of eyes
S.D. Standard deviation

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 [21]. 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 [14,22].

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. [23,24] 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) [25], *SRBD1, ELOVL5*, *CDKN2B/CDKN2B-AS1, SIX1/SIX6* and *ATOH7* genes [26], COL5A1 (rs1536478 and rs7044529) [27]. 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. [28] 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 **i**nferiorly 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.

5. 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.

ETHICAL APPROVAL

Ethical Review Committee of Ziauddin University, Karachi, Pakistan has approved the study.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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