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EDITORIAL COMMENTARY

Exploring the Association between G6PD Activity and Retinopathy of Prematurity: A Promising Connection or a Wild Goose Chase?

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Retinopathy of prematurity (ROP) is a vasoproliferative disease characterized by abnormal growth of blood vessels in the developing retina of premature infants receiving excessive oxygen therapy [1]. This can lead to various complications, including abnormal vascular shunts, neovascularization, and even retinal detachment resulting in significant ocular morbidity. Understanding its pathophysiology is crucial to comprehend this complex disease in order to develop evidence based interventions.

Normally, the relative hypoxic environment in fetus stimulates the release of vascular endothelial growth factor (VEGF), promoting retinal vessel growth. When premature infants are exposed to high oxygen levels causing increased reactive oxygen species (ROS), VEGF production decreases, resulting in the cessation of vessel growth and the formation of an avascular retina. Prolonged oxygen exposure leads to vasoconstriction and vessel obliteration, leaving the peripheral retina without adequate blood supply. Over time, the avascular retina becomes ischemic, leading to late VEGF production resulting in neovascularization [1, 2]. Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme that plays a crucial role in converting glucose-6-phosphate to glucose and generating reduced glutathione (GSH), an important antioxidant which directly neutralises excess ROS implicated in the pathogenesis of ROP [2, 3].

In a case-control study by Paulpandian et al. published in Indian Journal of Pediatrics, the researchers aimed to explore the relationship between G6PD activity and ROP [4]. They hypothesized that lower levels of G6PD enzyme activity would increase the risk of ROP, as no previous studies had examined this association. The study found that infants with ROP had slightly higher median G6PD activity compared to those without ROP, although the difference was not statistically significant. However, there was a trend of increasing G6PD activity with more severe forms of ROP. The researchers also found that both G6PD activity and gestation independently predicted the development of ROP on multivariable analysis.

This unexpected finding of higher G6PD activity being associated with ROP, contrary to the initial hypothesis, was explained by the researchers as a significant association that is less likely to be due to chance, considering the observed dose-responsiveness among different severity levels of ROP. The study design used a case-control methodology, which allowed for a comparison of G6PD activity between infants with and without ROP while controlling for potential confounding factors.

However, there are few limitations to consider. The sample size was relatively small, which may affect the generalizability of the findings. A larger sample size would provide more statistical power and strengthen the conclusions. Additionally, the study focused only on inborn boys, so the applicability of the results to entire population may be limited. Due to the case-control study design, severe cases of ROP and those who received blood transfusions, which likely included cases with more advanced stages of ROP, were excluded, and milder forms of ROP were lost during follow-up. This exclusion may have led to an overrepresentation of moderate cases of ROP that required treatment. Additionally, the authors were unable to measure the variation between different observers when staging ROP, all of which could have resulted in selection bias among the participants. The article would benefit from a more thorough discussion of the potential mechanisms underlying the observed association between G6PD activity and ROP.

Although there is limited knowledge regarding normal G6PD levels at different gestational ages in neonates, previous studies have shown an inverse linear relationship between G6PD levels and gestation, with the highest levels found in infants born before 29 wk of gestation, gradually

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decreasing by term gestation [3, 5]. In the current study, the average gestational age of "controls" were almost two weeks more than the "cases" and this difference was statistically significant. Therefore, caution should be exercised when interpreting the current results.

Nevertheless, this study provides valuable insights into the potential association between G6PD activity and ROP, shedding light on the role of oxidative stress in the development of this condition. Despite contradicting previous knowledge, it adds an interesting twist to the complex understanding of ROP's pathophysiology. Further exploration of this association is warranted to fully comprehend the role of G6PD activity in the development of ROP.

Declarations

Conflict of Interest None.

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