Retinopathy of Prematurity

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Abstract:

The incidence of premature births and their improved survival rates have led to an increasing number of cases diagnosed with Retinopathy of Prematurity. There is an ever-increasing need of awareness amongst Ophthalmologists and Pediatricians, to diagnose and treat these babies timely, in order to prevent advanced visual loss. This article highlights the extent of the disease and the importance of prompt diagnosis and intervention. Diagnosis is done by Retcam or indirect ophthalmoscopy and laser photocoagulation and anti-VEGF therapy have been the mainstay of treatment in these cases. Meticulous follow-ups are of paramount importance, as there is a very small window between when to treat and when to defer. Even after a successful treatment these babies have to be closely followed up till the retinal vascularization is complete. The comorbidities have to be taken into account while treating. Tele medicine plays an important role in reaching out to the periphery, and hence the need to introduce it far and wide.

Keywords- Retinopathy of prematurity,Retcam, Laser photocoagulation for ROP, Anti -VEGFs in ROP

Introduction :

Retinopathy of prematurity (ROP) is a fibrovascular proliferative disorder which affects the developing peripheral retinal vasculature of premature infants. Improved neonatal care and better neonatal survival rate has led to the diagnosis of increasing number of cases of ROP.[1] Identifying and screening of at-risk premature infants by an experienced ophthalmologist is the most important strategy in the management of ROP. ROP is a preventable cause of blindness and remains one of the leading causes of visual loss in children. STOP-ROP trial has shown that supplemental oxygen is not the sole cause of the disease;[5]studies support that both hyperoxia and hypoxia seem to be important factors in the pathogenesis of ROP, their effects being mediated by vascular endothelial growth factor, which is produced by muller cells and astrocytes. In the rural population an experienced ophthalmologist may not be available, and availability of Retcam can prove beneficial in such areas. Screening pictures of retina taken by Retcam can be sent via telemedicine to higher centers and a diagnosis made. If treatment is warranted ,the patient can be advised to come to higher centers. The mainstay of treatment has been laser photo coagulation to the avascular retina, although anti vascular endothelial growth factor injections have shown promising results in posterior disease.[6]

With the rising rate of prematurity and improving survival ,the need for ongoing ROP screening ,treatment options and long term follow up is greater than ever.

Incidence : In India, incidence of ROP varies from 38-51.9 % among low birth weight babies.[1] Approximately 2 million babies out of 26 million live births annually are born with birthweight <2000 gms and are at risk of developing ROP. According to WHO,India has the highest number of preterm births in the world.[7]

Risk Factors

- Low Gestational age
- Low Birth weight
- Number of days oxygen administered

Less common risk factors include -

- Multiple births
- Blood transfusions
- Respiratory distress syndrome
- Sepsis
- Intra uterine growth retardation(IUGR)
- Anemia
- Seizures

Whom To Screen (Recommended by American academy of ophthalmology and pediatrics)

Fundus examination of all infants with birth weight< or equal to 1500 gms or Gestational age < or equal to 30 weeks should be done. Babies between 1500-2000 gms or >30 weeks with an unstable clinical course should also undergo screening fundus examination.

Screening Criteria According To Indian Scenario

All infants with birth weight< or equal to 1700 gms or Gestational age<34 weeks should be screened for ROP. All infants requiring supplemental oxygen or with unstable neonatal course, irrespective of GA or BW should also have a screening fundus examination. This is called **SICKNESS**

CRITERIA.[9]

When to Screen

Initial eye examination should be done at 31 weeks post menstrual age or 4 weeks of chronological age whichever is earlier. The first retinal examination should be done in the first month of life.

How to Screen

Screening is done in a temperature controlled room or a nursery in the presence of a neonatologist. Such babies are susceptible to hypothermia, bradycardia, apnoiec episodes and fall in oxygen saturation. A monitor should be there to monitor the heart rate and oxygen saturation throughout the course of examination.

Instrumentation

1. Retcam-It is a digital camera for screening, provides instant and accurate documentation and provides state of the art wide field pediatric retinal imaging(130 degrees).It is a useful tool which can be used in peripheral areas, where a trained ophthalmologist is not available. A nurse or a technician can also do screening with a retcam, capture photographs and send over to an ophthalmologist. This tele screening program has been successfully implemented in Karnataka internet assisted diagnosis of retinopathy of prematurity (KIDROP) by Vinekar et.al.[4]

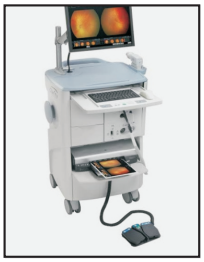

Figure 1: Retcam

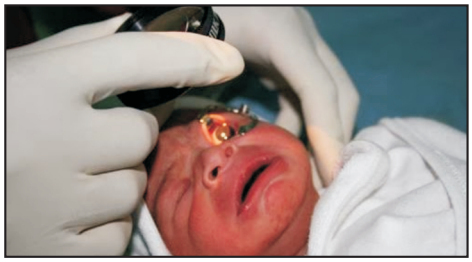

Figure 2: Examination with Indirect Ophthalmoscope

2. If a retcam is not available an indirect ophthalmoscope,a scleral depressor and a pediatric speculum is used.
3. Topical anaesthesia is given with 0.5% proparcaine eye drops.
4. Dilatation is done with half strength tropicamide plus eye drops,instilled not more than three times every 15 minutes,before the examination.Punctal occlusion may be done to avoid systemic absorption.[2]

Classification of Disease

Classification of disease is based on three clinical parameters:

» **Location of disease:**

- Zone 1-With disc as centre and twice the distance from disc to fovea , the circle formed is zone 1
- Zone 2-Extends from the peripheral border of zone 1 to nasal ora serrata and corresponding area temporally.
- Zone 3-Remaining temporal crescent of retina anterior to zone 2.

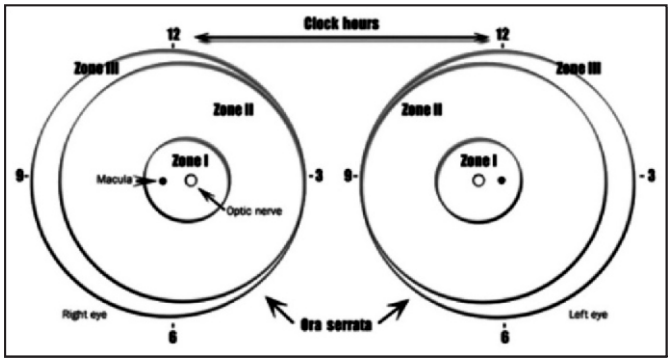

Figure 3: 3 zones of retinal involvement are recognized,each centered at the disc

» **Extent of disease:** This is defined by the number of clock hours of involvement.

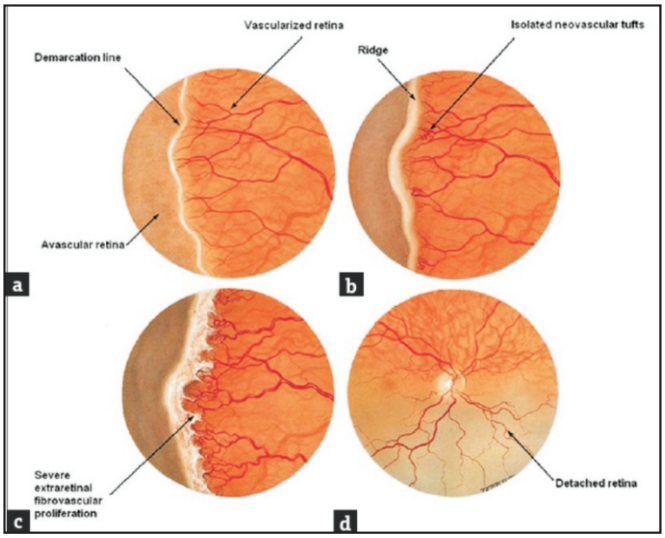

Figure 4 : Stages of ROP

Staging of Disease

Stage 1- Demarcation Line-It is a thin, flat white line within the plane of retina that separates a vascular retina anteriorly from vascularised retina posteriorly.

Stage 2- Ridge-It arises in the region of demarcation line, has a height and width and extends above the plane of retina.

Stage 3- Extra Retinal Fibrovascular Proliferation-It extends from the ridge into the vitreous.

Stage 4- Partial Retinal Detachment-Retinal detachment that may or may not involve the fovea.

Stage 5- Total Retinal Detachment-It is generally tractional and may occasionally be exudative.

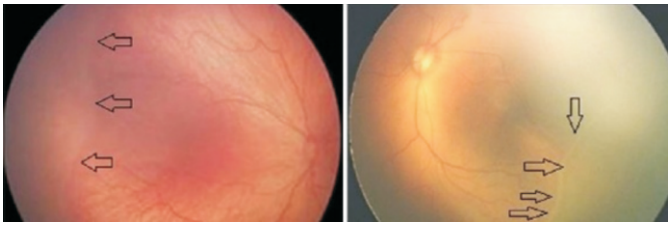

Figure 5: Stage 1-Demarcation line, Stage 2-Ridge

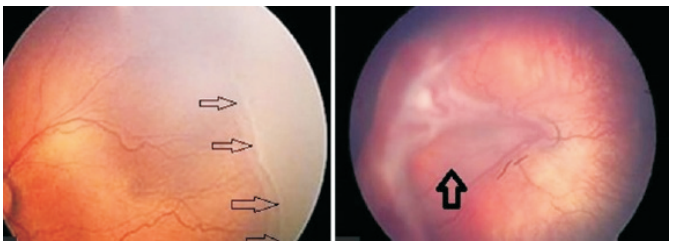

Figure 6 : Stage 3-Fibrovascular proliferation, Stage 4-Partial retinal detatchment

- **Aggressive posterior ROP-(AP-ROP)-**It is a rapidly progressing severe form of ROP.It is located posteriorly and has a prominence of plus disease.It is commonly seen in zone 1.
- **PLUS DISEASE-**There is increased venous dilatation and arteriolar tortuosity,and may include iris vascular engorgement and vitreous haze.
- **PRE-PLUS DISEASE-**This is defined as vascular abnormalities of posterior pole insufficient for the diagnosis of plus disease but demonstrate more arterial

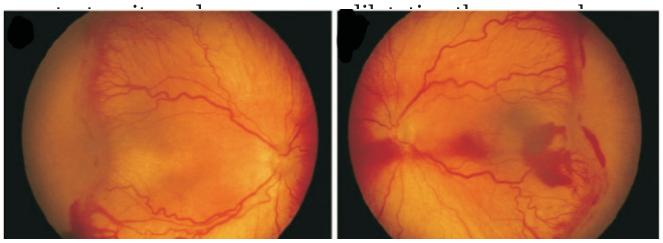

Figure 7 : Stage 3, Zone 2 with plus disease

When To Treat

Threshold disease: As per CRYO-ROP study,it is defined as stage 3 in zone 1 or 2 involving >5 contiguous or 8 cumulative clock hours with plus disease.

Pre-threshold disease: Early treatment ROP study has revised the treatment guidelines. The study proved that earlier treatment has a better outcome.

High risk pre-threshold

- Zone 1 any stage with plus disease
- Zone 1 stage 3 without plus disease
- Zone 2 stage 2 or 3 with plus disease.

Low risk pre-threshold

- Zone 1 stage 1 or 2 without plus disease
- Zone 2 stage 3 without plus disease

How To Treat

Different modalities of treatment are-

1. *Cryotherapy*- Thismodality of treatment is rarely used these days.

2. *Laser photocoagulation*- This the most widely used modality of treatment. Peripheral laser is done to stop neo vascularization. If done adequately and at the right time, the disease regresses and does not come back. The success rate has been quoted to beover 90%.[3] The peak incidence of treatment is usually 35-36 weeks, the child is followed upto 50 weeks. The long-term benefits of treatment are that it protects a against peripheral retinal tears. However there are certain risks, which should be kept in mind. Some institutes require laser to be done under general anaesthesia which has its own risks in a premature infant. It is usually done under topical anaesthesia in the presence of an anaesthetist, in NICU, with the monitors in place.

In roughly 5 percent of the cases treatable areas can be missed. In posterior disease, one can easily ablate two thirds of the retina ,which might lead to loss of peripheral field of vision[3] in some cases. The retina is ablated upto the ora serrata from the ridge. In severe cases laser may be done over the ridge also, to facilitate regression .[2] Follow-ups are done weekly, till the disease regresses completely and vascularization reaches the temporal ora.

3. *Anti -VEGF Therapy*- VEGF plays a significant role in both ischaemic and vasoproliferative phases of the disease, and anti -VEGFs play an important role in treatment of the disease. Its easy to use and has a rapid response, sometimes the result is evident within a day of injection whereas it usually takes a week to see the result of laser therapy .[3] Another advantage of anti -VEGF therapy is that it promotes near normal vascularization and hence preserves peripheral field of vision.

Two year follow up of BEAT-ROP study showed a lower incidence of myopia after anti VEGF therapy. In a study conducted at Bayer college of medicine, investigators found a mean incidence of myopia to be 0.9 d in anti VEGF group, while it was 4.4 d in the laser group .[3] However, in patients treated with anti VEGF, it took longer for the retina to develop normal vascularization. The retina remained a vascular for a long time and there was an increased chance of recurrence, sometimes even at 60 to 70 weeks .[10] A longer follow up of these infants was therefore required. VEGF is required for organogenesis and vasculogenesis. Systemic absorption of anti VEGFs may cause delayed vascular development in other organs. Hence it is not recommended as a first line of therapy. BEAT -ROP study showed promising results of Bevacizumab monotherapy in stage 3 disease in Zone 1. Laser treatment has been found to be

less effective in zone 1 disease. In all such cases bevacizumab injection followed by laser has shown to improve the efficacy of laser, with reduced need for extensive laser in the posterior pole. Anti VEGFs were found to be risky in children with comorbidities like Bronchopulmonary dysplasia. In fact four out of five deaths in BEAT -ROP study were pulmonary deaths. The optimal dosage of anti VEGF used in BEAT-ROP study was 0.625 mg .

4. *Surgery*- Indications for surgery are partial and total retinal detachment. Lens sparing vitrectomy has shown good results in stage 4.Bhende et.al have shown 82% success rate in stage 4A and 50 % success rate in stage 4B.[8] Stage 5 has been associated with poor surgical outcomes.

Sequelae

ROP babies have a strong association with development of myopia. About 65% develop myopia by 9 months of age. About 26% of babies treated for high risk pre threshold retinopathy ,have been found to develop more than 5 D of myopia in the ETROP study .[1] These patients also have a high incidence of amblyopia, strabismus and nystagmus. Parents of these babies should be explained the possibility of development of all these sequelae in their childhood years, hence the importance of regular eye checkups.

Examination Schedule

Following schedule should be followed for babies who do not need ablative treatment:

» One week or less follow up
  - Stage 1 or 2,zone 1 ROP
  - Stage 3,zone 2 ROP

» One to two week follow up—
  - Immature vascularization zone 1—No ROP
  - Stage 2, zone 2 ROP
  - Regressing ROP, zone 1

» Every two week follow up
  - Stage 1,zone 2 ROP
  - Regressing ROP zone 2

» Every two-three week follow up-
  - Immature vascularisation zone 2-No ROP
  - Stage 1or 2 zone 3ROP
  - Regressing ROP zone 3

Follow up examinations are done till complete retinal vascularisation.

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Can you find the answers to following Riddles?

1. Your hands have ten, and ten has two, and two has one, and that's your clue.
2. What's not a game, but can be played; is never seen, but often made?
3. I run but never walk, have a mouth but never talk, have a bed but never sleep, have a head but never weep. What am I?
4. The more there is, the less you see. What is it?
5. Say my name and I disappear. What am I?

Source: MSN