Long-term Evaluation of Refractive Status and Optical Components in Eyes of Children Born Prematurely

Ta-Ching Chen, Tzu-Hsun Tsai, Yung-Feng Shih, Po-Ting Yeh, Chang-Hao Yang, Fu-Chang Hu, Luke Long-Kuang Lin, and Chung-May Yang

PURPOSE. To evaluate the refractive status and optical components in school age children born prematurely and to examine the risk factors associated with refractive errors.

METHODS. The participants were a cohort of children aged 7 to 9 years with gestational age less than 35 weeks or birth weight less than 1500 g. The participants' neonatal histories were reviewed; their refractive status and optical components were measured. The study results were compared with the results of age-matched children from a national survey.

RESULTS. Of the 108 children studied, 48 (44%) had retinopathy of prematurity (ROP); 29 (27%) had ROP ≥ stage 3. Compared with the control subjects, the study cases showed higher prevalence of myopia (48% vs. 29%), hyperopia (23% vs. 15%), and astigmatism (73% vs. 41%). Common ocular features included shallow anterior chamber depth (ACD), thick lenses, and steep corneal curvature. The hyperopic cases had the shortest axial length (AL), whereas the myopia cases had significantly shallower ACD and greater LT. Those with a history of ROP had more prominent changes in the anterior segment. Generalized estimating equations showed that refractive errors could be predicted by a combination of optical components.

CONCLUSIONS. In children born prematurely, the development of myopia is mainly influenced by anterior segment components, whereas hyperopia is mainly attributable to short AL. Astigmatism is primarily cornea-related. A combination of various optical components results in complicated refractive outcomes. The presence of ROP may be associated with significantly shorter ACD, thicker lens, and higher myopia and astigmatism. (ClinicalTrials.gov number, NCT01045616.) (Invest Ophthalmol Vis Sci. 2010;51:6140–6148) DOI:10.1167/iovs.10-5234

Ophthalmic problems are common among children born prematurely or with low birth weight. Refractive error is particularly common and may cause visual problems. Numerous reports have disclosed the refractive status and amblyogenic factors in the population with low birth weight. Myopia is one of the most well-known ocular abnormalities associated with premature birth. Some studies have shown that the prevalence of myopia correlates negatively with birth weight and gestational age, but positively with increasing severity of retinopathy of prematurity (ROP). In addition to myopia, children born prematurely also tend to develop other refractive errors, such as hyperopia, astigmatism, and anisometropia. However, the risk factors of these problems have not been fully investigated. Moreover, most studies were focused on preschool children. Studies of the refractive status of schoolchildren born prematurely remain limited.

The incidence of myopia in schoolchildren in Taiwan is much higher than that in other countries. An investigation of refractive error and optical components in children born prematurely and a comparison of the study results with the data obtained from the general child population could help to understand how prematurity affects refractive status. In this study, we evaluated the refractive status and optical components in eyes of schoolchildren who were born prematurely. The study results were compared to the results of age-matched, term-born control subjects. The purpose of our study was to advance our knowledge regarding the relationship between preterm birth, ROP, ocular development, and long-term refractive status.

METHODS

Children of premature birth who were born between January 1, 1999, and December 31, 2001, at the National Taiwan University Hospital (NTUH) were selected for this retrospective cohort study. Infants born at postconception age of less than 35 weeks or with a birth weight of less than 1500 grams were initially included. After those without complete medical records and ophthalmic records and those who had died were excluded, 153 patients were obtained. Forty-five cases were further excluded because they were either lost to follow-up or were unable to perform the tests in the ophthalmic examinations because of cognitive factors. Overall, a total of 108 children completing the follow-up examinations were enrolled in this study. The latest follow-up was performed in 2008 when the participants' ages ranged between 7 and 9 years. Written, informed consent was obtained from the parents of the study participants. The study conformed to the tenets of the Declaration of Helsinki and was approved by the Research Ethics Committee of NTUH. We reviewed the birth history and neonatal ophthalmic records of the 45 children not studied. There were no significant differences in gestational age, birth weight, and maximum ROP stage between these 45 children and our 108 cases.

All patients underwent a complete ophthalmic examination, including best corrected visual acuity (BCVA), cycloplegic refraction, indirect fundus examination, and the measurement of optical components. Stereopsis was examined with the National Taiwan University Random-dot Stereograms, 300 sec arc (NTU 300 test), which is a screening tool designed for nationwide screening of school and preschool children. Failing the test suggests a defect in binocular vision and higher risks of amblyopia, strabismus, severe anisometropia, or extremely poor vision caused by retinal disease or optic neuropathy. The corneal radius (CR) and refractive status were measured with an autorefractor (RK-8100);
Topcon, Tokyo, Japan). The biometric profile, including anterior chamber depth (ACD), lens thickness (LT), axial length (AL), and central corneal thickness (CCT), was obtained with ocular ultrasound (Pascal 300AP; Sonomed, Lake Success, NY). Landolt-C optotypes were used for the measurement of visual acuity. Visual acuity was then converted to logarithm of the minimum angle of resolution (LogMAR) for statistical analysis.

Medical records were reviewed to collect data regarding birth history—gestational age (GA), birth weight (BW), presence of neurologic deficits and events, and the occurrence of circulatory insufficiency, such as cyanotic heart disease and severe anemia—stage of ROP and treatments received, and important complications developing in the neonatal period. ROP was categorized by the stage of maximum severity in the acute phase. Eyes with severe ROP received laser treatment or surgical repair. The timing and indications for laser treatment depended on the development of threshold disease, similar to the conventional treatment group in the ET-ROP study.\textsuperscript{18,19} The threshold disease is defined by the CRYO-ROP Study as a stage 3+ ROP in zone I or II, involving at least five contiguous clock-hour sectors or at least eight interrupted clock-hour sectors.\textsuperscript{20} In these 108 cases, all children ($n = 27$) categorized with stage 3 ROP received laser treatment, and two others with stage 4+ ROP received surgical treatment.

To study the refractive changes and the associated factors, we divided the patients into three groups according to their refractive status: myopia, emmetropia, and hyperopia. Myopia and hyperopia were defined as a spherical equivalent (SE) less than $-0.5$ D (myopia) or more than $0.5$ D (hyperopia). Emmetropia was defined as an SE between $-0.5$ and $0.5$ D. One hundred children had symmetric fundus presentation after birth. In these children, we chose the information in the right eye for statistical analysis. Eight of the 108 children had different stages of ROP between the right and the left eyes. In these cases, the information on the eye with more advanced ROP (right eye in five, left eye in three) was chosen for analysis.

To examine the effect of ROP on refraction, we compared refractive status and optical components in patients with ROP with that in patients without ROP, and the data from advanced ROP cases (defined as ROP of stage 3 or above) were further compared with those in cases of mild ROP. Data collected in a 2006 national survey in Taiwan (managed by the Department of Health, Executive Yuan, Taiwan, performed by Ophthalmology Department, NTUH, Taiwan) from students aged 7, 8, and 9 years, including 532, 540, and 552 girls, and 468, 420, and 485 boys, respectively, were used as the age-matched control.\textsuperscript{21} The same instruments and visual acuity test for the study group had been used in the children in the control group.

**Statistical Analysis**

A computerized database was established to facilitate data management and statistical analysis. Subsequent data analysis was performed with commercial software (Excel 2007; Microsoft Corp., Redmond, WA, and SPSS 12.0; SPSS, Inc., Chicago, IL, and SAS 9.1.3, SAS Institute Inc., Cary, NC). Two-sample $t$-tests were used for comparing mean values of continuous variables between the study group and the age-matched control group. The $\chi^2$ test or Fisher’s exact test was used to examine the associations between categorical variables. The comparisons of refractive errors and optical components among the three refractive groups—myopia, emmetropia, and hyperopia—were accomplished by using one-way analysis of variance (ANOVA).

A multivariate statistical analysis was performed to identify factors that predicted the severity of myopia, hyperopia, and astigmatism. The factors analyzed included patients’ neonatal history (GA, BW, ROP stage, and major neurologic and circulatory diseases) and ocular components (optical components, visual acuity, and eye alignment). A marginal linear regression model was used, with general estimating equations (GEEs) to control for between-eye correlations. In the GEE analysis, if the exchangeable correlation structure fit our clustered data well, the model-based estimates of SE were used; otherwise, the empirical (robust) estimates of SE were reported instead, assuming that the sample size of 108 subjects was large enough. If the observations did not correlate, the GEE analysis would revert to the standard regression analysis.

The goal of the regression analysis was to find one or a few parsimonious regression models that fit the observed data well for outcome prediction or effect estimation. To ensure the quality of the results of the analysis, we performed basic model-fitting techniques for variable selection, goodness-of-fit (GOF) assessment, and regression diagnostics. Specifically, the stepwise variable selection procedure (with iterations between the forward and backward steps) was applied to obtain the candidate final regression model. All the relevant variables, regardless of the significance during the univariate analyses, were included in the variable list to be selected, and the significance level for entry (SLE) and for stay (SLS) was set at 0.15 or larger. Then, with the aid of this substantive knowledge, the best final regression model was identified manually in a backward fashion (i.e., removing one statistically nonsignificant covariate at a time) by reducing the significance level to 0.05 corresponding to the chosen $\alpha = 0.05$ level. Any discrepancy between the results of univariate and multivariate analysis was probably due to the confounding effects of the uncontrolled covariates in the univariate analysis. The coefficient of determination, $R^2$, which is the square of the Pearson correlation between the observed and predicted values of the continuous response variable, was used to assess the GOF of the fitted linear regression model. The statistical tools for regression diagnostics such as residual analysis, detection of influential cases, and examination on multicollinearity were used to discover any problems within the data or model.

**RESULTS**

**Demographics and General Information**

Among the 108 children, there were 67 boys and 41 girls. The average age at the latest follow-up was $8.06 \pm 0.85$ years (35 children at 7, 31 at 8, and 42 at 9 years of age). The average GA was $29.32 \pm 2.86$ weeks and average BW was $1162 \pm 340$ grams. Of the premature children 78% (84/108) were born before the postconception age of 32 weeks and 56% (60/108) weighed less than 1000 grams at birth. Twelve children had circulatory insufficiency, including cyanotic congenital heart disease and severe anemia; 7 had a seizure history in during infancy, and 15 were documented to have a brain abnormality, including hydrocephalus, intraventricular hemorrhage, ventriculomegaly, and periventricular leukomalacia in the neonatal period. Sixty (56%) of the eyes had no ROP, whereas 48 (44%) eyes had documented ROP, including 11 at stage 1, 8 at stage 2, 27 at stage 3, and 2 above stage 3.

The average spherical equivalent refractive error of the 108 children was $-1.02$ D. One hundred four of the children received a BCVA examination and 80% (83/104) of those achieved a logMAR visual acuity of less than 0.2 ($>20/30$). Among the four children who failed to have their BCVA evaluated, two had mild cognitive problems, one had clinically suspected autism, and one had difficulty in expression and verbal communication. Screening of strabismus in 106 children showed that 9 (8%) had esotropia (ET) and 7 (6%) had exotropia (XT) of more than 10 prism diopters. One hundred two children underwent the NTU 300 Random-dot stereopsis examination. Of those, 21 (20%) failed the test. Among those failing the test, six had anisometropia more than 3 D, and eight had amblyopia in clinical diagnosis. Eight of nine children with ET and two of seven with XT failed this examination. Intraocular pressure was checked in 89 children; 7 of them had an IOP $>20$ mm Hg, with a maximum of 24. All these 7 children had a CCT greater than 570 \textmu m. Except for two (1.8%) children with dragged retinal vessels, all had a normal macular appearance.
Refractive Status

Evaluation of the refractive status showed an average spherical equivalent of \(-1.02 \text{ (± 3.53, SD)} \) D. At the latest follow-up, there were 51 cases of myopia, 32 cases of emmetropia, and 25 cases of hyperopia. No significant difference was found in GA and BW among these three groups. Most of the children (76%, 22/29) with ROP of stage 3 or above were myopic. Children with no ROP or only stage I ROP showed similar prevalence of myopia, emmetropia, and hyperopia (Table 1).

Figure 1 shows a comparison of the distribution of SE between cases and age-matched controls. In the control group, the distribution peaked at emmetropia (more than half of the population had a refraction of 0 to \(-1.00 \text{ D}\)). Less than 5% of the children in the age-matched control group had myopia of more than \(-3 \text{ D}\) or hyperopia of more than \(+2 \text{ D}\). On the other hand, the distribution of the children born prematurely had a lower and leftward shift in the peak. More than 15% of the study cases had myopia of more than \(-3 \text{ D}\), and approximately 15% of them had hyperopia of more than \(+1 \text{ D}\). Eight percent of the study cases had a high myopia of more than \(-6 \text{ D}\), suggested by the small peak of the SE distribution curve at the left side. The two distributions were significantly different (\(P < 0.001\)). When subjects were divided into those with ROP (the gray area in data bars of the study cases) and those without ROP (the black area in data bars of the study cases), the results showed that the peak in high myopia was entirely attributable to ROP. Except for the peak in high myopia, the SE distribution in the ROP group was similar to that in the non-ROP group, and both groups were consistent in the high proportion of mild myopia. The ROP and non-ROP distributions of SE were statistically significant (\(P = 0.008\)).

Figure 2 shows the difference in distribution of astigmatism in the study participants and the age-matched schoolchildren (\(P < 0.001\)). Over 40% of the study participants (44/108 cases) had astigmatism of more than \(-1 \text{ D}\), and the range of distribution was wide. On the other hand, more than 80% of the normal population had astigmatism of less than \(-1 \text{ D}\). Nearly 70% (76/108) of the children showed with-the-rule (WTR) astigmatism, whereas 25% (27/108) of them had oblique (OBL) astigmatism, and less than 5% (5/108) had against-the-rule (ATR) astigmatism.

Characteristics of Optical Components in Groups with Different Refractive Status

Various parameters were compared among the three groups (Table 2). The mean refraction was \(-3.22, -0.02, \text{ and } 2.15 \text{ D}\) in the myopia, emmetropia, and hyperopia groups, respec-

---

**Table 1. Baseline Characteristics of the Study Sample**

<table>
<thead>
<tr>
<th>Cases, n</th>
<th>Myopia</th>
<th>Emmetropia</th>
<th>Hyperopia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>8.06 ± 0.83</td>
<td>8.22 ± 0.87</td>
<td>7.88 ± 0.83</td>
<td>8.06 ± 0.85</td>
</tr>
<tr>
<td>GA, wk</td>
<td>29.51 ± 2.70</td>
<td>29.44 ± 2.77</td>
<td>29.20 ± 3.37</td>
<td>29.32 ± 2.86</td>
</tr>
<tr>
<td>BW, g</td>
<td>1161 ± 322</td>
<td>1187 ± 391</td>
<td>1134 ± 314</td>
<td>1162 ± 340</td>
</tr>
<tr>
<td>Neonatal ROP stage*</td>
<td>0</td>
<td>24</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>5</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>4, 5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

* If stages in the two eyes were discordant, the eye with more advanced stage was chosen.

---

**Figure 1.** Distribution of refractive status between preterm study cases and age-matched schoolchildren (study cases, \(n = 108\); age-matched control, \(n = 2997\)). Data of the normal age-matched control group are from a 2006 national survey in Taiwan.

**Figure 2.** Distribution of astigmatism between study cases and age-matched schoolchildren (study cases, \(n = 108\); age-matched control, \(n = 2997\)). Data of the age-matched control group are from a 2006 national survey in Taiwan.
The degree of astigmatism was highest in the myopia group (−1.56 D), followed by the hyperopia group (−1.03 D) and the emmetropia group (−0.80 D; P = 0.01). The average BCVA was found to be significantly poorer in the myopia group (logMAR 0.22) than in the other two groups (P = 0.045). Myopic eyes had shallower ACD (5.29 mm) and greater LT (3.76 mm; P < 0.05). On the other hand, the AL was shortest in the hyperopia group (21.93 mm), followed by the emmetropia group (22.98 mm) and the myopia group (23.39 mm; P < 0.001). All three groups showed a similar CCT. Keratometry examination showed a flatter curvature in the emmetropia group than in the other two groups, but the difference did not reach statistical significance. Similar to the results of cylindrical refractive error, myopic eyes had the most severe corneal astigmatism, with an average of −1.82 D.

Comparison between Cases with or without ROP and between Cases with Mild or Advanced ROP

To further evaluate the influence of ROP and the severity of ROP on ocular development, we compared refraction and optical components between the ROP and non-ROP groups (Table 3A). The ROP group consisted of 29 boys and 19 girls with a positive ROP record in the neonatal period, and the non-ROP group consisted of 38 boys and 22 girls. Neither distribution of the sexes nor the average age at the latest follow-up was different between the two groups, but significantly smaller GA and BW were found in the children with ROP (P < 0.001 for both). Comparison of refraction and optical components showed that the degree of myopia and astigmatism was higher in the ROP group. Significantly shallower ACD, greater LT, and higher corneal astigmatism were found in the ROP group (all P < 0.05), and on average, the degrees of myopia and astigmatism were higher in the ROP group than in the non-ROP group.

We further compared the refractive error and optical components between the different ROP stages. Children with ROP were divided into mild ROP (stages 1 and 2) and advanced ROP (stage 3 or above; Table 3B). Of note, eyes with more advanced ROP appeared to have an even shallower ACD, greater LT, and higher degree of myopia and astigmatism (all having P < 0.05). However, similar AL was found regardless of the presence and the extent of ROP. Keratometry showed a similar pattern of steep corneal curvature in all groups.

Comparison with Age-Matched Control Subjects

Data of the boys and the girls were separated for further analysis. Table 4 summarizes the detailed results of these components between the study cases and the age-matched schoolchildren. Compared with the controls, both the study boys and the girl showed significantly shallower ACD (boys, P = 0.048; girls, P < 0.001), greater LT (boys, P < 0.001; girls, P < 0.001), and smaller CR (steeper corneal curvature) (boys, P < 0.001; girls, P = 0.02) than the age-matched controls. The differences in ACD and LT were more prominent in the children with ROP (all P < 0.001).

Despite the similarity in average AL between the study group and the age-matched control, the distribution of AL differed between the groups (Fig. 3A). The distribution pattern in the age-matched controls was close to a normal distribution and was centralized in 22.5 to 23.0 mm. However, in the study group...
cases, more of the children had an AL of less than 21.5 mm, and the peak fell between 23.0 and 23.5 mm. Furthermore, the distribution pattern was similar between the ROP and non-ROP groups, except that the children with ROP were more likely to have elongated ALs (non-ROP group versus control group, \( P = 0.49 \)).

Linear regression was conducted to further clarify the relationship between AL and spherical equivalence in our cases (Fig. 3B). Although the more severely myopic eyes tended to show elongated ALs compared with the emmetropic or hyperopic eyes, the difference was much less than the results predicted from the normal population, which estimated an approximately 0.37 mm axial elongation with a 1-D myopic shift.22,23 The regression equation showed only a 0.21- to 0.22-mm elongation with a 1-D myopic shift, and the correlation coefficient suggested only mild to moderate correlation \( (R^2 = 0.36) \). Comparisons among different refractive groups showed that children with shorter ALs tended to develop hyperopia (Fig. 3C). However, no significant difference in AL was found between myopia and emmetropia cases \( (P = 0.07) \).

### Predictors of Refractive Error

GEEs were used to further clarify the risk factors and predictive parameters associated with high incidence of refractive errors in children born prematurely. All categorized or quantified data were incorporated in the equation for analysis. In the analysis of predictors for myopic shift, the children with myopic and emmetropic eyes were included; with respect to the analysis of hyperopic shift, the children with hyperopic and emmetropic eyes were included. Factors demonstrating strong correlations with the refractive outcomes are listed in Table 5, and the equations are displayed below.

Based on the results of the analysis, the severity of myopia can be predicted by the following equation:

Spherical equivalent (D) = \( 32.0266 + 1.1931 \times \text{ACD} (\text{mm}) - 2.2015 \times \text{AL} (\text{mm}) - 0.5125 \times \text{VCR} (\text{mm}) - 7.7223 \times \text{HCR} (\text{mm}) - 3.1325 \times \) \( \text{esotropia} > 10 \) D

\[ R^2 = 0.8717 \]

The \( R^2 \) of this equation was 0.87, suggesting a predictive rate of more than 93%.

The degree of hyperopia can be predicted by the following equation:

Spherical equivalent (D) = \( 10.1988 + 1.7315 \times \text{ACD} (\text{mm}) + 1.8941 \times \text{AL} (\text{mm}) + 3.5579 \times \text{HCR} (\text{mm}) + 0.7915 \times \) \( \text{esotropia} > 10 \) D

\[ R^2 = 0.7693 \]
The \( R^2 \) of this equation was 0.77, indicating that the Pearson correlation between the observed and predicted values was more than 0.87.

The degree of astigmatism can be predicted by the following equation:

\[
\text{Cylinder dipters (D) = } -5.0947 + 0.8549 \times ACD (\text{mm}) + 0.5054 \times LT (\text{mm}) - 0.1828 \times AL - 4.8499 \times HCR + 5.4557 \times VCR - 0.5159 \] (in the worse eye in highly anisometropic children)

where highly anisometropic children are defined as having a difference of \( >5 \) D in spherical equivalent between the two eyes; the worse eye is the eye with more absolute refractive error; and the adjusted \( R^2 \) of this multiple linear regression model is 0.79, suggesting that the Pearson correlation between the observed and predicted values are >0.88.

Some variables of birth history such as GA and BW do not contribute to these equations. However, further analysis of the study cases showed that children with shorter GA or lower BW tended to have shallower ACD and greater LT (Table 6, all \( P < 0.01 \)). Other variables regarding birth history (neurologic deficits, cyanotic heart disease, and severe anemia) and results of ocular examinations (stereopsis and CCT) did not correlate with refractive outcomes.

**DISCUSSION**

Ocular structures go through a continuous development and remodeling process before and after birth.\(^{24-30}\) Premature departure from the intrauterine environment may affect ocular development or later emmetropization.\(^{3,9,25,26,31}\) Postnatal stress or diseases may also alter the normal process of ocular development.\(^{32,33}\) Most reports analyzing the refractive status of children born prematurely.\(^{3,34,35}\) However, some studies suggested that the early refractive errors may not provide enough information in predicting the later refractive outcome.\(^{9,11}\) Whether these factors play significant roles in determining refractive errors in older children is disputable, as the process of emmetropization continues after 5 years of age. Therefore, we enrolled a complete cohort of children born prematurely and aged between 7 and 9 years, to evaluate the effect of preterm birth on long-term ocular development.

We found a very high proportion of ametropia in our patients of preterm birth. Previous studies have shown that most school myopia resulted from elongated AL.\(^{15,14,16}\) However, prematurity may have a significant influence on optical components, and premature birth may have a more complicated mechanism that affects the development of refractive status. O’Connor et al.\(^4\) studied the refractive state in children aged 10 to 12 years with a BW of less than 1701 g, and both myopic shift and significant shorter AL were found. Past studies also showed that preterm infants may develop so-called myopia of prematurity (MOP) secondary to arrested development of the anterior segment.\(^{56}\) MOP is independent of ROP status and is characterized as having a low AL-to-power ratio, a shallow ACD, and a thicker lens.\(^{37}\) These studies suggested that the ocular biometry and the mechanism of refractive error were different in patients of preterm birth.

In our study, we confirmed that the significant steep corneal curvature, shallow ACD, and greater LT noted in the study cases, regardless of sex (Table 4), suggested that characteristic of anterior segment may persist until school age. The average AL in the three groups showed a progressive increase, ranked from the hyperopia followed by the emmetropia and the myopia groups. However, no significant difference in AL was found between myopia cases and emmetropia cases (\( P = 0.07 \); Fig. 3C). Although the average AL in our study group was not different from that of the control group, the ALs were much more variable in the preterm group (Fig. 3A). A larger proportion of the children with small AL tended to develop hyperopia, whereas some of the children with mildly elongated AL presented a leftward shift in refractive distribution. The different distribution in AL and the abnormal growth of anterior segment may account for the different ametropic outcome in our patients. It appears that no single optical component was significant enough to explain the diverse refractive status in children born prematurely. Our GEE equations also confirmed that multiple factors were involved in predicting refractive status.

Corneal curvature may be influenced by prematurity. Another study showed that preterm infants had a steeper corneal curvature than did full-term infants.\(^{7,8,56}\) Some studies have suggested that the abnormally steep curvature disappears gradually in infancy.\(^{38,39}\) However, in our long-term follow-up, steep corneal curvature was a common finding in these cases, regardless of sex, ROP severity, birth GA/BW, or refractive status. Our study showed that the corneal curvature of children born prematurely did not flatten to the same extent as that in children of full-term birth.

In the present study, 48 (44\%) of the 108 children had ROP, whereas the other 56\% did not. The prevalence of ROP in our cohort was similar to that in previous studies with the same GA range as in our study.\(^7,40\) Twenty-nine (27\%) of the 108 children had ROP of stage 3 or above. ROP is known to have a significant impact on optical components. Majima\(^41\) and Hino et al.\(^42\) reported that at least some ROP-afflicted children had myopia secondary to a combination of increased LT, decreased ACD, and increased AL. Laws et al.\(^43\) found that infants with more severe ROP had shorter AL. In this study, we observed that the children with ROP had shallower ACD and greater LT, but there was no significant difference in AL or CR, compared with those parameters in other children of premature birth. The shallow ACD and thick lens became more prominent in the advanced ROP cases, regardless of AL, and the combination of these changes resulted in significant myopia. Shallow ACD and thick lens may lead to angle-closure glaucoma. Michael et al.\(^44\) reported 10 cases of late-onset angle-closure glaucoma associated with ROP, with onset between 12 and 45 years. In general, even though the myopic population seldom develops angle-closure glaucoma due to long ALs, the same situation cannot be guaranteed in the ROP-related myopic cases.

Our study provided a detailed analysis and several unique findings about the refractive development of children born prematurely. Figure 4 shows the components associated with premature birth and the features of different types of refractive errors. In contrast to normal control eyes, the eyes of our students showed steeper corneal curvatures, shallow anterior chambers, thick lenses, and variable ALs. Hyperopic status largely resulted from a short AL, whereas the development of myopia was mainly attributable to the anterior segment factors. Eyes with a history of advanced ROP tended to develop severer

<table>
<thead>
<tr>
<th>GA (wk)</th>
<th>BW (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACD, mm</td>
<td>( R = 0.278 (P = 0.007) )</td>
</tr>
<tr>
<td>LT, mm</td>
<td>( R = -0.359 (P &lt; 0.001) )</td>
</tr>
</tbody>
</table>
myopia, which was due to even shallower AC and greater LT, although elongated AL was simultaneously observed in some cases. In a study of low-birth-weight children (<1701 g) at 10 to 12 years of age, O’Connor et al. found that preterm birth leads to shorter AL on average, but those with higher myopia (more than −3.0 D) had elongated AL. In their study, children of myopia had similar ACD with those of emmetropia but longer ACD than those of hyperopia. However, our results suggested similar average AL between preterm and full-term children. In addition, we noted that children with myopia had significantly shorter anterior chambers (P = 0.02) and thicker lenses (P = 0.03) than those with emmetropia or hyperopia. Although long ALs were found in extremely myopic eyes, the elongation of the eye was not the major contributor to myopia. In contrast, AL played an important role in children with hyperopia, who had significantly shorter ALs than the emmetropic and myopic children.

Most children of premature birth developed astigmatism in the present study. Those with ROP tended to have more astigmatism, especially in cases with advanced ROP. High astigmatism with divergent axes had been reported in children of ROP residua and cryotherapy. In our cases, the treatment of ROP was uniformly laser photocoagulation rather than cryotherapy. Most patients achieved good anatomic outcome without ROP residua. Unlike previous reports, our study showed that most of the study cases (76/108 children, 70%) exhibited WTR astigmatism, and the extent correlated well with corneal astigmatism.

In the present study, we applied statistical methods based on basic model-fitting techniques for regression analysis to calculate the GEEs to evaluate the refractive status and possible risk factors of refractive errors. The predictive equation for myopia showed that ACD, AL, and VCR were three major factors in determining refractive status in mild myopia. If an advanced stage of ROP and abnormal systemic conditions after birth such as seizure episodes were found, certain constants had to be added to the equation to make the result much more accurate. The GEEs to evaluate the refractive status and possible risk factors of refractive errors. The predictive equation for myopia showed that ACD, AL, and VCR were three major factors in determining refractive status in mild myopia. If an advanced stage of ROP and abnormal systemic conditions after birth such as seizure episodes were found, certain constants had to be added to the equation to make the result much more accurate.
the optical characteristics of the children were compared to those of an age-matched normal population from a national survey. Therefore, the results could provide more information concerning the significance of various optical components found in children born prematurely. Furthermore, our study was the first to use GEEs to set up a predictive model for different refractive errors. This statistical method could provide a more accurate analysis of risk factors than the traditional regression method. Given the moderate number of subjects, the power of our analyses would be adequate for the statistically significant findings, but caution should be used in the interpretation of negative results, as some factors may become statistically significant if the sample size is larger.

In conclusion, our study demonstrated the increased incidence of myopia, hyperopia, and astigmatism in schoolchildren with preterm birth. These patients were characterized as having shorter ACVs, greater LTs, and steeper central corneas, compared with age-matched control subjects. Myopia is mainly attributable to anterior segment components, rather than to increased AL. A combination of the anterior segment components with different ALs results in varied refractive outcomes.

The existence of ROP may be associated with significantly shorter ACV and greater LT, and higher myopia and astigmatism (Fig. 5). Patients born prematurely should be informed of the possible risks of certain ocular diseases that may accompany refractive and ocular component changes. The importance of long-term follow-up should be emphasized. Future study is needed to examine the refractive error changes in preterm patients during their adolescence to adult ages.

References


