Longitudinal Development of Refractive Error in Children With Accommodative Esotropia: Onset, Amblyopia, and Anisometropia

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Purpose. We investigated longitudinal changes of refractive error in children with accommodative esotropia (ET) throughout the first 12 years of life, its dependence on age at onset of ET, and whether amblyopia or anisometropia are associated with defective emmetropization.

Methods. Longitudinal refractive errors in children with accommodative ET were analyzed retrospectively. Eligibility criteria included: initial hyperopia $\geq$+4.00 diopters (D), initial cycloplegic refraction before 4 years, at least 3 visits, and at least one visit between 7 and 12 years. Children were classified as having infantile ($N = 30$; onset $\leq$12 months) or late-onset ($N = 78$; onset at 18–48 months) accommodative ET. Cycloplegic refractions culled from medical records were converted into spherical equivalent (SEQ).

Results. Although the initial visit right eye SEQ was similar for the infantile and late-onset groups (+5.86 $\pm$ 1.28 and +5.67 $\pm$ 1.26 D, respectively), there were different developmental changes in refractive error. Neither group had a significant decrease in hyperopia before age 7 years, but after 7 years, the infantile group experienced a myopic shift of −0.43 D/y. The late-onset group did not experience a myopic shift at 7 to 12 years. Among amblyopic children, a slower myopic shift was observed for the amblyopic eye. Among anisometropic children, the more hyperopic eye experienced more myopic shift than the less hyperopic eye.

Conclusions. Children with infantile accommodative ET experienced prolonged hyperopia followed by a myopic shift after 7 years of age, consistent with dissociation between infantile emmetropization and school age myopic shift. In contrast, children with late-onset accommodative ET had little myopic shift before or after 7 years.

Keywords: refractive error, development, ocular, accommodative esotropia, amblyopia

Abnormal emmetropization has been reported in children with accommodative esotropia (ET), including persistent hyperopia.[1–5] These reports focused on emmetropization during infancy to 3 to 6 years of age, but did not track refractive changes into the school-age years when a myopic shift may commence.[6] According to the age of onset, accommodative ET often is classified into infantile accommodative ET for those children who have accommodative ET during infancy (before 1 year of age), and late-onset accommodative ET. There is evidence that age of onset of accommodative ET may influence its clinical course.[7] Yet, most previous studies of refractive error in accommodative ET combined data from children with infantile and late-onset.

Two recent studies reported a continuous decrease in hyperopia in children with accommodative ET.[8,9] In these studies, refractive error data were reported as years after spectacle prescription. Because age at initial spectacle prescription varied from 6 months to 6 years, refractive error data from children with widely disparate ages were averaged.[8,9] Therefore, the observed continuous decrease in hyperopia over time may have been a spurious result of averaging refractive errors and blurring the influence of distinct periods of eye component growth.[10]

Children with accommodative ET experience decorrelation of binocular vision, and approximately one-third of them suffer amblyopia.[4,11] Amblyopia has been hypothesized as the most important factor that disrupts the regulation of ocular growth during emmetropization.[8] Asymmetric emmetropization and the onset of anisometropia secondary to ET also have been reported.[1,3] Anisometropia, in turn, is associated with increased risk for amblyopia in children with accommodative ET.[12,13] Because previous studies often reported results based on one eye, longitudinal anisometropia data in children with accommodative ET are limited. None are available for children older than 6 years of age,[1,3] so the relationship of anisometropia

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to emmetropization and amblyopia remains unclear in populations with accommodative ET.

We investigated longitudinal changes of refractive error and anisometropia in children with accommodative ET throughout the first 12 years of life, and whether age at onset (infantile versus late-onset), amblyopia, or anisometropia is associated with defective emmetropization.

Methods

This research protocol observed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center and Indiana University, and conformed to the requirements of the United States Health Insurance Portability and Privacy Act.

Participants

Patients were referred to the Retina Foundation of the Southwest by 16 Dallas-Fort Worth pediatric ophthalmologists. Patients from Indiana University were diagnosed and treated by pediatric ophthalmologists in the Riley Hospital for Children. Cycloplegic retinoscopy (1% cyclopentolate) was performed by the referring pediatric ophthalmologists as part of routine medical care.

Eligibility criteria were: (1) Hyperopia in spherical equivalent (SEQ) at initial visit in the right eye ranged from +4.00 to +10.00 diopters (D). The lower cutoff was chosen to define a homogeneous group of children with accommodative ET who all were prescribed spectacle correction on their initial visit and to exclude those children who received this diagnosis solely on the basis of a high AC/A ratio. Either of these factors may be associated with a distinct pattern of refractive development. (2) Initial cycloplegic refraction occurred before 4 years of age. (3) All were followed up for a minimum of 3 years with at least one additional cycloplegic refraction between ages 7 and 12 years. Each patient had at least three visits on record. Such criteria can ensure a medical record window with enough longitudinal range to demonstrate a developing trend for each patient. None of the patients had known developmental delays, or concurrent ophthalmic or systemic diseases. None of the children was born preterm (≤36 weeks).

Patient Care

Patient care was at the discretion of the referring ophthalmologists, within the guidelines of the American Academy of Ophthalmology Preferred Practice Pattern: Esotropia and Exotropia.[14]

Optical Correction and Amblyopia Treatment. Briefly, initial management included full correction of hyperopic refractive error with spectacles and amblyopia treatment (patching and/or atropine penalization) if indicated.

Surgery. Only after refractive and amblyopia treatment, if needed, was surgery performed to correct ocular alignment.

Onset of Accommodative ET

Patients were classified into two groups: those with infantile ($N = 30$; onset ≤12 months) and late-onset ($N = 78$; 18 < onset ≤ 48 months) accommodative ET. For the infantile-onset group, only children who had accommodative ET diagnosed by a pediatric ophthalmologist by 12 months of age were eligible. For the late-onset group, only children whose parents and primary care doctors first noticed ET after 18 months of age were eligible after accommodative ET was diagnosed by a pediatric ophthalmologist. While this does not absolutely exclude patients who had a delayed diagnosis in the late-onset group, the infantile-onset group was composed solely of children with early onset.

Visual Acuity

Visual acuity was measured at the last visit using a logMAR letter chart. Unilateral amblyopia was defined as an interocular visual acuity difference in best-corrected visual acuity of ≥0.2 logMAR (2 or more lines) with the fellow eye's visual acuity of ≤0.2 logMAR (20/30); bilateral amblyopia was defined as visual acuity in both eyes of ≥0.3 logMAR (20/40).

Data Analysis and Statistics

Cycloplegic refraction data were recorded originally in conventional form as sphere (S), plus cylinder (C), and axis (α). Using a custom spreadsheet (Excel; Microsoft, Inc., Redmond, WA, USA), they were converted into their power vector components: M (SEQ), J_0 (positive J_0 indicates with-the-rule [WTR] astigmatism, negative J_0 indicates against-the-rule [ATR] astigmatism), and J_{45} (oblique astigmatism; positive J_{45} indicates 135° astigmatism while negative J_{45} indicates 45° astigmatism).[15] To calculate anisometropia, the absolute value of the SEQ interocular difference was calculated. In this study, significant anisometropia is defined as anisometropia ≥1 D. To delineate refractive development, SEQ, SEQ at the initial visit, and SEQ at the final visit were analyzed. Myopic shift was defined as the SEQ difference between the initial and final visits ($SEQ_{initial} - SEQ_{final}$). Therefore, a positive myopic shift means decreased hyperopia. To evaluate longitudinal changes in refractive error, we analyzed our data according to age subgroups: 3, 6, 9, and 12 months, and 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 years.

Descriptive statistics are presented as mean ± SD. To compare results from the initial and last visits, a paired *t*-test was applied. To estimate the rate of individual refractive error change (SEQ, J_0, and J_{45}) with age, we used a mixed effect model, which uses longitudinal information from each individual. The onset was treated as a fixed effect and individual as a random effect. The model provides comparisons within each group as well as comparisons between infantile and late-onset groups.

Longitudinal refraction data from all individuals in each group initially were fitted with a linear and bilinear model, using the iterative weighted least square (IWLS) method. The transition point for the bilinear model was set at 7 years based on substantial data demonstrating that a myopic shift in refractive error occurs between ages 7 and 12 years for children with or without ET.[6,16,17] Thus, using the IWLS method, the bilinear model was used to describe two linear relations between refractive error and age, one for ages less than the transition point (<7 years) and one for ages beyond the transition point (≥7 years). The likelihood ratio was used to determine whether the linear or bilinear model provided a better fit for the cycloplegic refraction data, with a critical rejection value of 3.84 for the χ^2 distribution with 1° of freedom at 5% type I error. Similar analyses were conducted for astigmatism (J_0 and J_{45}) and anisometropia.

Results

Data from 108 patients (53 from the Indianapolis site and 55 from the Dallas site) were analyzed. Results from the right eye were highly correlated with those from the left eye. The correlation between right and left eye initial SEQ was 0.82 ($N = 108$, $t = 14.75$, $P < 0.0001$), and for final SEQ it was 0.86 ($N = 108$, $t = 17.3$, $P < 0.0001$). Therefore, with the exception of

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TABLE 1. Demographic and Clinical Characteristics of the Infantile and Late-Onset Accommodative ET Cohorts (mean ± SD, 95% CI)

Group	N	Sex, F/M	Age at Initial Visit, y	Age at Last Visit, y	Initial Visit SEQ, D	Amblyopia at the Initial Visit	Amblyopia at the Last Visit	Anisometropia at the Initial Visit (≥1D)	Anisometropia at the Last Visit (≥1D)
Infantile	30	14/16	0.8 ± 0.48 (0.63–0.97)	10.3 ± 1.65 (9.71–10.89)	5.86 ± 1.28 (5.4–6.32)	7	11	1	6
Late-onset	78	39/39	3.1 ± 0.79 (2.92–3.28)	9.5 ± 1.41 (9.19–9.81)	5.67 ± 1.26 (5.39–5.95)	37	45	23	29
Total	108	53/55	2.5 ± 1.23 (2.27–2.73)	9.8 ± 1.51 (9.52–10.08)	5.72 ± 1.26 (5.48–5.96)	44	56	24	35

anisometropia and amblyopia, refractive error data are reported for the right eye only.

Table 1 summarizes demographic and clinical findings for the cohort studied. Table 2 shows the number of patients at each age subgroup. Our cohort was 80% Caucasian and 20% Asian, African-American or Black, More Than One Race, or Other. The infantile group had an initial visit at 0.8 ± 0.5 years of age and was followed for 9.5 ± 1.8 years, with 7.4 ± 2.1 visits; the late-onset group had an initial visit at 3.1 ± 0.8 years of age and was followed for 6.5 ± 1.6 years, with 4.8 ± 1.4 refraction visits.

Refractive Error on the Initial Visit

At the initial visit, children with accommodative ET in this cohort had a mean SEQ of 5.75 ± 1.26 D; there was no significant difference in SEQ between the infantile and late-onset groups (Table 1). In the infantile group, 15 patients (50%) had high hyperopia, with an SEQ ≥ +6.00 D, while 34 (44%) in the late-onset group had high hyperopia. At the initial visit, 16/30 (53%) in the infantile group and 25/78 (32%) in the late-onset group had significant astigmatism (J_0 or $J_{45} \geq 0.375$ D, which corresponds to C ≥ 0.75 D). Only 1/30 (3%) in the infantile group had anisometropia on the initial visit compared to 26/78 (33%) in the late-onset group.

Refractive Error Changes With Age

Individual data for children in the infantile and late-onset groups are shown in Figure 1. According to the SEQ difference between the initial and the final visits, patients were classified into three trend subgroups: increasing ($SEQ_{initial} - SEQ_{final} \leq -1.00$ D), no change (-1.00 D $< SEQ_{initial} - SEQ_{final} < 1.00$ D), and decreasing ($SEQ_{initial} - SEQ_{final} \geq 1.00$ D) in both groups.

Generally, children in the infantile and late-onset groups retained their hyperopia through age 7. At 7 years, mean SEQ was 5.5 ± 1.48 D in the infantile group ($N = 19$) and 6.0 ± 1.42 D in the late-onset group ($N = 47$). Only 27% in the infantile group had a decrease in hyperopia of ≥ 1.00 D before 7 years, but by the time of the final visit 16/30 (53%) had a myopic shift of ≥1.00 D. In contrast, only 13.5% in the late-onset group had a decrease in hyperopia of ≥1.00 D by 7 years, and this percentage did not change significantly by the time of the final visit (19%).

Figure 2 shows the SEQ from initial and final visits for each individual in both groups. Overall, SEQ at the final visit was significantly correlated with SEQ at the initial visit ($r = 0.44$ for the infantile group and $r = 0.46$ for the late-onset group; $P < 0.05$ for both groups). Myopic shift was defined as the SEQ difference between the initial visit and the final visit ($SEQ_{initial} - SEQ_{final}$). The proportion of children who experienced a myopic shift of ≥1.00 D was significantly higher in the infantile group compared to the late-onset group ($Z = 3.5$, $P < 0.001$). On average, myopic shift in the infantile group was 1.45 ± 2.16 D, significantly more than the mean myopic shift of –0.02 ± 1.48 D observed in the late-onset group (independent t-test, $t_{106} = 4.06$, $P = 0.001$; Table 3). There was no significant correlation between baseline SEQ and myopic shift for either the infantile or late-onset group.

Refractive Development Model

Figure 3 shows the average SEQ based on right eye longitudinal cycloplegic refraction data across age categories for the infantile and late-onset groups.

For the infantile group, the bilinear model provided a significantly superior fit to the SEQ data compared to the linear

Table 2. The Number of Patients With Accommodative ET on Each Age Subgroup

	Age, y															
	0.25	**0.5**	**0.75**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Infantile	6	9	8	11	15	20	18	23	17	13	19	16	16	10	11	9
Late-onset						19	51	61	48	22	50	55	37	26	16	10

model ($P < 0.05$ for the likelihood ratio test; χ^2 distribution with 1° of freedom at 5% type I error). Using the bilinear model, SEQ for the infantile group was fit by (Fig. 3):

$$SEQ_{\text{infantile}}(\text{Age}) = 5.95 - 0.04 \times \text{Age} \qquad \text{for Age} \leq 7 \text{ years;}$$

$$SEQ_{\text{infantile}}(\text{Age}) = 8.66 - 0.43 \times \text{Age} \qquad \text{for Age} > 7 \text{ years.}$$

The initial SEQ estimated by the model was +5.95 D. Before 7 years of age, the rate of SEQ change was not significantly different from zero (–0.04 D/y; $t_{106} = -0.86$, $P = 0.39$). After 7 years of age, SEQ decreased significantly at –0.43 D/y ($t_{97} = -6.57$, $P < 0.001$).

Spherical equivalent for the late-onset group was best fit by a linear model (Fig. 3):

$$SEQ_{\text{late-onset}}(\text{Age}) = 5.94 - 0.012 \times \text{Age.}$$

The initial SEQ for the late-onset group was estimated as +5.94 D by the model. The rate of change in refractive error (slope) of –0.012 D/y was not significantly different from zero ($t_{77} = -0.47$, $P = 0.63$), indicating that SEQ in the late-onset group remains hyperopic with little change.

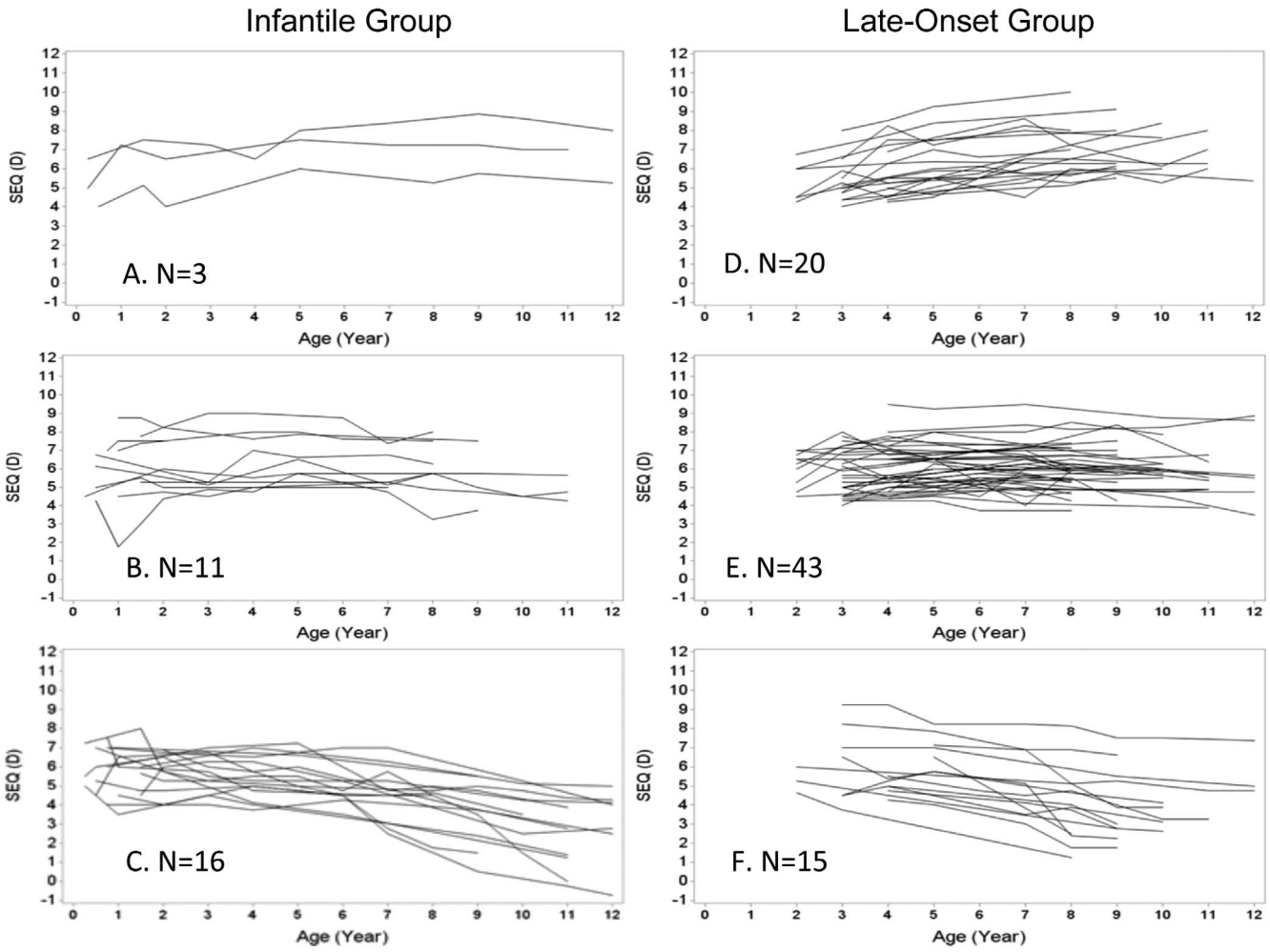

Figure 1. Spherical equivalent spline plots for individual patients; *lines* connect raw data points. According to the SEQ difference between the initial and final visits, patients were classified into three groups: increasing (**A**, **D**), no change (**B**, **E**), or decreasing (**C**, **F**) in the infantile and late-onset groups. The *left column* shows the infantile group (**A–C**); the *right column* shows the late-onset group (**D–F**). Note that three of the infantile onset patients were initially diagnosed and treated by pediatric ophthalmologists who were not part of our study group; therefore, although they met the eligibility criteria of diagnosis by 12 months of age, the first refraction data collected at our study site was only available after they changed their eye care provider at 14 to 18 months.

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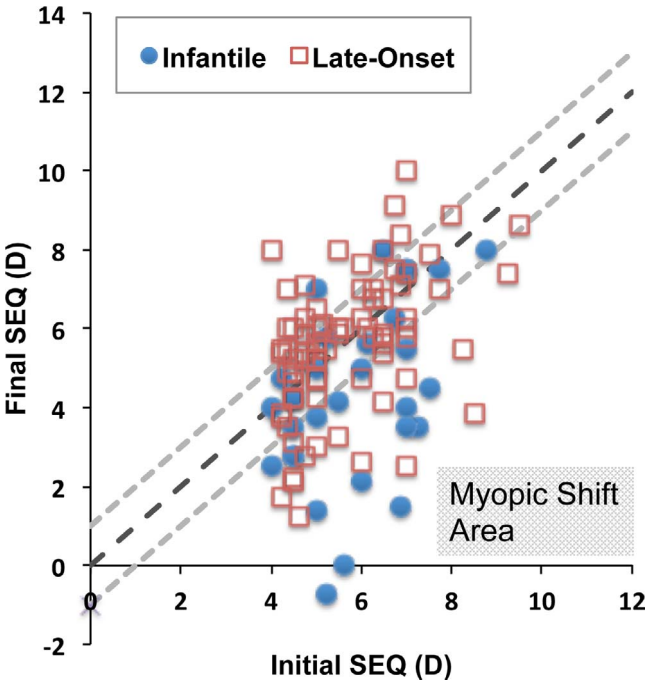

FIGURE 2. Spherical equivalent at the final visit versus SEQ at the initial visit for the individuals in both groups. The *black dashed line* indicates the equal line. When a data point is below the equal line, it indicates SEQ has myopic shift. The infantile group is represented by *solid blue circles* and the late-onset group by *empty red squares*.

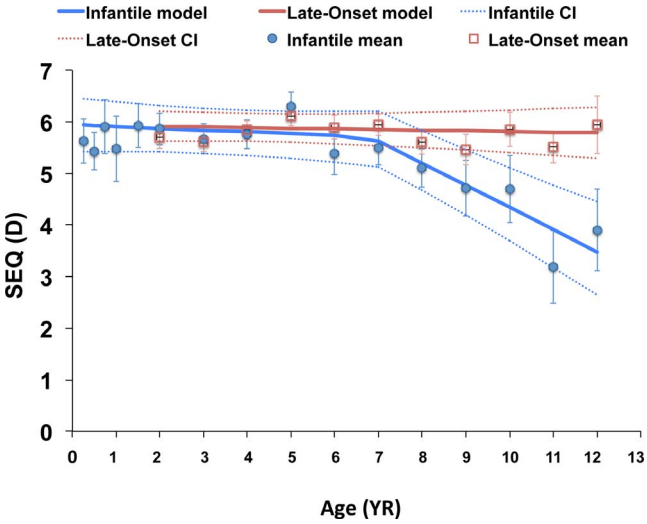

FIGURE 3. The best fit models for SEQ with the 95% confidence interval (CI) based on right eye longitudinal cycloplegic refraction data. The corresponding *blue* and *red bold lines* show the best fit models for the infantile group and for the late-onset group, respectively. The *fine dashed lines* indicate the CI for the infantile group in *blue* and for the late-onset group in *red*. Means and standard errors (SE) of age subgroups from both groups are overlapped with the models. The infantile group is represented by *blue circles* and the late-onset group by *squares* in *red*.

Astigmatism

In the infantile group, 16 (53%) children had significant astigmatism at the initial visit. Of the 16 children, 11 had significant WTR astigmatism ($J_0 \geq 0.375$ D), 1 child had ATR astigmatism ($J_0 \leq -0.375$ D), and 5 children had oblique astigmatism ($J_{45} \geq 0.375$D); note, 1 child had J_0 and J_{45}. At the final visit, 10 of these 16 children remained astigmatic. In addition, 9 children in the infantile group suffered astigmatism during follow-up, yielding a total of 19 (63%) children in the infantile group with significant astigmatism at the final visit.

In the late-onset group, of the 25 (32%) children who had significant astigmatism at the initial visit (21 had WTR, 2 had ATR, and 2 had oblique astigmatism; note, 1 child had J_0 and J_{45}), 22 remained astigmatic at the final visit. In addition, 22 children in the late-onset group had astigmatism during follow-up, for a total of 44 (56%) children in the late-onset group with significant astigmatism at the final visit.

Combining the infantile and late-onset groups, cylinder magnitude at the final visit was significantly correlated with cylinder magnitude at the initial visit ($N = 108$, $r = 0.35$, $P < 0.001$).

Figure 4 shows the average J_0 across age. Both groups demonstrated an increasing trend toward WTR astigmatism.

J_0 was fit by a linear model (Fig. 4) for the infantile group:

$$J_{0_{\text{infantile}}}(\text{Age}) = 0.24 + 0.032 \times \text{Age}$$

and for the late-onset group:

$$J_{0_{\text{late-onset}}}(\text{Age}) = 0.14 + 0.028 \times \text{Age}.$$

The baseline of J_0 astigmatic error (0.24 D) significantly differed from zero ($t_{106} = 3.58$, $P < 0.001$) and baselines were not significantly different for the two groups ($t_{402} = -1.16$, $P = 0.25$). The rate of J_0 astigmatic error (0.032 D/y) in the infantile group significantly increased ($t_{106} = 2.50$, $P = 0.01$). The rates of increase in mean J_0 astigmatic error were not significantly different for the two groups ($t_{402} = -0.27$, $P = 0.79$), which indicates the rate of J_0 in both groups increase similarly.

The average J_{45} error was negligible and there was no significant change in J_{45} with age.

Anisometropia

The mean anisometropia at the initial and final visits is shown in Table 3. In the infantile group, the prevalence of significant anisometropia increased from 3% ($N = 1$) at the initial visit to

TABLE 3. Mean Refractive Errors (±SD) at the Initial and Final Visit

Group	N	Initial Visit SEQ, D	Final Visit SEQ, D	Myopic Shift, D	Initial Visit J0, D	Final Visit J0, D	Initial Visit Anisometropia, D	Final Visit Anisometropia, D
Infantile	30	5.86 ± 1.28	4.41 ± 2.31* †	1.45 ± 2.16†	0.31 ± 0.47	0.54 ± 0.57*	0.23 ± 0.28†	0.64 ± 0.83*
Late-onset	78	5.67 ± 1.26	5.69 ± 1.73	−0.02 ± 1.48	0.21 ± 0.37	0.39 ± 0.57	0.73 ± 0.97	0.83 ± 0.73
Total	108	5.72 ± 1.26	5.34 ± 1.99	0.39 ± 1.81	0.24 ± 0.40	0.43 ± 0.57	0.59 ± 0.86	0.77 ± 0.76

* Initial visit versus final visit ($P < 0.05$).
† Infantile group versus late-onset group ($P < 0.05$).

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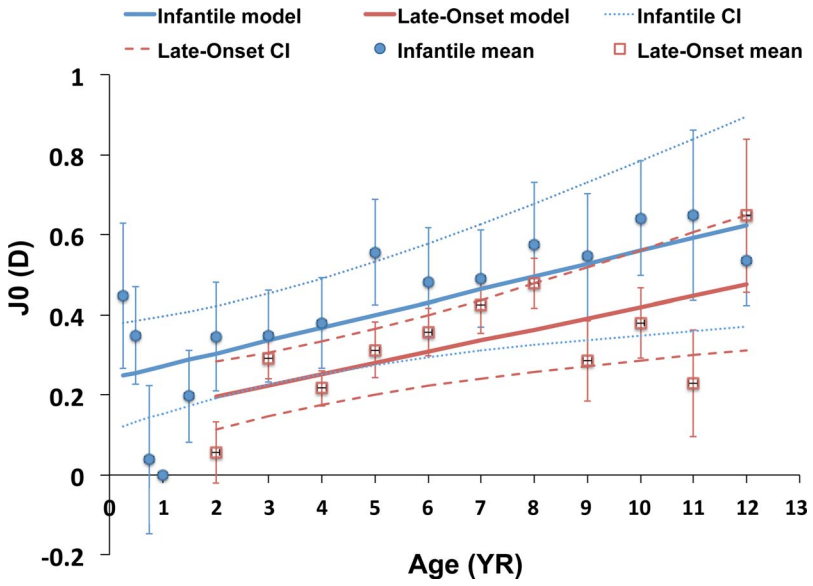

FIGURE 4. The best fit models for J_0 with the 95% CI based on right eye data. The corresponding *blue* and *red bold lines* show the best fit models for the infantile group and for the late-onset group, respectively. The *fine dashed lines* indicate the CI for the infantile group in *blue* and for the late-onset group in *red*. In addition, means and SEs from age subgroups are plotted.

20% ($N = 6$) at the final visit. In the late-onset group, the prevalence of significant anisometropia changed little during follow-up, 29% ($N = 23$) at the initial visit and 37% ($N = 29$) at the last visit. Interestingly, within the infantile group, anisometropia at the initial visit was not correlated significantly with anisometropia at the final visit ($r = 0.19$, $P = 0.3$). Within the late-onset group, anisometropia at the final visit was significantly correlated with anisometropia at the initial visit ($r = 0.67$, $P < 0.001$); at last visit, 17 of 23 patients with initial significant anisometropia had maintained or increased anisometropia. In other words, children who had large amounts of anisometropia tended to have persistent anisometropia in the late-onset group.

Anisometropia was fit by a linear model (Fig. 5) for the infantile group:

$$Anisometropia_{\text{infantile}}(\text{Age}) = 0.27 + 0.04 \times \text{Age}$$

and for the late-onset group:

$$Anisometropia_{\text{late-onset}}(\text{Age}) = 0.65 + 0.01 \times \text{Age}.$$

In the infantile group, the magnitude of anisometropia significantly increased with age ($t_{106} = 4.17$, $P < 0.001$). The initial anisometropia (0.65 D) in the late-onset group was significantly higher than that in the infantile group ($t_{378} = 2.97$, $P = 0.003$), and the rate of change in anisometropia (0.01 D/y)

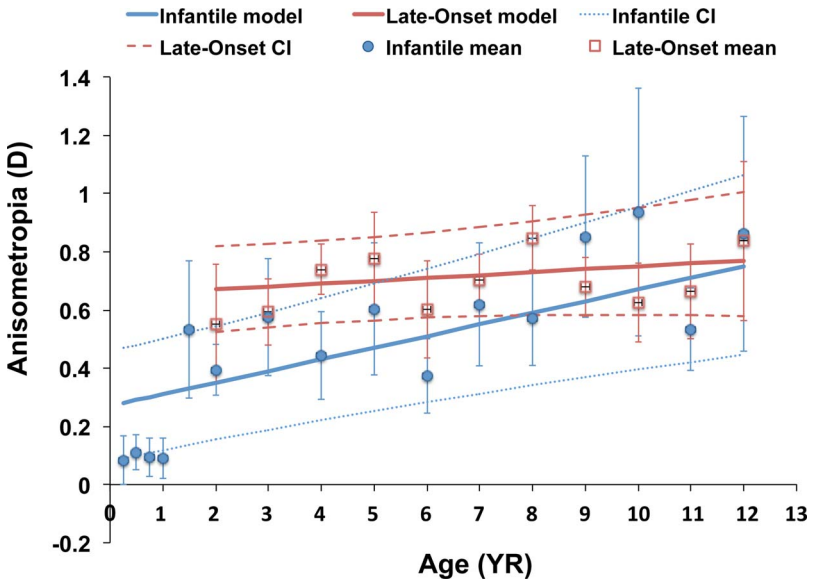

FIGURE 5. The best fit models for anisometropia with the 95% CI. The corresponding *blue* and *red bold lines* show the best fit models for the infantile group and for the late-onset group, respectively. The *fine dashed lines* indicate the CI for the infantile group in *blue* and for the late-onset group in *red*. Means and SEs of age subgroups from both groups are overlapped within the models.

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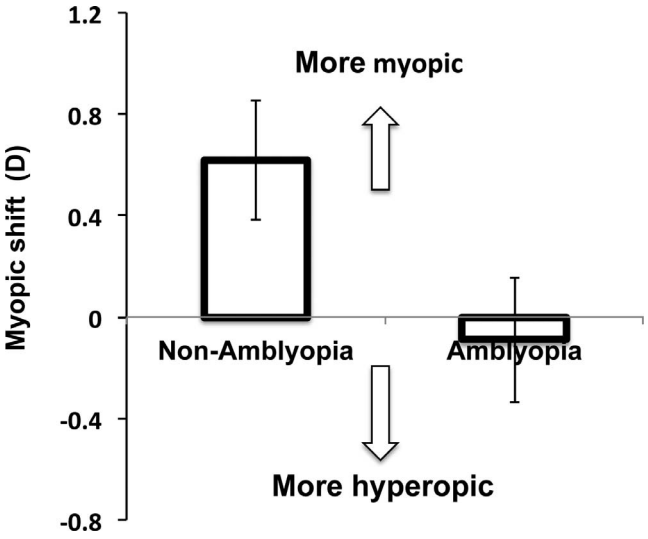

FIGURE 6. According to initial amblyopia, mean and SEs of myopic shift for children with initial amblyopia and those without initial amblyopia.

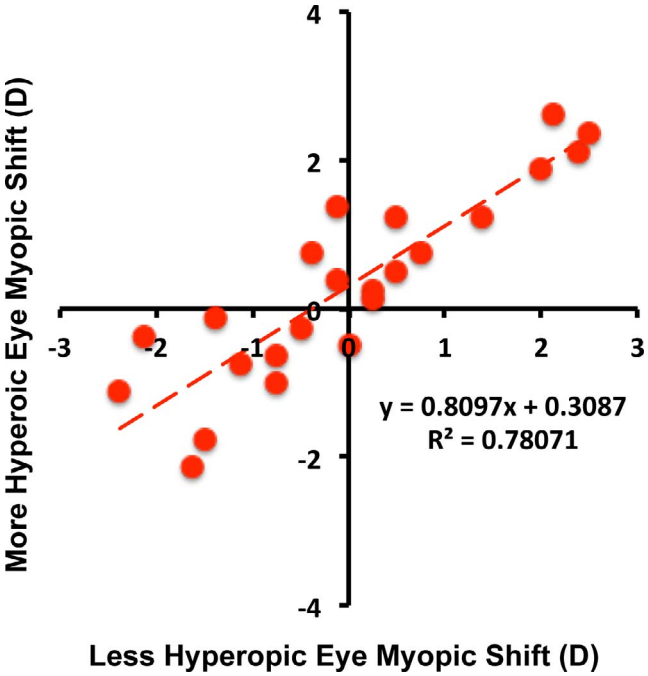

FIGURE 7. According to relative hyperopic magnitude, myopic shift for patients with significant anisometropia ($N = 23$) in the late-onset group.

was significantly slower than in the infantile group (0.04 D/y; $t_{378} = -2.04$, $P = 0.04$).

Myopic Shift and Amblyopia

At the initial visit, 2 of 108 children had bilateral and 42 of 108 (39%) had unilateral (20 on the right eye and 20 on the left eye) amblyopia, and the remaining 64 children were nonamblyopic. Figure 6 shows that the eyes with initial amblyopia had significantly less myopic shift ($N = 44$, –0.09 ± 1.64 D) than eyes without initial amblyopia ($N = 64$, 0.62 ± 1.89 D; $t_{106} = 2.00$, $P = 0$ .04). Note that a positive number of myopic shift indicates more myopic direction, while the negative number indicates more hyperopic direction.

At the final visit, the range of visual acuity was 20/20 to 20/400; 4 of 108 children had bilateral and 52 of 108 (48%) had unilateral (23 on the right and 29 on the left eye) amblyopia, and the remaining 52 children were nonamblyopic.

To compare longitudinal data, the amblyopic and nonamblyopic eyes in the 42 patients, SEQ was fit by a linear model for the unilateral amblyopic eye:

$$SEQ_{\text{amblyopic}}(\text{Age}) = 6.22 + 0.007 \times \text{Age}$$

and for the nonamblyopic eye:

$$SEQ_{\text{nonamblyopic}}(\text{Age}) = 5.72 - 0.026 \times \text{Age}.$$

The intercept or baseline SEQ is significantly lower in the nonamblyopic eye compared to the amblyopic eye (approximately 0.5 D, $t_{345} = 3.24$, $P = 0.0013$). Both slopes were not significantly different from zero.

Myopic Shift and Anisometropia

Because there are few children with significant anisometropia at the initial visit in the infantile group, we only analyzed the impact of initial anisometropia on myopic shift in the late-onset group ($N = 23$). Figure 7 shows that myopic shift significantly differs for the "less hyperopic eye" and the "more hyperopic eye" (paired t-test, $t = 2.3$, $P = 0.03$). The best fit equation is $Y = 0.81 \times x + 0.31$ ($r = 0.88$; $P < 0.0001$). Children with initial significant anisometropia have less myopic shift in the "less hyperopic eye" (–0.01 ± 1.40 D), and more myopic shift in the "more hyperopic eye" (0.30 ± 1.28 D).

Effect of Missing Data

Not all of the children provided data in every age group, and not every child was followed up to age 12 years. For our data set, it is reasonable to assume data were missed at random. This is why we used the mixed-effect model, which is one of the preferred methods when data are missing at random. However, we noted that there were less follow-up data after 9 years. To evaluate the effect that missing data may have had on our model, we repeated the analysis using only the data up to 9 years old. Using the bilinear model, SEQ for the infantile group was fit by:

$$SEQ_{\text{infantile}}(\text{Age}) = 6.00 - 0.05 \times \text{Age} \qquad \text{for Age} \le 7 \text{ years};$$

$$SEQ_{\text{infantile}}(\text{Age}) = 8.46 - 0.40 \times \text{Age} \qquad \text{for Age} > 7 \text{ years}.$$

The initial SEQ estimated by the model was +6.00 D. Before 7 years of age, the rate of SEQ change was not significantly different from zero (–0.05 D/y; $t_{105} = -1.09$, $P = 0.28$). After 7 years of age, SEQ decreased significantly at –0.40 D/y ($t_{83} = -3.30$, $P = 0.001$).

Spherical equivalent for the late-onset group was best fit by a linear model:

$$SEQ_{\text{late-onset}}(\text{Age}) = 5.81 + 0.01 \times \text{Age}.$$

The initial SEQ for the late-onset group was estimated as +5.81 D by the model. The rate of change in refractive error (slope) of 0.01 D/y was not significantly different from zero ($t_{76} = 0.49$, $P = 0.63$), indicating that SEQ in the late-onset group remains hyperopic with little change. If we compare the 9-year-old model to the 12-year-old model side-by-side, results and conclusion are very similar. The slope of the late-onset group became +0.01 D/y, instead of –0.01 D/y in 12-year-old model.

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Neither slope is significantly different from zero. Thus, we concluded that missing data after 9 years of age had little effect on our modeling.

Discussion

Children with accommodative ET experienced little change in SEQ during the first 7 years of life. Between 7 and 12 years of age, those with infantile accommodative ET (onset of strabismus during the first year of life) experience a significant myopic shift of −0.43 D/y. In comparison, there was no significant decrease in hyperopia in the late-onset accommodative ET group between 7 and 12 years of age. The prevalence and magnitude of astigmatism increased with age. The prevalence of anisometropia among children with accommodative ET (20%–40%) was approximately 10-fold higher than the prevalence in population-based studies (1.6%–4.3%).[18,19] Further, amblyopia and anisometropia were associated with deficient emmetropization in children with accommodative ET.

Note that in this study, we only evaluated those whose initial refractive error ranged from +4.00 to +10.00 D. We selected patients with such criteria mainly for two reasons: (1) There lacks a consensus among practitioners and researchers alike for the appropriate threshold at which to prescribe correction; however, at +4.00 D all were treated with spectacles at their initial visit to a pediatric ophthalmologist. (2) This criterion served to exclude children who received a diagnosis of accommodative ET solely on the basis of high AC/A ratio to allow us to evaluate a more homogeneous cohort of children with accommodative ET associated with moderate to high hyperopia. The higher amount of hyperopia present in our cohort at the initial visit may contribute to the slight differences between the myopic shift observed in this study and in previous studies.[8,9,20] Our cohort, which was 80% Caucasian, showed a similar distribution to that observed in US children with higher magnitude hyperopia.[9,11] Nonetheless, patients who fit these criteria are representative of patients who seek clinical care.

Refractive Error Development Trends and Models

There are various descriptions of development trends for refractive error in children with accommodative ET. We observed three patterns (increase, decrease, no change) in individuals with accommodative ET, which is similar as literature reported.[20,21] Berk et al.[20] reported that the direction of change (increase, decrease, no change) in 59 patients with 3 years of follow-up was 17.8%, 56%, and 26.3%.[20] Our study defined "no change" as "no change over ±1 D," and our data for all patients were 21.3%, 28.7%, and 50%. Mulvihill et al.[22] described that spherical equivalent in 103 patients in their cohort barely changed over at least 4.5 years of follow-up. Raab et al.[21] also reported direction of change (increase, decrease, no-change). Interestingly, they reported that refractive error increased with an annual change of 0.19 ± 0.36 D before 7 years, then between ages 7 and 13 years, and decreased −0.18 ± 0.25 D per year.[21] This report provided one rationale for our choice of 7 years as the turning point for fitting the model of refractive development. In addition, a large volume of literature exists about myopia development that supports age 7 years as a critical turning point for refractive development.[23,24]

Most studies in the literature tracked changes in refractive error according to "time after spectacles prescribed."[8,9] These studies also included children with ≤+3.00 D hyperopia and there is no consensus on whether to prescribe glasses immediately. Thus, refractive errors likely were averaged over children who varied widely in age in many of the earlier studies. In the present study, we analyzed refractive error according to years of age and this approach may have enabled us to appreciate the myopic shift that begins after 7 years of age. Lambert et al.[9] suggested that lower magnitude hyperopia is associated with fast myopic shift. Our study excluded children with hyperopia ≤+4.00 D, and we found that myopic shift is associated with onset age.

Why does the onset matter? Possibly, better vision due to early spectacle correction in the infantile onset group is associated with emmetropizing ocular growth. To understand the mechanism of different trends in children with accommodative ET, we currently are evaluating ocular shape (relative peripheral hyperopia) and accommodative lag as signals that may guide different patterns of refractive development in the infantile accommodative ET versus late-onset accommodative ET. For the infantile onset group, we collected data from those patients whose parents reported ET occurring before 12 months old confirmed by a pediatric ophthalmologist. While our eligibility criteria for the late-onset group should define a cohort of primarily late-onset accommodative ET, we cannot absolutely exclude the possibility that a few patients had delayed diagnosis of infantile accommodative ET in the late-onset group. On the other hand, the infantile onset group should have solely early onset accommodative ET.

Astigmatism is relatively prevalent in children with accommodative ET. Our data showed a significant increase of astigmatism in the infantile group, but not in the late-onset group. Lambert et al.[25] reported that cylinder power increased with age in their two younger groups. Park et al.[8] showed higher prevalence of astigmatism in children with accommodative ET and cylinder power did not change significantly over age. Although these studies did not elaborate on their results with axis of astigmatism, our results showed, similar to that found in their study, that WTR astigmatism was dominant and increased with age in both accommodative ET groups. Further, our study showed that the final astigmatism is correlated significantly with initial astigmatism.

Amblyopia, which is a commonly observed condition in children with accommodative ET,[4,11,20] could be an important factor influencing refractive error development. Previously, Park et al.[8] investigated the development in the amblyopic eye and nonamblyopic fellow eye ($N = 20$).[8] Our results ($N = 42$) on the amblyopic eyes agreed with their report that the amblyopic eye is more hyperopic than the fellow nonamblyopic eye. However, our model did not show significantly decreasing slope as that in their study. The major reason for explaining such difference could be that: (1) one criterion for our cohort is ≥ 4 D and (2) our cohort differs in race/ethnicity from the cohort described by Park et al.,[8] which included only Asian children, who generally show larger and earlier myopic shifts than other races.[26–28] Compared to the initial visit, our cohort also showed slightly more patients had unilateral amblyopia. It might be related to changed refraction or increased anisometropia during follow-up.

Children with hyperopia and anisometropia are at greater risk for strabismus than those with hyperopia alone.[29,30] Our results showed that the prevalence of anisometropia among children with accommodative ET (20%–37%) was approximately 10-fold higher than the prevalence in population-based studies (1.6%–4.3%).[18,19] Further, a study reported that the prevalence of anisometropia increases between 5 and 15 years in normal children; anisometropia at the initial visit is associated with later anisometropia and elevated risk for amblyopia.[31] For our sample, anisometropia at the final visit was associated with anisometropia at the initial visit in the late-onset group, but not in the infantile group. For our data,

interestingly, the "less hyperopic eye" did not have as large myopic shift as the "more hyperopic eye" on average.

Limitations of Models Derived in This Study

Although we assumed data were missing at random, there were frequent missing data in this cohort and models derived in this study should be interpreted with caution. In addition, the hyperopia cutline was +4.00 D, so the model derived here can be applied only to predict refractive development for children with moderate and high hyperopia. Compliance with spectacle wear could be a factor that affects refractive error development. In this study, there was no formal assessment of compliance with spectacle wear. However, there is no reason to suspect that the cohort study is atypical, so the data should be representative of typical refractive error development trends.

Clinical Meaning of This Study

Long-term refractive error management is important for resolution or deterioration of accommodative ET.[11,32,33] Our study focused on patients who had hyperopia ≥+4.00 D, which is a population that present in clinics. Our findings could provide reference for clinicians to describe longitudinal prognosis of spectacle correction for patients with accommodative ET.

Conclusions

Children with infantile onset accommodative ET experience prolonged hyperopia followed by a significant myopic shift after 7 years of age. In contrast, children with late-onset accommodative ET have less a significant myopic shift after 7 years of age. Also, WTR astigmatism and anisometropia increase with age in children with accommodative ET.

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