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Abnormal vasculogenesis in retinopathy of prematurity : a clinico-pathological study

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ABSTRACT

Retinopathy of Prematurity (ROP) is a proliferative condition of the retina in preterm infants where there is abnormal vasculogenesis. When preterm and low birth weight infants are exposed to high concentrations of oxygen in incubators, the immature retina undergoes a state of static, followed by uncontrolled neovascularisation which proliferates into the vitreous, leading to complications like retinal detachment. An increase in the number of neonatal care units has lead to an increase in the survival rates of low birth weight and premature babies who are at a higher risk of developing Retinopathy of Prematurity. Knowledge of the anatomical manifestations in the different stages of the disease is a must for early detection and proper management of this condition.

KEYWORDS Retinopathy of Prematurity, neovascularization, retinal detachment, laser therapy, low birth weight

Retinopathy of prematurity (ROP) is a potentially blinding, vasoproliferative retinopathy affecting premature infants of very low birth weight who have been exposed to high ambient oxygen concentration[1]. It is mainly seen in infants of gestational age less than 32 weeks and birth weight less than 2000gms. It features an abnormal proliferation of developing blood vessels at the junction of vascular and avascular retina.

ROP was first described by Theodore Terry in 1942 as 'retrolental fibroplasia' [2]. The term ROP was later coined by Heath in 1951 [3]. In the same year Campbell suggested that uncontrolled oxygen was responsible for the epidemic of ROP [4].

It's been described as an epidemic as there has been an increase in the number of neonatal care units. This has led to an increase in the survival rates of premature infants, who are at a greater risk of developing ROP if they are not detected and treated at the initial stages [5].

The incidence of ROP was 47% in infants whose birth weight was between 1000 grams to 1251 grams, and it was 81.6% for infants weighing less than 1000g at birth[6].

MICROSCOPIC ANATOMY

The retina is unique among tissues in that it has no blood vessels until the fourth month of gestation, at which time vascular complexes in the form of 'spindle cells' from the adventitia of hyaloid vessels at optic disc grow towards the periphery[7]. These cells canalize and metamorphose into mature vessels and reach the nasal ora serrata by 36 weeks and temporal retina around 39-41 weeks of gestation. This probably accounts for the preponderance of the disease to temporal retina as it develops at a later date.

PREDISPOSING FACTORS

1) Prematurity
2) Low birth weight
3) Alternating hyperoxia-hypoxia
4) Mechanical ventilation, apnea, sepsis.

MECHANISM

In prematurity due to ventilation with increased concentrations of oxygen there is hyperoxia leading to a decrease in Vaso-Endothelial Growth Factor (VEGF). But as the metabolic demands of the eye ball increases with growth there is an increase in the VEGF leading to abnormal proliferation of immature vessels[8].

PATHOGENESIS OF ABNORMAL VASCULOGENESIS

1) As the retina is not fully vascularized and there are increased levels of oxygen during ventilation, the newly formed capillaries are obliterated as their endothelium is damaged.

2) The surviving mesenchymes and the mature arteries and veins unite via remaining few channels.

3) The mesechyme stops its peripheral advancement and piles like a shelf forming the mesenchymal arteriovenous shunt[9]. This demarcates the vascular from the avascular retina. This shunt is fed and drained by dilated irregular vessels which lose their clear identity as arterioles or venules.

4) After a brief period of a few days to months the shunt thickens to form a ridge. It is during this period that the real fate of the eye depends. The cells of the shunt can divide and differentiate into normal capillary endothelium to form primitive endothelial tubes. This is called regression of ROP which is self limiting and fortunately occurs in more than 90% of cases.

5) In the remaining 10% there is extra retinal neo vascular proliferation leading to end stage disease. Here the primitive cells of the shunt multiply, break through internal limiting membrane of the retina but do

not differentiate into normal endothelium. Instead they grow into the vitreous forming a membrane which later contracts and leads to tractional retinal detachment. Late events include secondary glaucoma, vitreous hemorrhage, synechiae formation, and phthisis bulbi. The scar tissue gets pulled up behind the lens and appears as a white fibrovascular mass, also known as "Retrolental Fibroplasia".

International Classification of Retinopathy of Prematurity [ICROP] classifies the entity based on: zones, stages, extent of the stage and presence or absence of plus disease [10].

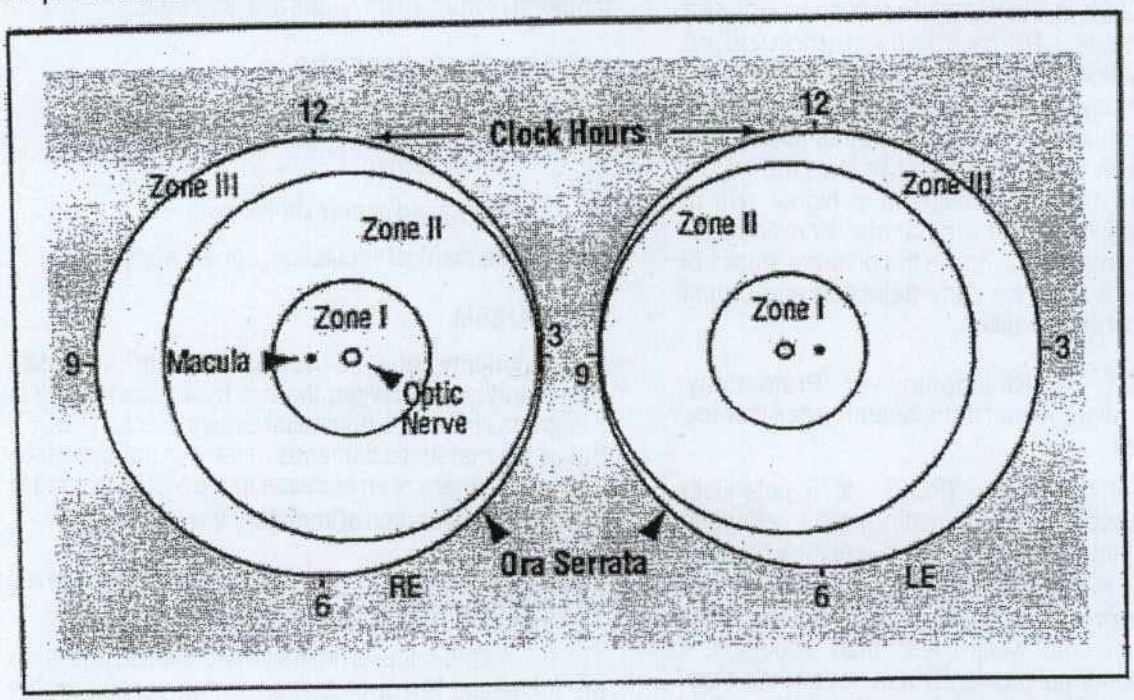
There are 3 zones:

Zone 1: is bounded by an imaginary circle, the radius of which is twice the distance from the disc to the macula[11].

Zone 2: extends concentrically from the edge of zone 1; its radius extends from centre of the disc to the nasal ora serrata.

Zone 3: consists of a residual temporal crescent anterior to zone 2

It has 5 stages.



Stage 1: Demarcation line between the vascular and avascular retina.

Stage 2: Development of a ridge from the demarcation line with isolated neovascular tufts posterior to it which extends above the plane of the retina.

These 2 stages can regress without developing into severe ROP.

Stage 3: Extraretinal fibrovascular proliferation extending from ridge into the vitreous, a feature of

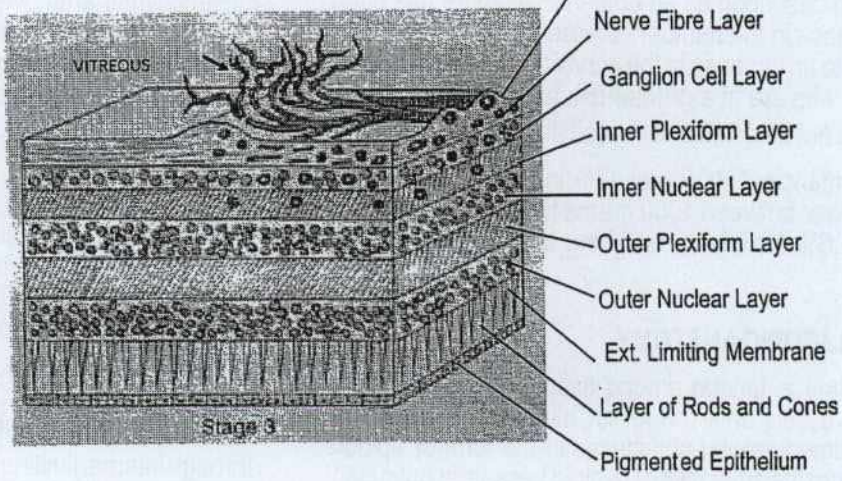


Fig 2: Neovascular tufts proliferating into the Vitreous

severe ROP.

Stage 4: Partial retinal detachment.

Stage 5: Total retinal detachment.

The extent of ROP is indicated by the number of clock hours of a stage.

Plus disease is the presence of dilated and tortuous retinal vessels along with pre retinal and vitreous hemorrhage and is a feature of severe ROP[12].

Aggressive Posterior Retinopathy Of Prematurity (APROP) also called Rush disease is characterised by increased dilatation and tortuosity of vessels in all 4 quadrants.

TREATMENT

In about 90% of cases, ROP regresses spontaneously by a process of involution from a vasoproliferative to fibrotic phase leaving few, if any, residua.

In case the disease is active then treatment modalities include:

Laser Photocoagulation of the avascular immature retina. This is successful in 85% of cases. Laser therapy has largely replaced cryotherapy because visual and anatomical outcomes are superior, and laser induces less myopia 13.

Lens Sparing Pars Plana Vitrectomy can be done for tractional retinal detachment not involving the macula.

SCREENING

Babies born at or before 31weeks gestational age, or weighing 1500g or less, should be screened for ROP by an ophthalmologist with expertise in ROP. This may involve indirect ophthalmoscopy with a 20D lens or a wide field retinal camera (Retcam 120)14. Screening should begin within 4 weeks of birth. Subsequent review should be at 1-2 weekly intervals, depending on severity.

SUMMARY

Retinopathy of Prematurity is gaining importance as the survival rates of preterm infants is increasing. As the pathogenesis is irreversible and the present treatment modalities only prevent the progression of the disease but do not repair the damage already done there is a need to diagnose it at its earliest stage. The anatomical modifications like ridge formation between the vascular and avascular retina and neovascular growth into the vitreous should be taken into account in the screening process for early detection and proper management.

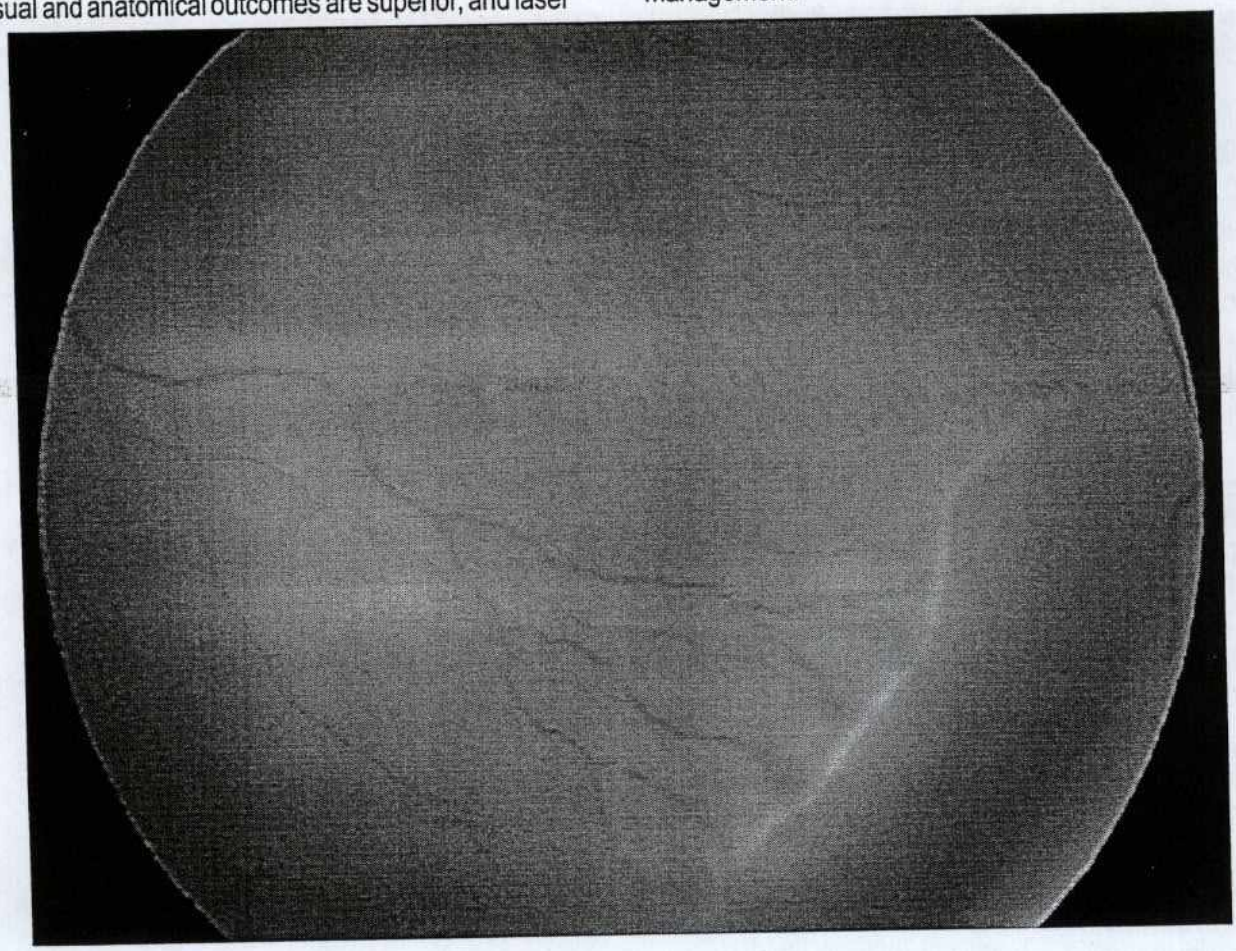


Fig 3: Ridge between upper vascular and lower avascular retina in stage 2

LEGENDS

1. Fig 1: Illustration shows division of the retina into different zones which is used for marking the extent of the disease during screening.

2. Fig 2: Illustration shows uncontrolled proliferation of the immature vessels from the retina into the vitreous which leads to haemorrhages, scar tissue formation and later into retinal detachment.

3. Fig 3: Illustration shows stage 2 where a ridge demarcates the vascular from avascular retina.

REFERENCES

1. Patz A. The role of oxygen in retrolental fibroplasia. Trans Am Ophthalmol Soc: 1968;66: 940-985.

2. Terry TL. Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens: A Preliminary report. Am J Ophthalmol: 1942;25: 203-204.

3. Heath P. Pathology of Retinopathy of prematurity, RLF. Am J Ophthalmol: 1953;34: 1249.

4. Campbell K. Intensive oxygen therapy as a possible cause of neonatal fibroplasia: a clinical approach. Med J Aust: 1951;2: 48.

5. Gibson DL, Sheps SB, Schechter MT. Retinopathy of prematurity: a new epidemic? Pediatrics: 1989;83: 486-492.

6. Recchia F M, Capone A. Retinopathy of Prematurity. In: Yanoff M, Duker J S. (eds). Ophthalmology. 2nd Ed Mosby. St.Louis, 2004, pp. 870-876.

7. Azad RV. ROP: Vasculogenesis. In: Azad RV. Retinopathy of Prematurity: A Text and Atlas. 1st Ed Jaypee. New Delhi, 2006, pp. 9-12.

8. Mc Colm JR, Hartnett ME. Retinopathy of Prematurity: Current Understanding Based on Clinical Trials and Animal Models. In: Text book of Pediatric Retina. 1st Ed Lippincot Williams and Wilkins. Philadelphia, 2005, pp. 387-409.

9. Natarajan S, Dutta B. Retinopathy of Prematurity. In: L C Dutta. Modern Ophthalmology. 3rd Ed Jaypee. New Delhi, 2005, pp. 838-848.

10. The committee for the classification of retinopathy of prematurity. An international classification of retinopathy of prematurity. Arch Ophthalmol: 1984; 102:1130-1134.

11. Jack. J. Kanski. Retinopathy of Prematurity. In: Jack. J. Kanski. Clinical Ophthalmology. 6th Ed. Elsevier Publications. Edinburg, 2008, pp. 606-611.

12. Early Treatment of Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity. Arch Ophthalmol: 2003; 121: 1684-1696.

13. Fallah N, Lynn MJ, Aaberg TM, Lambert SR. Clinical Outcome of Confluent Laser Photoablation for Retinopathy of Prematurity. J AAPOS: 2002; 6: 81-85.

14. Shah PK, Narendran V, Saravanan VR, Raghuram A, Chattopadhyay A, Kashyap M. Screening for retinopathy of prematurity - a comparison between binocular indirect ophthalmoscopy and RetCam 120. Indian J Ophthalmol: 2006;54: 35-38.

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