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Inflammation and Retinopathy of Prematurity

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Retinopathy of prematurity (ROP) is a disorder of retinal vasoproliferation that occurs mainly in extremely preterm infants [1]. The long-term visual outcome among children with ROP includes a prominently increased risk of a range of visual disabilities [2]. Understanding the etiology and pathogenesis of ROP is crucial for the design of strategies to prevent and treat this potentially disabling disease.

Less than a decade ago, one review included the statement “only low birth weight, low gestational age, and supplemental oxygen therapy following delivery have been consistently associated with disease” [3]. This statement was made despite the recognition by others that other antecedents might be important, including insufficient levels of vitamin E, indomethacin treatment for patent ductus arteriosus, hypercapnia, maternal aspirin use, and transfusion of blood and blood products or the need for such transfusions [4].

While immaturity at birth and exposure to supplemental oxygen unquestionably play important etiologic roles in ROP [5], the possibility that exposures to infectious and inflammatory stimuli contribute to ROP is only gradually receiving attention. As recently as 2003 one review included the statement that “the relationships between infections and the development of ROP remain unclear” [6], while another stated that “the role of an inflammatory reaction in the pathophysiology of ROP has not been thoroughly investigated” [7].

Exposure to infection and elevated concentrations of inflammation-related proteins in the placenta and/or neonatal body fluids are associated with an increased risk for preterm delivery [8], respiratory dysfunctions [9], as well as brain damage and subsequent disability among preterm infants [10]. This concept that fetal/neonatal inflammation has adverse effects has been expanded to include ROP and other visual disturbances in preterm infants [11]. Indeed, some of the data in papers discussed below support the impression that ROP pathogenesis begins *in utero*.

The current pathogenetic model

In brief, the current pathogenetic model of ROP postulates that early neonatal exposure of the immature retina to high levels of oxygen reduces the retinal level of pro-angiogenic

growth factors such as vascular endothelial growth factor (VEGF), leading to cessation of vessel growth [12]. Subsequent relative hypoxia then leads to relatively higher VEGF levels and an overgrowth of retinal vasculature. Aspects of vulnerability include genetic components [13] and the relative inability to sustain normal vascularization in the face of adversity (e.g., low levels of VEGF [14] and insulin-like growth factor (IGF) [15].

Infection and ROP

Multiple studies suggest that neonatal infection is a risk factor for ROP. *Candida sepsis* is associated with a more than fourfold increased risk for ROP (stage 3 or higher) in a multivariable analysis that adjusted for birth weight, gestational age, days on supplemental oxygen, and 5-minute Apgar score [16]. Neonatal sepsis in general (not restricted to *Candida*) is also associated with ROP [17]. Among more than 15,000 very low birth weight infants from the Israel Neonatal Network, those who had early sepsis were twice as likely to develop severe ROP as their peers who did not have early sepsis [18].

Inflammation and ROP

If hyperoxia and infection are viewed as distal causes of ROP, then oxidative stress and inflammation are the more proximal causes. Oxidative stress, which can be a consequence of inflammation [19], has long been implicated in ROP etiology [20]. Inflammatory processes might interfere with normal retinal vascularization in the most vulnerable retinas. For example, in a murine hyperoxia model of ROP [21], knock-out mice that lack the strongly pro-inflammatory cytokine tumor necrosis factor- α (TNF α) appear to be relatively protected [22]. In another study of hyperoxia-induced ROP, omega-3-polyunsaturated fatty acids decreased the size of the avascular area and this protective effect appeared to be mediated, at least in part, via suppression of TNF α [23].

Evidence is just beginning to accumulate that markers of inflammation appear to be associated with ROP in human studies. So far, we know of one report of an association between *histologic chorioamnionitis* and ROP based on a univariable data analysis [24]. Additional support comes from a more recent and larger observational study of more than 800 extremely low birth weight infants [25]. Over the first three postnatal weeks, the systemic levels of eight cytokines and chemokines were significantly different in infants with ROP compared to controls. For example, the immuno-modulatory interleukin 18 was significantly lower on the first postnatal day, while elevated on days 7, 14, and 21 in infants who later developed severe ROP compared to controls.

Multi-factorial models of disease causation tend to require multiple “hits” [26]. Our data support the hypothesis that multiple hits increase ROP risk. We found that the co-occurrence of immaturity plus pro-inflammatory “hits,” such as clinical chorioamnionitis and neonatal systemic *inflammation* is associated with an increased risk for ROP [27]. Moreover, we also identified interactions beyond additive (and even multiplicative) patterns among the three “hits” neonatal sepsis, oxygen exposure, and low gestational age (Minghua Chen, personal communication).

Recent evidence supports the notion that poor neonatal weight gain predicts ROP [28]. It will be important to explore to what extent what is attributed to poor neonatal weight gain in ROP etiology should instead be attributed to antecedents of poor weight gain, (e.g., intrauterine inflammation) [29].

Summary and conclusion

In sum, increasing evidence suggests a role for neonatal infection and perinatal inflammation in ROP pathogenesis. The exact mechanism and timing of this inflammatory component of ROP pathogenesis remain to be elucidated, but might deserve the attention of those who wish to prevent ROP and its devastating consequences.

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