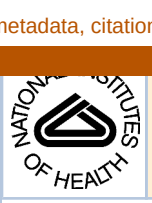

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RETINAL FEATURES PREDICTIVE OF PROGRESSIVE STAGE 4 RETINOPATHY OF PREMATURITY

M. ELIZABETH HARTNETT, MD and **JANET R. MCCOLM, PhD**

From the Department of Ophthalmology, University of North Carolina, Chapel Hill, North Carolina.

Abstract

Purpose—To determine the retinal features predictive of progressive stage 4 retinopathy of prematurity (ROP) after laser treatment for threshold ROP.

Methods—Retrospective review of 72 eyes of 37 infants after laser treatment for threshold ROP between 1993 and 2002. Retinal features were abstracted from examinations made within 1 week of development of stage 4A ROP or 2 weeks after laser treatment in eyes with regressed threshold disease. Predictive features of progressive stage 4 ROP were determined using a generalized estimating equation model to account for within-subject variability.

Results—The generalized estimating equation showed that vitreous state, ridge elevation of six or more clock hours, and two or more quadrants of plus disease predicted progressive retinal detachment, whereas two or more quadrants of neovascularization did not.

Conclusions—Progressive stage 4 ROP requiring surgical intervention was predicted by the absence of clear vitreous, ridge elevation of six or more clock hours, and two or more quadrants of plus disease, but not by neovascularization. These results may be useful in the management of eyes after laser treatment for threshold ROP.

Keywords

features; predictive; retinal detachment; retinal surgery; retinopathy of prematurity; surgical intervention

In eyes that develop progressive stage 4 retinopathy of prematurity (ROP) after laser treatment for threshold ROP,[1,2] vitreoretinal surgery is considered to prevent or repair retinal detachment.[3–7] For the best visual potential, surgery should achieve retinal attachment, be performed before macular detachment,[4] and spare the lens to permit visual rehabilitation in the phakic eye.[3,7] However, surgical complications of cataract,[8] aphakia, and peripheral retinal breaks have vision-threatening consequences, including profound amblyopia and inoperable retinal detachment,[5] which are unique to the developing infant compared with the adult. In addition, because approximately 70% of eyes treated for threshold ROP[1,2] and some eyes with stage 4A ROP do not progress,[9] recognition of retinal features predictive of progression of stage 4 ROP may facilitate early treatment of eyes at risk for vision loss and also minimize treatment of some low-risk eyes.

Reprint requests: M. Elizabeth Hartnett, MD, Department of Ophthalmology, University of North Carolina, 5109D Bioinformatics Building, 130 Mason Farm Road, Chapel Hill, NC 27599-7040; e-mail: hartnet@med.unc.edu.

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We performed this study to determine the characteristics predictive of progression of stage 4 ROP in infants who had been adequately treated for threshold ROP. We abstracted features from retinal drawings made at the time of examinations performed within 1 week of developing partial retinal detachment (stage 4A ROP) or 2 weeks after laser treatment in eyes that showed regression of disease. We developed a generalized estimating equation (GEE) model that accounted for within-subject variability of the eyes[10] to determine predictive features of progressive stage 4 ROP in eyes after laser treatment for threshold ROP.

Methods

Patients and Setting

Thirty-six infants (72 eyes) referred to one physician (M.E.H.) from 1993 to 2002 for management of stages 3, 4, and 5 ROP were studied. Twenty-one infants (42 eyes) had laser treatment performed by pediatric ophthalmologists credentialed for the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity Study (CRYO-ROP) and were referred specifically for the management of stages 4 and 5 ROP, and 15 infants (30 eyes) had laser and postlaser management, including surgery performed by the same physician (M.E.H.). All infants had carefully recorded examinations with retinal drawings before and after laser treatment for threshold ROP performed by physicians who were credentialed examiners for the CRYO-ROP study.[1] The age when surgery was performed was recorded as postmenstrual age in weeks (gestational age plus chronologic age). Human subjects' approval for exempt status was obtained to gather data retrospectively from patient charts. All patients received full examinations, including assessment of adequacy of laser treatment and the presence of skip lesions.

Observation Procedures

The examination sheets, based on forms from the International Classification of Retinopathy of Prematurity,[11] were developed to record retinal features before and after treatment for threshold ROP. Features were recorded within 1 week of developing partial retinal detachment (stage 4A ROP) or 2 weeks after laser treatment if regression of ROP occurred. Retinal characteristics included zone and stage of ROP, vascular engorgement and plus disease, ridge elevation, vitreous state, and clock hour or quadrant extent of retinal features.[1]

During the course of the study, surgical management developed and changed. To ensure uniformity for feature abstraction for every infant, sequential weekly examination forms were available for all study infants. Thus, for infants who had developed stage 4 or 5 ROP, retrospective retrieval of feature data was possible within 1 week of development of retinal detachment regardless of the stage at which the surgery was ultimately performed. Data within 1 week of stage 4A ROP was collected when possible, unless progression to stage 4B ROP occurred between two sequential weekly examinations. Uniformity of feature abstraction also applied to infants who developed stage 4 ROP and had regression without need for surgical intervention and for infants who had regressed threshold ROP without developing retinal detachment. For infants who had regression of threshold ROP, however, we chose the time of 2 weeks after laser treatment to abstract features for analysis. Features of all infants were available from records except for two eyes of one infant (Table 1), whose examination report lacked the number of quadrants of plus disease 1 week before developing stage 4 ROP; this was accounted for in the statistical analysis. The indication for surgery was progressive stage 4 ROP threatening the macula. All infants were followed up for 4 months after laser treatment to detect late development of stage 4 or 5 ROP.

Retinal Characteristics

Ridge elevation was defined as per the International Classification of Retinopathy of Prematurity,[11] a thickened structure arising from the retinal surface at the junction of the avascular and vascularized retina. Ridge elevation was considered independent from neovascularization or retinal detachment. When ridge elevation, retinal detachment (retinal elevation between the ridge and optic nerve), or neovascularization was present at the same time, each was noted separately. Ridge elevation was observed to be new if flattening of the ridge was observed after laser treatment and then recurred, or to be persistent if ridge elevation remained for longer than 2 weeks after laser treatment. Ridge elevation and its clock hour extent were recorded for every eye. The status of the vitreous was graded from 0 to 4 (0, clear; 1, hazy; 2, limited hemorrhage obscuring part of the ridge; 3, hazy vitreous and grade 2 hemorrhage; and 4, organization of vitreous with evidence of condensation within the vitreous cavity). Plus disease was recorded as the number of retinal quadrants in which the dilated retinal arteries and veins were observed. When the retinal veins were dilated in one quadrant but the arteries appeared normal, the feature was recorded as half a quadrant of vascular dilatation. The quadrants of pre-retinal neovascularization were also recorded.

Statistical Analysis

Statistical Analysis System (SAS Institute, Cary, NC) was used for analyses, including a GEE model that accounted for within-subject variability of the eyes.[10] The outcome was progression to retinal detachment requiring surgery and the predictor variables were vitreous score, clock hours of ridge elevation, and quadrants of plus disease and neovascularization. All *P* values given for predictors in the GEE model are from Wald statistics on the model parameters.[12] Odds ratios (OR) were determined from the GEE model parameters, and 95% confidence intervals (CIs) are given.

Results

Patients

This study included 72 eyes (36 right eyes and 36 left eyes) of 36 infants (13 girls and 23 boys). The median birthweight was 670 g (interquartile range [IQR], 613–748 g), and the median gestational age was 24 weeks (IQR, 24–25 weeks). In all but one eye that developed vitreous hemorrhage before threshold ROP, previous laser treatment for threshold ROP was performed as recommended.[1,2] Except for two infants (four eyes) treated with cryotherapy in addition to laser, all infants were treated with laser only. No apparent skip lesions in laser treatment were noted in any eye. All eyes, except one, that developed stage 4A ROP did so 2 or more weeks after laser treatment. In the one exception, the infant developed a stage 4B tractional retinal detachment within 1 week of laser treatment.

Features

Table 1 lists the number and frequency of retinal features and progression to retinal detachment or regression of disease. In both eyes of one patient, an assessment of plus disease could not be made from the records.

Thirty-four eyes developed progressive stage 4 ROP and required surgery, whereas 38 eyes showed regression of stage 3 (32 eyes) or 4 (six eyes) ROP. Because of the referral nature of the practice, the frequency of retinal detachment was higher than that reported in other studies.[1,2] For example, some patients who received laser treatment by outside ophthalmologists were never referred because threshold disease regressed without the development of stage 4 ROP. Twelve infants required surgery in both eyes, 10 in one eye only, and 14 in neither eye. Ridge elevation occurred in 34 eyes that required surgery, compared with 18 eyes that did not

progress. Of those eyes with ridge elevation that required surgery, 74% (26 of 34) had six or more clock hours of ridge elevation, whereas in eyes with regressed ROP, only three (8%) of 38 eyes had six or more clock hours of ridge elevation.

We used a GEE model that included within-subject assessment of variance. Features present after laser treatment for threshold ROP that predicted progression to retinal detachment requiring surgical intervention were six or more clock hours of ridge elevation ($P = 0.0248$), absence of clear vitreous on examination ($P = 0.0039$), and two or more quadrants of plus disease ($P = 0.0490$). OR estimates were six or more clock hours of ridge elevation (OR = 33.6; 95% CI, 1.56–722.9), absence of clear vitreous on examination (OR = 32.6; 95% CI, 3.1–347.8), two or more quadrants of plus disease (OR = 4.95; 95% CI, 1.01–24.34). Neovascularization in two or more quadrants extent was not a significant predictor ($P = 0.9609$). Fewer clock hours of ridge elevation or variations in the number of quadrants of plus disease or neovascularization were not significant.

Discussion

Early surgical intervention in stage 4 ROP can be critical to preserve vision for certain eyes, but there are few specific guidelines to determine eyes at risk of progressive ROP after laser treatment for threshold disease.[1–3,7,13] We studied retinal features that confront the ophthalmologist monitoring eyes after laser treatment for threshold ROP. These features were recorded within 1 week of the development of stage 4A ROP or 2 weeks after laser treatment in eyes that showed regression of threshold ROP. The outcome was progression of stage 4 ROP requiring surgery for threatened macular detachment. Features that predicted progressive stage 4 ROP were absence of clear vitreous, plus disease in two or more quadrants, and six or more clock hours of ridge elevation. Neovascularization or fewer than six clock hours of ridge elevation or two quadrants of plus disease were not predictive of disease progression.

As with any retrospective study, potential flaws exist. First, data abstraction from drawings can result in data error because of differences in interpretation of an image by the same observer or multiple observers. However, feature detection from fundus drawings of infants has been the standard in large multicenter clinical trials for ROP,[1,2] and all drawings in our study were performed by ophthalmologists credentialed for the CRYO-ROP study. Second, sometimes features may not be recorded with sufficient detail to be analyzed. In our study, only one infant examination (two eyes) (Table 1) lacked sufficient information about one feature (i.e., the number of quadrants of plus disease) and was accounted for in the GEE. Third, many retrospective studies present only case series. This study, though retrospective, did provide a reasonable control group for comparison, namely infants who received laser treatment for threshold ROP, were diagnosed and treated by ophthalmologists credentialed for the CRYO-ROP study, and had regression of threshold disease. The controls were also not historic, in that they were selected from the same period as the study group, thus reducing possible error associated with changes in management. Finally, most studies of stage 4 ROP fail to consider the effect of within-subject variability of the eyes, thereby adding error to the analysis of infants with ROP, because of the high correlation in disease severity between eyes.[14] To avoid this, we used a GEE model to account for within-individual variability and included infants who had received laser treatment in both eyes for threshold ROP.[15] We found significance, although the small numbers provided wide confidence intervals.

The causes of these late-onset features predictive of retinal detachment are unknown. There is evidence that increased vitreous haze may occur from breakdown of the blood–retina barrier related to vascular endothelial growth factor–induced permeability.[16] Several growth factors, including vascular endothelial growth factor, platelet-derived growth factor, and hepatocyte growth factor,[17] induce cell proliferation and migration[18] and may promote the thickening of

the ridge. Cell proliferation and migration onto the ridge and into the vitreous can produce visible vitreous membranes connecting the peripheral retina to anterior ocular structures. Later contraction of these membranes would detach the peripheral retina. We found that fewer than six clock hours of ridge elevation did not predict progressive retinal detachment. Perhaps when the process of vitreoretinal contraction is limited in clock hour extent, the forces acting to detach the retina are offset by the forces to maintain retina attachment.

Possible factors contributing to plus disease are also complex and may involve those that affect vascular diameter and blood flow,[19] such as nitric oxide[20] and endothelin-1.[21] That neovascularization was not predictive of retinal detachment is contrary to current clinical expectations. Our findings may indicate that changes that occur to neovascularization after laser treatment, such as early regression, may not be apparent by clinical observation alone. Regardless of the reasons, neovascularization after adequate laser treatment, without skip lesions, was an insensitive clinical marker for progression of retinal detachment in this study.

This retrospective study provides statistical support regarding guidelines for eyes at risk for progressive stage 4 ROP after treatment for threshold disease. It also provides pilot data for a large, prospective, multicenter study to assess anatomic and visual outcomes in stage 4 ROP and include an analysis of retinal features after laser treatment for threshold ROP that were predictive of progressive retinal detachment. Guidelines from such a study would aid in determining the timing of surgery for stage 4 ROP and would facilitate and improve the clinical management of infants with ROP.

From our study, we provide evidence that features of hazy vitreous, plus disease in two or more quadrants, and ridge elevation of six or more clock hours may herald the need for surgical intervention for retinal detachment in ROP. We did not find a predictive value of progressive retinal detachment from ridge elevation of fewer than six clock hours, plus disease in fewer than two quadrants, or neovascularization.

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Table 1

Retinal Features of Retinopathy of Prematurity in Eyes that Regressed or that Required Surgical Intervention

Retinal Feature	Progressed and Required Surgery, n (%)	Regressed, n (%)
Plus disease		
<2 quadrants	7 (10)	28 (39)
≥2 quadrants	25 (35)	10 (14)
Vitreous state (score)		
Clear (0)	8 (11)	35 (49)
Hazy +/or vitreous hemorrhage (1, 2, 3)	15 (21)	2 (3)
Obvious organization of vitreous (4)	11 (15)	1 (1)
Ridge elevation		
<6 clock hours	9 (12)	35 (49)
≥6 clock hours	25 (35)	3 (4)
Neovascularization		
<2 quadrants	13 (18)	34 (47)
≥2 quadrants	21 (29)	4 (6)