Development of Refractive Error in Individual Children With Regressed Retinopathy of Prematurity

Jingyun Wang,[1] Xiaowei Ren,[2] Li Shen,[3] Susan E. Yanni,[4] Joel N. Leffler,[5] and Eileen E. Birch[4,5]

[1]Eugene and Marilyn Glick Eye Institute, Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, Indiana
[2]Department of Biostatistics, Indiana University School of Public Health, Indianapolis, Indiana
[3]Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, Indiana
[4]Crystal Charity Ball Vision Evaluation Center, Retina Foundation of the Southwest, Dallas, Texas
[5]Department of Ophthalmology, University of Texas Southwestern Medical Center, Dallas, Texas

Correspondence: Jingyun Wang, Eugene and Marilyn Glick Eye Institute, Department of Ophthalmology, Indiana University School of Medicine, 1160 W. Michigan Street, Indianapolis, IN 46202; jingyun.wang@gmail.com.

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Purpose. We investigated longitudinally the refraction development in children with regressed retinopathy of prematurity (ROP), including those with and those without a history of peripheral retinal laser photocoagulation.

Methods. Longitudinal (0–7 years) cycloplegic refraction data were collected prospectively for two groups of preterm children: severe ROP group included those with regressed ROP following bilateral panretinal laser photocoagulation ($n = 37$; median gestational age [GA] = 25.2; range, 22.7–27.9 weeks) and mild/no ROP group included those with spontaneously regressed ROP or no ROP ($n = 27$; median GA = 27.1; range, 23.1–32.0 weeks). Analyses were based on spherical equivalent (SEQ), anisometropia, astigmatism, and age (corrected for gestation).

Results. The prevalence, magnitude, and rate of myopic progression all were significantly higher in the severe ROP group than in the mild/no ROP group. Longitudinal SEQ in the severe ROP group were best fit with a bilinear model. Before 1.3 years old, the rate of myopic shift was −4.7 diopters (D)/y; after 1.3 years, the rate slowed to −0.15 D/y. Longitudinal SEQ in the mild/no ROP group was best fit with a linear model, with a rate of −0.004 D/y. Anisometropia in the severe ROP group increased approximately three times faster than in the mild/no ROP group. In the severe ROP group, with-the-rule astigmatism increased significantly with age.

Conclusions. The severe ROP group progressed rapidly toward myopia, particularly during the first 1.3 years; anisometropia and astigmatism also increased with age. The mild/no ROP group showed little change in refraction. Infants treated with laser photocoagulation for severe ROP should be monitored with periodic cycloplegic refractions and provided with early optical correction.

Keywords: myopia, refractive error development, retinopathy of prematurity, laser photocoagulation

Retinopathy of prematurity (ROP) is one of the leading causes of childhood visual impairment and blindness in the United States. The prevalence of myopia has been reported to vary with severity of ROP, ranging from 0% to 16% for preterm infants with no ROP[1–3] to 21% to 100% for children whose severe ROP was laser-treated.[1–4] The prevalence of myopia in children with severe ROP is astonishingly high, especially in those who received peripheral laser-photocoagulation.[4–6] The Early Treatment of Retinopathy of Prematurity (ETROP) study found that, between six and nine months, the prevalence of myopia in infants with severe ROP (and laser-photocoagulation at either high-risk prethreshold or at threshold) increased from ~60% to ~70%, with little further change in prevalence between 9 months and 3 years.[5] The prevalence of high myopia (≥−5.00 diopters [D]) steadily increased from 17% to 26% at 6 months to 51% at 3 years.[5] However, little is known about the developmental time course of myopia or changes in the magnitude of myopia with age in individuals who were treated by laser photocoagulation for severe ROP. The prevalence of myopia is much lower among preterm children with no/mild ROP. Two birth cohort studies have reported that only 14% of preterm children who had no ROP had myopia,[7] and that the prevalence of myopia is relatively stable at 20% to 29% between 6 months and 6 years of age.[7,8] A longitudinal study of 62 preterm children with mild/no ROP reported that 24% had myopia during early childhood and only 11% had high myopia.[9] This study will focus on comparing longitudinal changes in refractive error of individual preterm children who had severe ROP (treated with laser-photocoagulation) and those with mild/no ROP.

To our knowledge, previous studies have not offered a model to predict an individual's development of refractive error because they did not track individual myopic progression. As a result, gaps remain in our understanding of refractive error development in individual children with ROP. Furthermore, it is well-known that there is a high prevalence (6-fold higher than

in the general population) of anisometropia associated with ROP,[10] and a prevalence as high as 47% in laser-treated children.[11] However, the developmental pattern of anisometropia, one important cause of amblyopia, has not been investigated in individual children with ROP to our knowledge. Lastly, the prevalence of astigmatism (>1 D) in children with severe ROP has been reported as 42% at 4 years and 52% at 6 years.[12] Yet, little is known about when astigmatism develops and whether its magnitude increases with age in individual children with ROP.

The aim of our study was to investigate the development of refractive error longitudinally in two groups of preterm children with regressed ROP, those with and those without a history of severe ROP and peripheral retina laser-photocoagulation. In each group, we answered four questions: (1) What is the initial refractive state? (2) What is the best model to describe the myopic progression pattern? (3) When does anisometropia appear and how does it change with age? (4) When does astigmatism appear and how does it change with age?

Methods

This research protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center and conformed to the requirements of the United States Health Insurance Portability and Privacy Act. The research adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from one or both parents before each infant's enrollment.

Participants

Patients were enrolled in an ongoing prospective study of visual development in preterm infants and children at the Retina Foundation of the Southwest. They were referred by one pediatric ophthalmologist, who conducted ROP screenings in multiple Dallas-area neonatal intensive care units. Inclusion criteria were birth ≤32 weeks after conception; normal-appearing posterior poles on ophthalmoscopy; initial cycloplegic refraction completed at age ≤2 years, at least 3 cycloplegic refractions by age 7 years; and a minimum of 1.5 years of follow-up. Exclusion criteria were retinal detachment, macular dragging, intraocular surgery, optic nerve hypoplasia, malformations of the eye, hydrocephalus, cortical visual impairment, other ocular diseases or syndromes, cerebral palsy, developmental delay, and seizure disorders.

Preterm children were classified into two groups. Group 1 (severe ROP) had bilateral threshold ROP or high-risk prethreshold ROP that regressed following panretinal laser treatment[13,14] ($n = 37$; median gestational age (GA) = 25.2; range, 22.7–27.9 weeks). Group 2 (mild/no ROP) included preterm children who had mild ROP that regressed without treatment and preterm children born with incompletely vascularized retinas who never had ROP (sometimes called stage 0 ROP) ($n = 27$; median GA = 27.1; range, 23.1–32.0 weeks). Cycloplegic refraction data were collected prospectively. GA, sex, stage of ROP, and treatment history were obtained from medical records.

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), they were converted into their power vector components: M (spherical equivalent [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] The M component, that is, SEQ, was used to estimate myopic progression. To estimate anisometropia, the absolute value of the SEQ interocular difference was calculated. J_0 was used to estimate WTR astigmatism. J_{45} was used to estimate oblique astigmatism.

In our study, corrected age was used for all analyses. Corrected age equals postnatal age minus the difference between term (40 weeks) and gestational age (GA) at birth ($Corrected\ Age = Postnatal\ Age - [Term - GA]$). For instance, the corrected age of an infant born at 26 weeks' GA and tested at postnatal age 24 weeks is 10 weeks: $24 - (40 - 26) = 10$. We refer to "corrected age" as "age" in this report.

To estimate the rate of individual myopic progression (i.e., SEQ) with age, a linear mixed effect model was used. The mixed effect model is a model that uses longitudinal information from each individual. The severity of ROP was treated as a fixed effect and individual as a random effect. The model provides comparisons within each group as well as comparisons between groups. Refraction data initially were fit with a bilinear model, using the iterative weighted least square (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 and one for ages beyond the transition point. The Akaike information criterion (AIC),[16] a widely used method for model selection that considers the model complexity and goodness of fit of the model to the data, was used here to optimize the selection of the transition point with the following procedure: (1) set the search interval as [0, 2]; (2) test 30 uniformly distributed locations by fitting the model and calculating the AIC value; (3) update the search interval by a narrower range, including the smallest AIC value, and its left and right neighbors; (4) repeat steps (2) and (3) until the AIC values in the new interval converge. In any case where we observed no significant difference (by *t*-test of the mixed effect model) between the slopes of the two lines in the bilinear fit, data were reanalyzed using a simple linear model fit by the IWLS method. We conducted similar analyses on anisometropia and astigmatism (J_0 and J_{45}).

Results

Results from the right eye were similar to those from the left eye. Only results from right eyes will be reported in detail. For the severe ROP group, the median number of visits was 5 (range, 3–10) and the median length of follow-up was 4.6 years (range, 1.5–6.6 years). For the mild/no ROP group, the median number of visits was 4 (range, 3–8) and the median length of follow-up was 4.0 years (range, 1.5–6.3 years). The Table provides the number of subjects in each group by age range. For detailed individual data, we plotted the longitudinal data for both eyes of each individual subject in two Supplementary Figures; Supplementary Figure S1A shows data for the 37 subjects in the severe ROP group, while Supplementary Figure S1B shows data for the 27 subjects in the mild/no ROP group.

In the severe ROP group, on the initial visit, 10 of 37 (27%) children had hyperopic refractive error (SEQ ≥+1.00 D), 17 of 37 (46%) children had myopia (SEQ ≤−1.00 D), and the remaining 10 children (27%) were emmetropic (−1.00 <SEQ <+1.00 D). At the final visit, 4 children (11%) had hyperopia, 28 of 37 children (76%) had myopia, and 5 children (13%) had emmetropia. Notably, within the group of 28 myopic children, 20 of them had high myopia (SEQ ≤−5.00 D). For 34 children who had data before 9 months of age (≤0.8 year),

TABLE. The Number of Patients in Age Subgroups of Both Groups

	Age Subgroup								
	<0.5	<1	<1.5	<2	<3	<4	<5	<6	<7
Severe ROP	31	26	27	16	31	22	19	16	5
Mild/no ROP	15	11	19	9	21	20	12	8	5

14 children had myopia (SEQ ≤–1.00 D) and 20 did not. All 14 children (100%) who had infantile myopia had myopia at the final visit and 11/14 (79%) had high myopia (SEQ ≤–5.00 D). Among the 20 children who did not have infantile myopia, 8 (40%) were myopic at the final visit and only 1 (5%) had high myopia. The proportions of children who were myopic at the final visit and who had high myopia were significantly larger in the subset with infantile myopia than the subset who did not have infantile myopia ($z = 3.60$, $P = 0.0003$; $z = 4.42$, $P < 0.0002$). The prevalence of myopia at the final visit was significantly higher than at the initial visit in the severe ROP group (McNemar χ^2 test, $P = 0.001$). Results for left eyes were similar; 24 of 37 of children (65%) had myopia by the final visit.

In the mild/no ROP group, on their initial visit, 20 of 27 children (74%) had hyperopic refractive error, 2 children (7%) were myopic, and 5 children (18.5%) were emmetropic. The prevalence of hyperopia in the mild/no ROP group was significantly higher than in the severe ROP group (McNemar χ^2 test, $P = 0.001$). At the final visit, 17 children (63%) were hyperopic, 3 children (11%) were myopic, 7 children (26%) were emmetropic. Prevalence of hyperopia did not change significantly from the initial visit to the final visit (McNemar test, $P = 0.28$). Results for left eyes were similar; 3 children (11%) in the mild/no ROP were myopic at the final visit.

Refractive Error Development Model

The right eye SEQ for the severe ROP group was fit by a bilinear model (Fig. 1A):

$$\text{SEQ}_{\text{severe}}(\text{Age}) = -4.69 \times \text{Age} + 0.19 \text{ for Age} \leq 1.29 \text{ years};$$
$$\text{SEQ}_{\text{severe}}(\text{Age}) = -0.15 \times \text{Age} - 5.64 \text{ for Age} > 1.29 \text{ years}.$$

The baseline SEQ estimated by the model was +0.19 D. The transition point in the bilinear model at 1.29 years (95% confidence interval [CI], 1.25–1.33 years, we round it up to 1.3 years in the following text) can be interpreted as a critical age in myopia progression. The SEQ at 1.29 years is –5.86 D. Before the critical age, the rate of myopia progression (–4.69 D/y) was approximately 30 times faster than after the critical age (–0.15 D/y). Results for left eyes were similar, with a transition point at 1.23 (95% CI, 1.21–1.26) years, and rates of myopia progression of –4.00 and –0.01 D/y before and after the transition point.

The right eye SEQ for the mild/no ROP group was fit by a linear model (Fig. 1A):

$$\text{SEQ}_{\text{mild/no}}(\text{Age}) = -0.004 \times \text{Age} + 2.10.$$

The baseline SEQ for the mild/no ROP group was estimated by the model as +2.10 D. This is significantly different from the baseline SEQ of +0.19 for the severe ROP group ($t_{160} = 2.65$, $P = 0.009$). The rate of change in refractive error (slope) of –0.004 D/y was not significantly different from zero ($t_{26} = 0.04$, $P = 0.97$); that is, the SEQ remained hyperopic and changed little across age. Results for left eyes were similar, with a rate of change in refractive error –0.08 D/y, which also was not significantly different from zero ($t_{26} = 1.05$, $P = 0.30$). The severe ROP and mild/no ROP groups had significantly different rates of change (slopes) for refractive error before 1.3 years, ($t_{160} = 4.76$, $P < 0.0001$).

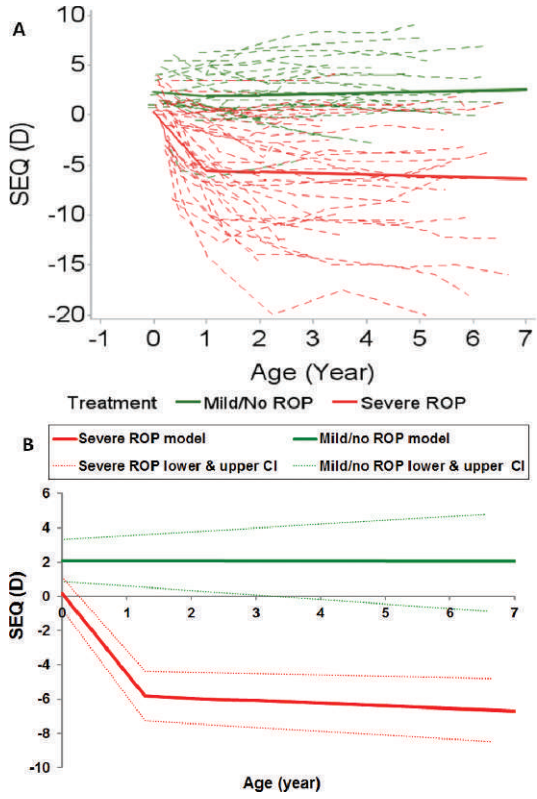

FIGURE 1. (**A**) SEQ for the right eye of each patient plotted against corrected age. The *red dashed lines* indicate individual patients in the severe ROP group ($n = 37$); *the green dashed lines* indicate individual patients in the mild/no ROP group ($n = 27$). The corresponding *red* and *green bold lines* show the best-fit models for the severe ROP group and for the mild/no ROP treated group. (**B**) The best fit models with the 95% CIs. The corresponding *red* and *green bold lines* show the best-fit models for the severe ROP group and for the mild/no ROP treated group. The *fine dashed lines* indicate the CI for the severe ROP group in *red* and for the mild/no ROP treated group in *green*.

Confidence intervals are shown in Figure 1B.

Anisometropia

Of 37 children in the severe ROP group, 14 (38%) had anisometropia (SEQ difference ≥1.00 D) at their initial visit. At the final visit, 20 of 37 children (54%) had anisometropia. The prevalence of anisometropia in the severe ROP group was not significantly different between the initial and final visits (McNemar test, $P = 0.16$).

Six of 27 children (22%) in the mild/no ROP group had significant anisometropia at their initial visit. At the final visit, 7 children (26%) had anisometropia. The prevalence of anisometropia in the severe ROP group was higher than that in the mild/no ROP group (McNemar test, $P = 0.02$).

Anisometropia was fit by a linear model (Fig. 2A) in the severe ROP group:

$$\text{Anisometropia}_{\text{severe}}[\text{Age}] = 0.31 \times \text{Age} + 1.13$$

and in the mild/no ROP group:

$$\text{Anisometropia}_{\text{mild/no}}[\text{Age}] = 0.11 \times \text{Age} + 0.47.$$

The magnitude of the initial anisometropia observed in the severe ROP group was approximately two times that observed

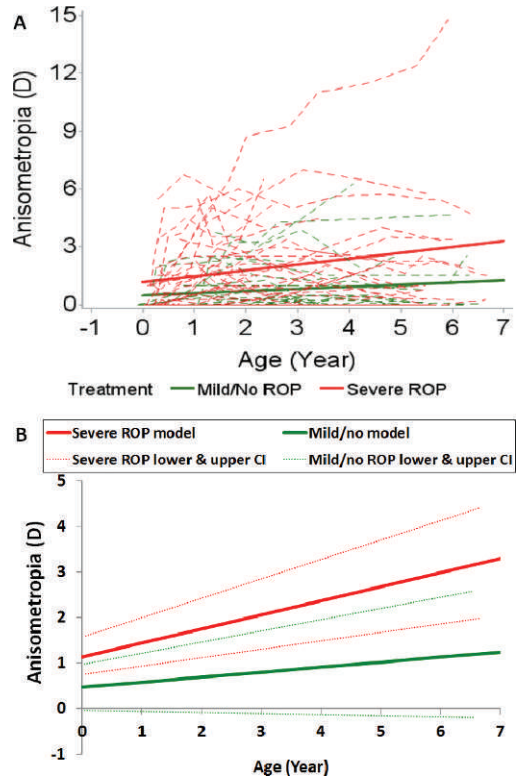

FIGURE 2. (**A**) Magnitude of anisometropia for each patient plotted against corrected age. The *red dashed lines* indicate individual patients in the severe ROP group ($n = 37$); *the green dashed lines* indicate individual patients in the mild/no ROP group ($n = 27$). The corresponding *red* and *green bold lines* show the best-fit models for the severe ROP group and for the mild/no ROP treated group. (**B**) The best fit models with the 95% CIs. The corresponding *red* and *green bold lines* show the best-fit models for the severe ROP group and for the mild/no ROP treated group. The *fine dashed lines* indicate the CI for the severe ROP group in *red* and for the mild/no ROP treated group in *green*.

in the mild/no ROP group ($t_{222} = 1.96$, $P = 0.05$). Although there was no statistical difference between the slopes of these two models ($t_{222} = 1.38$, $P = 0.1702$), the rate of anisometropia progression in the severe ROP group (0.31 D/y) was approximately three times that of the mild/no ROP group (0.11 D/y). Confidence intervals are shown in Figure 2B. For detailed individual anisometropia data, Supplementary Figures S1A and S1B illustrate the difference between the right and left eye.

Astigmatism

On the initial visit, only 1 of 37 (3%) children in the severe ROP group had significant WTR astigmatism ($J_0 \geq 0.5$D, which corresponds to CYL ≥ 1 D), 2 children (5%) had significant ATR astigmatism ($J_0 \leq -0.5$ D, which corresponds to CYL ≥ 1 D), and one child had significant oblique astigmatism ($J_{45} \geq 0.5$ D or $J_{45} \leq -0.5$ D). At the final visit, 13 of the 37 children (35%) had significant WTR astigmatism and one child (3%) had ATR astigmatism, while 6 children (16%) had oblique astigmatism. A total of 15 children (40.5%) had astigmatism (note, some children had significant J_0 and J_{45}). The number of children in the severe ROP group with WTR astigmatism increased from 1 to 13 between the initial and final visits; this increase in prevalence was significant (McNemar test, $P < 0.001$).

In the mild/no ROP group, at the initial visit, 3 of 27 (11%) children had WTR astigmatism, 3 had ATR astigmatism, and 2 had oblique astigmatism. At the final visit, five children (18.5%) had significant WTR astigmatism, one child (3.7%) had ATR astigmatism, and one child (3.7%) had oblique astigmatism. A total of 7 children (26%) had astigmatism. The prevalence of astigmatism in the mild/no ROP group was not significantly different between the initial and final visits (McNemar test, $P = 0.22$). At the final visit, there was no significance between the prevalence of astigmatism in the severe ROP group and that in the mild/no ROP group (McNemar test, $P = 0.31$).

J_0 was fit by a linear model (Fig. 3) in both the severe ROP group:

$$J_{0severe}[\text{Age}] = 0.04 \times \text{Age} + 0.005$$

and in the mild/no ROP group:

$$J_{0mild/no}[\text{Age}] = 0.08 \times \text{Age} + 0.02.$$

The initial J_0 observed in the severe ROP group was not different from that in the mild/no ROP group ($t_{222} = -0.18$, $P = 0.86$). There was no statistical difference between the slopes of these two models, and J_0 of both groups increased significantly with age ($t_{222} = 3.85$, $P < 0.001$), indicating a trend toward WTR astigmatism in both groups. Results for left eyes were similar, with a rate of 0.03 D/y in J_0 in the severe ROP group and 0.08 D/y in the mild/no ROP group, which also showed significant trends toward WTR astigmatism. There was no significant difference between two groups.

Since the prevalence of oblique astigmatism was <16%, there was no significant result to report.

DISCUSSION

In our study, longitudinal refractive error data of individual children with regressed ROP were used to define models of refractive error development for two groups of preterm children: severe ROP and mild/no ROP. In particular, the best-fit model in the severe ROP group delineated a phase of rapid myopia progression before a critical age of 1.3 years, and slower progression of myopia thereafter. Myopia present by 9 months of age in a child with a history of severe ROP was associated with long-term myopia and a high risk of development of high myopia. In addition, to our knowledge

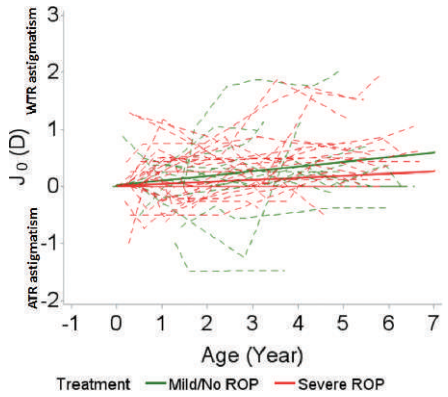

FIGURE 3. J_0 for each patient plotted against corrected age. The *red dashed lines* indicate individual patients in the severe ROP group ($n = 37$); the *green dashed lines* indicate individual patients in the mild/no ROP group ($n = 27$). The corresponding *red* and *green bold lines* show the best-fit models for the severe ROP group and for the mild/no ROP treated group.

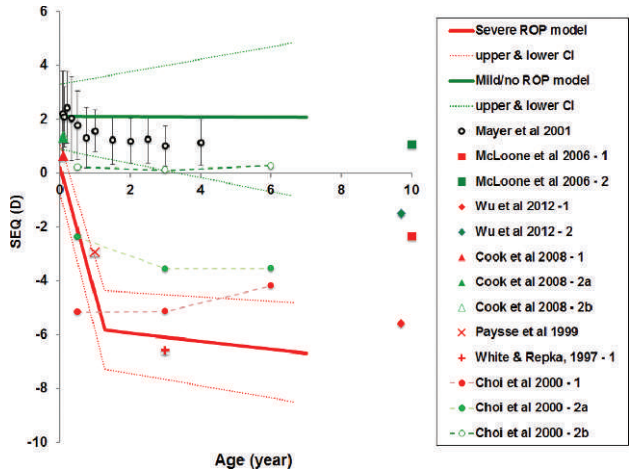

FIGURE 4. The best-fit models of our study, along with fifth and 95th percentiles CI derived from the models, presented with data from the literature.[7,8,17–19,41] Normal term-born control data from study of Mayer et al.[21] is plotted in *black circles* with CI. If the results from the literature are from the group similar to the severe ROP group, they are plotted in *red symbols* and end in "*1*" in the legend. If the results from the literature are from the group similar to the mild/no ROP group, they are plotted in *green symbols* and end in "*2*" in the legend. If the literature separated the "mild ROP" *in green-filled symbols* and "no ROP" group in *green open symbols*, we used "*2a*" and "*2b*" to note in the legend, too. Data from the studies of Lue et al.[9] and Holmstrom and Larsson[42] were not plotted here, since it is difficult to extract the corresponding numbers from their figures.

our study for the first time describes longitudinal changes in anisometropia and astigmatism in children with regressed ROP.

Refractive Error Development

The best-fit models derived from longitudinal data are consistent with most cross-sectional and longitudinal data reported in the literature (Fig. 4).[7,8,17–19,41,42] For the severe ROP group, the model predicts low hyperopia at corrected age = 0, consistent with published data from preterm infants at 40 weeks after conception.[7] The model also is consistent with prior reports of mean refractive error −3.00 D at 1 year of age,[17] −6.50 D at 3 years,[18] and −5.50 D at 10 to 12 years,[19] but differs from the report of −2.33 D mean refractive error in a small sample of children with regressed severe ROP.[20] For the mild/no ROP group, the initial visit refractive error of +2.00 D is close to the refractive error reported for the "No ROP" preterm group by Lue et al of +1.86 D,[9] and is similar to the average SEQ (+2.20 ± 1.60 D) reported for 1-month-old full-term control infants.[21]

In addition to the bilinear and linear models used to fit the refractive data in our study, it has been proposed that an exponential model may provide a good fit to myopic progression.[9] We did explore whether an exponential model might provide a better fit to the SEQ data in our study, but found that the exponential model did not provide as good a fit as the bilinear model (larger error term) and had a larger AIC value.

A few hypotheses may explain the myopic progression in the severe ROP group. First, following laser photocoagulation for severe ROP, there is extensive peripheral chorioretinal scarring with retinal atrophy and gliosis, loss of RPE, and extensive atrophy of the choroid and its vasculature.[22] These important anatomic features might alter retinal signaling for eye growth and/or alter the response of the sclera to growth signals (growth signal hypothesis). If myopic progression in laser-treated eyes is due to destruction of peripheral retina and choroid, we might expect that children treated with injection of bevacizumab who have healthy peripheral retina would not be myopic. A few studies have reported that postbevacizumab myopic refractive error was lower in magnitude than for children treated with laser photocoagulation, but the prevalence of myopia still was high. With a small sample size, at 10.5 months of corrected age, Harder et al. reported that the mean level of myopia in preterm infants treated with bevacizumab was −0.27 D ± 4.09 D in the right eye (range, −7.00 to +4.25 D), which is considerably lower than in our severe ROP group.[23] However, a recent case report described a preterm infant treated with bevacizumab who had high myopia.[24] A recent nonrandomized study reported that 5 of 9 eyes treated with bevacizumab were myopic at 5 years of age and the SEQ is approximately −1.75 D on average.[25] In summary, there are not enough data available to evaluate whether myopic progression is associated with laser photocoagulation or with severe retinopathy.

Second, rapid biological changes in optical elements, including axial length, corneal curvature, and lens power, normally occur during the first year of life.[26] Compared to term-born, control infants, steeper corneal curvature, shorter anterior chamber depth, and thicker crystalline lens have been reported in infants with severe ROP who receive panretinal laser treatment.[19,20,27–30] This suggests that severe retinopathy and/or its treatment may result in arrested anterior segment development. During the rapid eye growth at the early age, all these abnormal biometric parameters may come together and result in significant myopia progression in the severe ROP group.

Third, recent nonhuman primate studies conclude that peripheral retina has an important role in guiding the growth of ocular components during emmetropization (peripheral retina hypothesis).[31] Restricted peripheral vision beyond 24° to 37° induced axial elongation of the eye and myopia.[31] Because the visual field is reduced by peripheral retinal laser photocoagulation,[32] one could argue that reduced peripheral input results in myopia in laser-treated children. However, myopia of prematurity is not a result of axial growth. In addition, peripheral laser photocoagulation typically is applied at >70° retinal eccentricity, and it is not clear if regions this far even have an effect on myopic progression.

These hypotheses are not mutually exclusive and it is possible that any hybrid of these may explain myopic progression.

Anisometropia

Consistent with a study by Yang et al.,[11] we found a high prevalence of anisometropia (54%) in children with severe ROP. In the mild/no ROP group, the prevalence of anisometropia was higher than that in the term-born emmetropic children (2.8% ~ 3.4%[33,34]). Compared to the mild/no ROP group, the severe ROP group had higher baseline anisometropia and the magnitude of anisometropia progressed more rapidly (by a factor of 2) with age. Anisometropia could be associated with an imbalance of retinopathy severity between eyes, or because the laser treatment may not have been identical for the two eyes.

To address the potential effect of laser treatment on refractive status, we looked at data from four children who had severe ROP and laser treatment in only one eye. They were not included in the two groups we studied. Figure 5 shows all 4 children had anisometropia. In two cases (left column), the laser-treated eye was more myopic, while in the other two cases (right column) the laser-treated eye was less myopic.

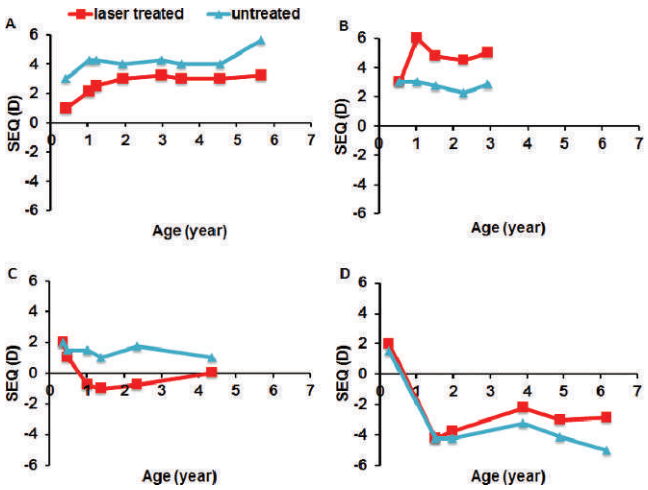

FIGURE 5. Four individuals who had laser treatment in one eye only (*red symbols*). For the two subjects shown on the *left* ([**A**] and [**C**]), the laser-treated eye is more myopic. For the two subjects shown on the *right* ([**B**] and [**D**]), the laser-treated eye is less myopic. All four patients became anisometropic.

Furthermore, the eye with more severe ROP and laser treatment was not consistently more myopic. These results suggested that neither severity of ROP alone nor laser treatment alone predict refractive outcome.

Astigmatism

In both the severe ROP group and mild/no group, the magnitude of WTR astigmatism (J_0) increased with age. The severe ROP group had a prevalence of 40% at the final visit, which occurred before 7 years of age, in agreement with the results of Davitt et al.[12] The mild/no group had a prevalence of 26% of astigmatism, which is higher than the term-born subjects (~15%).[21,35,36] After the age of 5, the severe ROP group had significantly higher WTR astigmatism (J_0) than the mild/no ROP group.

A limitation of our study is that the cohort is not a birth cohort; instead, the patients are those who were referred for and agreed to participate in an ongoing research study. Therefore, the prevalence of refractive errors in the cohort may not be representative of the general population of preterm children, and those with severe ROP are likely overrepresented because parents are more likely to volunteer if their child has refractive error and/or severe ROP. Nonetheless, we were able to look at how myopia developed across time in individuals and examine risk factors for rapid change of myopia of prematurity. Ideally, a normal full-term control group would enhance the study. However, there is abundant literature on normal children's refractive error development[21,37–40] and we are familiar with refractive error development features of full-term children.

We conclude that infants treated with panretinal photocoagulation for severe ROP are more likely to have early and rapidly progressive myopia. We found that before 1.3 years of age, the rate of progression was −4.7 D/y in laser-treated eyes, indicating an average increase of approximately −1.00 D every three months. We also found an average increase in anisometropia of 0.25 D per year. Preterm infants whose retinopathy was treated by laser should be monitored closely with periodic cycloplegic refractions and early optical correction to prevent visual deficits. Further studies are needed to investigate potential interventions that may slow the rapid myopia progression associated with severe ROP and laser treatment. The results of our study suggested that any such intervention should be applied before the child is 1.3 years old.

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