·Clinical Research·

Macular and peripapillary retinal nerve fiber layer thickness in children with hyperopic anisometropic amblyopia

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Abstract

• AIM: To compare the retinal nerve fiber layer (RNFL) thickness and macular thickness in the amblyopic eye with that in the sound eye of children with hyperopic anisometropic amblyopia using optical coherence tomography (OCT).

• METHODS: A prospective, nonrandom, intraindividual comparative cohort study includes 72 children with hyperopic anisometropic amblyopia in a single center. Macular thickness, macular foveola thickness, and peripapillary RNFL thickness were compared between the amblyopia eyes and the contralateral sound eyes.

• RESULTS: There were 38 male and 34 female patients, with a mean age as 9.7±1.9 years (range, 5-16 years). Hyperopic was +3.62±1.16D (range +2.00D to +6.50D) in the amblyopic eyes, which was significantly higher in the control eyes with +0.76±0.90D (range 0D to +2.00D) (P< 0.01). The mean peripapillary RNFL thickness was 113.9± 7.2μm and 109.2±6.9μm in the amblyopic eye and the normal eye, respectively, reaching statistical significance (P = 0.02). The mean macular foveola thickness was significantly thicker in the amblyopic eyes than the contralateral sound eyes (181.4±14.2μm *vs* 175.2±13.3μm, P<0.01), but the 1mm, 3mm or 6mm macular thickness central macular thickness was not significantly different. Degree of anisometropia in the contralateral eyes was not significantly correlated with differences of peripapillary RNFL, macular foveola thickness or central macular thickness.

• CONCLUSION: Eyes with hyperopic anisometropic amblyopia are found thicker macular foveola and peripapillary RNFL than the contralateral eyes in children.

• KEYWORDS: hyperopic anisometropic amblyopia; retinal nerve fiber thickness; macular thickness; optical coherence tomography; children

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INTRODUCTION

Amblyopia is a common disease in children, which is a visual disorder characterized by a reduction of vision that cannot be immediately improved by refractive correction or accounted for by clinically determined anatomic defects of the eye or visual pathway [1]. The pathophysiologic mechanisms of amblyopia were not elucidated. Strabismus, anisometropia, and form-vision deprivation are considered to be classic causes of amblyopia [1]. Each of these is thought to result in amblyopia *via* functional and morphologic effects on the visual cortex and lateral geniculate nucleus [2,3]. Yen *et al*[4] has hypothesized that amblyopia may affect the postnatal maturation of the retina, including the postnatal reduction of retinal ganglion cells, which would lead to a measurable increase in retinal nerve fiber layer (RNFL) thickness in amblyopic eyes.

Optical coherence tomography (OCT) is a rapid, non-invasive, office-based imaging technique allowing objective quantification of retinal structures with high resolution, including determination of peripapillary RNFL thickness and macular thickness. It has been applied successfully in young children in previous studies [5-7]. However, evidence for direct retinal changes in eyes with amblyopia has been controversial. In the present study, we compared peripapillary RNFL thickness, central macular thickness and foveola thickness of the normal fellow eyes to that of the amblyopic eyes using OCT in children with unilateral anisometropic amblyopia. Because early anatomic changes may be present in the retinas of children with axial myopia [8], only children with hyperopic anisometropic amblyopia were included in this study.

SUBJECTS AND METHODS

Subjects This comparative, observational, case series were performed from January 2010 to March 2012 at a single centre according to the tenets of the Declaration of Helsinki.

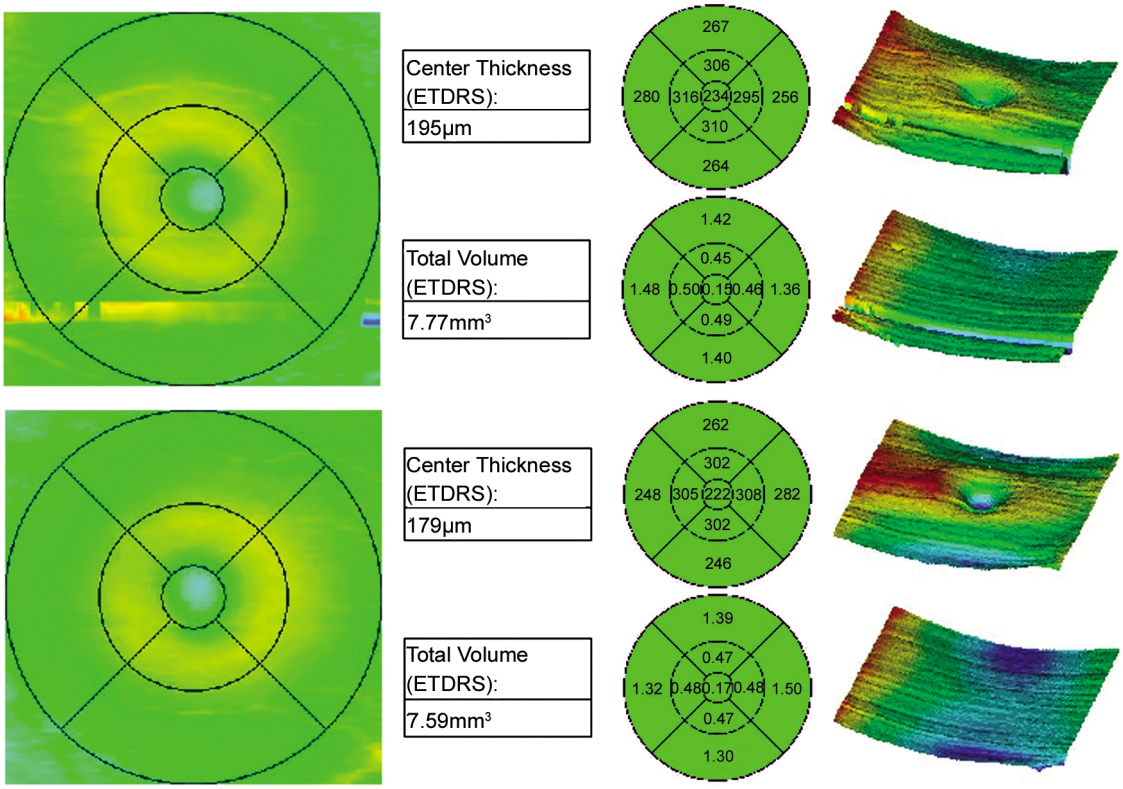

Figure 1 Macular optical coherence tomography in a patient with hyperopic anisometropic amblyopia (Top) Right eye, spherical equivalent as +4.00 diopter (D), best corrected vision acuity (BCVA) as 0.5. (Bottom) Left eye, spherical equivalent as +0.50D, BCVA as 1.0.

The institutional review board approved the study, and written informed consent was obtained from the parents or legal guardians of all patients prior to enrolment. All enrolled patients had unilateral hyperopic anisometropic amblyopia and normal vision in the contralateral eye. Anisometropic diopter was more than 2 diopter. The patients have not received treatment for amblypia in the initial visit. Patients with any of the following conditions were excluded: age less than 4 years or greater than 16 years, strabismus, eccentric fixation, not sufficiently cooperative for OCT examination, previous ocular surgery, neurological disease or other diseases of the visual pathways.

Methods

Main measurements All patients underwent a full ophthalmological assessment, including visual-acuity testing, slit lamp biomicroscopy, fundus examination, and evaluation of ocular alignment. Cycloplegic refraction was performed using retinoscopy 60 minutes after the instillation of 1% tropicamide by a same ophthalmologist (LWZ). The corrected visual acuities were transformed to a logarithmic scale (logMAR) for statistical analysis. All OCT scans were performed using a frequency-domain OCT (3D-OCT 1000; Topcon Inc, Paramus, New Jersey, USA). The measurements were done by a single skilled technician, who was masked to the diagnoses of the subjects. All patients were performed using the fast macular thickness and fast optic disc protocol. All scans had signal strength of at least 6 radial line scans, with axial resolution as 5μm, transverse resolution as 18μm, and probing depth as 2.3mm. Internal fixation was used for all scans. In the fast macular thickness protocol, 6mm lines in a radial spoke-like pattern are obtained in a continuous automated sequence. The foveola thickness, central macular thickness and four quadrants of the inner and outer macular thickness were measured for each subject. The central macular thickness is defined as the central circle of 1mm diameter in the macular image (Figure 1). The foveola thickness was corresponding to the central thickness in the macular image (Figure 1). Inner macula refers to the ring around the foveal area of 3mm diameter and outer macula refers to the ring around the inner macula of 6mm diameter (Figure 1). Peripapillary RNFL thickness was measured using the "fast RNFL thickness (3.4mm diameter)" scan protocol, which consisted of 6 radial line scans (Figure 2). This comprised 256 sampling points along a circular scan path. Three scans were performed, and the average was used in analyses.

Statistical Analysis Peripapillary RNFL thickness, central macular thickness, and macular foveola thickness were compared with Paired-$t$test.Correlations between continuous variables were obtained using Pearson's correlation coefficient for normal data. All tests were two-tailed, and a P value of less than 0.05 was deemed statistical significance.

RESULTS

At the end of this study, there were 72 patients (38 males

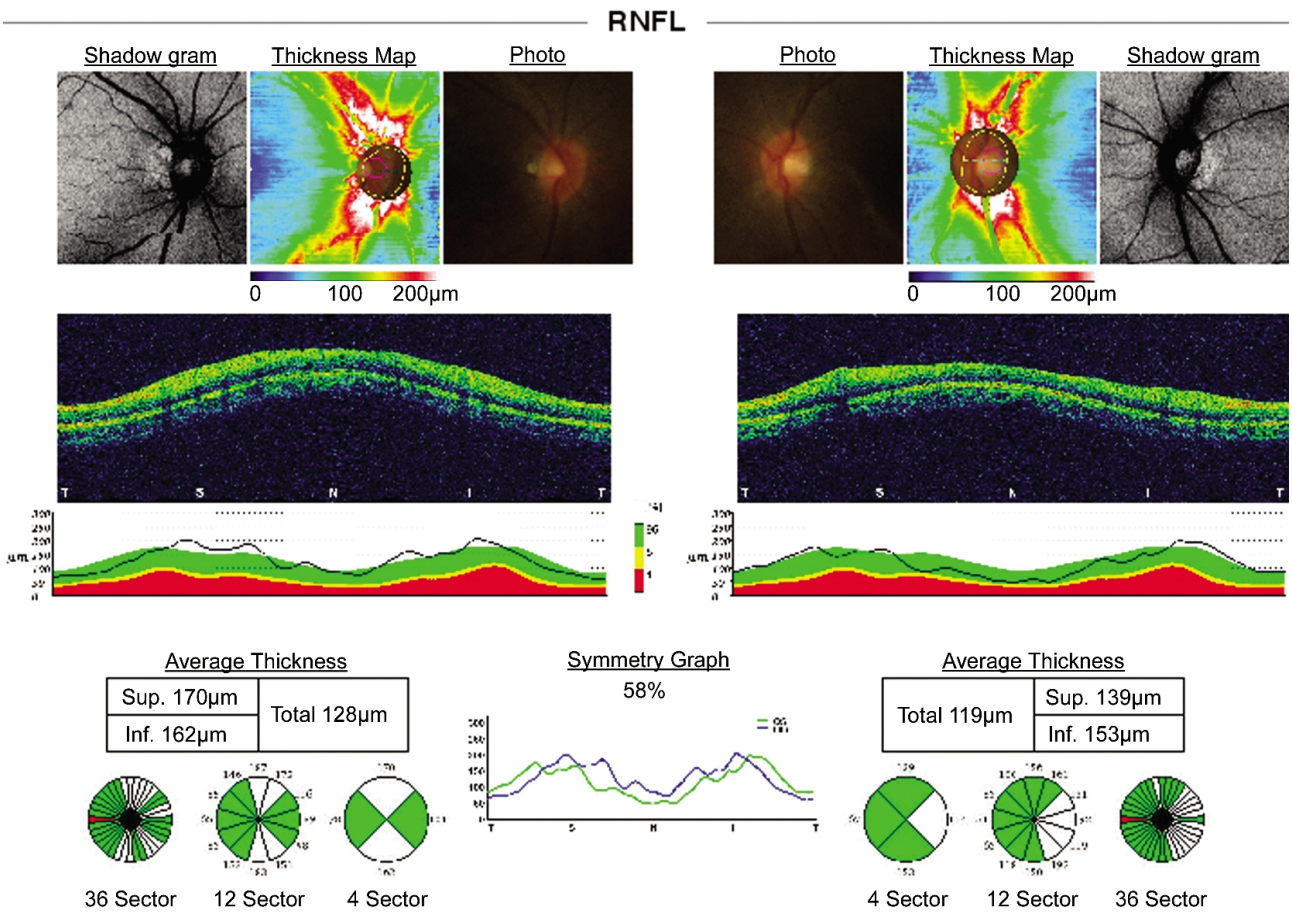

Figure 2 Optical coherence tomography of retinal nerve fiber layer (RNFL) in a patient with hyperopic anisometropic amblyopia
Right eye, spherical equivalent as +4.00 diopter (D), best corrected vision acuity (BCVA) was 0.5. Left eye, spherical equivalent was +0.50D, BCVA was 1.0.

and 34 females) included. The mean age of these patients were 9.7±1.9 years (range, 5-16 years). Hyperopic was +3.62 ±1.16D (range +2.00D to +6.50D) in the amblyopic group, which was significantly higher in the control group with +0.76±0.90D (range +0D to +2.00D) (P<0.01). The mean logMAR best-corrected visual acuity was 0.37 ±0.15 (range 0.15 ±0.70) in the amblyopic eyes and 0.02 ±0.07 (range 0.00-0.12) in the fellow eyes.

The mean peripapillary RNFL thickness was 113.9 ±7.2μm in the amblyopic eyes, which was significantly thicker than 109.2±6.9μm in the fellow eyes (P=0.02) (Table 1). The difference of peripapillary RNFL thickness between contralateral eyes was not significantly related with the degree of anisometropia (r=-0.068, P= 0.60) (Table 2).

The mean central macular thickness was 257.1 ±15.8μm in the amblyopic eyes and 258.6 ±13.9μm in the fellow eyes, which did not reach statistical significance (P =0.80), whereas the macular foveola thickness was significantly thicker in the amblyopic eyes than that in the fellow eyes (181.4±14.2μm *vs* 175.2±13.3μm, P<0.001) (Table 1). No significant differences were found in the four quadrants of the inner and outer macular thickness (Table 1). The degree of anisometropia between the contralateral eyes was not significantly correlated with the difference of the mean macular foveola thickness (r=-0.012, P=0.93) and the mean central macular thickness (r=-0.05, P=0.71) (Table 2).

Table 1 Peripapillary retinal nerve fiber layer thickness and macular thickness (μm, $\bar{x} \pm s$)

	Amblyopic eye (n=72)	Control eye (n=72)	P
Peripapillary RNFL thickness	113.9±7.2	109.2±6.9	0.02
Foveola thickness	181.4±14.2	175.2±13.3	<0.001
Central macular thickness (1mm)	257.1±15.8	258.6±13.9	0.80
Inner macula (3mm)			
Superior	307.3±12.7	302.8±9.6	0.10
Nasal	294.3±8.4	308.3±6.2	0.11
Inferior	286.5±3.9	302.5±7.9	0.06
Temporal	282.2±9.9	287.0±5.0	0.45
Outer macula (6mm)			
Superior	278.5±15.7	282.8±12.6	0.21
Nasal	286.5±21.0	291.3±12.7	0.54
Inferior	265.3±27.2	267.8±11.1	0.84
Temporal	267.8±17.0	261.8±13.1	0.11

Data were compared with Paired t- test. RNFL: retinal nerve fiber layer.

DISCUSSION

Previous literatures suggested that there were two or more nerve impulses from the retinal afferent lateral geniculate body and visual cortex in the visual transduction process [2,3]. Amblyopia has a deleterious effect on both the cell growth of

Table 2 Pearson's correlation between degree of anisometropia and differences of peripapillary and macular thickness in the contralateral eyes $\bar{x} \pm s$

	Mean±SD (Range)	*r*	*P*
Degree of anisometropia (D)	2.78±0.83 (1.25 to 5.00)		
Differences of peripapillary RNFL thickness (μm)	5.27±5.35 (-10.0 to 18.0)	-0.068	0.60
Differences of Central Macular thickness (μm)	-0.37±10.9 (-31.0 to 15.0)	-0.012	0.93
Differences of foveola thickness (μm)	6.05±8.31 (-9.0 to 33.0)	-0.05	0.71

RNFL: retinal nerve fiber layer; D: diopter; SD: standard deviation.

the lateral geniculate nucleus and the distribution of cortical neurons [2,3]. It has been found that lateral geniculate body layer of the amblyopic eye had anatomic changes: neuron of afferent fibers in the lateral geniculate body layer was smaller than that of the normal eyes, which was considered to be minor changes in ocular dominance columns in terms of occurring mechanism [1-3]. Histological study of the lateral geniculate nucleus of monkeys with strabismic, anisometropic, and visual deprivation amblyopia reveals marked shrinkage of cells that receive input from the amblyopic eye [2], and similar changes were found in human [9,10]. In patients with anisometropia, when the binocular refractive errors can not be corrected at the same time, the imaging of the same object on binocular retina was not same clear, even not same size when anisometropia was large. Therefore, binocular visual image can not be fused in the cortex. Cortical centers can only inhibit imaging from the eye with larger refractive errors and blur imaging, causing the eye amblyopia with a long period of suppression.

However, possible involvement of the retina in amblyopia has been controversial. Recently, the retinal structure can be measured reliably with OCT. Due to decreasing of RNFL thickness in macular and peripapillary in eyes with myopia, especially for hypermyopia, as reported in previous studies [8,11], we only included the patients with hyperopic anisometropia. Furthermore, comparison of amblyopic eye with contralateral eye can avoid the impaction of age and gender on this research.

There has been an interesting biological theory regarding differences in RNFL thickness in eyes with and without amblyopia. In humans, the total population of cells in the ganglion cell layer is highest between approximately weeks 18 and 30 of gestation and declines rapidly after there [12]. The number of axons in the human optic nerve also decreases during gestation [13]. If amblyopia affects the process of postnatal reduction of ganglion cells, RNFL thickness may be thicker than that in the normal eye. It may be also contributed to no apoptosis or less apoptosis of retinal ganglion cells in amblyopic eyes due to absence of normal vision stimulation, eventually leading to thicker RNFL of the amblyopic eye than non-amblyopic eye. The critical period of human was about 3-12 years, with rapid visual development in this stage [14]. In this period, the obstacles of normal visual environment are most likely to induce amblyopia, which may be accompanied with changes of the number, structure and function of cortical neurons and their synapse with the environment [14]. In the present study, we included children with hyperopic anisometropic amblyopia at 5-16 years old, and detected that the mean peripapillary RNFL thickness in the amblyopic eyes was significantly thicker than that of the fellow eyes (P<0.01). Similar results were also reported by other studies in children with ametropic amblyopia [15,16], but not agree with the study on adult with hyperopic amblyopia [17] and an epidemic study on children aged predominantly 6 and 12 years [7].

According to previous studies [12,18], macular differentiation has its own specialty: in the developing process, macular becomes thicker rather than thinning in the peripheral retina at 6-month embryos, manifesting slightly protruding. Macular fovea appears at 7-month embryos, with ganglion cell layer thinning in the macular central. We found that the foveola thickness was significantly thicker in the amblyopic eyes than that in the fellow eyes (181.4±14.2μm *vs*175.2± 13.3μm, P <0.01). We speculated that due to visual deprivation and binocular competing role, blurred vision led to no enough stimulation in the amblyopic eye, affecting the normal maturation of the macula, including movement of Henle's fibers away from the fovea and a decrease in foveal cone diameter, which would result in increased foveola thickness. As a relative larger area, the difference of 1-mm central macular thickness was not found in the amblyopic eyes and the fellow eyes. Our result was well consistent with Huynh's [7] and Yoon's [15], but it was disagreement with Walker's result [17]. Similiar findings were reported in amblyopic children with unilateral high myopia [19], suggesting probable parallel pathophysiologic mechanisms for hyperopic anisometropic amblyopia and myopic anisometropic amblyopia. The diameter of foveola is 0.35mm, less than the 1-mm central macular thickness. Therefore, different definition of macular thickness and foveola thickness was related to distinctive results in previous studies [7,15,17]. The disagreement results of foveola thickness and 1-mm central macular thickness need further investigation. We did not find correlation of severity of anisometropia and differences of peripapillary RNFL thickness, central macular thickness or foveal thickness in

the contralateral eyes, suggesting far more complex pathophysiologic mechanisms for anisometropic amblyopia than we have known.

An important limitation is that 1% tropicamide was used for pupil dilation, by which an exact cycloplegic refraction could not be acquired in children with high-degree hyperopia. Therefore, the relationship of the degree of anisometropia between the contralateral eyes and peripapillary RNFL and macular thickness needs further identification.

In conclusion, in children with hyperopic anisometropic amblyopia, there is a thicker peripapillary RNFL and foveola, but not 1-mm central macular thickness. This finding requires further histopathologic confirmation.

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