

Retinopathy of Prematurity: A Review

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Summary

Ajibode HA. Retinopathy of Prematurity: A Review. *Nigerian Journal of Paediatrics* 2004;31:61. Retinopathy of prematurity [ROP], previously called retrolental fibroplasia, is a vasoproliferative retinopathy that occurs principally, but not exclusively in premature and low-birth-weight infants. It occurs in two overlapping phases, namely, (a) an acute phase in which normal vasculogenesis is interrupted and a response to injury is observable in the retina and (b) a chronic or late proliferation of membranes into the vitreous during which tractional detachment of the retina, scarring of the macula and significant visual loss occur. More than 90 percent of cases of acute ROP regress spontaneously, healing with minimal scarring and little or no visual loss. Less than 10 percent of the involved eyes go on to significant cicatrization.

Introduction

TERRY in 1942,¹ advanced the belief that premature children may suffer a retinal disease, primarily as a complication of prematurity, when he described 'retrolental fibroplasia' for the first time. The estimated population of children blinded by retinopathy of prematurity (ROP) between 1943 and 1953 was about 10,000 worldwide, and approximately 70 percent of these were in the United States. A hectic search therefore started for possible causes. A paediatrician in Australia² provided the first substantial clinical clue by comparing the frequency of occurrence of ROP in three nurseries with variations in the ease of access to supplemental oxygen (O₂). She noted that each produced a different rate of ROP. Other studies followed which supported a possible aetiological role for oxygen. A randomized prospective trial³ of oxygen therapy soon after, clearly established that the incidence of ROP was related inversely to birth weight and increased in premature babies kept in an oxygen environment of more than 50 percent. Thus, it was generally agreed that although there is no established safe level of oxygen therapy, it should be given in the lowest concentrations for the shortest duration possible.

Unfortunately, although severe end-stage ROP all but disappeared with the restriction of inspired oxygen to 40 percent or less, the disease was replaced by increased incidence of brain damage and death among premature

infants. In fact, a study estimated that for every prevented case of blindness from ROP, 16 infants died in the US.⁴ Thus, a more rational and liberal policy of O₂ use in premature nurseries began in the mid-1960s. ROP reappeared; modern technology of life-support systems which could be applied to the tiniest infants who are at greatest risk for ROP, played a role in this reappearance.

In the 1980s,⁵ it was observed that infants weighing less than 1000gm, often with normal arterial oxygen levels, developed ROP and contributed to most of the cases. This led researchers to doubt the earlier concept that O₂ administration alone was responsible for ROP. Some infants even developed ROP without O₂ administration. Even infants with cyanotic heart disease and very low blood levels of O₂ developed ROP, as did babies suffering from hypoxia. This led to the realization that perhaps, prematurity itself was just one significant aetiological factor while other factors such as O₂ therapy were aggravating factors. A better understanding of the disease was also helped by the evolution of instruments for examining the eye. The initial classification failed in one respect or another to furnish the clinician with a complete picture of the disease. However, the classification improved after the invention of indirect ophthalmoscope, which now provides a view of the infant retina up to the ora serrata. Therefore, in 1984, the International Committee for Retinopathy of Prematurity [ICROP] reclassified ROP.⁶ This classification for the first time permitted direct and accurate comparison between centres and countries and provided the stimulus and basis for the Multicentre

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Study of Cryotherapy of Prematurity [CRYO-ROP Study].⁷

Epidemiology

The risk of ROP is inversely related to gestational age and birthweight.⁸ Greater proportions of very low birth weight [VLBW i.e. weight less than 1500gms at birth], and extremely low birth weight [ELBW i.e. weight less than 1000gms at birth] babies are surviving as neonatal services continue to improve. The population at risk is therefore increasing and there are some reports that blindness from ROP is increasing again.⁸ However, in the industrialized world, it is now restricted largely to infants in the ELBW group. Major risk factors of preterm birth and low birthweight are no longer in doubt. Fluctuating O₂ level has also been suggested by current studies⁹ as an important risk factor. This is because the infant retina is particularly susceptible to fluctuations in O₂ levels in the first few weeks of life. Studies in industrialized countries⁹ have shown that up to 60 percent of low birthweight babies develop ROP, and this rises to 72 percent in ELBW babies. The proportion of VLBW babies that develops stage III 'plus disease' and subsequent blindness can be as high as 11 percent and eight percent, respectively.

At the moment, there are very few reports from developing countries on the proportion of preterm babies who develop ROP; one of this came from a neonatology unit in India.⁸ Data from Europe show that 6-17 percent of blindness in children are due to ROP, and those from other regions of the world suggest that ROP may be emerging as an important cause of blindness in Latin American and other middle income countries.^{9,10} Furthermore, these findings are more commonly seen in urban centres than the rural communities. A recent study in a blind school in South Africa,¹¹ showed that 10.6 percent of the children were blind as a result of ROP. This is the only country in Africa where blindness from ROP has been reported. The prevalence of ROP and blindness from it in Nigeria can only be imagined. The only study available for review gives an impression that blindness from ROP is rare in Nigeria.¹² Many of the preterm, LBW babies probably do not live long enough for blindness to become apparent. However, it has to be borne in mind that the neonatal units in our tertiary institutions are probably enabling the survival of more ELBW and VLBW babies for long enough for ROP screening and intervention to become necessary.

Pathogenesis

Mesenchyme, the vascular precursor, pours out of the optic disc at 16 weeks of gestation and grows across

the surface of the retina in a wavelike fashion, reaching the edge of the retina [the ora serrata] on the nasal side, at about 36 weeks of gestational age. Because of the greater distance, it does not reach the temporal ora until about 40 weeks, which probably accounts for the preponderance of the disease in the temporal retina. The sequence of events to maturation of blood vessels is as follows: mesenchyme, to capillary meshwork, to mature arteries and veins. This is the popular theory today. To account for the ophthalmoscopic observations, the following sequence of events in vascular injury and response is postulated:

- 1] An injury from unidentified noxious agent[s] destroys the vascular endothelium where it has just differentiated from mesenchyme to form the primitive capillary meshwork.
- 2] The mesenchyme and mature arteries and veins survive and unite via the few remaining vascular channels to form the mesenchymal [A-V] shunts.
- 3] The mesenchymal [A-V] shunts form a distinct demarcation line between vascular and avascular retina. It is composed of a nest of primitive mesenchymal and maturing endothelial cells, fed by mature arteries and veins. No capillaries are found in the region of the shunt (the pathognomonic lesion of acute ROP). It has a location and extent in the retina, the more posterior the location and the greater the circumference of the developing vasculature involved, the more severe the prognosis for the eye.
- 4] There is a sessile period after the injury when all vascular development of the eye ceases. This period may last for days or months, during which there are few changes in the ophthalmoscopic findings.
- 5] Then, the tissues that form the shunt begin to thicken as vasculogenic activity resumes in the retina. This stage, in a very real sense, determines the fate of the eye.

[A] If the cells inside the shunt divide and differentiate into normal capillary endothelium; they then form primitive endothelial tubes which can be identified with fluorescein angiography as a regular 'brush' border of capillaries which over time grows into the avascular retina providing blood supply. This is referred to as regression. Fortunately, this happens in over 90 percent of cases of ROP.

[B] If, however, the primitive cells in the shunt multiply and break through the internal limiting membrane of the retina but do not differentiate into normal endothelium, they grow into the vitreous, over the surface of the retina and the ciliary body. It is this lack of differentiation and destructive proliferation of

cells and their invasion into spaces and tissues where they do not belong that leads to membrane proliferation and the traction detachment. This process can either be slow but inexorable [over weeks or months] or, as described by the Japanese may be a 'rush' disease, during which its progress can be compressed into a matter of days to weeks. In either event, the outcomes are identical: partial or total tractional retinal detachment with visual loss; this occurs in less than 10 percent of cases of ROP.

Classification

A group of ophthalmologists from 11 countries developed a new classification between 1984 and 1987;⁶ this is now the International classification of ROP. In this classification system, the specification of location and extent of the disease, its accurate staging, and its evolution to retinal detachment or regression are clearly shown. For specification of location of the disease, the retina is divided into three zones [Fig. 1]:

1. Zone I: Extends from the optic disc to twice the disc-macula distance = 30 degrees in all directions from the disc.
2. Zone II: The middle zone extends from the outer border of zone I to the ora on the nasal side and to approximately, the equator on the temporal side.
3. Zone III: Extends from the outer edge of zone II in a crescentic fashion to the ora serrata.

The extent of the vascular involvement is simply coded by the number of clock hours involved [see Fig 2].

Staging

It is more likely that one or two stages of the disease may be present at any given time. The stages are:

- Stage 1: Demarcation line. Distinct junction between vascularised and avascular retina.
- Stage 2: Ridge. The demarcation line has now acquired a volume, width and risen above the surface of the retina.
- Stage 3: Ridge with extraretinal fibrovascular proliferation. May be mild, moderate or severe.
- Stage 4: Subtotal retinal detachment [RD]. Tractional forces develop from proliferating tissue in the vitreous gel or on retinal surfaces resulting in a traction-type of RD.
- 4a) : Subtotal RD excluding the fovea.
- 4b) : Subtotal RD involving the fovea.
- Stage 5: Total RD.

This classification has as its unifying idea, a simple but powerful principle. The more posterior the zone, the more of the developing vasculature involved, and the more hours of the clock encompassed, the worse the prognosis is for the eye. Vitreous hemorrhage as well as exudative RD can occur in stages 3 to 5.

Plus disease, a term of importance that is emphasized in the international classification of ROP, is determined by the presence of retinal vascular dilation and tortuosity in the posterior pole. It is indicative of an actively progressing phase of the disease. If plus disease is

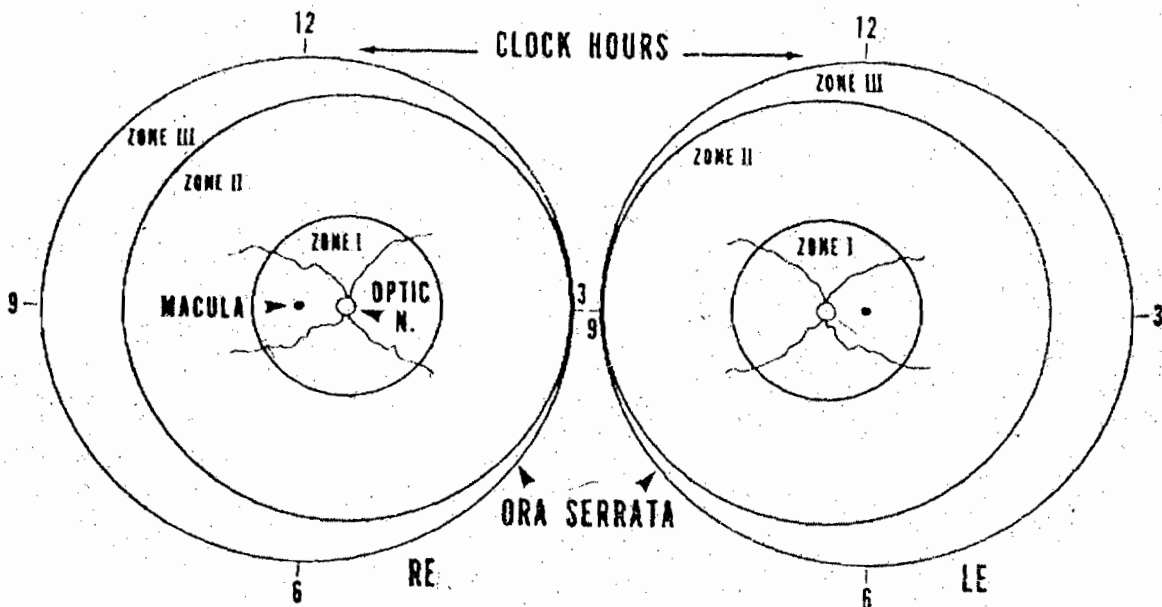


Fig 1. Zones of retinal involvement, illustration of the fundus with the zoning employed in conjunction with the new classification of ROP

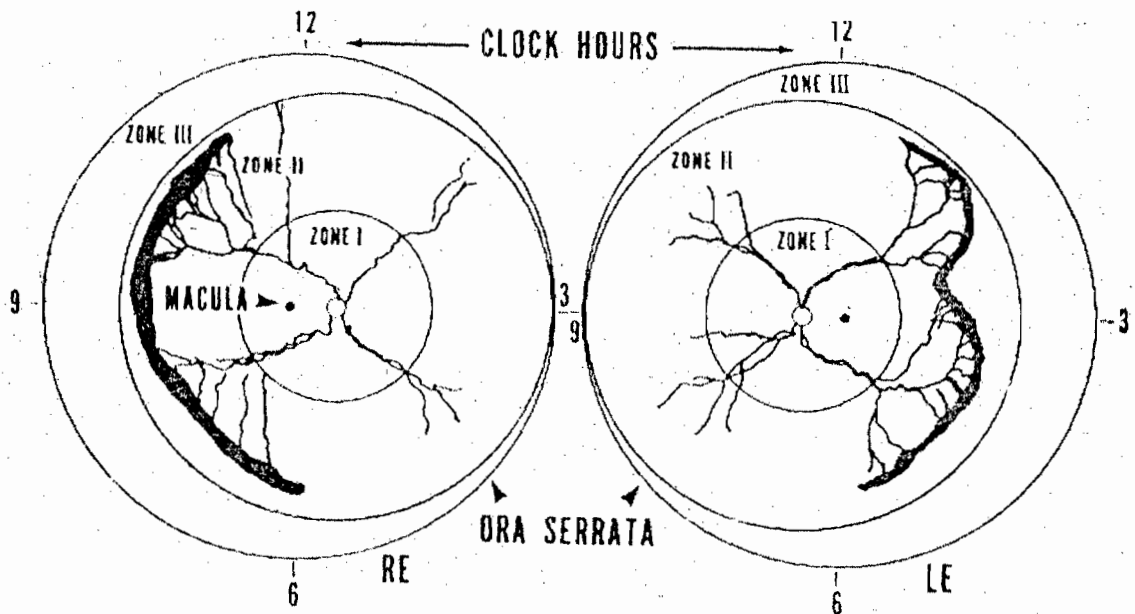


Fig 2. Extent of involvement. Bilateral zone 2 retinopathy of prematurity of 5 clock hours in the temporal retina of both eyes.

located in Zone I or posterior Zone II, there is a significant risk of a rapidly progressive disease [‘rush disease’]

Threshold disease: is characterized by Zone I or II ROP with plus disease, in combination with stage 3 involving five or more confluent clock hours or eight cumulative clock hours.

Predisposing Factors of ROP

The predisposing factors of retinopathy of prematurity are contained in Table X. It has been clear for a while, that birthweight and oxygen are by no means the sole factors that determine the occurrence of ROP. The condition has been reported in full term infants without O₂ therapy. In the early 1990s, it was observed that there were variations between ethnic groups. Some evidence suggests that African-American infants are less prone to severe outcome ROP than white infants.¹ This racial variation suggests that genetic, socioeconomic, or dietary factors may be involved. Thus, although O₂ has a long tradition of being implicated as a cause of ROP, it is clearly neither a necessary nor a sufficient cause of the disease. However, there is no doubt that the most vulnerable are infants with the lowest gestational age, lowest weight and the most ill.

Implications for Screening

An increased incidence of blindness from ROP can be expected in any area of any country where improved neonatal care is available. To prevent this, there is a need to promote some specific disease control measures

according to the VISION 2020 programme.⁸ Thus, there is a need to establish a screening programme at least in the tertiary and secondary health centres where neonatal and ophthalmic services are available.

Screening Schedule

The principle upon which a screening programme to detect ROP in infants at risk might be based include the following:¹⁴

Table X

Predisposing and Risk Factors in Retinopathy of Prematurity

Prematurity.
Low birthweight.
Oxygen therapy.
Sepsis.
Chronic hypoxia <i>in-utero</i>
Multiple blood transfusions [e.g. exchange blood transfusions]
Multiple births
Hyaline membrane disease
Drugs: e.g. Aminophylline, Antibiotics
Apnoeic spells
Metabolic acidosis
Ultraviolet light therapy
Cyanotic heart disease
Anencephaly
Intraventricular haemorrhage
Genetic

1. Infants with birthweights of 1500gms or less, those with gestational age of 28 weeks or less, and those over 1500gms who have unstable clinical course and are felt to be at high risk by the attending paediatrician, should have a dilated indirect ophthalmoscopic examination by an ophthalmologist experienced in the examination of preterm infants.
2. Examination should be carried out between the fourth and sixth weeks of chronological age or between 31 and 33 weeks post-conception age, as determined by the paediatrician.
3. Follow-up examinations are best guided by the findings at the first examination using the international classifications; for example, two to four-weekly examinations, until full vascularisation in those without ROP.
4. Infants with ROP but no threshold disease should be seen at one to two-weekly intervals until vascularisation enters zone 3.
5. Infants with threshold disease should be considered for ablative treatment of at least, one eye within 72 hours of diagnosis.
6. There should be detailed information on the ocular status of referred infants.

Requirements for Examination

The requirements for the ophthalmic examination which is best done in the Nursery, include the following:

- [a] Indirect ophthalmoscope
- [b] Paediatric lid-speculum.
- [c] Scleral indenter [cotton bud can suffice].
- [d] Prior pupillary dilatation with 0.5 percent cyclopentolate and 2.5 percent phenylephrine [or 1 percent tropicamide + 2.5 percent phenylephrine]. (Physicians should beware of possible adrenergic response by the infant)
- [e] Topical anesthesia before using the speculum.

Treatment Options

The aim of therapy is to treat the entire 360° of the avascular retina anterior to the ridge either by cryotherapy or laser. The result of the cryotherapy for retinopathy of prematurity trial⁷ indicated that treatment was associated with approximately 50 percent reduction in the occurrence of posterior retinal traction or detachment. There is a report from India⁸ where better results were obtained by treating patients with stage 3 + ROP in three contiguous or five cumulative clock hours in zones I to II. The stress induced by cryotherapy could lead to life threatening complications, thus the presence of the neonatologist and life support systems are

essential during the procedure.

Diode and argon laser through indirect delivery are now being used as an alternative method of treatment.¹³ Laser is easier for very posterior lesions, causes minimal reactions, pain and fewer systemic complications. Diode laser is preferred to argon, because it is cheaper, easy to maintain, portable and does not cause cataracts in an eye with a thick tunica vacuoles lentos. However, argon causes less pain. Despite the seeming advantages of laser treatment, cryotherapy is more commonly used because it is cheaper, more easily available and portable.

Surgery

Stages 4 and 5 diseases require surgery even though the results are very disappointing visually and anatomically.

Surgical options are (a) scleral buckling alone or (b) vitreo-retinal surgery with vitrectomy and lensectomy. Even reattached retinæ have only 10 percent of ambulatory vision.

Long-term follow-up

Long-term follow up is essential even for those who have regressed ROP. Problems that may arise in such eyes later include cataract, glaucoma, strabismus, amblyopia, myopia and anisometropia. Angle closure glaucoma can occur during the second to fifth decades, with a mean age of 32 years in affected eyes.

Conclusion

Although ROP has been recognized for some years as an important cause of blindness in developed countries, it is now becoming a significant condition in developing countries. The WHO's Vision 2020 programme targets ROP as an "avoidable disease" requiring early detection and treatment to prevent blindness and the inherent costs to the individual and the community. As a lower cost option for developing countries, screening only infants under 1200g may be more cost effective. Prevention remains the best strategy at present to avoid blindness; further research on preventive measures is still required.

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