Visual Outcome in Infants with Cicatricial Retinopathy of Prematurity

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Monocular grating acuities of preterm infants with retinopathy of prematurity (ROP) were measured using a forced-choice preferential-looking (FPL) procedure. Eyes were independently graded by a retinal specialist and/or pediatric ophthalmologist and assigned to anatomic outcome categories on the basis of cicatrical residua of ROP. Eyes assigned to the normal/regressed and peripheral retinal changes categories (n = 120) had normal posterior poles. The authors found that grating acuities in this group were slightly lower than those of age-matched healthy full-term infants, even when infants with amblyogenic or neurologic conditions were eliminated from the analysis. Grating acuity of eyes assigned to the macular ectopia, macular fold, partial detachment, or total detachment outcome categories (n = 60) had abnormal posterior poles, and grating acuity of these eyes was significantly related to anatomic outcome category (P < 0.001). Follow-up data from subsets of eyes at 6 months, 12 months, or 2-5 yr after the initial acuity test suggest that early FPL acuity tests may be predictive of long-term functional outcome (r = 0.75-0.87). Invest Ophthalmol Vis Sci 32:410-415, 1991

Preterm birth is associated with a higher prevalence of visual impairment than full-term birth, particularly in the very-low-birthweight group.1,2 Some common forms of visual disorders in the very-low-birthweight population are retinopathy of prematurity (ROP), refractive error, nystagmus, and strabismus.3-10 However, few quantitative data on monocular acuity development are available for well-defined populations of very low birthweight preterm infants.11-14 This study examined the degree of acuity deficit present in different grades of cicatrical ROP and the predictive validity of early forced-choice preferential-looking (FPL) acuity tests for long-term visual outcome.

Materials and Methods

Subjects

Infants with a history of ROP were referred by one of seven pediatric ophthalmologists and three retinal specialists (located in the Dallas–Fort Worth area 1982–1990) to our laboratory for acuity testing. Participating infants (n = 180 eyes; 135 infants) had gestational ages at birth ranging from 24–33 weeks and birthweights ranging from 420–1790 g. The mean age at initial acuity testing was 11.8 ± 13.1 months adjusted age (20.8 months post-conception). Eyes were independently evaluated for anatomic changes due to ROP by a retinal specialist and/or pediatric ophthalmologist. Eyes were graded by the examining ophthalmologist(s) on the basis of cicatrical residua of ROP. The following categories were used and adapted from those used by the national multicenter study of cryotherapy for ROP:15 normal/regressed (n = 99), peripheral retinal changes (n = 21), macular ectopia (n = 23), macular fold (n = 9), partial detachment or partial retrolental opacity (n = 11), or total detachment or complete retrolental opacity (n = 17). In addition to ROP, a variety of other visual disorders were present in this group: strabismus (n = 31 infants), nystagmus (n = 23 infants), myopia (n = 43 eyes; range: −0.5– −13.5; 12 eyes had 7 diopters or greater myopia), and anisometropia (n = 11 infants; range: 2–9.5 diopters). Forty-six eyes had been treated with cryotherapy (19 infants in both eyes, 8 children in 1 eye). Twenty-one eyes were treated with other ophthalmic procedures, including vitrectomy, scleral buckle, and eye muscle surgery.

Acuities of preterm infants were compared with

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* None of the infants were participants in the multicenter CRYO-ROP study; they were born before or after the recruitment period or were cared for in a non-participating nursery.
† Since participants in this study were a referral population, the prevalence of visual disorders among them is unlikely to be equivalent to the prevalence among all low-birthweight infants. The data summarized here are provided as a description of the population studied.
those of healthy full-term infants on the basis of post-conceptual age. A description of the healthy full-term population of infants and their monocular acuity data (n = 246 eyes, 1 eye per infant) have been published. Their gestational ages at birth ranged from 38–42 weeks (mean: 39.7 ± 1.2 weeks).

Informed consent was obtained from a parent or guardian of all infants before acuity testing.

Apparatus and Procedures

For infants aged 1–15 months, grating acuity was assessed by an FPL procedure. The infant was held over the parent’s shoulder or on the parent’s lap at eye level with two rear projection screens (11.5° diameter, 36° center-to-center separation) located in a dark room 50 cm away. High-contrast (≥ 90%) vertical gratings and paired gray fields were projected onto the screens. The gratings and gray fields were photometrically matched in space-averaged luminance (2.5 log cd/m²). On each trial, the infant was confronted with a grating vs gray field stimulus pair. The observer, without knowledge of the position of the grating, made a forced-choice judgment about which side the infant preferred to fixate. No feedback was given to the observer. On each trial, the grating appeared on a pseudo-randomly chosen side. Gratings ranging from 0.38 to 48 c/deg were presented in a transformed two-down-one-up staircase. Ten staircase reversals were obtained and grating acuity was defined as the average of the final eight reversal points. This staircase provided an estimate of threshold at 70.7% correct. For toddlers and young children, operant reinforcement was added to this procedure. For each stimulus pair, the child was required to point to the grating position and receive a food reward for each correct response. Children received a brief training period before they were tested and were required to accomplish six consecutive correct responses with coarse gratings (0.38 c/deg) before proceeding with the acuity test. Operant testing was conducted at 25 cm so that the children could reach the stimulus panel to point and collect food rewards. All other aspects of the operant procedure and stimuli matched those used in the FPL tests. Infants and children with significant refractive errors wore appropriate optical correction during acuity tests.

Analyses

For each eye tested, the grating acuity obtained on the initial visit was compared with the mean acuity of age-matched full-term infants. A difference score was calculated (acuity deficit in octaves) for each test. All statistical analyses were conducted using the intraclass correlation model described by Rosner.

Results

Normal Posterior Pole

One hundred twenty eyes had normal posterior poles: 99 classified as normal/regressed and 21 with anatomic changes limited to the peripheral retina (scarring primarily due to cryotherapy). The range of acuity deficits in the normal posterior pole group relative to healthy full-term infants is shown in Figure 1. The mean acuity deficit (using the intraclass correlation model) for these eyes was small, −0.279 octave; ie, slightly but significantly below the acuity of age-matched healthy full-term infants (t = 4.16, P < 0.001). Acuity deficit was not significantly rank-order correlated with gestational age at birth, birth-weight, or adjusted age at testing within either the normal/regressed or the peripheral retinal changes groups.

Some of the infants had ophthalmic conditions that may have been amblyogenic (eg, anisometropia, strabismus with fixation preference), neurologic conditions (eg, hydrocephalus, cerebral palsy, grade 3 or 4 intraventricular hemorrhage), or both conditions, which might have resulted in an acuity deficit independent of ROP outcome (Fig. 1). Acuity data from these eyes were deleted and the acuity deficits relative to full-term infants were re-analyzed. The mean acuity deficit decreased slightly, −0.197 octave, but

\[\text{Octaves Difference from Mean Normal}\]

\[\begin{array}{c}
\text{Both} \\
\text{Neurologic} \\
\text{Possible Amblyopia} \\
\text{None}
\end{array}\]

\[\text{Number of Eyes}\]

\[\begin{array}{c}
-3 \\
-2 \\
-1 \\
0 \\
1 \\
2 \\
3
\end{array}\]

Fig. 1. FPL acuity deficits of eyes with normal posterior poles (normal/regressed and peripheral retinal changes anatomical outcome categories). Four subgroups are shown: None, no other ophthalmic or neurologic condition is present; Possible amblyopia, an amblyogenic condition is present (anisometropia, strabismus with fixation preference, high myopia); Neurologic, a neurologic condition that may affect visual acuity is present (cerebral palsy, hydrocephalus, significant IVH, etc.); Both, both amblyogenic and neurologic conditions are present.
remained significantly different from that of healthy full-term infants ($t = 2.94$, $P < 0.005$).

Twenty-one of the eyes with normal posterior poles had been treated with cryotherapy; the remaining 99 eyes had regression of retinopathy. The acuity deficits of these two subgroups of eyes with normal posterior poles are shown in Figure 2. There was no significant difference in mean acuity deficit between eyes treated with cryotherapy and eyes with normal/regressed outcome ($t = 0.004$).

Abnormal Posterior Pole

Sixty eyes had abnormal posterior poles as a result of ROP. The mean acuity deficit for each anatomical outcome group is shown in Figure 3. For infants who had no consistent fixation response to even the coarsest grating (20/1600), an arbitrary but conservative value of six octaves acuity deficit was assigned. This was the maximum acuity deficit obtained from any child who responded to at least the coarsest grating. The severity of acuity deficit was directly related to the severity of anatomic outcome. As shown in Table 1, this relationship was statistically significant. Post-hoc tests, summarized in Table 2, showed significant difference between all pairs of outcome categories with the exception of two pairs: ectopia vs macular fold and macular fold vs partial detachment. For the abnormal posterior pole group as a whole, acuity deficit was not significantly rank-order correlated with gestational age at birth, birthweight, or adjusted age at testing.

Follow-up

The use of grating acuity tests in predicting long-term visual development was assessed by applying linear regression to first-visit data vs follow-up data from infants who were tested at least twice. These two occasions were separated by 6 months, 12 months, or 2-5 yr. Various anatomic outcome categories were represented at each retest interval. As shown in Figure 4, the acuity deficit found on the initial visit was predictive of later acuity deficit. Correlation coefficients were 0.845 ($P < 0.001$), 0.869 ($P < 0.001$), and 0.750 ($P < 0.001$) for the three follow-up intervals, respectively. Slopes of the best-fitting lines were near 1.0, ranging from 0.855-0.996, and intercepts were near 0.0, ranging from −0.870-0.151. These parameters were estimated standard errors of the means. To examine whether the arbitrary assignment of six octaves acuity deficit to those infants who did not respond to the coarsest grating may have influenced the statistical analyses, the data were analyzed with the nonparametric Kruskal–Wallis analysis of variance by ranks. Right and left eyes were analyzed separately since no intraclass correlation model was available for nonparametric ANOVA. Nonparametric statistical results were comparable to the parametric results for both right eyes ($H_{3,30} = 13.53$, $P < 0.005$) and left eyes ($H_{3,30} = 21.195$, $P < 0.0001$).

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**Table 1. Analysis of variance comparing acuity deficit among different anatomical outcome groups using the intraclass correlation model**

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between groups</td>
<td>115.27</td>
<td>3</td>
<td>38.42</td>
<td>16.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Between persons</td>
<td>90.51</td>
<td>39</td>
<td>2.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>within groups</td>
<td>18.08</td>
<td>17</td>
<td>1.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SS: sums of squares; df: degrees of freedom; MS: mean square.
ters indicate that there is little change in the absolute value of the acuity deficit at the various follow-up ages.

The concurrent validity of grating acuity test results was evaluated for 18 children (36 eyes) who were able to participate in Snellen acuity testing during a follow-up visit. Correlations between grating acuity and Snellen acuity for the first visit on which both tests were administered were high for both right and left eyes ($r = 0.92, P < 0.01$ and $r = 0.93, P < 0.01$).

**Table 2. Values of t-statistics and p-values for comparisons of specific outcome groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>Persons/eyes</th>
<th>Comparison group</th>
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<tbody>
<tr>
<td>Ectopia</td>
<td>-1.70</td>
<td>0.39</td>
<td>15/23</td>
<td>Ectopia</td>
</tr>
<tr>
<td>Fold</td>
<td>-2.86</td>
<td>0.58</td>
<td>7/8</td>
<td>Fold</td>
</tr>
<tr>
<td>Partial</td>
<td>-3.22</td>
<td>0.54</td>
<td>8/11</td>
<td>Partial</td>
</tr>
<tr>
<td>Total</td>
<td>-5.22</td>
<td>0.42</td>
<td>13/18</td>
<td>Total</td>
</tr>
</tbody>
</table>

Fig. 4. Relationship between FPL acuity deficit (octaves below mean normal) at the initial visit and at follow-up visits scheduled (A) 6 months, (B) 12 months, or (C) 2 to 5 years after the initial visit.
Discussion

Monocular grating acuities of eyes with normal posterior poles were slightly lower than acuities of age-matched healthy full-term infants. A recent report on grating acuity development in 17 infants with regressed stage 3 ROP has also shown an acuity deficit in eyes with normal posterior poles but has attributed this deficit to coexisting periventricular leukomalacia or significant intraventricular hemorrhage in some of the infants. In the larger group of infants reported here, a slight acuity deficit was found even when infants with ambylogeic or neurologic conditions were eliminated from the analysis. The source of this acuity deficit remains to be determined. Isenberg described a delay in macular development when ROP develops in preterm infants and has proposed that this delay may affect acuity development. Angiographic evidence of macular sequelae of ROP has also been reported. The question of whether the acuity deficit reported here is a functional consequence of differences in macular development between preterm and full-term infants or whether it results from other subclinical retinal or neurologic changes awaits further study.

The normal posterior pole outcome group consisted of all eyes in the normal/regressed category and eyes that had been treated with cryotherapy. Both subgroups showed a slight but significant acuity deficit relative to age-matched healthy full-term infants. Despite the fact that the sample sizes for the normal/regressed and cryotherapy groups were sufficient to detect a 0.5-octave difference at the $\alpha = 0.05$ level with a power of 0.99, no significant difference in acuities was found. This study was not designed to evaluate the overall efficacy of cryotherapy; however, the similarity of visual acuity outcomes for the normal/regressed ROP group and the successfully treated cryotherapy group suggests that cryotherapy itself has no adverse effect on visual acuity development.

For eyes in the abnormal posterior pole outcome categories, these data show that FPL acuity directly relates to the severity of anatomic outcome. In part, the variability of FPL results within an outcome category reflects the heterogeneity of anatomic changes subsumed within it. In addition, no attempt was made to exclude infants with concomitant disorders (16.3% of the infants had neurologic disorders, including cerebral palsy, hydrocephalus, developmental delay, and/or seizures; 16.7% of their eyes possibly had ambylogeic conditions, including high myopia, anisometropia, and/or strabismus with fixation preference). Grading of outcome solely on the basis of fundus appearance almost certainly increased the heterogeneity found in each outcome category. Despite this, a strong relationship was found between anatomic outcome category and FPL acuity. In the future, effects of heterogeneity within an anatomic category (e.g., degree of macular dragging) and the effects of other disorders will be examined in a larger group of preterm infants.

The longitudinal data presented here are preliminary but suggest the predictive value of FPL acuity. The acuity deficit found on the initial visit was significantly correlated with the acuity deficit found at later visits. The initial visit occurred at an average of 7 months adjusted age, with follow-up 6 months to 5 yr later. During this period, healthy full-term infants undergo significant improvement in FPL acuity, from approximately 20/100 at 5 months to 20/20 at 3–5 yr. The fact that the acuity deficit of the eyes studied remained approximately constant relative to full-term norms means that the FPL acuity of preterm infant eyes also showed improvement during the follow-up period. Good agreement between grating acuity and Snellen acuity was found among children who participated in both tests during a follow-up visit. Taken together, these results suggest that early FPL acuity results are predictive of long-term functional outcome.

Lastly, FPL acuity was useful in evaluating visual outcome in eyes with cicatricial ROP. The significant relationship between acuity outcome and anatomic outcome supports the concurrent validity of FPL acuity. The significant correlations between the acuity deficit on the initial visit and acuity deficits measured on follow-up support the predictive validity of FPL acuity. The availability of FPL acuity outcome data for infants and preverbal children with ROP may permit more rapid evaluation of treatment protocols for this group of high-risk infants.

Key words: retinopathy of prematurity, forced-choice preferential looking, visual development

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References