Retinopathy of Prematurity

Retinopathy of prematurity (ROP), initially described as retrolental fibroplasia by Terry in 1942 was the leading cause of blindness in children in the United States (US).[1] To date, three "epidemics" of blindness due to ROP have been described.[2][3] The first epidemic occurred in the 1940s-1950s in industrialized countries primarily due to unmonitored supplemental oxygen. Regulation and monitoring of high oxygen at birth caused ROP to virtually disappear, but as a result of advances neonatal care, premature infants survived at earlier gestational ages and lower birth weights, and ROP re-emerged to be a serious problem, leading to the second epidemic that began in the 1970s in industrialized countries. Then in mid-1990s, the third epidemic began in low and middle income countries (i.e. initially in Eastern Europe and Latin America, spreading to East and South Asia, and now in sub-Saharan Africa) due to both high rates of preterm birth and varying levels of neonatal care in these countries (some countries/regions within countries lack the technology and resources to optimize their care) where ROP is seen in larger and older infants exposed to unregulated oxygen (similar to that in the US in the 1940's and 50's).[4] In the US and developed countries, ROP affects extremely premature infants and involves incomplete vascularization of the retina as well as oxygen-induced damage, which is believed to play less a role now.[5] Therefore, the manifestation and timing of ROP differs greatly throughout the world.

Etiology

In utero, the fetus is in a hypoxic state in contrast to after birth. When infants are born prematurely, the relative oxygen level is increased sometimes even when oxygenation is at ambient level. High supplemental oxygen can be damaging to capillaries.

The cause of ROP is premature birth and additional factors that cause a mismatch between normal retinal vascularization and oxygen need by the developing retina.

Risk Factors

Key risk factors

- Low birthweight
- Young gestational age
- High, unregulated oxygen at birth
- Poor postnatal growth

Suggested risk factors

- Intraventricular hemorrhage, respiratory distress syndrome, sepsis, white race, blood transfusion, and multiple births. [6][7]
- A study found that 'prenatal steroid use, GA (gestational age), the duration of mechanical ventilation, and respiratory distress syndrome were associated with the development of

ROP. However, GA, bronchopulmonary dysplasia, the number of red blood cell units transfused, intraventricular hemorrhage, and periventricular leukomalacia were significantly correlated with ROP progression.'[8]

General Pathology

In histological studies of infants with ROP, the earliest lesions seen in acute phase were arteriovenous shunts. Other lesions include neovascularization that may penetrate the vitreous, microvascular changes including tufting, and obliteration of capillaries around arteries and veins.[9]

Pathophysiology

ROP occurs in premature infants who are born before the retinal vessels complete their normal growth.

Normal retinovascular development in the human is believed to occur initially through vasculogenesis, or de novo formation of vessels from precursor endothelial cells, at about 14-16 weeks gestation and vascularizing the posterior pole through 22 weeks gestation. Following this angiogenesis occurs budding from existing vessels to extend retinal vessels to the periphery and to the other plexi. Migrating endothelial cells are attracted by a gradient of vascular endothelial growth factor (VEGF) toward the ora serrata.

However, in ROP premature birth stops the process and other factors play a role in the initial halt in normal vascular development and possible oxygen-induced vascular injury. Risk factors can include high oxygen at birth, fluctuations in oxygenation, poor postnatal growth, possible oxidative stress. In developed countries, extreme prematurity related to low birth weight and young gestational age is highly associated. In countries lacking resources for ROP can occur in larger and older infants. The role of oxygen in the causation of ROP is complex. Studies have shown that keeping the oxygen saturation at a lower level from birth can reduce the rate of advanced ROP, but some have found increased mortality. [10]

Primary prevention

Screenings of infants at risk with appropriate timing of exams and follow up is essential to identify infants in need of treatment.[7] It is important to recognize that screening recommendations may vary by location. In India and Asia, ROP can occur in babies of older gestational age or larger birth weight.[11] The text and table below summarizes the current recommendations for the United States.[12]

The following infants should be screened for ROP:

- Low birthweight (1500 grams or less)
- Gestational age (30 weeks or less)
- 1500 grams < birthweight < 2000g grams or gestational age > 30 weeks who are believed by their pediatrician or neonatologist to be at risk for ROP (e.g. history of hypotension requiring inotropic support, received supplemental oxygen for more than a few days or without saturation monitoring

Infants should be screened "by an ophthalmologist who is experienced in the examination of preterm infants for ROP using a binocular indirect ophthalmoscope."[12]

Gestational Age at Birth	Postmenstrual age (PMA) (weeks)	Chronologic (weeks)
22 weeks	31	9, consider earlier screening per clinical judgment
23 weeks	31	8, consider earlier screening per clinical judgment
24 weeks	31	7
25 weeks	31	6
26 weeks	31	5
27 weeks	31	4
28 weeks	32	4
29 weeks	33	4
30 weeks	34	4
>30 weeks with high risk factors	-	4

Diagnosis

The International Committee for Classification of Retinopathy of Prematurity developed a diagnostic classification in 1984, and since has been further refined.[13][14][15] ROP is defined by location (Zone), severity (stage) and vascular characteristics in the posterior pole (normal, pre-plus, or plus disease).[15]

Location (Zone)

For the purpose of defining the location, three concentric zones were defined. Since retinal vascular development proceeds from the optic nerve to the ora serrata, the zones are centered on the optic disc rather than the macula.

Zone I: The area defined by a circle centered on optic nerve, the radius of which extends from the center of the optic disc to twice the distance from the center of the optic disc to the center of the macula.

Zone II: The area extending centrifugally from the edge of zone I to a circle with a radius equal to the distance from the center of the optic disc to the nasal ora serrata.

Zone III: The residual temporal crescent of retina anterior to zone II. By convention, zones II and III are considered to be mutually exclusive.

Zone is based on the most posterior zone (as the retina may be vascularized to different extents in different regions of the retina, i.e. nasal vs temporal vs superior vs inferior)

Disease Severity (Stage)

Prior to the development of ROP in the premature infant, vascularization of the retina is incomplete or "immature" (Stage 0).

Stage 1: Demarcation Line: This line is thin and flat (in the retina plane) and separates the avascular retina anteriorly from the vascularized retina posteriorly.

Stage 2: Ridge: The ridge arises from the demarcation line and has height and width, which extends above the plane of the retina. The ridge may change from white to pink and vessels may leave the plane of the retina posterior to the ridge to enter it. Small isolated tufts of neovascular tissue lying on the surface of the retina, commonly called "popcorn" may be seen posterior to this ridge structure and do not constitute the degree of fibrovascular growth that is a necessary condition for stage 3.

Stage 3: Extraretinal Fibrovascular Proliferation: Neovascularization extends from the ridge into the vitreous. This extraretinal proliferating tissue is continuous with the posterior aspect of the ridge, causing a ragged appearance as the proliferation becomes more extensive.

Stage 4: Partial Retinal Detachment: Stage 4, in the initial classification was the final stage and initially known as the cicatricial phase.[13] It was later divided into extrafoveal (stage 4A) and foveal (stage 4B) partial retinal detachments. Stage 4 retinal detachments are generally concave and most are circumferentially oriented. Retinal detachments usually begin at the point of fibrovascular attachment to the vascularized retina and the extent of detachment depends on the amount of neovascularization present.[14]

Stage 5: Total Retinal Detachment: Retinal detachments are generally tractional and usually funnel shaped. The configuration of the funnel itself is used for subdivision of this stage depending on if the anterior and posterior portions are open or narrowed.[14]

More than one stage may be present in the same eye, staging for the eye as a whole is determined by the most severe stage present.

Extent

The extent of disease is recorded as hours of the clock or as 30° sectors. As the observer looks at each eye, the 3-o'clock position is to the right and nasal in the right eye and temporal in the left eye, and the 9-o'clock position is to the left and temporal in the right eye and nasal in the left eye.[13]

Vascular characteristics in the posterior pole (normal, pre-plus or plus disease)

Plus disease

Additional signs of increased venous dilatation and arteriolar tortuosity of the posterior retinal vessels which can increase in severity to include iris vascular engorgement, poor pupillary dilatation, and vitreous haze was referred to as plus disease in the original classification.[13] Thus it is necessary to see all the patients with suspected ROP inclduing those with poor dilation of pupils after topical mydriatics to rule out plus disease and more importantly aggressive posterior ROP (APROP).

Subsequent clinical trials have used a "standard" photograph to define the minimum amount of vascular dilatation AND tortuosity that must be present in at least 2 quadrants that are required to make the diagnosis of plus disease.[16] Additional studies are being performed with contact cameras and methods to standardize features of plus disease using machine based learning.[17]

Pre-Plus disease

There is a spectrum of abnormal dilatation and tortuosity of which Plus disease is the severe form. Pre-plus disease was later described as vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arterial tortuosity AND more venous dilatation than normal.[15]

Aggressive Posterior ROP (AP-ROP)

An uncommon, rapidly progressing, severe form of ROP is designated AP-ROP was later added to the classification. [15] Characteristic features of this type of ROP are a posterior location, plus disease, and the ill-defined nature of the retinopathy, which usually progresses to stage 5 if untreated. This rapidly progressing has also been referred to as "Rush disease". There are vascular loops and no obvious demarcation line or ridge. Fundus fluorescein angiography may delineate the vascular changes more clearly in this disease.[18]

Diagnostic procedures

Following pupillary dilation using eye drops, the retina is examined using an indirect ophthalmoscope. The peripheral portions of the retina are pushed into view using scleral depression.

Either separate sterile equipment or appropriate cleaning protocols should be used to avoid possible cross-contamination by infectious agents between infants.[19]

Caution: When using dilation drops, be aware of possible adverse effects to the cardiorespiratory and gastrointestinal system of the infant.

Differential diagnosis

- Familal Exudative Vitreoretinopathy is a genetic disorder that appears similar to ROP but occurs in full-term infants. It may present early within the first week of life also.[20] Examination of family members is very important. Genetic counseling and testing can be helpful to identify gene variants in about 50% of patients.
- Persistent Fetal Vasculature (PFV) can cause a traction retinal detachment difficult to differentiate but typically unilateral and does not have a correlation to prematurity.
- Incontinentia pigmenti

Management

Ophthalmologists with adequate knowledge of ROP should perform retinal exams in preterm infants. The initial exam should be based on the infant's age (see table1). Follow up recommendations were updated in 2019 by the American Academy of Pediatrics and depend on the location and stage. [12]

The timing of follow up examinations[12] are based on retinal exam findings as classified by the International Classification of Retinopathy of Prematurity revisited.[15]

- Recommended follow up in 1 week or less:
    - Zone I: stage 0 (immature vascularization), 1, or 2 ROP
    - Posterior Zone II: immature vascularization
    - suspected presence of AP-ROP
- Recommended follow up in 1-2 weeks:
    - Zone I: unequivocally regressing ROP
    - Posterior Zone II: immature vascularization
    - Zone II: stage 2 ROP
- Recommended follow up in 2 weeks:
    - Zone II: Stage 0 (immature vascularization) or 1, or unequivocally regressing ROP
- Recommended follow up in 2-3 weeks:
    - Zone II: regressing ROP
    - Zone III: stage 1 or 2 ROP

Termination of acute retinal screening examinations based on age and retinal finding. Examinations can be stopped when:

- Retinal is fully vascularized
- Zone III retinal vascularization without previous ROP in Zone I or II (may need a confirmatory exam if PMA <35 weeks)
- PMA = 45 weeks and no type 2 ROP ("prethreshold disease") (i.e. stage 3 ROP in zone II, any ROP in zone I) or worse ROP

- If previously treated with anti-VEGF (vascular endothelial growth factor) injection, follow until at least PMA =65 weeks (FYI: infant needs close follow up during time of highest risk for disease reactivation PMA: 45-55 weeks)
- ROP has fully regressed (ensure there is no abnormal vascular tissue present that can reactivate and progress)

Long-term follow up:

After termination of acute retinal screening. Prematurely-born infants should be seen within 4-6 months after discharge from the NICU because they are at increased risk for developing strabismus, amblyopia, high refractive error, cataract, and glaucoma.

Surgery

The first surgical treatment for ROP accepted to be safe and effective was cryotherapy to the avascular retina as designated by the CRYO- ROP study in 1986. This produced a reduction in unfavorable outcomes in eyes with threshold ROP. [6] Threshold ROP is defined as 5 contiguous or 8 cumulative clock hours of stage 3 ROP in zone 1 or zone 2 with plus disease.[21] Subsequently, argon and diode lasers have been used similarly to treat the avascular retina to reduce unfavorable outcomes. The laser units are preferred because they are more portable and better tolerated by patients. [22] Currently ROP treatment guidelines are based on the Early Treatment of Retinopathy of Prematurity Study.[23]

Surgical treatment is currently recommended for the following (defined as **"type 1" ROP**):

- Zone I: any stage ROP with plus disease
- Zone I: stage 3 ROP without plus disease
- Zone II: stage 2 or 3 ROP with plus disease

Eyes meeting these criteria should be treated as soon as possible, at least within 72 hours.

The number of clock hours of disease is no longer a determining factor for treatment.

Anti-VEGF treatment has shown promise (compared to conventional laser therapy) for treatment of stage 3 ROP with plus disease in Zone I (not Zone II).[24] Recent clinical studies and trials have been done to test de-escalating doses of bevacizumab (reduced from the BEAT-ROP study)[25] or ranibizumab in the RAINBOW study[26] for type 1 or treatment-warranted ROP. Both studies have found efficacy with lower bevacizumab doses or with ranibizumab 0.2 mg in treatment warranted ROP.

Surgical follow up

Follow-up is recommended in 3-7 days following laser photocoagulation or anti-VEGF injection.[12] Surgically treated eyes must be watched carefully for regression. Very late recurrences of proliferative ROP have been reported following anti-VEGF therapy. Despite treatment, some eyes will progress to retinal detachment. In the CRYO-ROP study, approximately 30% of eyes progressed to posterior pole macular fold or retinal detachment.[16] These eyes may need vitreoretinal surgery. At the reported 15-year outcome from the CRYO-ROP study, "between 10 and 15 years of age, new retinal folds, detachments, or obscuring of the view of the posterior pole occurred in 4.5% of treated

and 7.7% of control eyes."[27] Thus, they recommended that eyes that experience threshold should have long-term, regular follow up.

Following anti-VEGF injections into the eyes of infants, examinations are often soon to assure reduction in retinal dilation and stage 3 ROP. Features can be reduced within a week. Also eyes are closely followed for possible endophthalmitis or other complications associated with intraocular injection, including damage to the retina or lens.

Complications

The most feared complication in ROP is retinal detachment or macular folds. There are a number of other complications related to this disease that can effect visual development. Myopia is a common finding in premature infants with our without ROP. Infants with regressed ROP also have an increased incidence of strabismus, amblyopia, and anisometropia.

Prognosis

If ROP progresses leading to retinal detachment, the outcome is visually devastating. The CRYO-ROP study showed that at the 15-year follow-up treatment reduces the risk of unfavorable outcome from 52% to 30%.[27] The same study showed improved outcomes in the treated group for visual acuity at the 3-year, 10-year, and 15-year follow-ups.

Additional Resources

- AAPOS Frequently Asked Questions about ROP
- Boyd K, Janigian RH. Retinopathy of Prematurity. American Academy of Ophthalmology. EyeSmart® Eye health. https://www.aao.org/eye-health/diseases/retinopathy-of-prematurity-list. Accessed March 25, 2019.

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