

An Unusual Manifestation: Retinopathy Of Prematurity in Late Preterm Infants A Case Series

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ABSTRACT

Background: Retinopathy of Prematurity (ROP) is a significant cause of preventable childhood blindness. ROP has been strongly associated with extreme prematurity and prolonged oxygen therapy. Recent reports indicate that ROP can occur even in late preterm infants without extended oxygen exposure, particularly when other perinatal risk factors are present. Early detection and timely intervention are crucial to prevent progression to severe stages that can result in permanent vision loss.

Case presentation: We present two neonates with retinopathy of prematurity.

Case 1: A male infant was born at 34 weeks of gestation via spontaneous vaginal delivery, with a birth weight of 1600 grams. Continuous positive airway pressure (CPAP) was initiated after birth due to dyspnea and grunting. The mother had a risk of infection with the leukocyte count of 17,000/mm³. Suspected intrauterine growth restriction (IUGR) was diagnosed. On the second week of life, a routine ophthalmologic screening revealed stage 2 retinopathy of prematurity in the posterior Zone II, bilaterally, without plus disease. The patient is scheduled for a repeat ROP examination in 1 week.

Case 2: A male infant was delivered at 34 weeks of gestation via cesarean section, with a birth weight of 1650 grams. The mother, 32 years old, G3P1102, had preeclampsia, anemia, hypoalbuminemia and a fetus with IUGR. CPAP was initiated due to dyspnea and grunting. On second weeks of life, ophthalmologic screening revealed stage 2 retinopathy of prematurity in the posterior Zone II, bilaterally, without plus disease. The patient is scheduled for a repeat ROP examination in 1 week.

Conclusion: ROP may develop in late preterm infants despite minimal postnatal oxygen exposure when prenatal risk factors such as intrauterine growth restriction and maternal comorbidities are present. Screening protocols based solely on gestational age and oxygen history may therefore fail to identify infants who remain at risk; a more individualized, risk-based approach to ROP screening is warranted.

Keywords: Retinopathy of prematurity, Neonate, Oxygen therapy.

INTRODUCTION

Retinopathy of Prematurity is a vascular retinal disorder that remains a leading cause of preventable childhood blindness worldwide, particularly affecting premature infants. The highest incidence of ROP is observed in infants born before 32 weeks of gestation or with a birth weight below 1500 grams, especially those exposed to prolonged oxygen therapy. However, emerging evidence suggests that ROP can also develop in late preterm infants and in those without significant oxygen exposure, particularly in the presence of additional risk factors such as perinatal asphyxia, intrauterine growth restriction (IUGR), or maternal complications.

Delayed diagnosis and intervention can allow ROP to progress to advanced stages, increasing the risk of retinal detachment and permanent visual loss. Therefore, a thorough understanding of the range of risk factors and clinical presentations of ROP in the premature population is essential to optimize screening and prevention strategies. Here, we present two cases of stage 2 ROP, identified at an unusually early age in late preterm infants, with a history intrauterine growth restriction.

CASE PRESENTATION

Case 1

A male infant was born at 34 weeks of gestation via spontaneous vaginal delivery, with a birth weight of 1600 grams. Apgar scores at 1 and 5 minutes were 5 and 7. The mother, 25 years old, G1P0000, had a risk of infection with the leukocyte count of 17,000/mm³. Suspected intrauterine growth restriction (IUGR) was diagnosed. The

infant was born with respiratory distress, as indicated by a Downe's score of 4 and required Continuous Positive Airway Pressure (CPAP) with the PEEP 7 cmH₂O and the FiO₂ 30% for respiratory support after birth. On the second week of age, a routine ophthalmologic screening revealed stage 2 retinopathy of prematurity in the posterior Zone II, bilaterally, without plus disease. The patient is scheduled for a repeat ROP examination in 1 week.

Case 2

A male infant was delivered at 34 weeks of gestation via cesarean section, with a birth weight of 1650 grams. The mother, 32 years old, G3P1102, had preeclampsia, anemia, hypoalbuminemia and a fetus with IUGR. At birth, the neonate did not cry immediately. After initial resuscitation steps, the infant had grunting and subcostal retractions. Continuous positive airway pressure was initiated (PEEP 7 cmH₂O, FiO₂ 30%). Apgar scores at 1 and 5 minutes were 5 and 7. On the second week of age, ophthalmologic screening revealed stage 2 retinopathy of prematurity in the posterior Zone II, bilaterally, without plus disease. The patient is scheduled for a repeat ROP examination in 1 week.

Table 1. Clinical characteristics

	Case 1	Case 2
Age of examination (days)	16	17
Gestational Age (weeks)	34	34
Sex	Male	Male
Birth Weight (grams)	1600	1650
Apgar Score	5/7	5/7
Mode of delivery	Spontaneous delivery	Cesarean section
Oxygen support	CPAP PEEP 7 cmH ₂ O/ FiO ₂ 30%	CPAP PEEP 7 cmH ₂ O/ FiO ₂ 30%
History of mother	25 years old, G1P0000, risk of infection	32 years old G3P1102, anemia, preeclampsia, hypoalbuminemia
Stage of retinopathy	OD: ROP stage 2 posterior Zone II OS: ROP stage 2 posterior Zone II	OD: ROP stage 2 posterior Zone II OS: ROP stage 2 posterior Zone II

DISCUSSION

Prematurity (< 32 weeks of gestation) or low birth weight (< 1500 g) infants are at higher risk of developing retinopathy of prematurity.^{1,2} Prolonged administration of supplemental oxygen increases this risk. Late prematurity is also associated with risk of ROP but the risk increases with decreasing gestational age. In the first case, the maternal risk factor was a leukocyte count of 17,000/mm³, and in the second case maternal comorbidities included preeclampsia, anemia and hypoalbuminemia. Both infants were 34 weeks gestational age and birth weight was > 1500 grams and had IUGR from prenatal ultrasonography and required non-invasive ventilation. Thus, even in the absence of classical risk factors such as extreme prematurity or prolonged exposure to oxygen, factors such as IUGR and maternal comorbidities may be involved in the development of ROP. The key is to find it early so that it can be diagnosed and treated early.

This case study is about two infants with retinopathy of prematurity (ROP) who were born at 34 weeks gestation with inspired oxygen fraction (FiO₂) below 40%. It is of interest to address this finding because, in the classic paradigm of ROP pathogenesis, the two major risk factors have been extreme prematurity and variable exposure to high oxygen.^{1,2} In the past, ROP has been reported in infants with much higher gestational ages (≥32 weeks), especially in low- to middle-income countries where most neonates with severe ROP are, in fact, born beyond conventional screening thresholds.¹ In these regions, more mature and larger birth weight infants may increasingly develop ROP as neonatal care capacity expands.³ Dammann et al. also described ROP in infants born at larger gestational ages, usually associated with more exposure to supplemental oxygen, although the phenotype and clinical course are quite different from ROP in extremely preterm children.¹ We now understand the pathogenesis of ROP as a multifactorial etiology, involving complex interplay between prenatal and postnatal variables rather than oxygen exposure alone.⁴ De las Rivas Ramírez et al. performed a retrospective cohort study of 452 premature infants and reported that gestational age was the strongest independent predictor of ROP

development, whereas duration of oxygen therapy was the strongest predictor of ROP progression: several additional factors, including the need for oxygen at day 28 of life, late-onset sepsis, need for non-invasive ventilation, mechanical ventilation duration, surfactant administration, and low birth weight at day 28 of life, also independently contributed to ROP development.⁴ The findings indicate that oxygen exposure is not the sole pathogenic pathway to ROP and that other risk factors, such as systemic inflammatory conditions like sepsis, can contribute to the development of ROP even without aggressive oxygen exposure.

Such rare findings are best explained by the concept of a prenatal origin of ROP. Woo et al. conducted a retrospective cohort study and found that increased levels of inflammatory mediators (interleukin [IL]-6 and IL-8) and angiogenic mediators (endoglin, endostatin and insulin-like growth factor binding protein-2 [IGFBP-2]) in amniotic fluid obtained before delivery were independently associated with the occurrence and progression of ROP in 175 premature infants after adjusting for postnatal confounding variables such as mechanical ventilation, surfactant administration and early sepsis.⁵ Woo et al. suggested that the pathophysiological events that predispose premature infants to ROP may begin before delivery.⁵ This framework can explain the infants in our report, who were born at a relatively mature gestational age (34 weeks) and were exposed to a brief period of low FiO₂ oxygen. Perhaps active inflammatory and/or angiogenic processes were present in the intrauterine environment, making the infants' retinæ intrinsically more vulnerable to vascularization disturbances despite minimal oxygen risk factors. Interestingly, the same research team did not find any association between systemic fetal cytokine levels at delivery, including IL-6, IL-8, and vascular endothelial growth factor [VEGF], and the risk of ROP in their previous study with umbilical cord blood samples (rather than amniotic fluid). However, the study did find a significant association between an increased risk of ROP and a clinical marker of maternal inflammation: a higher leukocyte count in the mother's blood at the time of hospital admission.⁶ The differences in results between the two biological compartments (amniotic fluid versus umbilical cord blood) suggest that the local intrauterine microenvironment, as reflected in the amniotic fluid, is probably a more sensitive marker of the pathogenic processes of ROP than the systemic fetal cytokine levels at a single point in time at birth.^{5,6} Although the samples examined in these two studies were of different biological compartments, both results offer strong support for the significance of prenatal inflammation as a major contributor to the pathogenesis of ROP, independent of classical oxygen pathways. Taken together, these observations suggest that gestational age and postnatal oxygen history alone may be insufficient to capture the full spectrum of infants at risk for ROP, particularly when prenatal inflammatory or growth-restricting conditions are present.⁵

CONCLUSION

These two cases illustrate that ROP may develop in infants born at 34 weeks of gestation despite minimal postnatal oxygen exposure, particularly when prenatal risk factors such as intrauterine growth restriction and maternal comorbidities are present. These findings challenge the conventional paradigm confining ROP predominantly to extremely preterm infants with prolonged high-concentration oxygen exposure. Screening protocols based solely on gestational age and postnatal oxygen history may therefore fail to capture infants who remain at risk, particularly in the presence of prenatal inflammatory or growth-restricting conditions. Our findings underscore the need for a more individualized, risk-based approach to ROP screening—one that incorporates relevant prenatal and maternal factors alongside conventional gestational age and birth weight criteria—to facilitate timely diagnosis and intervention.

Informed consent:

Written informed consent was obtained from the patients' parents for publication of this case report.

Patient Perspective:

Patient perspective could not be obtained because the patients were neonates.

Ethical considerations:

Ethical approval was waived because this study reports a case series and written informed consent was obtained from the patients' parents.

Conflict of Interest:

The authors declare that they have no conflict of interest.

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