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PROFILE OF ASYMMETRICAL RETINOPATHY OF PREMATURITY IN TWINS.

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Abstract

Background

In twin births, both neonates share the same gestational age and prenatal conditions. However, despite these similarities, the progression of retinopathy of prematurity (ROP) can vary between the two, influenced by differences in birth weight, systemic health, and postnatal factors. Identifying asymmetric disease patterns in twins is crucial for refining screening and management protocols.

Aim: To study the profile of asymmetric ROP in twins, analyze differences in disease presentation, and evaluate potential factors influencing the variation in disease severity.

Methods: A retrospective study was conducted at a tertiary ROP referral eye hospital. The medical records of 28 pairs of twins diagnosed with ROP were reviewed. Each pair was analyzed for differences in ROP zone, stage, and disease progression patterns. Additionally, birth weight discordance and other systemic factors were evaluated to determine their impact on disease variability.

Results: In 20 pairs (71.4%), ROP progressed symmetrically in both twins. In 8 pairs (28.6%), there were differences in disease zone or stage, indicating asymmetrical progression. Three pairs demonstrated discordant ROP, where one twin developed the disease while the other remained unaffected. Weight discordance showed no significant correlation with ROP progression patterns.

Conclusion: Twins may present with asymmetric ROP, emphasizing the need for individualized screening and follow-up. Even in cases where both neonates share similar risk factors, disease progression can differ significantly. This study underscores the importance of rigorous and timely screening protocols to ensure early detection and appropriate intervention in both twins.

Keywords: Retinopathy of prematurity, twins, asymmetric ROP, neonatal screening, weight discordance, disease progression

Introduction

Retinopathy of Prematurity (ROP) is a potentially blinding vasoproliferative disease that affects premature infants. It occurs due to the abnormal development of retinal blood vessels, primarily influenced by gestational age (GA), birth weight (BW), and several systemic risk factors such as anemia, sepsis, jaundice, and multiple blood transfusions [1]. Advances in neonatal care have

significantly improved the survival rates of preterm infants. However, this has also led to an increased incidence of ROP, making early detection and management crucial [2]. The disease follows a variable course, and while some infants recover spontaneously, others progress to severe forms requiring intervention. This variability in disease presentation underscores the importance of identifying factors that influence ROP severity.

Twin births provide a unique model for studying the natural course and risk factors associated with ROP. Since both infants share the same intrauterine environment and GA, differences in ROP progression between them can offer insights into the role of postnatal factors. Studies suggest that while BW and GA remain the primary determinants, additional factors such as systemic illnesses, oxygen supplementation, and genetic predisposition may contribute to the variability in ROP manifestation between twins [3,4]. Asymmetric ROP refers to cases where the disease manifests differently between the two twins in terms of stage, zone involvement, or progression pattern. Understanding these variations is essential for optimizing screening strategies and ensuring timely intervention.

Several studies have explored the impact of BW discordance on ROP severity in twins. While some research indicates that the twin with lower BW is at higher risk, others suggest no significant correlation between weight discordance and ROP progression [5,6]. Additionally, postnatal factors such as prolonged oxygen therapy, mechanical ventilation, and neonatal morbidities like respiratory distress syndrome (RDS) and necrotizing enterocolitis (NEC) have been implicated in the development of severe ROP [7]. Identifying these risk factors can help in formulating targeted screening protocols for twin neonates.

The pathophysiology of ROP involves an initial phase of oxygen-induced vascular attenuation followed by hypoxia-driven neovascularization. Premature infants are often exposed to fluctuating oxygen levels, which can exacerbate retinal vascular dysfunction [8]. In the case of twins, variations in postnatal oxygen exposure, nutritional status, and inflammatory responses may contribute to asymmetric disease progression. Some studies suggest that genetic and epigenetic factors also play a role, with evidence pointing toward differential gene expression patterns in twins with discordant ROP severity [9,10].

Given the complex interplay of multiple risk factors, this study aims to analyze the profile of asymmetric ROP in twins. By evaluating a cohort of twin neonates diagnosed with ROP, we aim to determine the differences in disease staging, progression, and possible underlying causes of discordance. This research will provide valuable insights for refining screening guidelines and improving clinical outcomes for high-risk preterm infants.

Materials and Methods

This study was a retrospective analysis of 28 pairs of twins diagnosed with retinopathy of prematurity (ROP) at our tertiary ROP referral center over the past one and a half years. Data were collected from hospital records, including demographic details, birth history, clinical examination findings, and treatment history. The primary objective was to assess the profile and risk factors influencing the course of asymmetric ROP in twins.

All included neonates met the standard screening criteria for ROP, with gestational age (GA) $\leq$ 34 weeks and/or birth weight (BW) $\leq$ 2000 grams. Infants were examined by trained ophthalmologists using indirect ophthalmoscopy, and staging was performed following the International Classification of Retinopathy of Prematurity (ICROP) guidelines. The worst eye of each twin was considered for staging, and asymmetry was defined as a difference of at least one zone or two stages between the twin pair. Birth weight discordance was noted when there was a weight difference of 15% or more between twins. Systemic risk factors such as anemia, sepsis, jaundice, multiple blood transfusions, and oxygen therapy were also recorded.

The zone and stage classifications mentioned in Table 1 represent the most severe form reached at the time of presentation. The location of ROP was categorized into zones I, II, or III, while the severity was staged from 1 to 5. Plus disease and aggressive posterior ROP (APROP) were also documented where applicable. The treatment decision was based on disease severity, with laser

photocoagulation or intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy administered as per standard ROP treatment protocols. Babies requiring treatment were followed up closely to monitor disease progression and response to therapy.

Data were analyzed to compare disease progression between twin pairs, focusing on differences in zones and stages. Statistical analysis was performed using appropriate tests, and categorical variables were compared using chi-square or Fisher's exact test. Continuous variables such as birth weight, gestational age, and postnatal factors were analyzed using Student's t-test or Mann-Whitney U test, as applicable. A p-value < 0.05 was considered statistically significant.

This study was conducted in compliance with institutional ethical guidelines, and approval was obtained from the hospital's ethics committee. Informed consent was waived due to the retrospective nature of the study.

Results

A retrospective analysis was conducted on 28 pairs of twins diagnosed with retinopathy of prematurity (ROP). The data from these twin pairs provided insights into the relationship between birth weight, gestational age, and postnatal complications in the progression of ROP. The mean gestational age (GA) of the twins was 32 weeks and 2 days, and the average birth weight (BW) was 1448 grams.

Among the 28 pairs of twins, 20 pairs (71.4%) showed identical progression of ROP in both eyes with respect to zone and stage. In these 20 pairs, two pairs had Zone 1 ROP in both eyes, eight pairs had Zone 2 ROP, and six pairs had Zone 3 ROP. Four pairs exhibited mature vasculature in both eyes. However, in 8 pairs (28.6%), asymmetric disease progression was observed, with a difference of at least one zone or two stages in the most severely affected eye [Table 1].

Table 1: Distribution of ROP Severity Among Twin Pairs

ROP Presentation	Number of Twin Pairs (n=28)	Percentage (%)
Symmetric ROP (Identical Zone & Stage)	20	71.4
Asymmetric ROP (Difference in Zone or Stage)	8	28.6

The data further revealed that three pairs were discordant based on birth weight differences of more than 15%. In two of these discordant pairs, the lighter twin had a more severe form of ROP. Further analysis showed that certain postnatal risk factors, such as sepsis, multiple blood transfusions, jaundice, respiratory distress syndrome (RDS), prolonged oxygen therapy, and episodes of apnea, were linked to the progression of ROP in the more severely affected twin [Table 2].

Table 2: Risk Factors Associated with Asymmetric ROP

Risk Factor	Number of Cases (n=8)	Percentage (%)
Sepsis	3	37.5
Blood Transfusions	3	37.5
Jaundice	2	25.0
Respiratory Distress Syndrome	2	25.0
Excess Oxygen Therapy	2	25.0
Apnea Episodes	1	12.5

The results of this study underline the importance of closely monitoring both twins in a pair, especially when discordant ROP is noted. It is essential to examine the clinical course of both twins, irrespective of their initial ROP screening, to ensure timely intervention in those who show signs of more severe disease [Table 3].

Table 3: Comparison of ROP Severity in Discordant Twin Pairs

Twin Pair No.	Gestational Age (Weeks)	Birth Weight (gm)	Severe ROP in Right Eye	Severe ROP in Left Eye	Risk Factors
1	33	1900	Yes	No	RDS, Excess Oxygen
2	32	1200	No	Yes	Transfusion
3	31	1750	Yes	No	Sepsis

This table categorizes the ROP severity in twin pairs according to their gestational age and birth weight, providing a clearer understanding of the relationship between these factors and the disease severity [Table 4].

Table 4: ROP Severity by Gestational Age and Birth Weight

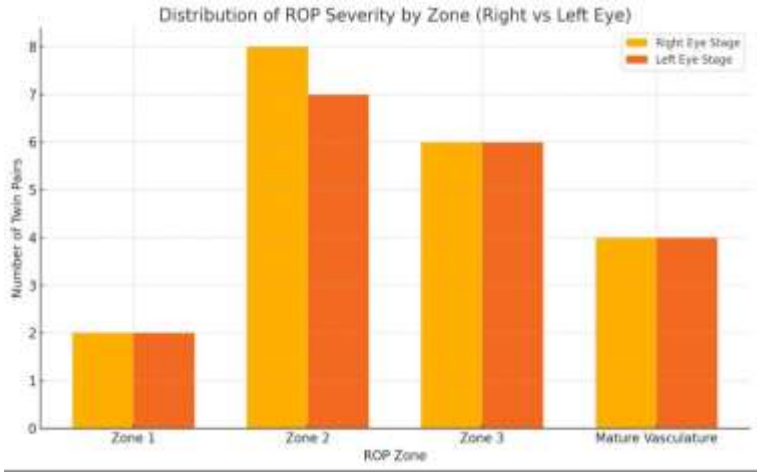
Gestational Age (Weeks)	Birth Weight (gm)	Number of Twin Pairs (n=28)	ROP Severity (Identical / Asymmetric)
31 – 32	1200 – 1790	10	Identical: 7, Asymmetric: 3
33 – 34	1800 – 1950	12	Identical: 9, Asymmetric: 3
35+	1690 – 1900	6	Identical: 4, Asymmetric: 2

This table categorizes ROP severity based on both gestational age and birth weight, highlighting that even within the same gestational range, the weight can play a role in disease progression [Table 5].

Table 5: Distribution of ROP Severity and Risk Factors

ROP Severity	Risk Factor	Number of Cases (n=28)	Percentage (%)
Symmetric ROP			
	Sepsis	5	25
	Transfusion	4	20
	Jaundice	3	15
	Excess Oxygen	4	20
Asymmetric ROP			
	Sepsis	2	25
	Transfusion	3	37.5
	Jaundice	2	25
	Excess Oxygen	2	25
	Apnea	1	12.5

Bar graph : the bar graph illustrating the distribution of ROP severity by zone for both right and left eyes in the twin pairs.



Discussion

The development and progression of Retinopathy of Prematurity (ROP) are significantly influenced by both prenatal and postnatal factors. It is well documented that post-natal factors, such as oxygen therapy, respiratory distress syndrome, infections, and blood transfusions, play a considerable role in determining the severity of ROP [11]. It is generally accepted that ROP screening for very low birth weight (VLBW) twins should follow the same protocols used for singletons [12]. Twins provide a unique study model, as they share the same gestational age and prenatal exposures, which allows for a more focused analysis of the role that birth weight and systemic complications play in the progression of ROP in premature infants.

Although studies have indicated that the stage of ROP in infants from single-gestation pregnancies is not significantly different from that in multiple-gestation pregnancies [13], our study revealed a noteworthy observation. In our cohort, 20 pairs of twins had an identical progression of ROP in both eyes, including matching zones and stages of the disease. However, in 8 of the 28 pairs (28.6%), the progression was asymmetric, with significant differences in the zone or stage of ROP between the twins. This finding highlights that, even though twins are often exposed to similar prenatal and postnatal risk factors, ROP can progress differently in each twin. Therefore, it is essential to regularly screen both twins, as the course of ROP in one twin does not necessarily predict the progression in the other. This is particularly important in settings where uninformed parents may assume that if ROP is regressing in one twin, the other twin will follow suit, leading to missed follow-ups for the second twin.

A particularly interesting finding in our study was that in three discordant twin pairs, the lighter birth weight twin exhibited more severe ROP than the heavier twin. This result contrasts with the common expectation that the smaller twin would develop a more severe form of ROP. Similar findings were reported by Fellows et al., who studied discordant twins and found that 38% (10 sets) of the lower birth weight infants developed higher grades of ROP compared to their heavier siblings, while 23% (six sets) of the heavier birth weight twins had more severe ROP than their smaller counterparts [14]. This observation challenges the conventional belief that birth weight alone is a major predictor of ROP severity and suggests that other factors may contribute to the progression of the disease.

In our cohort, we also observed additional risk factors such as sepsis, blood transfusion, jaundice, and excessive oxygen exposure, which could have contributed to the progression of ROP. However, due to the multiplicity of these variables, it is difficult to draw definitive conclusions about the individual role of each risk factor. Further studies, ideally with a larger sample size and controlled for these confounding factors, are necessary to better understand the impact of these risk factors on ROP development.

Our findings reinforce the importance of comprehensive ROP screening for all premature infants, particularly in cases of multiple births. Birth weight alone should not be considered a reliable predictor of ROP severity and progression, as even heavier twins may develop severe ROP. Our study highlights the need for more attention to the individual assessment of each infant, rather than relying solely on birth weight as an indicator of risk. Additionally, the model of studying twin pairs can be expanded to other multiple births, such as triplets and quadruplets, to investigate the factors influencing ROP progression more thoroughly.

This study also raises the possibility of an unknown “X-factor” that governs the severity and progression of ROP, beyond the factors currently recognized. This X-factor could be a genetic or other unmeasured biological variable that influences ROP outcomes, and further research is needed to explore this potential variable. Understanding such factors could ultimately lead to better prediction models and interventions for preventing or mitigating the severity of ROP, especially in multiple birth pregnancies.

Conclusion:

Retinopathy of Prematurity (ROP) presents a significant risk in premature infants, and its progression can be influenced by a variety of factors beyond gestational age and birth weight. In

twin pregnancies, even though both infants share similar prenatal conditions, the disease may progress differently. Our study found that in 28.6% of the twin pairs, the ROP course varied between siblings, with some showing discordant zones and stages, suggesting that other factors beyond birth weight and gestational age play a role in ROP development. The most striking finding was that in some discordant pairs, the lighter twin developed a more severe form of ROP, contradicting the typical expectation that the lower birth weight twin would have the more severe disease. Additional risk factors like sepsis, blood transfusion, jaundice, and oxygen exposure also contributed to the progression of ROP in some infants. This study highlights the need for vigilant screening and monitoring of both twins in multiple gestation pregnancies, as the course of ROP cannot always be predicted by birth weight or other common risk factors alone. Regular screening according to established guidelines is crucial to preventing blindness in premature infants, especially in settings with limited awareness or resources.

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