Development of Spherical Equivalent Refraction in Prematurely Born Children During the First 10 Years of Life

A Population-Based Study

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Objective: To evaluate the development of refraction, expressed as spherical equivalents, in prematurely born children during the first 10 years of life.

Methods: Retinoscopy in cycloplegia was performed at 6 months, 2.5 years, and 10 years of age in 198 prematurely born children from a previous population-based study on the incidence of retinopathy of prematurity. Spherical equivalents were calculated. Myopia was defined as a spherical equivalent of less than 0 diopters (D), clinically significant myopia at 10 years of age as −1 D or less, and moderate or high myopia as less than −3D. Hypermetropia greater than +3 D was regarded as significant.

Results: There were no significant differences during the refractive development between the various subgroups of retinopathy of prematurity. Cryotreated eyes had a wider distribution of refractive errors. A multiple regression analysis revealed that the spherical equivalents at 2.5 years of age predicted clinically significant myopia (≤−1 D) at 10 years of age.

Conclusions: Retinoscopies at 6 months, 2.5 years, and 10 years of age show a similar course of spherical equivalent refractive development regardless of the stage of retinopathy of prematurity. Refraction at 6 months of age is an unreliable predictor, but the refraction at 2.5 years of age seems to be a better tool for identifying refractive errors that will remain at 10 years of age.

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3.5 years of age, and they were finally called back at age 10 years along with a control group of children born at term. The refraction of the prematurely born children had been described at ages 6 months and 2.5 years and in both preterm and full-term children at age 10 years.4,5

Among the original study population of 260 children, 8 had died and 4 had been excluded in a previous follow-up because of ophthalmological or general diseases not related to prematurity.6 Of the remaining 248 children, refractions were measured at ages 6 months (247 children; both eyes), 2.5 years (228 children; 228 right eyes and 227 left eyes), and 10 years (213 children; both eyes). In the present study of the development of refraction, we included 198 children with retinoscopies on all of the occasions (198 right eyes and 197 left eyes). At 6 months of age, cycloplegic refractions were measured using eye-drops consisting of 0.5% cyclopentolate hydrochloride and 0.5% phenylephrine hydrochloride, and at the later examinations using 0.85% cyclopentolate hydrochloride and 1.5% phenylephrine hydrochloride. Spherical equivalents were calculated. Myopia was defined as a spherical equivalent of less than 0 diopters (D), clinically significant myopia as −1 D or less, and moderate or high myopia as less than −3 D. Hypermetropia greater than +3 D was regarded as significant.

For various analyses, ROP stages are grouped as no ROP, mild ROP (stages 1 and 2), and severe ROP (stages 3-5). Severe ROP is further divided into untreated and cryotreated ROP. The criterion for treatment was ROP stage 3 in at least 4 contiguous clock hours in zone II, even in the absence of plus disease.

The study was approved by the local ethics committee at Karolinska Institute, Stockholm. Informed consent was received from the families.

The Wilcoxon matched-pair signed rank test and the t test for dependent samples were used to compare the right and left eyes regarding various refraction variables. A 2-way analysis of variance was used to analyze the impact of the ROP stage on spherical equivalents during the first 10 years of life. Because the sample sizes were unbalanced and the variances were not homogeneous, an analysis of variance model with separate variance estimates was used (Proc Mixed in SAS statistical software [SAS Institute Inc, Cary, NC]).4 In the analysis of the prevalence of spherical equivalent refractive errors longitudinally, an analysis of variance for repeated measures was performed (SAS procedure GENMOD). A stepwise logistic regression analysis (combining backward elimination and forward selection methods) was performed to determine the most important risk factors for clinically significant myopia (≤−1 D) at 10 years of age.

RESULTS

The findings in the right and left eyes were analyzed separately. Since there were no significant differences between the eyes in the various analyses, only the results in the right eyes are presented.

BETWEEN-GROUP ANALYSES

The mean values of the spherical equivalents in the entire premature group declined significantly with time on the 3 retinoscopies.

A reduction of the mean values occurred with age (6 months, 2.5 years, and 10 years of age) in the ROP groups, regardless of the severity of ROP (Figure 1). Although children who had received cryotherapy generally had a significantly lower mean value (P = .03) of the spherical equivalents in all of the age groups, we found no significant differences in the course of refractive development between the various subgroups of ROP.

The distribution of the spherical equivalents in the right eye in various subgroups of ROP at the 3 ages is given in Figure 2. The prevalences of refractions between 0 D or greater and +3 D or less were similar throughout the study in all of the subgroups of ROP (Figures 2A-E). Changes in the distribution of hypermetropia in the entire group of prematurely born children were most marked between 6 months and 2.5 years of age (P < .001), after which the prevalence remained stable (P = .71) (Figure 2A). The prevalence of myopia of less than 0 D in all of the infants during this 10-year period increased slightly (P = .08) (Figure 2A). However, the prevalences of moderate or high myopia (≤−3 D) could not be statistically analyzed because of the small number of eyes. Regarding the various stages of ROP (Figures 2B-E), a significant difference of the prevalence of myopia (≤0 D) was found (P = .004), and the cryotreated eyes showed the highest prevalences, particularly of moderate or high myopia, in all of the age groups.

In a stepwise logistic multiple regression analysis of clinically significant myopia (≤−1 D) at 10 years of age (14 eyes), the gestational age at birth, birth weight, stage of ROP (including cryotreatment), and spherical equivalents at 6 months and 2.5 years of age were included as independent risk factors. In univariate analyses, all of the risk factors were statistically significant. However, in the multiple regression analysis, only the spherical equivalent at age 2.5 years was a significant risk factor for clinically significant myopia (≤−1 D) at age 10 years (P = .005). The risk of developing myopia of −1 D or less at age 10 years increased 9-fold with a reduction of each diopter of spherical equivalent at age 2.5 years. Further, the sensitivity and specificity at various cut-off points, ie, thresholds of refraction at age 2.5 years, with regard to myopia of −1 D or less at age 10 years were calculated (Table).
Figure 2. Prevalences of spherical equivalent refractive errors at ages 6 months, 2.5 years, and 10 years in the total study group (n=198) (A), with no retinopathy of prematurity (n=121) (B), with mild retinopathy of prematurity (n=42) (C), with severe, untreated retinopathy of prematurity (n=12) (D), and with cryotreated retinopathy of prematurity (n=23) (E). D indicates diopters.

Multiple regression analyses of moderate and high myopia (<−3 D) and hypermetropia (> +3 D) could not be performed because the number of eyes in these groups was too small.

INDIVIDUAL EYES

The course of refraction was studied in the right eyes of 198 children who had cycloplegic refractions measured at all of the 3 ages (6 months, 2.5 years, and 10 years).

Hypermetropia

Figure 3 shows the course of spherical equivalents of 26 eyes with hypermetropia of greater than +3 D at age 6 months. Twenty-one eyes (81%) had lost their hypermetropia at age 10 years. One eye developed clinically significant myopia (≤−1 D), and none developed moderate or high myopia.

In Figure 4, the findings in 8 eyes with hypermetropia of greater than +3 D at age 2.5 years are illustrated. Five of these eyes still had hypermetropia of greater than +3 D at age 10 years. Two eyes had developed hypermetropia for the first time at age 2.5 years, but they both lost it at age 10 years. No eye with hypermetropia had developed myopia at 10 years of age.

Figure 5 shows the course of spherical equivalents of 9 eyes with hypermetropia at 10 years of age. Five of these eyes had been hypermetropic on all of the retinoscopies, and the onset of hypermetropia greater than +3 D occurred after the examination at age 2.5 years in 4 children.

Myopia

The individual course of refraction in 16 eyes with myopia of less than 0 D at age 6 months is shown in Figure 6. In 4 eyes, the myopia was regarded as physiological, ie, it had disappeared on the retinoscopy at age 2.5 years. Four eyes had a slight myopia (<0 D and ≥−3 D) throughout the 10 years of the study. Three of the eyes with slight myopia progressed to moderate or high myopia at age 10 years. Two of the 3 children with moderate or high myopia (<−3 D) retained the same degree of myopia at age 10 years.

Figure 7 demonstrates the refractive development of 20 eyes with myopia (<0 D) at 2.5 years of age. Fifteen eyes remained myopic (<0 D) at age 10 years. Twelve of these eyes had clinically significant myopia (≤−1 D) at the examination at age 10 years. At the retinoscopy at age 2.5 years, moderate or high myopia was observed in 6 eyes, all of which retained the same degree of myopia at age 10 years.

Finally, Figure 8 shows the course of refraction in 14 eyes with clinically significant myopia (≤−1 D) at 10 years of age. Most (11 of 14 eyes) had myopia of less than
Moderate or high myopia at age 10 years had already been observed in 6 of 8 eyes at the examination at 2.5 years of age. The 2 remaining eyes had only slight myopia.

The individual course of spherical equivalents in the right eyes of 23 children who received cryotreatment and took part in all of the 3 refraction measurements is shown in Figure 9. In a majority of these eyes (20 of 23 eyes), there was a slight reduction of the refraction over time.

In the present study, we describe the development of refraction, expressed as spherical equivalents, in prematurely born children during the first 10 years of life. Analyses of retinoscopies at 6 months, 2.5 years, and 10 years of age revealed a similar refractive course regardless of the stage of ROP. The distribution of various subgroups of refractive errors in eyes with all stages of ROP was similar during this period, but the cryotreated eyes showed a different pattern.

In individual eyes, retinoscopy at age 6 months did not seem to predict subsequent spherical equivalent refractive errors at age 10 years, but the examination at age 2.5 years was a better tool. This was confirmed by a multiple regression analysis in which the spherical equivalent at 2.5 years of age predicted clinically significant myopia (−1 D or less) at 10 years of age.

Eighty percent (198 of 248) of the original population of prematurely born children underwent regular reti-
noscopy at ages 6 months, 2.5 years, and 10 years in the present population-based study, which permitted us to study the course of refraction. In the American Multicenter Trial of Cryotherapy for Retinopathy of Prematurity, Quinn et al. described the refractive development with an emphasis on myopia in prematurely born children with birth weights of less than 1251 g who were between 3 months and 5½ years of age, and also up to 10 years of age in treated and untreated eyes with threshold ROP. Other studies on the course of refraction in comparatively few children have also been performed. Lue et al. determined the course of myopia from ages 3 months to 13 years in 62 children with mild ROP. Fledelius described the individual course of refraction in eyes with myopia in 16 prematurely born children aged 3 to 9 years, and Choi et al. followed up the refraction in 65 prematurely born children from ages 6 months to 6 years.

It is noteworthy that all of the subgroups of ROP in the present study showed a similar course of refractive development in the 10-year period, although the cryotreated eyes had lower mean values of spherical equivalents on the 3 noscoscopic examinations. This does not agree with the findings by Lue et al., who described different courses of spherical equivalent, mostly toward myopia, in children with mild ROP as compared with those without ROP. In our study, the distributions of refractive errors were similar in the groups with no ROP, mild ROP, and severe, untreated ROP (Figure 2B-D). In the cryotreated eyes, however, a different pattern was found, with a wider distribution of spherical equivalent refractive errors and a higher prevalence of myopia (Figure 2E). This seems to be in accor-

Figure 5. Course of spherical equivalents of 9 eyes with greater than +3 diopters at 10 years of age.

Figure 6. Course of spherical equivalents of 16 eyes with less than 0 diopters at 6 months of age.
dance with the findings by Quinn et al.\textsuperscript{10} who described a similar distribution of refractive errors in eyes that did not develop ROP and in those with mild ROP, but a wider distribution in eyes with moderate (prethreshold) ROP. Prethreshold ROP is probably comparable to the stage of ROP in most of our cryotreated eyes, particularly since we treated ROP at a slightly earlier stage than that recommended by the American Multicenter Trial of Cryotherapy for Retinopathy of Prematurity.\textsuperscript{8,15}

When we analyzed the distribution of hypermetropia in all of the subgroups of ROP in the 10-year period, a reduction of hypermetropia between the first 2 retinoscopies was found, with stabilization thereafter (Figure 2). In the study by Quinn et al.,\textsuperscript{10} this change in hypermetropia was also seen in eyes with no ROP and mild ROP, but not in those with prethreshold ROP. The reason for disturbed emmetropization in their prethreshold eyes and not in our cryotreated eyes cannot be determined. The proportion of eyes with myopia (<0 D) increased slightly with age (Figure 2), unlike in the study by Quinn et al.,\textsuperscript{10} which may be owing to the fact that they only described refraction up to the age of 5\textfrac{1}{2} years.\textsuperscript{10}

In the present study, the refractive development in individual eyes (Figures 3-8) indicated that refraction at 6 months of age did not predict spherical equivalent refractive errors at 10 years of age, but most of the refractive errors at 10 years of age were found by the age of 2.5 years. This was illustrated by the fact that 21 (81%) of the 26 eyes with hypermetropia (greater than +3 D) at age 6 months had lost it by age 10 years, and that hypermetropia at age 10 years in only 4 of 9 eyes had not been diagnosed by the age of 2.5 years (Figure 3 and Figure 5). How-
ever, 3 of the latter children had strabismus and were already treated with glasses. Moreover, in 4 of 16 eyes, myopia at age 6 months appeared to be physiological and had disappeared by the examination at age 2.5 years (Figure 6). Most (11 of 14) of the eyes with clinically significant myopia (−1 D or less) at age 10 years had myopia of less than 0 D at age 2.5 years (Figure 8). This is in accordance with the views of Fledelius, who pointed out that physiological myopia in newborns is transient and that a diagnosis of myopia of prematurity must not be regarded as definitive before 2 years of age. Fledelius also states that myopia of prematurity is often severe and is diagnosed early in childhood, which was confirmed by our study (Figure 7 and Figure 8).

Description of the course of spherical equivalents in cryotreated eyes revealed that most eyes had a slight reduction of refraction during the study (Figure 9). However, 1 eye retained high hypermetropia throughout the study, and 2 eyes had a marked increase in their myopia. Comparison with the study by Quinn et al was not possible since that study did not discuss the spherical equivalent refractive development in individual cryotreated eyes.

Prematurely born, school-aged children have a higher prevalence of refractive errors than those born at term. Long-term follow-up is therefore warranted to identify children needing glasses to promote visual development and to prevent amblyopia. Previous studies in this population have described the results of cycloplegic refraction in the present cohort of prematurely born children with birth weights of 1500 g or less, at ages 6 months, 2.5 years, and 10 years. Children with cryotreated eyes ran the highest risk of developing refractive errors, but those with untreated ROP and without ROP also ran a higher risk than those born at term. Therefore, all of the prematurely born children screened for ROP should be included in an ophthalmological follow-up program.

To maximize the cost benefit, it also must be decided when follow-up examinations should be done. The present study with repeated retinoscopies permits us to analyze factors that predict spherical equivalent refractive errors. The results indicate that retinoscopy at age 6 months is unpredictable, which is in accordance with the findings of Fledelius, Quinn et al, and Choi et al. Retinoscopy at age 2.5 years, however, seems to be much more reliable for predicting clinically significant refractive errors and the need for glasses later. This was confirmed in a multiple regression analysis of clinically significant myopia (−1 D or less) at age 10 years in which spherical equivalents at ages 6 months and 2.5 years were added as independent risk factors together with gestational age at birth, birth weight, stage of ROP, and cryotreatment. With a certain reservation for the limited number of eyes and large confidence interval, only the spherical equivalent at age 2.5 years proved to be a significant risk factor.

To consider which threshold of spherical equivalent refractive error at age 2.5 years to follow up, the sensitivity and specificity at various cut-off points were calculated (Table). With a threshold at less than +1 D, no eyes with clinically significant myopia (−1 D or less) at age 10 years would be missed whereas further reduction would result in a few eyes that are missed. For example, a threshold of less than +0.5 D resulted in rea-

<table>
<thead>
<tr>
<th>Threshold of Refraction at Age 2.5 y (Eyes, No.)</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; +3 D (188)</td>
<td>100.0</td>
<td>5.5</td>
</tr>
<tr>
<td>&lt; +2 D (164)</td>
<td>100.0</td>
<td>18.5</td>
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<tr>
<td>&lt; +1 D (69)</td>
<td>100.0</td>
<td>70.1</td>
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<tr>
<td>&lt; +0.5 D (31)</td>
<td>85.7</td>
<td>89.7</td>
</tr>
<tr>
<td>&lt; 0 D (20)</td>
<td>78.6</td>
<td>95.1</td>
</tr>
<tr>
<td>&lt; −0.5 D (14)</td>
<td>78.6</td>
<td>98.4</td>
</tr>
<tr>
<td>&lt; −1 D (10)</td>
<td>71.4</td>
<td>100.0</td>
</tr>
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Abbreviation: D, diopter.
Prematurely born children have a higher risk of refractive errors, regardless of the severity of ROP. It is therefore important to identify those who need glasses to provide optimal visual development and to prevent amblyopia. The present population-based study of the course of refraction in prematurely born children shows that all of the subgroups of ROP have a similar rate of change in spherical equivalents over the first 10 years of life. Refraction at age 2.5 years is better than that at age 6 months for predicting the refractive status at age 10 years.

Finally, it should be emphasized that the present study only describes the spherical equivalent development. Definite recommendations for follow-up of refractive errors must also take into account astigmatism and anisometropia and will be forthcoming. Further, an increased risk of visual impairment, strabismus, and perceptual deficiencies, as well as the fundus appearance, must also be considered when designing general ophthalmological follow-up programs for prematurely born children.

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