Dark-Adapted Thresholds in Children With Histories of Mild Retinopathy of Prematurity

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Purpose. To test the hypothesis that rod-mediated visual thresholds at 10° eccentricity are elevated in children with histories of mild retinopathy of prematurity (ROP).

Methods. Dark-adapted thresholds for detection of 50 msec, 2° diameter spots at a 10° eccentric site, and at a peripheral reference site, 30° eccentric, were measured in 20 children with a history of mild ROP and known courses of refractive development. Ten myopic control subjects also were tested. The thresholds of the ROP and control subjects were compared.

Results. Six of the subjects with ROP had elevated thresholds at the 10° site. High myopia had been present since age 18 months or younger in each of the six. The thresholds of all other subjects with ROP, whose courses of refractive development had been toward emmetropia, and the control subjects with myopia were normal. In subjects with ROP, the association of early, persistent high myopia and an elevated threshold at 10° was significant (χ² = 20; P < 0.01). Among the subjects with ROP, refractive error and axial length were correlated.


Retinopathy of prematurity (ROP) has its onset preterm at ages when human rod outer segments are normally growing rapidly. In some children with histories of mild ROP, electroretinographic (ERG) a-wave responses to full-field stimuli indicate function of the outer segments is abnormal long after the ROP has resolved. Although electroretinography with full-field stimuli evaluates the function of the entire retina, it does not detect abnormalities specific to the macula, which is approximately the central 5% of the total retinal area. For instance, dense macular lesions have no demonstrable effect on ERG responses to full-field stimuli.

Psychophysical thresholds for detection of small test spots can assess rod-mediated visual function in the central as well as peripheral retinas of infants and children. We measured visual thresholds in children with a history of mild ROP to test the hypothesis that their rod-mediated visual thresholds at 10° eccentricity are elevated.

METHODS

Subjects

Children who had been diagnosed with mild ROP as infants were recruited. Letters were sent to the families...
TABLE 1. Clinical Characteristics of Subjects With ROP

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Gestational Age at Birth (weeks)</th>
<th>Birth Weight (g)</th>
<th>ROP (stage, zone, hours)</th>
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<td>1</td>
<td>25.0</td>
<td>810</td>
<td>2, 2, 12</td>
</tr>
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<td>32.0</td>
<td>1498</td>
<td>1, 2, 3</td>
</tr>
</tbody>
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ROP = retinopathy of prematurity.

of all children with regressed ROP (n = 62) who were
described in a recent study of the course of refractive
development in eyes with mild ROP.9 They included
patients from Children's Hospital who had all the fol-
lowing characteristics: birth dates from January 1,
1976, through December 30, 1988; noncicatricial
ROP; retinopathy specified as to severity and location
in the retina; explicit statements in the record that in
every eye, the retinal area within the temporal arcades,
the macula, was ophthalmoscopically normal at every
examination; normal globes except for refractive er-
rors and a history of mild ROP; at least two cycloplegic
refractions post-term; and normal general develop-
ment or only mild neuromotor handicaps. None of
the eyes of any of the children had macular pigmen-
tary disturbance, heterotopia, or retinal folds that
might cause mechanical disturbances of the photore-
ceptors in the central retina. None had optic atrophy
at any examination.

Twenty subjects with ROP participated (Table 1,
subjects 1 through 20). Although most were born be-
fore the International Classification of Retinopathy of
Prematurity classification system,10 records docu-
mented ROP consistent with zone 2 involvement, stage
1 to 3 in severity.9,10 The ROP was symmetric with the
same stage, zone, and number of hours of involvement
in the right and left eyes of each subject. None had a
history of plus disease10 or of laser or cryotherapy.
At the time of the threshold test, none had any ophthal-
moscopically visible disturbance of the peripheral ret-
ina.

The previously studied9 refractive courses of the
subjects with ROP are summarized in Figure 1. Six
were myopic in infancy and their high myopia per-
sisted (Fig. 1A). Glasses were first prescribed after age
6 months for myopia of −7.00 to −12.00 diopters. The
refractive courses of the other 14 subjects with ROP
were toward emmetropia (Figs. 1B, 1C, 1D), although
3 (Fig. 1B) were myopic at first refraction, and 6 had
"school myopia" (Fig. 1C). Five had normal courses of
refractive development (Fig. 1D).

Healthy myopes (n = 10) without a history of pre-
term birth also were studied (subjects 21 through 30).
They were recruited by "word of mouth." Their spherical
equivalents ranged from −2.50 to −15.25 (median,
−7.00) diopters. Their myopia had been discov-
red when they were 2 to 10 years of age.

The study conformed to the tenets of the Declara-
tion of Helsinki and was approved by the Children's
Hospital Committee on Clinical Investigation. In-
formed consent was obtained from the parents of the
children and from the adult myopes.

Ophthalmic Examination
An ophthalmic examination was conducted on the day
of the threshold test. Refractions were done with a

FIGURE 1. Summary of refractive courses in the subjects with retinopathy of prematurity. In
each panel, the spherical equivalent of the right eye is shown as a function of post-term age. The vertical bar at the left of each panel indicates the 99% prediction interval for spherical equivalent in normal infants at term.9 The patient's number is that indicated in Tables 1 and 2. For those with glasses, the black symbol indicates the age at which glasses were first prescribed. The age at which the threshold test was done is indicated by the last point plotted for each patient. (A) The courses of the six subjects with high myopia, subjects 1 through 6 in Tables 1 and 2, are shown. The early, rapid increase in myopia has been modeled as a simple exponential in another report.6 The heavy dashed line represents the course of normal refractive development.6 (B) Three patients had a course from myopia toward emmetropia. (C) Five patients had courses toward emmetropia, but then at 8 years of age or older returned with myopia. (D) Five patients have courses of refractive development indistinguishable from those of normal subjects.6
Canon R-1 autorefractor 30 to 45 minutes after instillation of 1% cyclopentolate. Matrix algebra was used to calculate the average of 10 refractions for each eye.

Axial lengths were measured in 17 of the subjects with ROP using a-scan ultrasonography (Model A 2500; Sonomed, Lake Success, NY) after topical administration of 0.5% proparacaine. The mean of five measures was obtained while the patient fixated a distant target. The corneal curvatures were measured in 17 of the subjects with ROP (EyeSys 1 Corneal Analysis...
The psychophysical procedure with which normal subjects and Myopic Control Subjects for each ROP subject was analyzed. The subject, with a binocular view of the screen, was instructed to look at the central fixation target. Then the fixation target was extinguished and a test stimulus was displayed. The stimuli were 2° diameter, 50-msec duration spots of blue light (Wratten 47B, \( \lambda < 510 \) nm) with centers 10° and 30° to the right or left of a 30° eccentricity, which had been studied 812 was used. The subject received feedback on every trial. Detection thresholds were calculated from the two principal meridians.

Corrected acuities were measured (ETDRS Log MAR chart; Lighthouse Low Vision Services, New York, NY) and reported in decimal notation with 20/ 20 = 1, 20/40 = 0.5, and so forth. To minimize possible effects of amblyopia, the better of the two acuities for each ROP subject was analyzed.

### Threshold Test Procedure
The psychophysical procedure with which normal development of rod-mediated vision at 10° and 30° eccentricities had been studied 812 was used. The subject was dark adapted for 30 minutes and then sat 50 cm from a rear projection screen, where the stimuli were displayed. The stimuli were 2° diameter, 50-msec duration spots of blue light (Wratten 47B, \( \lambda < 510 \) nm) with centers 10° and 30° to the right or left of a 30° eccentricity, which had been studied 812 was used. The subject received feedback on every trial. Detection thresholds were calculated from the two principal meridians.

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Thresholds in Children With Mild ROP

FIGURE 2. The distributions of Δ10-30 values in retinopathy of prematurity (ROP) and control subjects. The Δ10-30 values of the subjects with ROP (black bars) are distributed broadly. Six of the subjects with ROP have positive Δ10-30 values that indicate elevation of the threshold at 10° eccentricity. All other subjects with ROP have Δ10-30 close to those reported previously for normal adult control subjects (hatched bars) with a median Δ10-30 of zero. None of the control subjects with myopia (open bars) have elevated Δ10-30 values.

RESULTS

The data obtained on the day of the threshold test are summarized in Table 2. In Figure 2, the distributions of the Δ10-30 values in subjects with ROP and control subjects are shown. In the subjects with ROP, Δ10-30 ranges from -0.07 to +0.52 log unit. Six subjects with ROP have Δ10-30 of +0.31 to +0.52 (median, +0.42) log unit, indicating elevation of the threshold at 10° eccentric. The thresholds of the other subjects with ROP are approximately equal at the 10° and 30° sites with Δ10-30 close to zero (median, 0; range, -0.07 to +0.08 log unit). In control subjects with myopia, Δ10-30 also is close to zero (median, 0; range, -0.06 to +0.08 log unit) as reported previously for normal adult control subjects.

Each of the six subjects with ROP with elevated threshold at 10° (Table 2) has high myopia (median spherical equivalents: right eye - 8.91 diopters; left eye - 8.88 diopters) and has had more than -5 diopters of myopia in both eyes since age 18 months or younger (Fig. 1A). This early, persistent myopia and...
the elevated threshold at 10° are associated significantly ($\chi^2 = 20, df = 1, P < 0.01$). Other subjects with ROP who were myopic in infancy, but have had courses toward emmetropia (Fig. 1B) have normal thresholds.

For clarity, the spherical equivalents of the subjects with ROP at first and last refraction are summarized in Figure 3. Three of the six who were high myopes at the time of the threshold test (Fig. 3, left panel) have, in early infancy, spherical equivalents within the prediction interval\textsuperscript{9} for normal subjects (Fig. 1A). None of the six change toward emmetropia. Among the 14 subjects with ROP with normal thresholds, the distribution of spherical equivalents at first refraction is broad, +5.00 to −15.00 diopters (Fig. 3; right panel). Nevertheless, over the years, all 14 have changed toward emmetropia (Figs. 1B, 1C, 1D), although 6 (Fig. 1C) became myopic in the school years. For these 14, the median spherical equivalent of the right eye at the last refraction is −0.56 (range, −3.62 to +2.46) diopters; the median spherical equivalent of the left eye is −0.10 (range, +3.02 to +3.55) diopters and does not differ significantly from that of the right eye.

In the subjects with ROP, spherical equivalent and axial length (Table 2) for the right eye are correlated ($r = −0.85; P < 0.01; n = 17$); results are similar for the left eye ($r = −0.92; P < 0.01; n = 15$). The greater the myopia, the greater the axial length. Corneal power and spherical equivalent are not correlated.

In some individual subjects with ROP, the acuity of the eye with the better acuity is poorer than 1 (Table 2). Of the two acuities for each subject, the better acuities are significantly poorer in the six with elevated $\Delta_{10-30}$ than in those with normal $\Delta_{10-30}$ ($t = −2.44; df 18; P < 0.05$). Nevertheless, in five subjects with ROP (subjects 8, 9, 10, 15, and 16) with no elevation of threshold at 10°, both eyes have corrected acuities poorer than 1; their posterior poles are ophthalmoscopically normal. Two myopic control subjects (subjects 21 and 27) had acuity <1 in their better eye. Normal subjects in this age range have acuities of 1 or better.\textsuperscript{16}

**DISCUSSION**

The majority of the 20 subjects with ROP have normal, dark-adapted, scotopic thresholds for binocular detection of stimuli at both 10° and 30° eccentricities. Thus, ROP alone does not cause elevated thresholds. These
subjects with ROP had a history of symmetric ROP in right and left eyes and, on average, less than a half diopter of anisometropia.

Six of the subjects with ROP, however, have elevated scotopic thresholds for detection of the 2° stimulus at 10° eccentricity. Threshold elevation could occur if the rods’ ability to catch light were compromised. Other explanations, however, deserve consideration. For instance, staphylomatous stretching in eyes with myopia could cause greater center-to-center spacing of rods and apparent increase in the critical diameter, fewer rods activated by the stimulus, and consequent threshold elevation. The 2° stimulus is larger than the normal critical diameter in the posterior retina.\(^\text{17,18}\) Perhaps increased rod-to-rod spacing is an unlikely explanation because none of the control subjects with myopia have elevated thresholds. Additionally, normal photopic detection thresholds in young adults with myopia (−7.37 to −9.5 diopters spherical equivalent) speak against the stretching hypothesis.\(^\text{19}\) Neither myopia nor a history of mild ROP alone leads to the elevated thresholds. However, early, persistent myopia (Fig. 1A) and elevated threshold at 10° have a statistically significant association.

Previous ERG and anatomic studies suggest a photoreceptor basis for the elevated thresholds. In a rat model of ROP and in some children studied long after their active ROP had resolved, ERG results were similar. Both the saturated amplitude of the rod phototransduction and the gain of the activation of rod phototransduction were attenuated.\(^\text{3,4,20}\) Alterations in the post-receptoral b-wave parameters were explained mainly by receptor dysfunction.\(^\text{4}\) In the rat model, abnormalities in the outer segments including variable lengths, irregularly spaced discs, and highly variable absorbances by microspectrophotometry underlie the ERG results.\(^\text{21}\) Thus, we speculate such alterations in the rod outer segments underlie the rod dysfunction seen in subjects with ROP\(^\text{3,4}\) and is reflected in the elevated thresholds at 10° in the six subjects with high myopia. Rod outer segment material turns over regularly.\(^\text{22}\) Therefore, outer segments present in infancy during the time of active ROP would be long gone by the childhood years when the ERG\(^\text{3,4}\) and threshold tests were done. Thus, we suspect ROP, or the factors leading to ROP, damage the mechanisms controlling outer segment formation.\(^\text{23}\)

The threshold test detects no deficits in retinal sensitivity at 30° eccentricity in any of the subjects with ROP, including the six subjects with high myopia. Two of the subjects with high myopia (subjects 1 and 5) also participated in the ERG studies and had significant attenuation of saturated amplitude and gain of phototransduction in the rod cells. Thus, a normal visual threshold at 30° appears at odds with that of the ERG results.\(^\text{3,4}\) However, the relation between these ERG rod cell response parameters and visual detection of small spots of light remains to be defined. In a retina with abnormal ERG a-wave responses to full-field stimuli, some normally responding rods might be present within the 2° patch of retina under test at 30°. This could occur if the hypothesized alterations in the outer segments were heterogeneous across the retinal surface.\(^\text{21}\)

The myopia of the six subjects with ROP with elevated thresholds is axial. This implies enlarged globes and posterior segments. Although axial lengths were not measured at the time of the first refraction, the 20-diopter range of refractive errors near term (Figs. 1 and 3) suggests eye size was more variable among the subjects with ROP than that in term-born infants or in former preterms without a history of ROP.\(^\text{9}\) Thus, ROP, which has its onset preterm, may deregulate eye growth. In animals, the retina is the site of mechanisms that regulate eye growth.\(^\text{24–26}\) In subjects with ROP, photoreceptor dysfunction is consistent with retinal mechanisms that are involved in the regulation of eye growth.\(^\text{4}\) The photoreceptors are involved in experimental myopia.\(^\text{27–29}\)

The growth of rod outer segments in the central retina, which includes the 10° eccentric eye, has a slower developmental course than that in peripheral retina.\(^\text{1,2,6}\) Also rod-mediated visual sensitivity normally matures more slowly in the central than in peripheral retina. Specifically, when dark-adapted, 10-week-old infants are tested with stimuli that produce equal thresholds at 10° and 30° eccentricities in adults,\(^\text{8}\) the infants’ threshold at 10° is more elevated than at 30°. By age 6 months, the infants’ normal elevation of the threshold at 10° has vanished, and thresholds at both sites equal those in adults.\(^\text{15}\) Infants with a history of mild ROP have \(\Delta_{10-30}\) values of approximately +0.8 log unit, whereas normal infants have \(\Delta_{10-30}\) values of only +0.5 log unit.\(^\text{30}\) The discovery of threshold elevation in children (subjects 1 through 6) with a history of mild ROP and early persistent high myopia leads us to suspect some causative relation of the function of the developing rods and refractive development. However, we cannot rule out that some factor affects both rod function and refractive development.

The foveal cones, which have a prolonged course of development,\(^\text{31}\) also may be susceptible to the adverse effects of ROP because the acuities of some of these subjects with ROP with normal
general development are <1. In the current sample, acuity deficits in both eyes occurred not only in those with scotopic threshold elevation, but in five other subjects (subjects 8, 9, 10, 15, and 16) as well. Ophthalmoscopic evidence suggests ROP delays the development of the foveal pit. This, or other factors, such as cystoid macular edema noted in premature infants a few days after birth, before ROP has its onset, could account for the mild acuity deficits.

From a practical point of view, we note that the first refractions of these subjects with ROP do not forecast the spherical equivalent in childhood (Figs. 1A, 1B, 3). A normal spherical equivalent in early infancy does not guarantee emmetropia in childhood (Figs. 1A, 3, left panel), and myopia in infancy does not necessarily forecast high myopia in early childhood (Figs. 1B, 3, right panel). Normally, elevation of the scotopic threshold at 10° eccentricity disappears by age 6 months. Possibly excessive or persistent threshold elevation in infancy will predict high myopia in the preschool years. It may be possible to define a critical age by which Δ10−30 must reach zero for normal refractive development to proceed. Such information could affect the clinical management of patients with a history of mild ROP. A longitudinal study that monitored threshold and refractive development would yield information on this point.

Key Words
development, myopia, psychophysics, retinopathy of prematurity, rods

References
26. Wildsoet CF, Pettigrew JD. Kainic acid-induced eye


