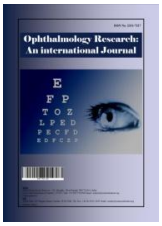

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Recognition and Prevention of Visual Loss Due to Retinopathy of Prematurity in High Risk Twin Infant Pairs: A Case Series with a Multi-specialty Approach

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Authors' contributions

This work was carried out in collaboration among all authors. Author RA performed screening, designed the study, performed the statistical analysis and wrote the first draft of the manuscript. Author KR performed data collection, wrote the protocol author MM checked and managed the analyses of the study. Author MM performed screening and follow up, managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: This study was performed to determine profile of asymmetry, newer differences in postnatal risk factors and effects of current laser treatment on retinopathy of prematurity (ROP) progression in preterm twin pairs.
Methods: A retrospective study was conducted on 250 infants (125 twin pairs) of premature birth, low weight or other infant risk factors at Sri Ramachandra hospital, a tertiary referral hospital in Chennai, India from May 2017 to April 2019. Indirect ophthalmoscopy with scleral indentation was performed on all babies under continuous monitoring of oxygen saturation using pulseoximeter in the presence of a neonatologist. Examination and analysis was done for stage and zone of ROP, systemic causes, spontaneous regression and need for treatment.
Results: Among 125 twin pairs, 38twin pairs (30%) had ROP which was asymmetrical in 27% and symmetrical in 4%. Disparity developed before 35 weeks when both twins had ROP. Two stage

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differences occurred in 84%. Both were statistically significant ($p<0.05$). Spontaneous regression occurred after 35 weeks and majority regressed by 40 weeks. Laser treatment was required in 36%. Risk factors were most commonly respiratory distress, patent ductus arteriosus, apnoea, variation of birth weight and gestational age.

Conclusion: Smaller gestational age is a good predictor of variability in progression of vascularization and along with birth weight and weight gain contributes to asymmetry. Respiratory distress has the highest risk. It is important to screen and follow up all twins irrespective of initial examination status and normal appearing retina in one twin, as transition from one stage to another can occur. Early detection with timely treatment will prevent irreversible visual loss.

Keywords: Retinopathy of prematurity; asymmetry; twin gestation; risk factors; plus disease.

ABBREVIATIONS

ROP : Retinopathy of prematurity
AP-ROP : Aggressive posterior retinopathy of prematurity
GA : Gestational age
IVH : Intraventricular haemorrhage
RDS : Respiratory distress syndrome
PDA : Patent ductus arteriosus
SGA : Small gestational age

1. INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disease that affects premature infants. It is one of the leading causes of preventable childhood blindness worldwide [1]. ROP is on the rise due to better neonatal survival rates and improved neonatal care. ROP occurs in premature babies who have been exposed to high ambient concentrations of oxygen. This may be required due to their preterm immature respiratory system. However, this oxygen supplied after birth can result in halting of retinal vascularisation. The pathogenesis is multifactorial and includes two phases. The first occurs typically between 22–30 weeks of gestational age and the second between 31–34 weeks of gestational age.

Plus disease indicates severe ROP with progressive changes in the posterior pole in extreme premature babies [2]. Aggressive posterior retinopathy of prematurity (AP-ROP) is the rapid progression of signs with involvement of zones 1 and 2 [3]. Early identification of retinal changes in at-risk premature infants remains the best strategy in the management of ROP. Known risk factors include small gestational age (GA) [4], anemia, blood transfusion, mechanical ventilation [5], hypoxemia [6], perinatal sepsis [7], use of inotropes [8], intra-ventricular hemorrhage (IVH), low birth weight [9], and postnatal exposures [10]. Limited literature is available regarding ROP development among twin pairs [11]. Our study aims to determine profile of asymmetry of ROP among twins the newer post natal risk factors and effects of current treatment responsible for the variability in ROP.

2. PATIENTS AND METHODS

2.1 Patients

An observational retrospective study was conducted on 250 infants (125 twin pairs) who were of premature birth, low weight or other infant risk factors at Sri Ramachandra hospital, a tertiary referral hospital in Chennai, India from May 2017 to April 2019. Objective of this study was to screen, treat and rehabilitate infants with a multidisciplinary approach.

2.2 Methodology

Apart from the clinical profile and contributing postnatal risk factors, spontaneous regression, resolution following treatment or progression of ROP were analysed. Twins were considered asymmetrical if there was a difference of at least two stages or one zone variation in involvement. Preterm infants with birth weight of less than 1500 grams or GA less than 32 weeks were screened according to the American Academy of Paediatrics guidelines [12]. The first screening was done at 3 weeks of postnatal age or 32 weeks whichever was later but earlier for babies with very low birth weight, gestational age < 28 weeks or high risk by babies [13]. Staging of ROP was recorded according to the revised International Classification of ROP [14]. Follow up was done weekly or biweekly until retinal vessels reached zone 3 or ROP regressed.

2.3 Examination Technique

Indirect ophthalmoscopy under continuous monitoring of oxygen saturation, respiration and cardiac status in the presence of a neonatologist.

2.4 Statistical Analysis

Results were analysed using chi square test. SPSS-15 software was used to analyse the distribution and prevalence. Sample size calculation was done with expected proportion 0.285, relative precision 20% and desired confidence level 95%. Inferences with P values equal to or less than 0.05 were considered statistically significant.

3. RESULTS

Out of 125 pairs of twins screened, 38 (30%) pairs developed ROP (Table 1), in which 33 (27%) pairs showed asymmetrical progression whereas 5 (4%) pairs showed symmetrical progression (Table 2). The average GA was 30weeks ± 2 and the average birth weight was less than or equal to 1500 grams.

Plus disease occurred in 5 babies (15%) (Fig. 1). Zone 2 stage 3 and zone 3 stage 3 involvement was seen in 2 babies and stage 4 in 1 baby.

In terms of asymmetry, one zone difference occurred in 2 twin pairs and one stage difference in 7 pairs. Up to two stage difference was noted in 84% (statistically significant, $p<0.02$).

When both twins developed ROP (16 pairs), asymmetry was noted before 35wks in 12 pairs and after 35wks in 4 pairs which was statistically significant $p<0.04$).

Significant systemic risk factors responsible for asymmetry were respiratory distress syndrome (RDS) (100%), patent ductus arteriosus (PDA) (57%) and apnea in (58%). Babies with low birth weight developing ROP was seen in 19 twin pairs (58%).

Spontaneous regression occurred in 61% and laser treatment was required in 36% and photocoagulation was most beneficial in zone 2 involvement (Fig. 2). Stage 4 disease was treated with a combination of intravitreal bevacizumab, laser and vitrectomy.

Table 1. Total no of twin pairs screened

No of twin pairs screened for ROP	125 pairs
No of twin pairs with ROP	38 pairs
No of twin pairs with NO ROP	87 pairs

Table 2. Total no of asymmetry or symmetry

No of twin pairs with ROP	38 pairs
No of twin pairs with asymmetrical ROP progression	33 pairs
No of twin pairs with symmetrical ROP progression	5 pairs

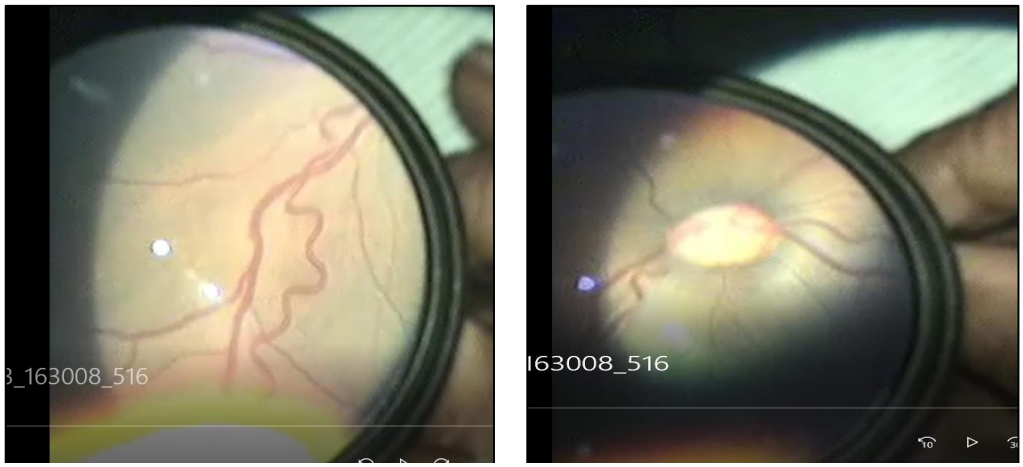

Fig. 1. Plus disease

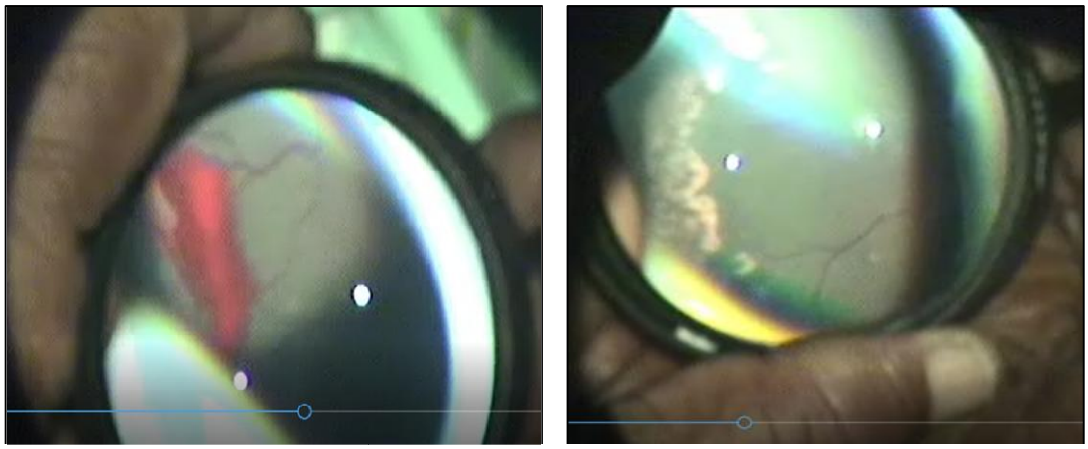

Fig. 2. Hemorrhage on the ridge in zone 2 before laser and resolution after laser

4. DISCUSSION

Twins provide a good study model since they have the same GA and are exposed to the same prenatal risk factors. Our study results suggest that variable courses of ROP were present in 33 of the 125 twin pairs (27%). This is useful information because it suggests that if ROP has a mild presentation and course in one twin, it is not necessary that the other twin will follow the same course. Thus, there is a need to examine and follow-up both babies regularly as per screening guidelines even if the initial examination was normal.

There is not much difference in asymmetry based on birth weight. Low birth weight was only marginally higher in our study, similar to the study done by Fellow et al. [15].

In our study, when one twin developed ROP the risk was mostly due to ventilation with oxygen for apneic episodes and respiratory distress syndrome. In keeping with previous studies, investigations of postnatal comorbidities among twins showed that the second delivered infant was associated with higher risks of RDS [16]. We found that a smaller GA, use of respiratory stimulant, invasive mechanical ventilation, PDA and blood transfusion in the baby are significant risk factors. In addition, we found that younger GA can itself perpetuate more damage from risk factors and thus GA determines the severity of ROP in twins but this did not explain the variability. More sensitive criteria for screening and detection of ROP are being developed [17]. It would be useful to be aware and to inform parents about the discrepancies that can occur because of antenatal risk factors, postnatal exposures, and differences in factors inherent to each twin [18]. We found that even the first born twin developed ROP and that birth weight in isolation was not a significant risk factor though small for gestational age (SGA) babies are definitely at risk.

We feel that prenatal and postnatal factors increase risk of severe ROP and can contribute to disease progression in babies especially if GA less than 28 weeks. On our assessment of other post-natal risk factors, respiratory stimulant (surfactant) and mechanical ventilation was given for 56%, anemia was present in 56%, blood transfusion given for 31%, IVH, sepsis and necrotizing enterocolitis was present in 13%.

A reverse association is now being reported in neonatal characteristics such as PDA and IVH in the absence of SGA or low birth weight [19]. However the twin with lower birth weight and PDA has greater risk of developing ROP. Lower birth weight predominantly occurred in the second twin which was at a greater risk of ROP.

Gestational age is considered a better indicator than weight gain for the development of ROP [20]. There has been an increased survival of preterm infants and this has probably increased the incidence of ROP. Although SGA babies were at risk because of immaturity, larger babies with greater SGA could develop ROP because of other comorbid illnesses [21]. We inferred from our patients that by large laser treatment has a good prognosis in ROP and in plus disease.

5. CONCLUSION

Smaller gestational age is a good predictor of progression of vascularization and along with birth weight and gain may contribute to

variability. Respiratory distress has the highest risk. This study highlight the importance of concurrence between the ophthalmologist and neonatologist during screening, detection and follow up in all twins irrespective of initial examination status and normal appearing retina in one twin.

CONSENT AND ETHICAL APPROVAL

Approval was obtained from the Institutional Ethics Committee of Sri Ramachandra Institute of Higher Education and Research, Chennai, India, where it was conducted. Informed consent had been obtained from the mother during examination for all the babies.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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