Retinopathy of Prematurity : Clinical Perspectives

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Introduction:

Retinopathy of prematurity (ROP) is a multifactorial retinal disorder primarily of low birth weight premature infants. It can be mild with no visual defects, or it may become aggressive with new vessel formation (neovascularisation) and progress to retinal detachment and blindness.The fundamental pathological process underlying ROP stems from incomplete vascularization at birth. Normal retinal vascularization progresses in-utero from the disc margin (16 weeks) and reaches the nasal ora serrata (by 36 weeks) and then temporally (by 39-41 weeks) to complete a mature vascular retina. Term infants have completely vascularized retina and hence are not at risk for developing ROP[1]. Premature infants have avascular or incompletely vascularized retina at birth; ROP evolves over 4-5 weeks after birth. This relatively slow evolution is however usually asymptomatic and the onus of whom to send for screening lies primarily with the neonatologist/childspecialist in order to effectively conduct retinal examinations and timely interventions to improve visual outcome and avoid irreversible blindness. The incidence of ROP in India is reported to vary between 38 – 51.9 % in low birth weight infants[2,3,4]. Out of the approximate 26 million annual live births in India, approximately 8.7% of newborns in India are < 2000 grams in weight[5]. This would imply that almost 2 million newborns are at risk for developing ROP

Risk factors (1)

Birth weight and gestational age

Infants with very low birth weight are at significantly higher risk of developing severe ROP that requires treatment. Similarly, the severity of ROP is inversely proportional to gestational age. Present evidence shows that low birth weight and gestational age are the most predictive risk factors for the development of ROP.

Oxygen Use

Oxygen therapy has been previously implicated in the aetiology of ROP. The use of supplemental oxygen neither caused progression of pre-threshold ROP nor significantly reduced the number of infants requiring peripheral ablative therapy. Recent evidence suggests that repeated hypoxic and hyperoxic episodes may be an important factor in the pathogenesis of ROP. Strict management of oxygen delivery without fluctuations and monitoring may be associated with decreased occurrence of ROP. One should also avoid SPO2 >94% in preterm babies. Although the exact relationship between oxygen therapy and ROP is currently not well established, oxygen therapy seemed to play an important role in the pathogenesis of ROP.

Other Risk Factors

The other risk factors that have been implicated in the development of ROP include use of, glucocorticoids , surfactant, indomethacin , xanthine and dopamine. In addition, ROP has also been associated with intra-ventricular haemorrhage, ante-natal blood loss requiring blood transfusions and surgery under general anaesthesia , sepsis ,candidemia , hypo/hypercarbia, raised serum bilirubin levels, and assisted conception .

However, there is insufficient evidence to determine the degree of importance of these risk factors in contributing to the pathogenesis of ROP.

There is no relation between ROP and bright light exposure, maternal smoking andmaternal PIH.

Classification of ROP[11]

ROP classification is based on the location of the disease into **3 zones** (**1-3**), extent of the disease based on **clock hours** (**1-12**), **stage** (**1-5**) and the presence of plus disease.

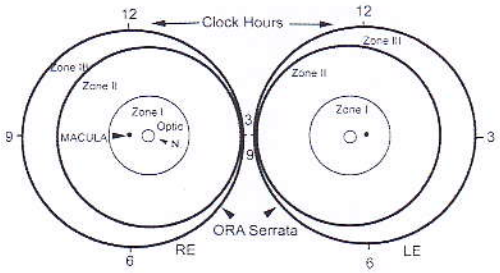
Location of ROP shown in figure 1.

a. Zone 1: innermost Zone , the radius of which is twice the distance from the centre of optic disc to macula

b. Zone 2: extends from Zone 1 to ora serrata of nasal side and about half the distance from ora serrata on temporal side.

c. Zone 3: residual crescent of retina on temporal side

Fig.1.



Extent (figure 1): it refers to the circumferential location of the disease and is reported as clock hours (1-12) in the appropriate zone.

Stage : it is divided into 5 stages

a. Stage 1: demarcation line that separates avascular retina anteriorly from the vascular retina posteriorly

b. Stage 2: ridge of scar tissue between the avascular retina and vascular retina

c. Stage 3: ridge with extraretinal fibrovascular proliferation or neovascularisation. Abnormal blood vessels extend into vitreous

d. Stage 4: partial retinal detachment due to pull of scar tissue. 4A- if detachment involves outside the fovea. 4B- if detachment involves fovea

e. Stage 5: total retinal detachment

Plus disease: it implies venous dilatation and arterial tortuosity of posterior retinal vessels, and later may include iris engorgement, rigid pupil and vitreous haze.

Pre-Plus disease: intermediate level of vascular dilatation and tortuosity between normal appearing posterior pole vasculature and frank plus disease

AP-ROP (Aggressive posterior ROP)

A rapidly progressive and severe form of ROP. The characteristic features are its posterior location, prominence of Plus disease, its ill-defined nature and rapid progression to stage 5. It is more common in

Indian babies and carries a worse prognosis as compared to classical ROP[6].

Threshold ROP

Threshold ROP is present if 5 or more contiguous or 8 cumulative clock hours(30-degree sectors) of stage 3 with plus disease in either zone 1 or 2 are present. This is the level of ROP at which risk of blindness is predicted to be at least 50% and at which the CRYO-ROP study showed that risk of blindness could be reduced to approximately 25% with treatment[7]

Pre threshold ROP

Any ROP in zone less than threshold ROP, and in zone 2, stage 2 ROP with plus disease, stage 3 without plus disease, or stage 3 with plus disease but fewer than the requisite clock hours that define threshold ROP.

Type 1 prethreshold ROP includes

i. In zone 1, any ROP and plus disease or stage 3 with/without plus disease
ii. In zone 2,stage 2 or 3 ROP with plus disease

Type 2 pretreshold ROP includes

i. In zone 1, stage 1or 2 without plus disease
ii. In zone 2, stage 3 without plus disease

Screening of ROP:*Theonus for referring patients for screening lies solely with the Neonatologist / Paediatrician.* The ideal setting for screening is under a radiant warmer in the NICU, under the guidance of the neonatologist. Discharged and stable babies may be screened in the trained ophthalmologist's clinic or in the NICU itself. The treating team should not forget to communicate with the parents regarding the risk of ROP; the need for screening preterm babies must be addressed along with the initial admission counseling itself. Documentation of such a communication is highly desirable. The baby should be swaddled and preferably fed one hour prior to examination. Pupillary dilatation should be performed about an hour prior to screening. A combination of **cyclopentolate 0.5% and phenylephrine (2.5%) drops is used two to three times about 10-15 minutes apart. Tropicamide 0.5-1% is an alternative to cyclopentolate**. The examination is carried out under topical anesthesia without any sedation, using the indirect ophthalmoscope and a 20 D or 28 D condensing lens. It must be remembered that retinal examinations are stressful and may be even painful to the infant. Swaddling the infant firmly in a thin blanket and administering 0.5-1 ml of 24% sucrose orally by syringe 1-2 minutes prior to the examination will help to provide comfort and relieve pain. Apnea and bradycardia may rarely develop during the examination in very premature babies. Resuscitation measures should be readily available. The pertinent questions regarding screening are**(1)** which neonates should be screened for ROP?**(2)** When should such screening be initiated? **(3)** How frequently should the infants be screened? **(4)**When is the screening complete?

Which infants should be screened for ROP? Screening for ROP should be performed in all preterm neonates who are < 34 weeks gestation and / or < 1750 grams birth weight. Apart from these infants, those preterm infants between 34 to 366/7 weeks gestational age or a birth weight between 1750 and 2000 grams with risk factors for ROP should also be screened[8,9,10].Risk factors for ROP in larger infants have not been clearly established. Multi-centre studies need to be undertaken to determine the incidence, risk factors and natural course of ROP in the larger preterm infants.

When should the first screening be done? The first screen should be performed not later than 4 weeks of age or 30 days of life in infants ≥ 28 weeks of gestational age. They may also be screened by the third week of life to enable diagnosis of AP-ROP[6].Infants <28 weeks or <1200 grams birth weight should be screened

early at 2-3 weeks of age, to enable early identification of AP-ROP.

How frequently should the infants be screened? Follow up examination intervals are based on the retinal findings; these findings are classified according to the revised International classification of ROP (ICROP)[11] Based on the retinal findings, the follow up examination schedule is suggested.

1 Week or less follow up
- Stage 1 or 2 ROP : zone I
- Stage 3 ROP : zone II

1 to 2 weeks follow up
- Immature vascularisation : zone I – no ROP
- Stage 2 ROP: zone II
- Regressing ROP : zone I

2 weeks follow up
- Stage 1 ROP: zone II
- Regressing ROP : zone II

2 to 3 weeks follow up
- Immature vascularization : zone II – no ROP
- Stage 1 or 2 ROP: zone III
- Regressing ROP: zone III

When should the screening be terminated? The following are the recommendations to guide when to stop further examinations[9].

a) Full retinal vascularization; this usually occurs at about the 40th week of postmenstrual age and mostly completes by the 45th week

b) Regression of ROP noted It is advisable to screen the baby every 1-2 weeks at least until the infant is 38-40 weeks of postmenstrual age.

c) When ROP has progressed to a stage when treatment is indicated.

Treatment of ROP when and how? Prior to December 2003, the CRYO-ROP treatment guidelines were followed. Only 'threshold disease' was treated. The Early Treatment for Retinopathy of Prematurity study (ETROP) [12] study showed that early treatment of Type 1 pretreshold ROP significantly reduced unfavorable outcomes to a clinically important degree. The guidelines from the above study are the currently recommended indications for ablative treatment and are summarized in table1. AP-ROP also needs early and aggressive laser treatment, often in multiple sessions to prevent retinal detachment .

Tab1. Treatement guidelines adopted from ET-ROP guidelines

Treatment of ROP			
ZONE 1	NO PLUS	Stage1	Follow
		Stage2	Follow
		Stage3	Treat
	PLUS	Stage1	Treat
		Stage2	Treat
		Stage3	Treat
ZONE 2	NO PLUS	Stage1	Follow
		Stage2	Follow
		Stage3	Follow
	PLUS	Stage1	Follow
		Stage2	Treat
		Stage3	Treat

The aim of the treatment is to ablate the entire avascular retina up to the ora serrata in a near confluent burn pattern getting as close to the edge of the ridge as possible. Laser photocoagulation delivered by the indirect ophthalmoscopic device is the mainstay of ROP treatment. Laser has supplanted cryotherapy due to better structural and functional outcomes. The child can be fed after about 30 minutes following completion of the procedure. Vital signs must be monitored. It is preferable that the child be under the supervision of the neonatologist or an anesthesiologist for at least 2-3 hours following the procedure. Post-treatment hypothermia and hypoglycemia are common and must be prevented. Mild conjunctival chemosis and hyperemia following the procedure may last for a few days and the parents must be counseled regarding this. Stage 4 or 5 ROP requires vitreo-retinal surgical intervention; retinal detachment carries a high risk of irreversible blindness. Visual rehabilitation must be offered to all visually challenged ROP babies.

Followup of ROP babies..

This may be typically scheduled after week 1, 2, 4 and 12 following treatment based on the findings recorded by the treating ophthalmologist.Infants with ROP, regardless of whether they have required treatment, are at risk for developing visual disorders such as strabismus, amblyopia, myopia and cataract;[13]. Retinal detachment may also occur during adulthood in infants with ROP. Moreover, prematurity may itself predispose to refractive errors, strabismus and lenticular opacities. Appropriate follow-up for these potential problems after discharge from the NICU is essential.Babies need to be under more intensive follow up for the first 6 months followed by a less intensive follow up schedule until young adulthood period to identify long term complications promptly.

Future of ROP screening: Photo-documentation and Tele-ophthalmology

The use of retinal wide field digital imaging (WFDI) using a portable pediatric fundus camera such as the RETCAM II, III and RETCAM shuttle (Clarity MSI, CA, USA) has become a useful adjunct to the documentation of ROP and as a screening and teaching tool[14] . The PHOTO-ROP study reports have shown that WFDI compares well with indirect ophthalmoscopy with a high diagnostic sensitivity[15]. In our country where trained ophthalmologists for ROP management are so few in number when the need is much more, the role of tele-ophthalmology in screening infants in peripherally situated semi-urban and rural centers by ROP experts in the tertiary care centers seems promising. This may enable timely referral of the affected infants to appropriate centers for further evaluation and treatment.

Summary:

ROP is emerging as one of the leading causes of preventable childhood blindness in India.

The responsibility of recognition of infants for screening lies with the pediatrician/neonatologist.

Screening for ROP should be performed in all preterm neonates who are born < 34 weeks gestation and/or < 1750 grams birth weight; as well as in babies 34-366/7 weeks gestation or 1750-2000 grams birth weight if they have risk factors for ROP.

The first retinal examination should be performed not later than 4 weeks of age or 30 days of life in infants born ≥ 28 weeks of gestational age. Infants born < 28 weeks or < 1200 grams birth weight should be screened early, by 2-3 weeks of age, to enable early identification of AP-ROP.

Communication with the parents regarding timely screening for ROP, seriousness of the issue, possible findings and consequences is extremely important.

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