Original Article

Peripapillary retinal nerve fiber layer thickness and central macular thickness in children with anisometropia

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ABSTRACT

Background: Anisometropia is associated with asymmetric ocular growth and may influence retinal structure, yet its impact on retinal nerve fiber layer thickness (RNFLT) remains incompletely understood. This study aimed to evaluate RNFLT and central macular thickness (CMT) in children with anisometropia and to examine their relationships with refractive error and ocular biometric parameters.

Methods: This cross-sectional study included children aged 5–16 years with anisometropia. Comprehensive ophthalmic evaluation included cycloplegic refraction, ocular biometry, and spectral-domain optical coherence tomography. Peripapillary RNFLT and CMT were measured and compared between worse and fellow eyes, as well as between amblyopic and non-amblyopic eyes. Correlations between spherical equivalent refraction (SER) and ocular parameters, including axial length, intraocular pressure, CMT, and RNFLT, were assessed.

Results: Among 46 children (median age 14 years), 45.7% (n = 21) had anisometropic amblyopia. Nasal RNFLT was significantly greater in worse eyes compared with fellow eyes ($P < 0.05$), while other quadrants and CMT showed no significant interocular differences. Amblyopic eyes showed higher RNFLT values than non-amblyopic eyes, reaching significance only in the nasal quadrant. SER showed a strong negative correlation with axial length (r = -0.91, $P < 0.001$) and moderate or weak positive correlations with quadrant-specific RNFLT, including inferior (r = +0.56, $P = 0.001$), superior (r = +0.67, $P < 0.001$), temporal (r = +0.59, $P < 0.001$), and nasal (r = +0.37, $P = 0.012$) quadrants, but not with CMT (r = -0.22, $P > 0.05$) or IOP (r = +0.19, $P > 0.05$).

Conclusions: Children with anisometropia exhibit selective regional RNFLT alterations, particularly involving the nasal quadrant, while macular thickness remains largely preserved. The observed associations between refractive error, AL, and RNFLT suggest that anisometropia may influence retinal structural development in a region-specific manner. Longitudinal studies are warranted to clarify the temporal relationship between refractive asymmetry and retinal structural remodeling.

KEYWORDS

anisometropia, anisometropic amblyopia, optical coherence tomography, peripapillary retinal nerve fiber layer thickness, macula luteas, eye axial length, ocular tonometry, intraocular pressures

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INTRODUCTION

Anisometropia is defined as a condition where the two eyes have different refractive errors, typically quantified as a difference in spherical equivalent refraction (SER) of at least 1.00 diopter (D) [1]. This is a unique presentation of ocular development where the eyes grow asymmetrically despite a shared genetic background and environment [2]. Anisometropia can be due to a difference in axial length (axial anisometropia) or differences in the optical power of the ocular media (refractive anisometropia) [3]. The condition is also frequently associated with high levels of astigmatism and differences in corneal toricity. Its prevalence varies with age [4, 5] and ethnicity [6].

Retinal nerve fiber layer thickness (RNFLT) is a key structural indicator for various ocular and central nervous system diseases, including glaucoma and myopic changes [7]. RNFLT is known to be thicker in the inferior and superior quadrants and thinner in the nasal and temporal quadrants [8]. Furthermore, factors like age, axial length (AL), and refractive status significantly influence RNFLT – for example, RNFLT increases with shorter AL and hyperopia, and decreases with increasing age, axial elongation, and myopia [9].

Anisometropia is frequently, though not invariably, associated with amblyopia. Both conditions are commonly detected during school vision screenings [5, 10]. While anisometropia is generally believed to contribute to amblyopia in the persistently defocused eye, definitive evidence supporting this causal relationship is lacking and has been questioned by several researchers [5, 10]. Additionally, multiple studies show that monocular deprivation can lead to the development of both anisometropia and amblyopia by disrupting ocular growth as well as synaptic and cortical development [5, 10, 11].

Given the possibility of structural asymmetry caused by anisometropia and the importance of RNFL integrity for vision, investigating RNFLT interocular symmetry is critical. There has been little detailed research into RNFLT and central macular thickness (CMT) in anisometropic amblyopia [12–14]. We aimed to assess RNFLT and CMT using optical coherence tomography (OCT) imaging to determine whether a significant difference exists between the two eyes in children with anisometropia; we also aimed to determine possible correlation of SER in anisometropia with RNFLT, CMT, AL, or intraocular pressure (IOP).

METHODS

A cross-sectional study was conducted at Port Said Ophthalmology Hospital, Port Said, Egypt, to evaluate refractive differences among pediatric patients visiting the outpatient ophthalmology clinic. The study was conducted between January and June 2025. The research protocol was prospectively registered in the Pan African Clinical Trial Registry (PACTR; registration number: PACTR202509889401810) and approved by the Ethics Committee of the Faculty of Medicine, Port Said University. All procedures were conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all participants prior to enrollment and before initiation of any study-related procedures.

A convenience sampling approach was used. Children aged 5–16 years were eligible for inclusion if they showed an interocular difference in SER greater than 2.0 diopters. Both male and female participants were eligible. Exclusion criteria included age younger than 5 years or older than 16 years, a history of ocular surgery, or the presence of ocular pathology, including glaucoma, cataracts, maculopathy, and corneal opacity.

Sample size estimation was performed using the formula for comparing two independent means: $n = 2[(Z\alpha/2 + Z\beta)\cdot\sigma / (\mu_1 - \mu_2)]^2$ [15]. The calculation was based on previously reported mean peripapillary RNFLT values of 113.9 ± 7.2 μm in amblyopic eyes and 109.2 ± 6.9 μm in normal eyes, which evidenced a statistically significant difference ($P = 0.02$) [12]. Given the comparable variability between groups, the standard deviation from the normal eye group ($\sigma = 7.2$ μm) was used as a representative estimate of measurement variability. This yielded a minimum required sample size of 37 participants. To account for a potential 10% attrition rate, the target enrollment was increased to 41 participants. Ultimately, 46 children were enrolled, exceeding the calculated sample size and ensuring adequate statistical power for the planned analyses.

A detailed medical and ophthalmic history was obtained for all participants. Each child subsequently underwent a comprehensive ophthalmological examination that included assessment of visual acuity, cycloplegic refraction, anterior and posterior segment evaluation, IOP measurement, ocular biometry, and OCT imaging. Uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) were measured monocularly for each eye using a Snellen chart (Topcon ACP-8 automatic chart projector, Topcon Corporation, Tokyo, Japan) and were converted to logarithm of the minimum angle of resolution (logMAR) units for statistical analysis.

Cycloplegic refraction was performed 30 minutes after instillation of 1% cyclopentolate hydrochloride eye drops (Plegica 1%, Egyptian Group for Pharmaceutical Industries [EGPI], Hikma Co., Egypt). Refractive error measurements were obtained using an automated refractometer (Topcon RM-8000B auto-refractometer, Topcon Co., Tokyo, Japan). Anterior segment evaluation was conducted using a slit-lamp biomicroscope (Topcon Co., Tokyo, Japan), and posterior segment examination was performed using a 90-diopter non-contact aspheric lens (Volk Optical, Inc., Mentor, OH, USA) under slit-lamp biomicroscopy. Intraocular pressure was measured using a non-contact air-puff tonometer (Topcon Co., Tokyo, Japan).

AL measurements were obtained using an optical biometer (Lenstar LS 900, Haag-Streit AG, Koeniz, Switzerland). CMT and peripapillary RNFLT were assessed using spectral-domain OCT (SD-OCT) with a Topcon 3D OCT system (Topcon

Corp., Tokyo, Japan) equipped with ImageNet 6 software (version R6 or later). OCT imaging was performed approximately 30–45 min following cycloplegic refraction. Peripapillary RNFLT measurements were analyzed across four quadrants: superior, nasal, inferior, and temporal.

Anisometropia was classified into three categories. Simple anisometropia was defined as a condition in which one eye was emmetropic while the fellow eye exhibited a refractive error, either myopia or hyperopia. Compound anisometropia was defined as the presence of refractive error in both eyes of the same type but differing in magnitude; this included anisomyopia, in which both eyes were myopic but one eye showed a greater degree of myopia, and anisohypermetropia, in which both eyes were hyperopic with differing refractive magnitudes. Mixed anisometropia was defined as the presence of myopia in one eye and hyperopia in the fellow eye [16]. Anisometropic amblyopia [16] was defined as a reduction in BCVA in the presence of any form of anisometropia.

In cases of simple anisometropia the ametropic eye was designated as the worse eye, whereas the emmetropic eye was considered the fellow eye. In anisomyopia the more myopic eye was classified as the worse eye and the less myopic eye as the fellow eye. In anisohypermetropia the eye with greater hyperopia was considered the worse eye, while the less hypermetropic eye served as the fellow eye. In cases of mixed anisometropia, the eye with the higher absolute refractive error was classified as the worse eye, and the contralateral eye as the fellow eye.

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Data distribution was assessed using the Shapiro-Wilk test. Quantitative variables were summarized using median and interquartile range (IQR). Comparisons between quantitative variables, including comparisons between worse and fellow eyes, were performed using the non-parametric Mann-Whitney U test. Associations between SER and quantitative parameters, including quadrant-specific RNFLT, CMT, AL, and IOP, were evaluated using Spearman's rank correlation coefficient. A two-tailed P-value < 0.05 was considered statistically significant.

RESULTS

A total of 46 children were included with a median age of 14 years (IQR 15.3, range 5–16 years). Compound anisometropia was the most prevalent subtype among participants—observed in 42 children (91.3%), followed by mixed anisometropia in three children (6.5%) and simple anisometropia in one child (2.2%). With respect to amblyopia status, 21 participants (45.7%) were diagnosed with anisometropic amblyopia, whereas 25 participants (54.3%) were classified as non-amblyopic.

Comparison of quadrant-specific RNFLT and CMT between worse and fellow eyes is presented in Table 1. Overall, most RNFLT parameters did not differ significantly between the two eyes. A statistically significant difference was observed in the nasal quadrant, where RNFLT was significantly greater in the worse eye compared with the fellow eye ($P < 0.05$). Although the superior and inferior quadrants displayed a tendency toward greater RNFLT values in the fellow eye relative to the worse eye, these differences did not reach statistical significance (all $P > 0.05$). Temporal quadrant RNFLT values were nearly identical between eyes ($P > 0.05$). Similarly, comparison of CMT between worse and fellow eyes revealed no statistically significant difference ($P > 0.05$).

Table 2 summarizes the comparison of quadrant-specific RNFLT and CMT between amblyopic and non-amblyopic eyes. RNFLT values across all quadrants were numerically higher in amblyopic eyes compared with non-amblyopic eyes, reaching statistical significance only in the nasal quadrant ($P < 0.05$). No statistically significant differences were observed between amblyopic and non-amblyopic eyes for inferior, superior, or temporal RNFLT measurements (all $P > 0.05$). Similarly, CMT did not differ significantly between amblyopic and non-amblyopic eyes ($P > 0.05$).

Correlation analyses between SER and other ocular parameters are presented in Table 3. A strong and statistically significant negative correlation was observed between SER and AL (r = -0.91, $P < 0.001$). In addition, SER showed significant moderate positive correlations with RNFLT in the inferior (r = +0.56, $P = 0.001$), superior (r = +0.67, $P < 0.001$), and temporal (r = +0.59, $P < 0.001$) quadrants. A weak yet statistically significant positive correlation was also observed between SER and nasal RNFLT (r = +0.37, $P = 0.012$). In contrast, no statistically significant correlations were identified between SER and IOP (r = +0.19, $P > 0.05$) or between SER and CMT (r = -0.22, $P > 0.05$).

Table 1. Comparing quadrant-specific RNFLT and CM between worse eye and fellow eye

Variable	Worse Eye	Fellow eye	*P*-value
Inferior RNFLT (μm), Median (IQR)	131.5 (146.0)	136.0 (143.3)	0.586
Superior RNFLT (μm), Median (IQR)	124.0 (131.5)	127.1 (133.5)	0.060
Nasal RNFLT (μm), Median (IQR)	84.0 (87.0)	78.0 (81.3)	**0.020**
Temporal RNFLT (μm), Median (IQR)	70.0 (75.0)	70.0 (72.3)	0.707
CMT (μm), Median (IQR)	261.1 (267.7)	259.4 (267.6)	0.566

Abbreviations: RNFLT, retinal nerve fiber layer thickness; CMT, central macular thickness; μm, micrometers; IQR, interquartile range. Note: *P*-value < 0.05 is shown in bold.

Table 2: Comparing quadrant-specific RNFLT and CM between amblyopic and non-amblyopic eyes

Variable	Non-amblyopic	Amblyopic	*P*-value
Inferior RNFLT (μm), Median (IQR)	130.0 (139.0)	146.0 (152.0)	0.558
Superior RNFLT (μm), Median (IQR)	120.0 (128.0)	124.0 (124.0)	0.060
Nasal RNFLT (μm), Median (IQR)	80 (84.5)	86 (91.5)	**0.020**
Temporal RNFLT (μm), Median (IQR)	69 (73.0)	71 (80.5)	0.707
CMT (μm), Median (IQR)	260.7 (267.8)	261.5 (267.8)	0.566

Abbreviations: RNFLT, retinal nerve fiber layer thickness; CMT, central macular thickness; μm, micrometers; IQR, interquartile range. Note: *P*-value < 0.05 is shown in bold.

Table 3. Correlation of SER to other ocular parameters in study participants

Variables	r-value	*P*-value
Axial Length	- 0.91	**< 0.001**
IOP	+ 0.19	0.076
Inferior RNFLT	+ 0.56	**0.001**
Superior RNFLT	+ 0.67	**< 0.001**
Nasal RNFLT	+ 0.37	**0.012**
Temporal RNFLT	+ 0.59	**< 0.001**
CMT	- 0.22	0.148

Abbreviations: SER, spherical equivalent refraction; IOP, intraocular pressure; RNFLT, retinal nerve fiber layer thickness; CMT, central macular thickness. Note: *P*-values < 0.05 are shown in bold; correlation coefficients (r) and corresponding *P*-values were calculated using Spearman's rank correlation.

DISSCUSSION

In this study, children with anisometropia showed selective structural retinal differences, with significantly increased nasal RNFLT in the worse and amblyopic eyes, while other quadrants and CMT remained comparable. SER showed strong or moderate correlations with AL and quadrant-specific RNFLT, highlighting the influence of refractive status on retinal architecture. These findings suggest that anisometropia is associated with localized alterations in RNFLT rather than diffuse retinal changes, supporting a region-specific structural response to refractive imbalance.

Thank to recent progress in OCT, retinal structures can be measured reliably. OCT is widely used to investigate how the retina and optic nerve are involved in anisometropic amblyopia [12–14] In contrast to population-based studies by O'Donoghue et al. [17] and Huynh et al. [18], which emphasized refractive and AL asymmetry in anisometropic eyes, and biometric analyses by Kim et al. [19] showing that anisomyopia severity is primarily related to interocular differences in vitreous chamber depth, our study extends these observations by identifying localized nasal RNFL alterations in anisometropic eyes with and without amblyopia, suggesting downstream retinal structural effects beyond ocular biometry alone.

Previous studies report inconsistent structural findings in anisometropic amblyopia. In concordance with Wu et al. [12], we observed increased RNFLT in amblyopic anisometropic eyes; however, this increase was confined to the nasal quadrant, with no accompanying changes in foveal or central macular thickness, indicating a localized effect. In contrast to Al-Haddad et al. [20], who reported increased macular thickness with comparable RNFL measurements, our findings evidence preserved macular thickness alongside selective nasal RNFL thickening, underscoring regional rather than diffuse retinal structural involvement.

Amblyopic eyes often have thicker retina or RNFL [12, 20, 21]. Yen et al. [21] evaluated RNFLT in unilateral amblyopia and showed significantly increased RNFLT in anisometropic amblyopia, but not in strabismic amblyopia, compared with fellow eyes. The authors hypothesized that this RNFL thickening may reflect arrested postnatal ganglion cell pruning in refractive amblyopia, while acknowledging the absence of histopathologic confirmation. Yoon et al. [23] reported significantly increased peripapillary RNFLT in eyes with hyperopic anisometropic amblyopia compared with fellow eyes, while macular retinal thickness remained unchanged, suggesting selective involvement of the peripapillary RNFLT rather than the macula. As most of our anisohypermetropic participants evidenced increased RNFLT in amblyopic eyes, our findings are consistent with previous reports by Yen et al. [21] and Yoon et al. [23] supporting the concept that refractive amblyopia is associated with RNFL thickening, although the distribution of this effect may be region-specific.

Prior studies report heterogeneous findings regarding retinal structural changes in amblyopia. Choi et al. [23] showed that increasing myopia is associated with peripapillary RNFL thinning and increased foveal thickness, underscoring the influence of refractive status rather than amblyopia per se. In unilateral strabismic amblyopia, Altintas et al. [24] found no significant differences in RNFL or macular parameters between amblyopic and fellow eyes. Similarly, Kee et al. [25] reported no overall significant differences between amblyopic and normal children; however, subgroup analyses revealed significant distinctions between anisometropic and strabismic amblyopia, where children with anisometropic amblyopia displayed thinner foveal thickness and greater RNFL thickness compared to those with strabismic amblyopia [25]. In this context, our

findings of selective nasal RNFL thickening in anisometropic eyes—particularly in amblyopia—suggest that retinal structural changes may be subtype-specific and regionally localized rather than diffuse.

Previous studies report variable retinal structural changes in anisometropia and amblyopia. Yalcin and Balci [26] evidenced increased foveal thickness without significant RNFL changes in hypermetropic anisometropic amblyopia, whereas our findings revealed preserved macular thickness with selective nasal RNFL thickening, indicating regional rather than global RNFL involvement. Jiang et al. [27] reported parafoveal thinning with preserved foveal thickness in myopic anisometropia. In our cohort, central macular thickness did not differ significantly across anisometropia subtypes, consistently with findings by Dickmann et al. [28] in anisometropic amblyopia. The relatively small number of eyes with mixed anisometropia in the present study highlights an area for future investigation.

A major strength of this study is the detailed quadrant-specific OCT analysis combined with comprehensive ocular biometry in children with anisometropia, offering clinically relevant insights for pediatric imaging. Nonetheless, the modest sample size and absence of an age-matched control group limit generalizability. Future large-scale, population-based and longitudinal studies incorporating control cohorts and additional parameters such as corneal curvature are warranted to refine OCT interpretation in pediatric anisometropia, amblyopia, and glaucoma assessment.

CONCLUSIONS

A selective increase in nasal quadrant RNFLT was observed in the worse eyes of patients with anisometropia and in amblyopic eyes. In contrast, no significant interocular differences were detected in CMT or in RNFL measurements across the remaining quadrants. The observed associations between refractive error, AL, and RNFLT suggest that anisometropia may influence retinal structural development in a region-specific manner. Our findings could indicate that anisometropia is associated with subtle, localized RNFL alterations rather than diffuse retinal structural remodeling, while overall macular architecture appears to be largely preserved. Clinically, these results underscore the importance of considering refractive status and anisometropia subtype when interpreting OCT-derived RNFL measurements, particularly in pediatric patients evaluated for amblyopia or glaucoma-related changes. Further longitudinal studies are warranted to elucidate the developmental trajectory and clinical relevance of these localized changes.

ETHICAL DECLARATIONS

Ethical approval: The research protocol was prospectively registered in the Pan African Clinical Trial Registry (PACTR; registration number: PACTR202509889401810) and approved by the Ethics Committee of the Faculty of Medicine, Port Said University. All procedures were conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all participants prior to enrollment and before initiation of any study-related procedures.

Conflict of interests: None.

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