Aggressive posterior retinopathy of prematurity in large preterm babies in South India

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ABSTRACT

Objective To describe aggressive posterior retinopathy of prematurity (APROP) in a subset of premature babies, having gestational age (GA) of ≥28 weeks and birth weight (BW) of ≥1000 g.

Design Retrospective observational case series.

Setting and Patients Case records of 99 babies, who were diagnosed to have APROP between July 2002 and October 2010 were reviewed. Fundus fluorescein angiography (FFA) was carried out in 19 babies.

Results The mean GA was 31.7 weeks (range 28–35 weeks) and mean BW was 1572 g (range 1000–2310 g). All these babies received supplemental unblended oxygen 3 days or longer after birth. Of the 52 babies who had an eye exam in the neonatal intensive care unit prior to discharge, 35 babies had loss of vascularised retina from zone II to zone I and four babies from zone III to zone I, when examined as an outpatient. FFA revealed large geographic areas of vaso-obliteration (more than 30 disc areas) posterior to the shunt vessels within vascularised retina.

Conclusions Features of severe capillary bed loss in the vascularised retina were seen in our cases. Oxygen could be a precipitating factor in causing this retinopathy of prematurity in large babies.

INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of retina occurring in premature children. It usually regresses but can lead to irreversible vision loss if there is progression from retinal neovascularisation to retinal detachment. Aggressive posterior ROP (APROP) is an uncommon, rapidly progressing, severe form of ROP first described in 2005. If untreated, it usually progresses to stage 5 and blindness. The characteristic features of this type of ROP are its posterior location, prominence of plus disease and the ill-defined nature of the retinopathy. In developed economies, it is usually seen in extremely premature babies having gestational age (GA) ≥28 weeks and birth weight (BW) <1000 g. We describe APROP in premature babies, having GA ≥28 weeks and BW ≥1000 g.

METHODS

Preterm babies, who presented with APROP between July 2002 and October 2010, were included in this study. All these babies were from six neonatal intensive care units (NICU). There was considerable disparity in the APROP cases seen from each NICU. Approval from the Institutional Review Board was obtained and tenets of declaration of Helsinki were adhered. The first examination was done at the NICU before discharge, which in some cases was as early as a couple of days after birth. This screening was done mainly to create awareness among the parents and paediatricians of the need for further exams. Subsequent examinations were done at the base hospital at 4 weeks of age. Clinical examination was performed with an indirect ophthalmoscope using a 28 D lens, lid speculum and scleral depressor. ROP was classified according to the revisited international classification of ROP. Stage 1 is a demarcation line, which is a thin but definite structure that separates the avascular retina anteriorly from the vascularised retina posteriorly. Stage 2 is a ridge which arises in the region of the demarcation line, has height and width, and extends above the plane of the retina. In stage 3, extraretinal fibrovascular proliferation or neovascularisation extends from the ridge into the vitreous. Stage 4 has partial retinal detachment and is divided into extrafoveal (stage 4A) and foveal (stage 4B) partial retinal detachments. Stage 5 is total retinal detachment. APROP was the new stage introduced in this classification. As 50 babies of the 99 APROP babies were seen before the publication of this revisited classification, that time we had classified them as ‘Fulminate ROP’. We reclassified them as APROP while doing this retrospective analysis. Retcam (Clarity Medical Systems, Pleasanton, California, USA) was used to photograph the posterior pole and as much as possible of the periphery for all the cases examined at the base hospital. Fundus fluorescein angiography (FFA) was carried out in 19 babies. Retinal laser photocoagulation was done within 72 h of diagnosis of APROP, using diode laser (Oculight SLx, Iridex, California, USA). Treated eyes received photocoagulation of the entire avascular retina...
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with near confluent burns. All lasers were done under topical anaesthesia with neonatologist standby. Two babies were given intravitreal bevacizumab (Avastin, Genentech, San Francisco) as a rescue treatment wherein one developed bilateral anterior segment ischaemia following extensive laser therapy and second child had total capillary loss on FFA. An unfavourable outcome was defined in the same manner as in the multicentre trial of cryotherapy for ROP.5

RESULTS

Ninety-nine babies were diagnosed to have APROP. Six cases were excluded from analysis as they had GA <28 weeks or BW <1000 g. The mean GA was 31.7 weeks (range 28–35 weeks) and mean BW was 1572 g (range 1000–2310 g). The biggest baby having APROP had a GA of 35 weeks and BW of 2290 g. All these babies came from NICU’s which used unmonitored unblended oxygen, 2–5 l/min immediately after birth, for 3 days or longer. Manual ventilation was carried out with the gas flowing only through a small water chamber (for humidification) directly into the child. As no oxygen blenders are used, 100% oxygen was administered. Thus, the fraction of inspired oxygen is 1.0, which is highly abnormal, especially when the child has healthy lungs. Even if oxygen saturation is monitored in some, it is of little use as the paediatricians in these NICU’s aimed at maintaining it at 100%. Details regarding number of days oxygen was given was available in 73 babies. The average number of days oxygen given was 11.7 (range 2–26 days). Seventy-four (74.7%) APROP were from a single unit, of whom

Figure 1  (A) Oxygen administration to babies with a non-re-breather funnel mask. (B) Oxygen administration via a hood.

Figure 2  (A,B) Fundus picture with fundus fluorescein angiography (FFA) picture of RE of a child with aggressive posterior retinopathy of prematurity (ROP). This child was born at gestational age of 33 weeks and birth weight of 1625 g and was given oxygen for 12 days. FFA was taken at post natal age of 22 days (10 days after stopping oxygen). There was total capillary drop out till the disc and only few large blood vessels are seen. Areas of blocked fluorescence nasal and inferior to disc signify haemorrhages. Interestingly the other twin which was sicker and was given oxygen for a longer duration, developed less severe conventional ROP (stage three in zone two with plus). (C) Fluorescein angiogram taken at 2 weeks after single injection of intravitreal bevacizumab. Capillary network is seen growing (white arrows). (D) Fluorescein angiogram taken at 12 weeks show fovea revascularised with vessels going till zone 2.
36 (48.6%) were seen between June 2002 and December 2003. During that time, the unit was administering 100% oxygen to the babies using a non-re-breather funnel mask (figure 1A). When they changed oxygen delivery from funnel to hood type (figure 1B), which is a crude form of blending oxygen, not a single baby was seen with APROP from that NICU in 2004 and the remaining 38 (51.4%) were seen subsequently over 5 years. Thus, it appears that the incidence of this condition was directly related to delivery of oxygen to these premature babies. Table 1 shows varying incidence of APROP according to mode of oxygen delivery. As the rule of the thumb, some NICU’s give unblended oxygen to all premature babies born at 36 weeks or less for at least 2 to 6 h, immediately after birth, irrespective of whether they require it or not.

Fifty-two babies had an eye exam before discharge (from 2 days to 3.5 weeks after birth). All had immature vessels either in zone II or III. When seen at base hospital as an outpatient, at 4–5 weeks after birth, 39 (75%) had loss of vascularised retina. Thirty-five had retraction from zone II to zone I and four had from zone III to zone I. All had severe plus disease and although the avascular retina extended till zone I, there were loops of large vessels seen reaching peripherally in a few cases, especially on nasal side. FFA revealed large geographic areas of vaso-obliteration posterior to the shunt vessels within otherwise vascularised retina with thrombosed vessels in some cases (figures 2A, B and 3A, B). Primary laser was deferred in the case depicted in figures 2 and 3 due to severe ischaemia extending till disc margins, where in primary laser would have meant ablating even the fovea. Thus, intravitreal bevacizumab was given as a rescue treatment following which the capillary network and vessels started growing and even the thrombosed vessels opened up (figures 2C, D and 3C, D). This child
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has completed more than 1 year follow-up and the vessels have not only progressed till anterior zone II without any laser or repeat injection of bevacizumab, but the child also has good vision. The average postnatal age (PNA) and postmenstrual age (PMA) at laser was 3.8 weeks (range 1.5–9.3 weeks) and 35.7 weeks (range 30.5–40.4 weeks), respectively. Fifty-five babies (59.1%) were lasered before 4 weeks and 23 (24.7%) before 6 weeks of age. Average laser spots given were 3678. Laser had to be given extensively, even within the vascular loops (figure 4). Twenty-seven eyes had unfavourable outcome. Thirteen had stage 5 and seven had stages 4a and 4b. The total unfavourable outcome for APROP was 13.7%.

In addition to these 93 babies who required laser, there were seven babies who had features of APROP to begin with, but these regressed without any treatment. All these babies had lesser amount of plus disease (preplus). Interestingly, there were islands of avascular retina seen in vascularised retina and these also disappeared over time without treatment.

When we analysed babies who had conventional ROP (high-risk prethreshold or threshold ROP), the mean GA was 30 weeks (range 24–35 weeks) and mean BW was 1327 g (range 600–2250 g). Of these 134 babies, 19 had APROP to start with, which got converted to conventional ROP over time. Average PNA at laser was 7.1 weeks (range 3.3–17 weeks) and the average PMA at laser was 57 weeks (range 30–40 weeks). Average laser spots given were 1845. Sixteen eyes had unfavourable outcome. Of these eight eyes that had stage 5, five had stage 4a and three had stage 4b.

**DISCUSSION**

Fluorescein angiograms of APROP cases in our study, showed decreased central as well as peripheral perfusion where there was total capillary drop out and even the large radial vessels in a few cases showed blocked fluorescence with no flow of dye in them (suggesting thrombosis) along with retinal haemorrhages (figure 3A,B).

Similar findings on fluorescein angiography were observed by Yokoi et al in three babies having APROP. However, all three were extremely premature. Their mean GA and BW was 24 weeks and 600 g, respectively compared with 31.7 weeks and 1572 g in our study. In their study, even when ROP stabilised after laser or surgical treatments, vascular abnormalities remained; including hypoplastic macular vessels while in our cases the non-perfusion areas vascularised after a good aggressive laser or bevacizumab as shown in one case. They concluded that because of poor macular function, long-term good visual acuity was doubtful. However, when we analysed our data of 34 babies with APROP, successfully treated with laser, at a mean follow-up of 3 years, 92% had visual acuity ≥20/60 (data not shown). This means that babies in our study had good macular perfusion at birth. Supplemental oxygen in premature infants interferes with normal vascular endothelial growth factor–driven vascular development which leads to cessation of normal vessel growth and regression of existing vessels subsequently. Thirty-nine babies in our study had loss of vascularised retina based on zone. When examined as an outpatient, they presented with severe vascular dilatation and tortuosity with large areas of capillary non-perfusion posteriorly in zone I. Our average postnatal age for laser was only 3.8 weeks and a few babies needed treatment as early as 1.5 weeks. Four to 6 weeks is when routine ROP screening starts in the west. It is impossible for us to get the exact percentage and oxygen saturation from the paediatricians as there are no proper records maintained in these NICU’s. Oxygen is given more liberally with the object of preventing cyanosis rather than treating it. When contacted, one of the treating paediatricians felt that it reduced the stay of the child in the hospital.

In our study, we saw seven cases of APROP which regressed spontaneously. All of these cases had lesser degree of plus disease in them. However, the APROP cases in our study had good vision at the last follow-up.
disease (preplus). Nineteen babies with APROP got converted to conventional ROP. All of them were large babies. Also the average GA and BW of babies with APROP was much higher than babies with conventional ROP which is very unusual and they also presented earlier. This could be because these babies were given oxygen unnecessarily. Thus we feel, oxygen is an important cause of ROP in large babies, but may not be a sufficient single cause in smaller ones. 10 It is known that SpO2 levels >95% are potentially dangerous in infants breathing supplemental oxygen. 11

Our study shows that when the care of preterm babies is appropriate and of high quality, then degree of prematurity is the major ROP risk factor and the risk of sight-threatening ROP for babies >30 weeks and 1500 g is very low. But when unblended oxygen is administered, then this swamps all other risk factors and the degree of prematurity is less important than the amount of oxygen. This is what Kinsey had found in the cooperative study of retrolental fibroplasia and the use of oxygen in 1956. 12

There are several drawbacks of this study. First, it is a retrospective one. Second, the exact oxygen saturation for all cases is lacking. Third, there is no photo documentation of retraction of retinal vessels between NICU screening before discharge and examination as outpatient later.

Incidence of ROP is on the rise in emerging economies. 13 There have been similar reports of ROP in larger premature babies from many developing countries like Vietnam, 14 Thailand, 15 China, 16 India 17 18 and Guatemala. 19 All of them speculate the cause towards high amounts of supplemental oxygen. Some have even named them as ‘smouldering ROP’ 20 or ‘hybrid ROP’. 21 In our study we could substantiate oxygen as the cause probably because of earlier screening, FFA documentation and mainly drop in the incidence of these cases when oxygen delivery was altered. The disease that was caused by oxygen as retrolental fibroplasia in 1950s is now being repeated again in these nations. Thus, a large preterm baby developing severe ROP before 4 weeks of age, oxygen toxicity should be suspected. It is simpler to alter a known factor (oxygen in this case) rather than go around looking for that unknown one. Having broader screening guidelines and screening more babies 22 in developing nations could be avoided with a little help from our paediatric colleagues. Thus cutting down unnecessary oxygen and using oxygen blenders, could prevent this epidemic of ROP in large preterm babies in these nations and end history from repeating itself. 16 23

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REFERENCES
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