Retinopathy of Prematurity Care: Screening to Vitrectomy

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Retinopathy of prematurity (ROP) was originally described in 1942 by Terry[1] and at that time, no treatment was available. Formerly known as retrolental fibroplasia, ROP is a major cause of blindness in children worldwide, despite current surgical treatment in the early and late stages of the disease.[2] Major advances in ROP treatment with cryotherapy and laser photocoagulation for ablation of the avascular retina has shown to be partially effective in preventing blindness in ROP infants.[3] Without treatment, at least 47.4% of eyes go on to have permanent visual loss.[3] The trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) treatments can reduce the incidence of blindness by 50% in infants with stage 3 and plus disease.[3,4]

Epidemiology

CRYO-ROP, a multicentered prospective trial, examined 4009 infants weighing <1251 grams. These infants received an initial examination at 4 to 7 weeks after birth and defined intervals thereafter. The trial demonstrated that 65.8% of premature infants developed some degree of ROP and 6% reached threshold. Multiple births and birth outside a study hospital were associated with an increased risk of severe disease.[5,6] The incidence and severity of disease were closely correlated to lower birth weights and earlier gestational age. The incidence of ROP was 47% in infants with birth weights between 1000 and 1251 g and 81.6% in infants weighing <1000 g at birth. Sixty percent of infants born at 28 to 31 weeks developed ROP and over 80% of infants born at <28 weeks developed ROP.[7] Similar findings were reported in a more recent

INTERNATIONAL OPHTHALMOLOGY CLINICS
Volume 51, Number 1, 1–16

study involving 2528 infants: no infant born after 32 weeks of gestation developed ROP, and stage 3 disease was not seen in infants with birth weights greater than 1500 g.[8]

It has been estimated that ROP causes visual loss in 1300 children and severe visual impairment in 500 children born each year in the United States.[9] As technological advances have made survival for extremely premature infants possible, it would seem likely that the number of infants with ROP would be likely to rise. Other studies have suggested that even with an increase in survival of these high-risk neonates, this may not be the case.[8,10–13] This trend may reflect improvements in ventilation techniques and perinatal care, with the use of prophylactic surfactant and the maternal use of antenatal steroids.[13,14]

■ Pathogenesis

Hypoxia is a common precursor to the abnormal neovascularization seen in many retinal diseases. Michaelson's hypothesis of an angiogenic chemical messenger secreted in response to tissue hypoxia has led to the identification of numerous angiogenic factors.[15–17] Increased attention has been focused on vascular endothelial growth factor (VEGF).[18] Vitreous levels of VEGF are elevated in patients with a variety of proliferative retinopathies, including ROP, and vitreous fluid from these patients stimulates growth of endothelial cells in vitro.[19] Vitreous samples taken from stage 4 or 5 eyes at the time of surgical repair were analyzed and compared with those found in the vitreous of age-matched children undergoing cataract surgery. VEGF levels were found to be dramatically elevated in the ROP eyes compared with controls, and eyes demonstrating persistent vascular activity had even higher concentrations.[20]

In the mouse model of ROP, VEGF is expressed in normal postnatal retina just anterior to developing capillaries.[21] High levels of oxygen decrease VEGF expression and lead to regression of retinal capillaries, whereas relative hypoxia induces a prompt 3-fold increase in VEGF expression and abnormal angiogenesis.[21–23] Dysregulated VEGF expression may lead to vaso-obliteration or exaggerated vasoproliferation. Studies in which there are fluctuations in oxygen levels have shown more severe ROP.[24] Serum levels of VEGF are significantly higher in infants with stage 3 and threshold ROP than in those with less severe disease. The peak difference occurs at 36 weeks postconceptional age, which is, coincidentally, the median onset of the active neovascularization of threshold disease.[25] Surgical eyes average a postconceptual age of 45 weeks and eyes with persistent vascular activity maintain significantly elevated VEGF levels in the vitreous.[26]

Histologically, stage 1 ROP is characterized by hyperplasia of the primitive spindle-shaped cells of the vanguard mesenchymal tissue at the demarcation line.[26] The ridge of stage 2 consists of further hyperplasia of the spindle cells and proliferation of the endothelial cells of the rearguard mesenchymal tissue. Extraretinal vascular tissue emanates from the ridge in stage 3. Proliferation of endothelial cells and small, thin-walled vessels occurs and represents abnormal angiogenesis. In the later stages, condensation of the vitreous into sheets and strands oriented anteriorly toward the equator of the lens occurs and tractional forces draw the retina anteriorly, leading to retinal detachment.

■ Clinical Features

In normal retinal development, vessels begin to migrate from the optic disc to the ora serrata at 16 weeks of gestation.[27] Vasculogenesis, the de novo synthesis of vascular channels, transforms precursor mesenchymal spindle cells into capillary networks. Mature vessels differentiate from these networks and extend to the nasal ora serrata by 36 weeks and to the temporal ora serrata by 39 to 41 weeks gestational age. The fundamental process underlying the development of ROP is incomplete vascularization of the retina at the time of birth. The location of the interruption of normal vasculogenesis is related to the time of premature birth.

The International Classification of Retinopathy of Prematurity was established in 1984, revised in 1987, to provide standards for the clinical assessment of ROP based on the severity (stage) and anatomic location (zone) of disease.[28,29] The first sign of ROP, stage 1, is the appearance of a thin, flat, white structure (demarcation line) at the junction of vascularized retina posteriorly and avascular retina anteriorly. In stage 2, the demarcation line develops into a pink or white elevation (ridge) of thickened tissue. Vessel growth into and above the ridge (extraretinal fibrovascular proliferation) characterizes stage 3 (Fig. 1). This fibrovascular proliferation may extend into the overlying vitreous and cause vitreous hemorrhage. With progressive growth into the vitreous, contraction of fibrovascular proliferation exerts traction on the retina, leading to partial retinal detachment (stage 4), either without foveal involvement (stage 4a) (Fig. 2) or with foveal involvement (stage 4b). Stage 5 denotes a total retinal detachment. These funnel-shaped detachements have configuration that can be further described as open or closed anteriorly and open or closed posteriorly. During the acute phases of ROP, progressive vascular insufficiency at the edge of the abnormal vasculature may lead to increasing dilatation and tortuosity of peripheral retinal vessels, engorgement of iris vessels, pupillary rigidity, and vitreous haze.[29] ''Plus disease'' occurs when the peripheral vascular

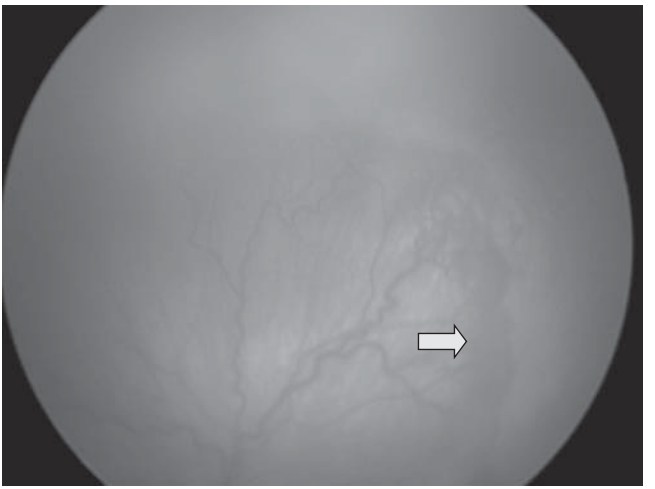

Figure 1. *Fundus photograph of premature infant eye. Vessel growth at and over ridge demonstrated in stage 3 retinopathy of prematurity. The arrow is pointing to the neovascularization seen in stage 3 retinopathy of prematurity.*

shunting of blood is so overwhelming that it leads to marked venous dilatation and arterial tortuosity in the posterior pole and is the hallmark of rapidly progressive ROP.

ROP is also classified by anatomic location (zone). The most anterior abrogation of normal retinal vascularization is identified and assigned a zone. A direct correlation exists between severity of disease and amount of

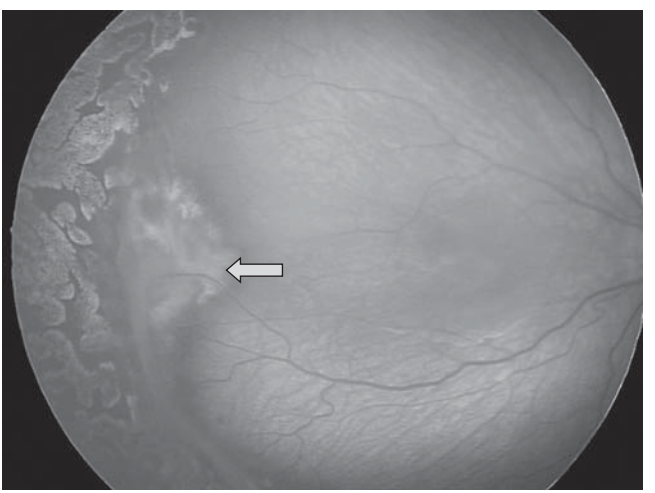

Figure 2. *Fundus photograph of premature infant eye. Retinal detachment without foveal involvement owing to contraction of fibrovascular proliferation—stage 4A retinopathy of prematurity. The arrow is pointing to the nonmacular involving retinal detachment.*

avascular retina; hence, the location of the border between vascularized and avascular retina is an important prognostic sign. Zone 1 is defined as a circle, the center of which is the disc, and the radius of which is twice the distance of the disc to the fovea. Zone 2 is a doughnut-shaped region that extends from the anterior border of zone 1 to within one disc diameter of the ora serrata nasally and to the anatomic equator temporally. Zone 3 encompasses the residual temporal retina. ROP descriptions include a stage, the posterior most zone containing disease, and a comment on the presence or absence of vascular activity (plus disease).

The determination of "threshold ROP," defined as stage 3+ ROP in zone 1 or 2 occupying at least 5 contiguous clock hours or 8 noncontiguous clock hours of retina, in CRYO-ROP sought to define the severity of ROP for which a given eye had an equal chance of spontaneous regression or progression to an unfavorable outcome.[30] In eyes with zone 2 ROP, this estimation was quite precise: 62% of untreated eyes with threshold ROP went on to a poor visual outcome; however, the estimation of a 50 of 50 threshold for eyes with zone 1 ROP was off the mark: untreated threshold zone 1 eyes had a 90% chance of unfavorable outcome.[31,32]

The Early Treatment for Retinopathy of Prematurity Cooperative Group sought to reevaluate the timing of intervention in eyes with ROP.[4,7] Two categories of prethreshold disease were created and management dictated by high-risk (type 1) or low-risk (type 2) prethreshold disease. When compared with the results of the CRYO-ROP study, the Early Treatment for ROP Cooperative Group study demonstrated fewer unfavorable outcomes, suggesting that prethreshold intervention with laser ablation is reasonable.

■ Screening

Ophthalmoscopic evaluation of the premature infant may be performed in the Neonatal Intensive Care Unit or in the office. Examination of the anterior segment is performed with specific attention to the iris vessels, lens, and tunica vasculosa lentis. Funduscopy is performed with an indirect ophthalmoscope and a 28D or 30D condensing lens. The posterior pole is examined without depression for the presence or absence of plus disease then with scleral depression to examine the temporal and nasal retina. The following guidelines have been set for screening[4]:

1. Screening for ROP should be performed in all infants with a birth weight <1500 g or a gestational age of 32 weeks or less, as well as in infants weighing between 1500 and 2000 g with an unstable clinical course and who are believed to be at high risk.
2. In most cases, at least 2 examinations should be performed. One examination may suffice, if it shows unequivocally that retinal

vascularization is complete bilaterally. The first examination should be performed between 4 and 6 weeks of postnatal age, or between the 31st and 33rd week of postconceptional age, whichever is later.
3. Infants with immature retinas (no ROP) vascularized into zone 2 or 3 may be examined at 2-week intervals.
4. Infants with type 2 prethreshold disease require weekly or twice weekly examinations.
5. Infants with type 1 prethreshold disease should be considered for peripheral laser ablation.

ROP care has evolved greatly over the last 2 decades. Interventions for ROP are based on appropriately timed and well-documented screening.[3] Unfortunately, not every premature child has access to appropriate screening and steps are being taken to ensure that screening is available to them. Screening by the qualified specialists involves incorporating bedside examinations as well as state-of-the-art photographic imaging.[33]

The key to an effective screening program is prompt identification of ROP severe enough to require treatment. Increasing the frequency of examinations is recommended as the disease approaches "threshold" so that swift treatment can be delivered.[34–36] The benefits of accurately screening and treating ROP include the prevention of severe vision loss and possible financial burdens for the infant and society. Utility analysis, used to describe the effect of an illness and medical intervention on an individual's quality of life over the course of a lifetime, for ROP has demonstrated that screening and treatment for threshold ROP is very cost effective.[37]

■ Photographic Imaging

The daunting task of screening all at risk infants for ROP poses multiple challenges. Ideally, an ROP expert would be available to perform each infant's screening examination. The limited number of physicians performing screening has been reduced. Many examiners claim fear of litigation as the reason they have stop performing screening examination.[38] A review of closed Ophthalmic Mutual Insurance Company (a risk retention group) ROP malpractice claims illustrated the multiple medical and logistical issues involved in the care of premature infants.[39] Reynolds[40] noted that a majority of the ROP malpractice cases involved a "failure to refer/missed window of opportunity." This combination of factors has fueled an interest in a photographic approach to ROP screening. The Photographic Screening for Retinopathy of Prematurity Study and that of Ells et al[41] evaluated and confirmed the utility of photographic imaging in ROP screening.[33]

This photographic imaging allows a very good representation of the posterior pole and the midperiphery of the eyes of premature infants. Photographic documentation in diabetes, age-related macular degeneration, and other retinal vascular disease is well known.[42–44] Photographic documentation of ROP has been available for several years and treatment in ROP in large part is driven by zone 1 and particularly zone 2 findings, well seen with photography.[33]

The interpretation of these pictures requires they be obtained and managed in a timely fashion and read by a qualified reader. ROP is a time-dependent disease, allowing development of stage 1 to stage 5 to occur in as little as 2 weeks.[45–47] FocusROP (FocusROP, LLC, Troy, MI), an internet-based, Health Insurance Portability and Accountability Act-compliant, secure website using certified and expert readers, has been developed to handle these images. This website, www.FocusROP.com (Fig. 3), receives the uploaded digital information obtained by trained individuals in the neonatal care centers and immediately notifies a previously certified local ophthalmologist to read these images. The follow-up algorithm contained in the software program allows only a very conservative examination schedule (Fig. 4).

Though bedside examinations allow a more extensive examination of the periphery, photographic screening has its advantages. Such advantages include an excellent view of the most severe aggressive posterior ROP and the ability to compare, side-by-side, the current examination with the previous one. The coupling of this remote management by photographic images as well as bedside examinations gives perhaps the ideal screening mechanism for the early stages of ROP. Implementation of a longitudinal digital imaging paradigm with remote image interpretation (ie, a reading center) has the potential to maximize utilization of the physician's time, broaden the availability of high-level ROP diagnostic expertise, and provide excellent patient care.

Figure 3. *Website home page. FocusROP website receives uploaded digital photographs and sends notification to the reader—who logs in to access photographs.*

Figure 4. *Website patient screen. The trained reader, via a secured website, accesses the photographs and checks the appropriate box findings. The follow up schedule is generated from these findings.*

Photographic screening does not replace the bedside examination but can be sufficient for screening to provide care for the patient and protect the hospital and doctor in malpractice cases.

■ Treatment

The goals of ROP treatment are prevention of retinal detachment or scarring and optimization of visual outcome. Treatment involves ablation of avascular retina by cryo or laser photocoagulation. Few indications remain for using cryotherapy over laser in the management of ROP: poor fundus visibility, lack of availability of laser, and a treating physician's unfamiliarity with indirect laser techniques.

■ Cryotherapy

Cryotherapy has been used to treat ROP since 1972.[48] It may be performed under topical, local, or general anesthesia, either transconjunctivally or transclerally after a conjunctival peritomy (as is necessary for posterior disease). The probe should be removed periodically for several minutes to avoid prolonged ocular hypertension. A favorable response usually occurs within 1 week.

The CRYO-ROP randomized eyes with threshold ROP to either cryotherapy or observation, to establish whether treatment reduced the occurrence of an unfavorable visual outcome (20 of 200 or worse) or unfavorable structural outcome (retinal fold, retinal detachment, or

retrolental fibroplasia).[30,31] At 10-year follow-up, eyes treated with cryotherapy were less likely to be legally blind (44% vs. 62%), and were less likely to have an unfavorable structural outcome. However, total retinal detachment still occurred in 22% of treated eyes.[49] Cryotherapy did not seem to cause significant detriment to visual field or contrast sensitivity.[50,51]

■ Laser Photocoagulation

As the inception of the CRYO-ROP study, argon laser and diode laser indirect ophthalmoscope systems have been developed. Advantages of photocoagulation include ease of treatment, portability, and fewer systemic complications. Photocoagulation is delivered through a dilated pupil with a 20D or 28D condensing lens. The endpoint is near confluent ablation, with burns spaced one-half burn width apart, from the ora serrata up to, but not including, the ridge for 360 degrees.[52] The retina should be inspected for skip areas, and the infant should be reexamined within 1 week. Persistent plus disease or fibrovascular proliferation is an indication for additional treatment. Complications of laser treatment include anterior segment ischemia; cataract; and burns of the cornea, iris, or tunica vasculosa lentis.[53,54]

Laser photocoagulation has been shown to be at least as effective, if not more effective than cryotherapy for threshold disease.[55–59] In one series of 61 eyes treated exclusively with diode laser, only 3 eyes (5%) progressed to stage 4 disease.[60] In another series of 120 eyes followed for at least 12 months, 91% had favorable structural outcomes.[58] In the largest, prospective, randomized comparison of laser photocoagulation with cryotherapy (25 infants followed for at least 4 years), eyes treated with cryotherapy were significantly more likely to have visual acuity of 20/50 or better and were significantly less myopic.[59] Laser photocoagulation is most effective for posterior (zone 1) disease: favorable anatomic results have been reported in 83% to 85% of eyes.[61,62] Cryotherapy, by contrast, provided favorable outcomes in only 25% of eyes with zone 1 disease.[63]

■ Surgery

Although retinal ablation is effective in a majority of cases of threshold ROP, a significant number of these eyes progress to retinal detachment. Detachment is most commonly tractional, originating at the ridge in a circumferential, purse-string pattern that draws the retina anteriorly and centrally.

The advanced stages of ROP (stages 4A, 4B, and 5) are poorly understood. Common misconceptions are that macula-sparing (stage 4A)

partial retinal detachments are largely benign, that surgery should be deferred until the macula is detached, that scleral buckle is the preferred retinal reattachment procedure, and that useful vision cannot be obtained in eyes with total (stage 5) detachments.

ROP-related detachments may seem stable in the first few weeks or months after peripheral retinal ablation. Yet neither the stability of partial detachment nor visual acuity is predictable from retinal appearance in infants with ROP.[31,64] This is particularly true for untreated eyes or those with incomplete peripheral retinal ablation.[31] Visual outcome of eyes with even partial ROP-related retinal detachment is generally poor by 4.5 years of age: in the cohort of 61 eyes from the CRYO-ROP study with partial retinal detachment 3 months after threshold, only 6 eyes had vision of 20/200 or better at age 4½.[5,65]

The goal of intervention for ROP-related retinal detachments varies with the severity of the detachment. The goal for extramacular retinal detachment (stage 4A ROP) is an undistorted or minimally distorted posterior pole, total retinal reattachment, and preservation of the lens and central fixation vision. Scleral buckling and vitrectomy have been used to manage stage 4A ROP.[66–68] Vitreous surgery can interrupt progression of ROP from stage 4A to stage 4B or 5 by directly addressing transvitreal traction resulting from fibrous proliferation.[69] A review of stages 4A and 4B detachments repaired with vitrectomy showed an 86% retinal attachment rate. Fix and follow behavior was noted in 78% of these infants.[70] Prenner et al[71] reported normal macular structure in 83% stage 4a detachments after vitrectomy with an average vision of 20/58. Disadvantages of scleral buckling for stage 4A ROP are the dramatic anisometropic myopia and the second intervention required for transection or removal so that the eye may continue to grow.[72] A direct comparison of stage 4 detachments repaired by vitrectomy or scleral buckle found a 73% retinal attachment rate in the eyes treated with lens sparing vitrectomy versus 31% in the scleral buckle group.[73]

Surgery for tractional retinal detachments involving the macula (stage 4B ROP) is performed to minimize retinal distortion and prevent total detachment (stage 5). The functional goal is ambulatory vision. In earlier studies, visual outcome for retinal detachment beyond stage 4A was quite poor. More recent reports demonstrate that form vision can be obtained by vitrectomy for stage 5 ROP.[64,66] Maximal recovery of vision after the insult of macula-off retinal detachment and interruption of visual development in infants may take years.

Retinal folds or tractional retinal detachments can occur in the setting of ROP. Lens sparing vitrectomy is an effective surgical treatment for such folds. The preservation of the lens during visual development may lead to better functional outcomes.[71] Retinal folds may closely approximate or contact the posterior lens capsule making surgical management difficult without performing a lensectomy to gain posterior

access. Ho et al[74] described a modification of a lens-sparing vitrectomy technique , ab interno incision, used when the surgical entry between the lens and the retina is too small for current vitrectomy instrumentation. Anatomically, the pars plana is not developed until 8 to 9 months in a postterm infant. Sclerotomies are created through the pars plicata approximately 0.5 to 1 mm posterior to the limbus. Once the sclera is entered with the microvitreoretinal blade, the blade is directed posterior and then inserted into the space between the retina and lens. Once there, anterior retinal traction is relieved and a posterior relaxation is noted. Sweeping in the surgical space parallel to the lens like a saw to releases tractional vectors.[74]

■ Future Therapies

With greater knowledge of the pathophysiology of ROP at the genetic and cellular level, comes the possibilities of novel and more effective therapeutic strategies. Pharmacologic stabilization of aberrant angiogenesis may be one approach. In the murine model of ROP, retinal neovascularization is inhibited by oligodeoxynucleotide antagonists of VEGF, by competitive blockade of VEGF receptors, and by intraperitoneal injection of pigment epithelium-derived factor, a natural antiangiogenic factor.[75–77] With the advent of anti-VEGF therapies for the treatment of age-related macular degeneration this is now a possibility. The bevacizumab eliminates the angiogenic threat of ROP study (ClinicalTrials.gov Identifier: NCT 00622726), a phase II study of intravitreal bevacizumab injections versus conventional laser surgery for ROP, has the purpose of exploring the safety and efficacy of avastin as a single injection (0.625 mg) into the vitreous cavity versus standard laser therapy while randomizing both eyes of every infant into either the avastin or the laser-treated group. The end point is the development of a primary recurrence of ROP at a minimum of 1 week.[78,79] Avastin appears, in small studies, to be potentially beneficial in stage 3 ROP but may be detrimental in stages 4 and 5 ROP.[78,80] Intravitreal avastin has also been explored as an adjunct to laser therapy.[81,82] Other therapies include adenovirus-mediated gene transfer into hyaloid and preretinal blood vessels of a rat model of ROP.[83] Such an approach may hold promise as an efficient method of delivering antiangiogenic therapies or molecules which will reestablish appropriate retinal development to a targeted location.

Our understanding of ROP continues to evolve, from expanding the methods and access to screening and the best indications and techniques for improving visual outcomes. A campaign to increase awareness starts with the interactions between the parents, the hospital, and ophthalmologist. Continued prospective studies are needed to explore the treatments on the horizon.

Dr Michael T. Trese holds financial interest (equity partner and consultant) in the FocusROP website and software.Dr Lisa J. Faia has no financial interests.

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