Anomalous relation between axial length and retinal thickness in amblyopic children

Pauline H. B. Kok, MD,[a] Roy de Kinkelder, MSc, PhD,[b] Yvette C. Braaksma-Besselink, MSc,[a] Jeroen Kalkman, MSc, PhD,[b] Liesbeth J. J. M. Prick, MD, PhD,[a] Marije L. Sminia, MD, PhD,[a] Maarten Ph. Mourits, MD, PhD,[a] and Frank D. Verbraak, MD, PhD[a,b]

PURPOSE To investigate the relationship between retinal thickness and axial length in amblyopic eyes compared to healthy eyes.

METHODS In this observational, transversal study, 36 amblyopic children and 30 healthy controls underwent full ophthalmological and orthoptic examinations, volume scanning of the macula with spectral domain optical coherence tomography (3D OCT-1000; Topcon Corporation, Tokyo, Japan), and measuring of axial length using the IOLMaster (Carl Zeiss Meditec AG, Jena, Germany). The average pericentral retinal thickness was calculated.

RESULTS A strong correlation was observed between the axial lengths of both eyes in the control group ($R = 0.98$, $P < 0.01$) and between the axial lengths of the amblyopic and fellow eye in the amblyopic group ($R = 0.77$, $P < 0.01$); the amblyopic and their fellow eyes were significantly shorter than the nonamblyopic control eyes. The pericentral retinal thickness of both eyes of an individual is highly correlated in nonamblyopic controls ($R = 0.92$, $P < 0.01$) and in amblyopic children ($R = 0.82$, $P < 0.01$). There is no significant difference in mean pericentral retinal thickness between healthy, amblyopic, and fellow eyes. In healthy eyes a moderate inverse correlation exists between axial length and pericentral retinal thickness ($R = -0.41$, $P = 0.02$); this relationship was not found in the amblyopic eyes or the normal fellow eye.

CONCLUSIONS In this patient cohort, there was an anomalous relation between the axial length and the pericentral retinal thickness in both amblyopic and their fellow eyes. (J AAPOS 2013;17:598-602)

Optical coherence tomography (OCT) has been used to study macular retinal thickness in amblyopic eyes[1-11] and in most studies amblyopic eyes tended to have a thicker retina and/or retinal nerve fiber layer (RNFL).[4,7,9,10,11] Yen and colleagues[9] postulated that amblyopic eyes have a thicker retina due to the arrest of the physiological postnatal ganglion cell reduction.

Retinal thickness in healthy eyes is determined by several factors, including age, sex, and axial length. Relatively greater axial length in healthy subjects has been shown to be significantly correlated with a thin retina and RNFL. Because amblyopic eyes tend to be hypermetropic, axial length can be a confounder in studies measuring retinal thickness in these patients.[11-15] The purpose of this study was to investigate the relationship between axial length and pericentral retinal thickness in the amblyopic and fellow eyes of children with amblyopia and compare the results to the same measurements in both eyes of healthy children. We analyzed the pericentral part of the retina since changes in the ganglion cells due to disease are most pronounced in this area of the retina.

Author affiliations: [a]Department of Ophthalmology, Academic Medical Center, Amsterdam, the Netherlands; [b]Biomedical Engineering & Physics, Academic Medical Center, Amsterdam, the Netherlands

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Correspondence: Pauline H. B. Kok, MD, Department of Ophthalmology, Room: D2-146, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands (email: p.h.kok@amc.nl).

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Subjects and Methods

The ethics committee of the Academic Medical Center in Amsterdam approved this observational, transversal study. All research adhered to the tenets of the Declaration of Helsinki, and all parents and guardians provided informed consent. Amblyopic patients seen at the Academic Medical Center (Amsterdam, the Netherlands) were asked to participate. Children with a history of amblyopia but a difference in visual acuity between eyes of <2 lines after treatment at the time of testing were assigned to the amblyopic group, which comprised children with mild or moderate amblyopia. Anisometropic amblyopic eyes had a difference in refraction between both eyes of at least 2 D sphere and/or at least a 2 D astigmatic difference. Strabismic amblyopia was defined as a manifest ocular deviation or eccentric fixation, with a visual acuity difference present or recorded in the past. Patients in whom amblyopia was caused by strabismus as well as by

Table 1. Parameters of amblyopic patients and healthy subjects

Parameters	Amblyopic eyes (n = 36)	Fellow eyes (n = 36)	Healthy eyes (n = 30)	*P* value	
Sex (M:F)	21:15	21:15	14:16	0.35[a]	
Age, mean ± SD	7.6 ± 1.7	7.6 ± 1.7	8.3 ± 1.5	0.12[a]	
Visual acuity, logMAR ± SD	0.20 ± 0.13	0.04 ± 0.84	0.09 ± 0.12	<0.01[b]	<0.001[a]
Spherical equivalent	3.1 ± 3.2	2.7 ± 2.2	–0.9 ± 2.5	0.14[b]	<0.001[a]

[a]Amblyopic eyes versus healthy eyes, independent *t* test.
[b]Amblyopic eyes versus fellow eyes.

anisometropia were included in a combination group. Healthy children were recruited during the same period from among children referred for a suspected visual acuity disorder that proved absent on examination. Healthy controls were orthotropic, although patients with short-term phorias were not excluded. All study participants had to be at least 3 years old and cooperative.

All subjects and controls underwent standard orthoptic examination as well as spectral domain optical coherence tomography (SD-OCT; 3D OCT-1000, software version 3.01; Topcon Corporation, Tokyo, Japan), and measurement of axial length with the IOLMaster (Carl Zeiss Meditec AG, Jena, Germany), which measures axial length to within 0.02 mm.[27,28] All participants also underwent additional ophthalmological examination, consisting of inspection of the ocular media and fundus examination to rule out intraocular pathology. The orthoptic examination consisted of testing binocular single vision using the TNO or Titmus fly binocular vision test, determining any ocular deviation by cover testing at near (30 cm) and at distance (2.5 m and/or 5 m) and testing best-corrected visual acuity (logMAR) with Lea symbols or ETDRS chart.

After pupil dilatation, an experienced examiner performed volume scanning of the macula with SD-OCT. A fast-volume scan of the macula with 32 b-scans consisting of 512 a-scans was chosen to overcome motion[16] and blinking artifacts in these young children. Due to incapacity of the built-in OCT software to correct for eccentric fixation using this faster scan protocol, the foveal retinal thickness, pericentral retinal thickness, and peripheral retinal thickness were calculated using a customized program (MATLAB; MathWorks Inc, Natick, MA) after exporting the acquired thickness data from the SD-OCT system.

Statistical analysis was performed using SPSS 16.0 (SPSS Inc, Chicago, IL). An independent *t* test was used to assess differences in mean age and sex between the amblyopic group and controls. Mean visual acuity and spherical equivalent were compared between amblyopic, fellow, and healthy eyes using analysis of variance (ANOVA) followed by a Bonferroni post hoc analysis to correct for multiple comparisons. A P value of <0.01 was considered statistically significant. The axial length and retinal thickness for amblyopic and healthy subjects were tested for normal distribution using a Shapiro-Wilk test. To compare means of the axial length and the thickness parameters (foveal retinal thickness, pericentral retinal thickness, and peripheral retinal thickness) between groups, a parametric and nonparametric (paired and unpaired) *t* test was performed, with a P value of <0.05 considered statistically significant. The axial length and the pericentral retinal thickness of the amblyopic eye versus the fellow eye of the amblyopic group and of the right eye versus the left eye of the control group were fitted with a linear regression model and a correlation coefficient was calculated. To correlate retinal thickness with axial length a correlation coefficient was calculated for the healthy eyes, the fellow eyes, and the amblyopic eyes.

Results

A total of 36 children diagnosed with amblyopia caused by an anisometropia (n = 17), strabismus (n = 11), or a combination of the two (n = 8) were enrolled in this study; 30 healthy children were enrolled as the control group. There was no significant difference in age and sex between groups. There was a significant difference in mean visual acuity and spherical equivalent between the amblyopic and the healthy eyes ($P < 0.01$) but no significant difference in spherical equivalent between the amblyopic and the fellow eye ($P = 0.14$). See Table 1. The axial length for the fellow eye in the amblyopic group and the axial length and retinal thickness for both eyes in the control group are distributed normally (Shapiro-Wilk test, $P > 0.05$). The axial length for the amblyopic eye is not distributed normally ($P = 0.02$).

Axial Length and Retinal Thickness Measurements

We found a statistically significant difference between the axial length of the amblyopic eyes compared to the axial length of healthy subjects (right eye, $P < 0.01$) and a statistically significant difference between the axial length of the fellow eyes and the axial length of healthy subjects (right eye, $P < 0.01$). There was no significant difference in axial length between the amblyopic eyes and their fellow eyes and between the left eye and right eye of healthy subjects ($P = 0.23$ and $P = 0.76$, resp.). See Table 2.

Figure 1 shows the axial length of the amblyopic eye versus the axial length of their fellow eyes (open triangles). The slope of the linear regression is 0.79 ± 0.15. The Spearman correlation coefficient of the linear regression model is 0.77 ($P < 0.01$). The mean axial length of the amblyopic eye is 22.00 mm; of the fellow eye, 22.18 mm. Figure 1 shows the axial length of the subject's right eye versus the axial length of the subject's left eye of the healthy subjects (black dots). The linear regression model gives a slope of 0.99 ± 0.03. The axial length of right eye is highly correlated with the axial length of left eye (Pearson's $R = 0.98$, $P < 0.01$). The mean axial length of the right eye is 23.28 mm; of the left eye, 23.29 mm.

Table 2. Comparison of axial length and retinal thickness values between groups

Parameters	Amblyopic eyes, mean (SD) N = 36	Fellow eyes, mean (SD) N = 36	*P* value[a]	Right healthy eyes, mean (SD) N = 30	Left healthy eyes, mean (SD) N = 30	*P* value[a]	*P* value[b]	*P* value[c]
AL, mm	22.00 (1.14)	22.18 (0.96)	0.23	23.28 (1.38)	23.30 (1.40)	0.76	<0.01	<0.01
Foveal RT, μm	230 (22.6)	231 (21.3)	0.41	231 (17.0)	231 (17.6)	0.89	0.71	0.92
Pericentral RT, μm	300 (14.2)	299 (14.0)	0.96	295 (13.2)	296 (13.2)	0.38	0.19	0.18
Peripheral RT, μm	262 (13.3)	260 (12.6)	0.35	259 (13.4)	258 (12.7)	0.86	0.37	0.48

AL, axial length; *RT*, retinal thickness.
[a]Parametric paired *t* test of, respectively, amblyopic eyes versus fellow eyes and right healthy eyes versus left helathy eyes.
[b]Parametric unpaired *t* test amblyopic eyes versus right healthy eyes.
[c]Parametric unpaired *t* test fellow eyes versus right healthy eyes.

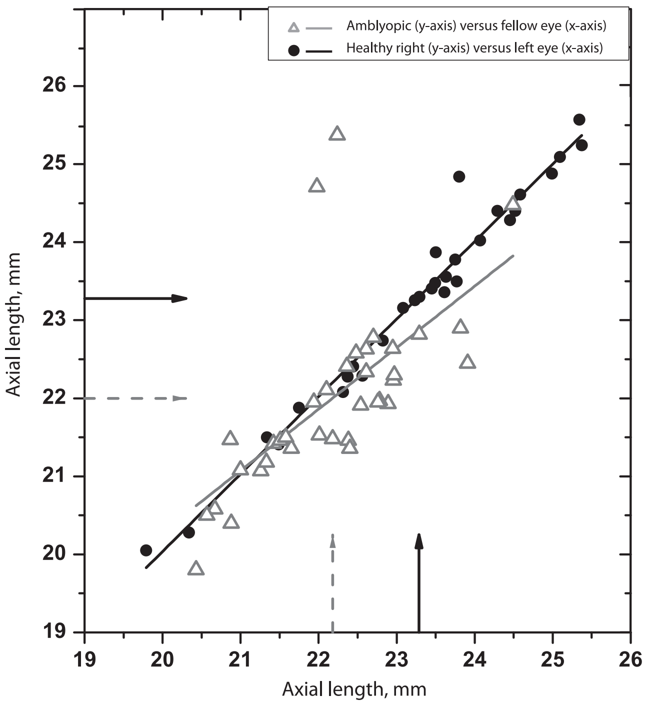

FIG 1. Axial length correlation between right and left eyes of control and amblyopic subjects. The axial length of the amblyopic eye versus the fellow eye is shown with open gray triangles. The slope of the linear fit is 0.79 with a y-axis intercept of 4.5. Black dots show the axial length of the right eyes versus the left eyes of the control subjects. The slope of this linear regression model is 0.99. The mean value of the axial length of the eye (arrows) show that amblyopic eyes are significantly smaller than healthy eyes.

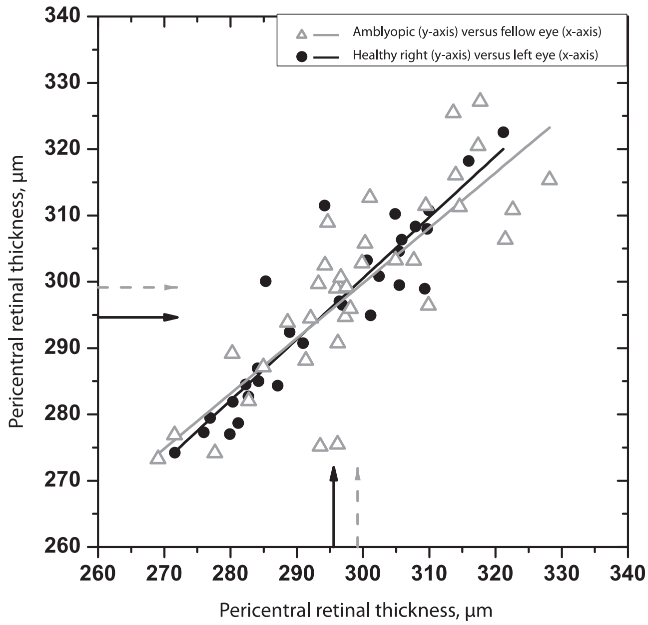

FIG 2. Retinal thickness correlation between right and left eyes of control and amblyopic subjects. The pericentral retinal thickness of the amblyopic eye versus the fellow eye are displayed with open gray triangles. The slope of the linear fit is 0.92. Black dots show the retinal thickness of the right eyes versus the left eyes of the control subjects. The slope of this linear regression model is 0.83. The mean value of the axial length of the eye (arrows) indicate no interocular difference.

The mean pericentral retinal thickness for the amblyopic eye was 300 μm; for the fellow eye, 299 μm. These measurements are slightly thicker than the mean pericentral retinal thicknesss for the normal group but not significantly different ($P = 0.19$). As seen in Figure 2, the data for the amblyopic subjects show a similar distribution to the data for the controls. The statistical analysis shows no difference in retinal thickness between groups (Table 2). Figure 2 shows the pericentral retinal thickness of the subject's right eye versus the left eye for the healthy subjects (displayed as black dots). The slope of the linear fit is 0.92 $\pm$ 0.07 (Pearson's $R = 0.92$, $P < 0.01$). The mean retinal thickness of right eye and left eye are 295 and 296 μm, respectively. The pericentral retinal thickness of the patient's amblyopic eyes are displayed in grey versus the retinal thickness of the fellow eyes. The slope of the linear fit is 0.83 $\pm$ 0.1 (Pearson's $R = 0.82$, $P = 0.01$).

Finally, we investigated the relation between retinal thickness and axial length for healthy, amblyopic, and fellow eyes. Figure 3 shows the retinal thickness versus axial length for healthy subjects (only right eye is used in this analysis) in black. A moderate linear correlation (Pearson's $R = 0.41$, $P = 0.02$) can be observed. The slope of the linear fit describing the relationship between retinal

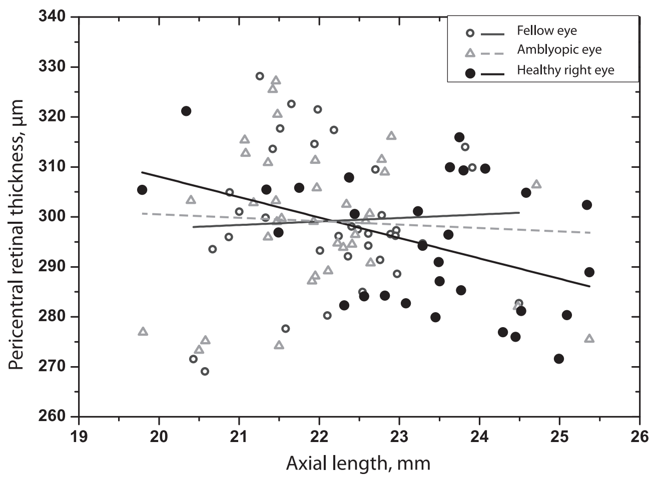

FIG 3. Correlation between axial length and retinal thickness of right control eyes, amblyopic eyes, and fellow eyes. For normal eyes (black closed dots) a correlation was found between thinning of the pericentral retinal thickness with increasing axial length ($R = 0.41$). This correlation could not be found in amblyopic eyes (light gray open triangles; $R = -0.04$) and their fellow eyes (dark gray open circles; $R = 0.05$).

thickness and axial length is -4.09 ± 1.64 [μm/mm]. The negative sign indicates that eyes with a short axial length tend to have a thicker retina. However, this relationship is not found in the amblyopic or in the fellow eyes of amblyopic patients: for amblyopic eyes the Spearman correlation coefficient is -0.04 ($P = 0.82$). For fellow eyes a similar result was found (Pearson's $R = 0.05$, $P = 0.78$).

Discussion

This study found an anomalous relation between axial length and retinal thickness in the eyes of amblyopic children. No significant differences in foveal, pericentral, and peripheral retinal thickness were found between the amblyopic eye and the fellow eye of amblyopic children, although the axial length of the amblyopic eyes and fellow eyes are significantly shorter compared to healthy eyes. In amblyopic children, for the axial length and pericentral retinal thickness separately, a strong linear correlation exists between the amblyopic eye versus the fellow eye, comparable to the correlation between both eyes of healthy subjects. If a strong relation existed between axial length and retinal thickness, as Ueda and colleagues[17] found, and as in the healthy eyes examined in the present study, then Figure 2 would have shown the amblyopic eyes primarily at the extremes of the retinal thickness range, similar to the distribution in Figure 1. Surprisingly, due to an anomalous relation between axial length and retinal thickness in amblyopic children, retinal thickness cannot be predicted from the axial length, contrary what was demonstrated in the healthy eyes (Figure 3).

An anomalous relation between axial length and retinal thickness in amblyopic children has not been described previously in the literature. Moreover, the findings of the present study support previous studies that found no differences in retinal thickness measurements. Altintas and colleauges[1] reported no significant difference in mean macular retinal thickness between the amblyopic and fellow eye in 14 unilateral strabismic amblyopic patients. Kee and colleagues[5] also found no differences in foveal retinal thickness and RNFL thicknesses between normal children and children with amblyopia. However, strabismic amblyopic eyes showed a thicker foveal retinal thickness but thinner RNFL thickness compared to the eyes of anisometropic children. Yoon and colleagues[10] described a thicker RNFL thickness and also no differences in mean macular retinal thickness when comparing amblyopic with fellow eyes in 31 hyperopic anisometropic patients. Dickmann and colleagues[3] found that the foveal retinal thickness and mean macular retinal thickness of strabismic amblyopic eyes are significantly higher than those of anisometropic children. The same study group later reported no difference in retinal structure between healthy children and those with amblyopia.[18] Al-Haddad and colleagues[11] described macular retinal thickness and RNFL thickness in amblyopia and, contrary to our findings, found a significantly increased foveal retinal thickness in 31 anisometropic amblyopic patients (anisometropia was defined as an interocular spherical equivalent of $\geq$1.0 D, aged $\geq$6 years) compared to fellow eyes using SD-OCT. No significant differences were noted between hyperopic and myopic subjects, and anisometropia without amblyopia did not yield significant differences in foveal retinal thickness. Huynh and colleagues[4] described differences in retinal thickness resulting from the Sydney Childhood Eye Study in 53 amblyopic children compared to 3,185 healthy children. After adjusting for age, sex, ethnicity, height, axial length, and cluster sampling, amblyopic eyes proved to have a statistically significant increased foveal retinal thickness and a thinner pericentral retinal thickness. No explanation is offered for this thinner pericentral retinal thickness found in amblyopic eyes. As an explanation for the increase in foveal retinal thickness, the authors of both studies[4,11] mentioned that the physiological postnatal ganglion cell reduction could be inhibited in amblyopia, as hypothesized by Yen and colleagues.[9] A recent paper on maturation of the human fovea demonstrated that a postnatal reduction in ganglion cell layer plus inner plexiform layer occurs from 110 μm to 80 μm, partly explained by a shift of ganglion cell bodies to the periphery.[19] We could not demonstrate differences in foveal retinal thickness in the present study. Our finding of an anomalous relation between axial length and pericentral retinal thickness in both the amblyopic and the fellow eyes of amblyopic children could be due to a disturbed development of the retina in these eyes, although a hypothetical arrest of the normal postnatal ganglion cell reduction is expected to lead to an abnormally thick retinal thickness, especially the pericentral retinal thickness.

Our study has several limitations. The small number of patients in this study did not permit subgroup analysis based on amblyopia type. The study included mostly patients with a relatively mild amblyopia, which may have affected our study results; due to the effectiveness of amblyopia screening system in the Netherlands and the generally prompt treatment of amblyopia, we did not encounter deep amblyopic patients. We felt justified in including patients with a history of amblyopia because any retinal change that might have developed during the critical period in the amblyopic process would still be detectable later on, even if they might not be categorized as amblyopic based on visual acuity at the time of testing. In 2010 Miki and colleagues[20] found no significant change in retinal nerve fiber layer thickness between the affected and fellow eyes in patients with persistent amblyopia and in those who had been successfully treated. There was also no significant difference between the amblyopic eyes of patients with persistent amblyopia and the previous amblyopic eyes of patients with recovered amblyopia. The recent SD-OCT study in an Italian population also did not encounter deep amblyopic patients, which supports the statement that deep amblyopia is rare nowadays.[18] Finally, this study focuses on pericentral retinal thickness measurements and did not include RNFL thickness measurements.

In conclusion, although a moderate correlation between axial length and pericentral retinal thickness was found in healthy eyes, this correlation was anomalous in amblyopic or in fellow eyes.

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