

Analysis of retinal nerve fibre layer changes in anisometropic amblyopia by Heidelberg retina tomograph

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Abstract

Objective: To identify if anisometropic amblyopia is associated with changes in optic disk morphology.

Methods: The study comprised a total of 80 eyes recruited from Shifa Foundation Community Health Centre and the Pakistan Institute of Medical Sciences, Islamabad between May and October 2012. Anisometropic amblyopia was the only cause of disability (visual acuity $\geq 6/12$) in amblyopic eyes whereas normal eyes had a best corrected visual acuity of 6/6 and no morbidities. Patients with other causes of amblyopia, co-morbid ocular diseases, and in whom a good-quality image could not be obtained were excluded. Mean retinal nerve fiber layer thickness was analysed using Heidelberg retina tomograph. Analysis of frequency distribution, probability and regression were run on the data collected during the study using SPSS version 15.0.

Results: The mean age of the patients was 23.85 ± 5.85 years. The retinal nerve fibre layer thickness ranged between 0.09mm and 0.35 mm (mean: $0.23\text{mm} \pm 0.07$) in amblyopic eyes, and between 0.18mm and 0.36mm (mean: $0.25\text{mm} \pm 0.05$) in normal eyes. The difference was not statistically significant ($p=0.087$). No association was found between the retinal nerve fiber layer thickness or the age and refractive error of patients.

Conclusion: The optic disk does not appear to be the site of morphological changes in amblyopia.

Keywords: Amblyopia, Retinal nerve fibre layer, Heidelberg retina tomography. (JPMA 63: 1491; 2013)

Introduction

Amblyopia is a visual impairment secondary to abnormal visual experience during early childhood that cannot be corrected by glasses alone.¹ Anisometropic amblyopia can result from a difference of refractive error of $\geq \pm 1$ Diopters between the two eyes.² Changes in the structure of the visual cortex and lateral geniculate nucleus have traditionally been used to explain the pathogenesis of amblyopia.³⁻⁶ Recent evidence suggests that morphological changes in the retinal and peri-papillary-nerve fibre layer may have a role in the etiology of amblyopia.⁷⁻¹⁰ However, not all published literature supports this.¹¹

Heidelberg Retina Tomograph (HRT) has been extensively used to study the optic disk characteristics.¹² With its ability to objectively measure optic disk parameters, the instrument is ideally suited to studying the changes in the optic disk, if any, in anisometropic amblyopia.

The purpose of this study was to investigate the peri-papillary retinal nerve fiber layer thickness using HRT in patients with anisometropic amblyopia to identify if amblyopia is associated with changes in optic disk

morphology. This has not been published before in adult amblyopic patients in South Asia in Medline indexed literature.

Patients and Methods

The study was conducted between May and October 2012 on patients recruited from Shifa Foundation Community Health Centre and Pakistan Institute of Medical Sciences, Islamabad. After approval from the institutional review board, the sample size was calculated using the 'sample size for comparing two means' function of Epidemiologic Statistics for Public Health package using a confidence interval (CI) of 95%, power 80% and ratio of sample size in two groups as 1:1. The value of mean $\pm$ standard deviation retinal nerve fibre layer thickness (RNFLT) was taken from Miki A et al.⁵ A total of 80 eyes; 40 amblyopic and 40 normal were recruited from the 2 clinical sites. For this study, anisometropic amblyopia was defined as the difference in refractive error of $> \pm 1$ Diopter between the two eyes with concurrent visual disability defined as Snellen's visual acuity of 6/12 (0.50) or worse; the anisometropia being exclusively responsible for the visual disability. Inclusion criteria for recruitment comprised age > 18 years and < 40 years. For amblyopic eyes, the anisometropic amblyopia was the only cause of decreased visual acuity. The normal eye was defined as an eye with best corrected visual acuity of 6/6 and no morbidities. Patients with bilateral visual disability, a history of amblyopia therapy, other forms of

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**Heidelberg Retina Tomograph
Initial Report**

HEIDELBERG
ENGINEERING

Patient:

Sex: DOB: Pat-ID: Ethnicity:

OD

Examination:

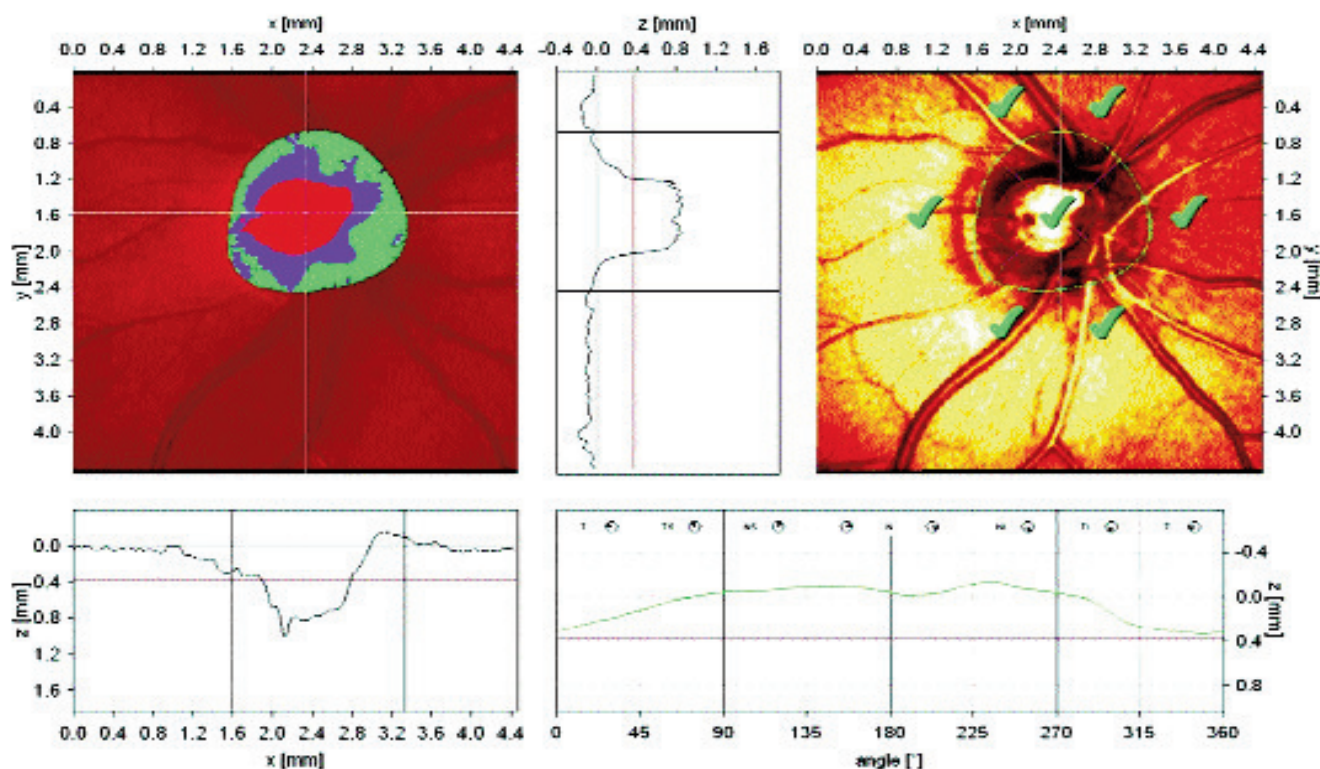
Date:

Scan:

FOCUS:

Depth:

Operator:



Stereometric Analysis ONH	Normal Range	
Disc Area	2.50 mm ²	1.53 - 2.63
Cup Area	0.69 mm ²	0.15 - 1.04
Rim Area	1.82 mm ²	1.22 - 1.75
Cup Volume	0.20 mm ³	-0.02 - 0.27
Rim Volume	0.60 mm ³	0.24 - 0.52
Cup/Disc Area Ratio	0.27	0.13 - 0.39
Linear Cup/Disc Ratio	0.52	0.36 - 0.63
Mean Cup Depth	0.31 mm	0.13 - 0.28
Maximum Cup Depth	0.83 mm	0.40 - 0.73
Cup Shape Measure	-0.19	-0.25 - -0.10
Height Variation Contour	0.46 mm	0.29 - 0.49
Mean RNFL Thickness	0.32 mm	0.19 - 0.32
RNFL Cross Sectional Area	1.82 mm ²	0.94 - 1.61
Reference Height	375 μm	
Topography Std Dev.	9 μm	
FSM	2.69	
RB	1.83	

Moorefields Classification: Within normal limits (*)

(*) Moorefields regression classification (Optometry 1996;105:1507-1503). Classification based on statistical diagnosis is physician's responsibility.

Comments:

Date: **Signature:**

Figure: Stereometric Analysis of optic nerve head by Heidelberg Retinal Tomograph.

Software Version: 2.1/3515

amblyopia, or amblyopia with co-morbidities (glaucoma, media opacities, oculo-motor imbalance and neurologic disease) were excluded from the study as were patients in whom a good-quality image could not be obtained. A full disclosure of the study was made to the patients and informed consent was obtained from them. Explanation concerning anisometropic amblyopia, the instrument and image acquisition procedure was provided to all the patients. All patient queries were answered to their satisfaction. After a detailed history, the patients underwent a complete ocular and orthoptic examination.

Heidelberg Retina Tomograph (version 3.0, Heidelberg Engineering, Heidelberg, Germany) was used for image acquisition in all patients by a doctor who had more than 4 years' experience in operating the instrument and was blind to the nature of the visual disability of the patient as well as to the study itself. The pupils of all patients were dilated using Tropicamide (1%) eye drops. The patients were given a visual demonstration of what they would expect to see during image acquisition by explaining to them the 'patient fixation guide' provided by the manufacturer of the instrument. The patients' refractive error, age, gender and intra-ocular pressure were entered in the database maintained for the study. Patients with astigmatism of $\geq \pm 1$ Diopter cylinder were asked to wear their spectacle correction for good-quality image acquisition. The quality of the image was assessed by uniformity of illumination of the image, focus and overall clarity as quantitatively indicated by a standard deviation of image. A standard deviation of ≤ 30 microns (as indicated by the software) was accepted for analysis.

The optic disk contour was subsequently drawn by a doctor who was experienced and was blind to the study.

Stereometric analysis of the optic nerve head was performed in software (Figure). Mean peri-papillary RNFLT

Results

A total of 80 eyes, 40 (50%) amblyopic and 40 (50%) normal, were included in the study. In each group, there were 29 (72.5%) males and 11 (27.5%) female. Overall mean age of the patients was 23.85 ± 5.85 years (range: 18 to 35 years).

The Snellen's Visual Acuity (VA), mean spherical equivalent refractive error and mean RNFLT of amblyopic and normal eyes were calculated (Table-1), and so were the mean RNFLT comparison along gender lines (Table-2).

The VA in the amblyopic eye was between 1/60 (0.02) and 6/12 (0.50). In amblyopic eyes, the range of refractive error was between +8.0 Diopters (D), and -5.50D. Hypermetropic refractive error was responsible for amblyopia in 31 (77.5%) eyes, the range of error being +1.50D to +8.00 D. Myopic refractive error was responsible for amblyopia in 9 (22.5%) eyes, the range of error being -3.00D to -5.50D. In normal eyes, the range of refractive error was between +0.50D and -1.250D. Hypermetropic refractive error was present in 4 (10%) eyes, the range being +0.50D to +1.00D, myopic refractive error was present in 7 (17.5%) eyes, the range of error being -1.00D to -1.250D. All normal eyes had a best corrected visual acuity of 6/6 (1.0).

The RNFLT in amblyopic eyes varied between 0.09mm and 0.35mm (mean: $0.23\text{mm} \pm 0.07$), while the normal eyes had an RNFLT that ranged between 0.18mm and 0.36mm (mean: $0.25\text{mm} \pm 0.05$). The expected range of RNFLT, as reported by HRT, was 0.19mm to 0.32mm (mean: $0.25 \pm 0.04\text{mm}$).

The difference in the mean RNFLT between amblyopic eyes compared to the mean RNFLT of normal eyes and expected RNFLT was not statistically significant ($p=0.087$; $p<0.20$ respectively).

Table-1: Mean Snellen's Visual Acuity, Spherical equivalent refractive error and mean Retinal Nerve Fiber Layer Thickness (RNFLT) of amblyopic and normal eyes.

Mean Visual Acuity		Refractive Error (Diopters)		Mean RNFLT (mm)	
Amblyopic eyes	Normal eyes	Amblyopic eyes	Normal eyes	Amblyopic eyes	Normal eyes
0.16 (± 0.13)	1.0 (± 0)	Myopes -4.34 (± 0.90) Hypermetropes +4.04 (± 1.65)	Myopes -1.03 (± 0.09) Hypermetropes +0.87 (± 0.25)	0.23 (± 0.07) P=0.087	0.25 (± 0.05)

of amblyopic eye and normal eyes were entered into the database. Independent sample and one sample t-tests (test value 0.25) were performed to compare RNFLT between normal and amblyopic eyes and the expected value of RNFLT as reported by HRT respectively. For all tests, $p<0.05$ was taken to be significant. The level of significance was set at 5%.

Table-2: Mean RNFLT in amblyopic and normal eyes of Males and Females.

Mean RNFLT in Amblyopic eyes (mm)		Mean RNFLT in Normal eyes (mm)	
Males	Females	Males	Females
0.25mm (± 0.07)	0.18mm (± 0.05)	0.26 (± 0.05)	0.25mm (± 0.05)
P<0.01		P<0.75	

RNFLT: Retinal Nerve Fibre Layer Thickness.

Multiple regression analysis showed a negative but insignificant association between refractive errors ($p < 0.71$; beta coefficient = -0.06), age ($p < 0.51$; beta coefficient -0.11) and mean RNFLT. There was no significant association between the type of refractive error and mean RNFLT ($p < 0.97$ for hypermetropic errors, and $p < 0.62$ for myopic refractive errors) in amblyopic eyes.

Discussion

The mean RNFLT in this study was calculated using HRT. Changes in the morphology of RNFLT, as indicated by its thickness, may help establish an association between changes in optic disk morphology and amblyopia.

The variability of mean RNFLT in amblyopic eyes was low (± 0.10 mm) for the study group. Mean RNFLT in anisometropic amblyopic eyes was less (0.23 ± 0.07 mm) compared to mean RNFLT in normal eyes (0.25 ± 0.05 mm). However, the difference was statistically insignificant ($p < 0.087$).

The results of studies that have investigated RNFLT in amblyopic patients have been inconsistent.^{10,13,14}

Yen et al showed that the RNFLT in anisometropic amblyopia was thicker than normal a finding that they attributed to retardation in the postnatal reduction in ganglion cells.¹⁰ These findings are similar to those reported by Yoon et al.¹³

Mean RNFLT has been shown to be lower in amblyopes compared to normal individuals by Duranoglu.¹⁴ However, a definitive cause-and-effect relationship between amblyopia and the findings of his study could not be assigned.

The results of the current study are similar to those that showed no statistically significant difference in mean RNFLT in patients with amblyopia.¹⁵⁻¹⁸

In this study regression analysis showed that mean RNFLT was not associated with the refractive status of the patient. This is in agreement with published literature when assessing optic disk by HRT for amblyopia.¹⁵

In our patients, amblyopia was seen to be induced by myopic refractive errors of -3.5D which is supported in published literature.^{2,19,20} A relatively large portion of our population had myopia as a cause of amblyopia (22.5%). Similar results have been reported by Sethi et al²¹ and Patwardhan²² while studying amblyopic populations.

In our study, the mean RNFLT, of amblyopic eyes, in males was 0.25 ± 0.07 mm, while in females the mean thickness was 0.18 ± 0.05 mm which was statistically significant ($p < 0.01$). This has not been specifically studied in

literature for amblyopic populations. The normal eyes in the current study also exhibited a thinner mean RNFLT for female population, a difference which was not statistically insignificant ($p = 0.75$) and was in agreement with published literature which showed that females have thinner mean RNFLT, but not statistically significant.^{23,24}

In this study, the mean RNFLT showed a negative (Pearson Correlation factor -0.12), but statistically insignificant correlation with age ($p < 0.44$) in the amblyopic eyes. In the normal eyes, the mean RNFLT also showed a negative and statistically insignificant correlation with age (Pearson Correlation factor -0.14; $p = 0.37$). RNFLT association with age has not been studied in amblyopic populations, but has shown to be significantly (and negatively) correlated with advancing age in normal individuals.^{25,26} The narrow age group of patients in this study (mean age 23.85 ± 5.88 years: range 18 to 35) is likely to be responsible for the statistical insignificance of these results.

We also found that the left eye was more affected by anisometropic amblyopia compared to the right; 65% of the patients had amblyopia in the left eye compared to 35% of patients who had amblyopia in the right eye. Factors that influence laterality in determination of amblyopia include microtropia, sighting dominance, developmental or neurological factors and laterality in the development of refractive error.²⁷

The majority of patients recruited in this study were males. This is likely to be due to the fact that patients with amblyopia in Pakistan present to an eye clinic when seeking employment abroad after being referred by relevant medical testing and screening facilities. They are usually not aware of their disability until it is detected during the screening process. As almost all of the candidates seeking employment abroad are males, they constituted a majority of the patients in this study.

This study compared the mean RNFLT of amblyopic eye to that of normal eye and also to the expected value as reported by HRT. No benchmark for normal mean RNFLT values is available for Pakistani population. To identify whether the RNFLT in eyes in our study was within the normal range, we also included the parameter of expected RNFLT as reported by HRT. We found no significant difference in the mean RNFLT in amblyopic eyes of patients in this study compared to the expected value reported by HRT ($p = 0.20$).

The limitation of the current study included a larger male population which was reflective of the demographics seeking medical attention for amblyopia. The age range of the patients was also narrow. Paediatric age group was

excluded to rule out age-associated growth changes in the mean RNFLT.²⁸ Adults with age >40 years were excluded from the study as their RNFLT might be influenced by glaucomatous damage that is not clinically apparent.¹⁰ Older adults who were on amblyopia therapy or had amblyopia therapy were also excluded in order to ensure that the impact of therapy on retinal morphology, including RNFLT, did not confound the results. Thus, only newly diagnosed cases of unilateral amblyopia were recruited for the study. This necessitated selecting patients within a much stricter criterion with a resultant narrow age band.

Conclusion

There appears to be no morphological change in the RNFLT in the eyes of patients with anisometropic amblyopia. The study adds to a growing pool of evidence that the mean RNFLT, factoring in predictors of refractive error and age, is not significantly affected in anisometropic amblyopia. Future therapies might gain benefit from this study by focussing on components of the visual system that are shown to be affected by amblyopia.

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