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Perinatal infection, inflammation, and retinopathy of prematurity

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Summary

The major known risk factors for retinopathy of prematurity (ROP) are extremely low gestational age, exposure to high levels of oxygen early after birth (phase I) and relatively lower oxygen levels later (phase II). In this review, we summarize recent data suggesting that exposure to perinatal infection/inflammation is associated with an increased risk for ROP. Part of this effect might be due to direct exposure of the developing retina to circulating products of infection and/or inflammation. Another potential mechanism that deserves exploration is that inflammation and/or oxidative stress can modify the known increased risk of oxygen-associated ROP. Taken together, accumulating evidence suggests that prenatal, perinatal, and postnatal systemic inflammation contribute to a 'pre-phase', sensitizing the pre-ROP retina for subsequent insults, setting the stage for what are now called phase I and phase II of ROP pathogenesis. Strategies targeting inflammatory responses might help reduce the risk for ROP in extremely low gestational age newborns.

Keywords

Infection; Inflammation; Retinopathy of prematurity

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the developing retina that mainly occurs in preterm newborns.¹ The long term visual outcome among children with ROP includes a marked increased risk for blindness² and visual disability.³ Identifying the antecedents and clarifying the pathogenesis is crucial for preventing and treating ROP.

Current pathogenetic model

ROP develops in two sequential phases. The first phase involves the cessation of normal retinal vascularization in the setting of hyperoxia. The second phase results in abnormal

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Conflict of interest statement

None declared.

neovascularization of the retinal vessels.⁴ The current understanding of the etiology of ROP is that 'only low birth weight, low gestational age, and supplemental oxygen therapy following delivery have consistently been associated with disease.'⁵ Indeed, the major pathogenic factor appears to be exposure of the immature retina to a succession of changing levels of oxygen, culminating in abnormally low/high levels of retinal growth factors, such as vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF). These, in turn, lead to a dysregulation of retinal vascularization.⁴

This two-phase model of ROP pathogenesis has been studied extensively, but does not include the important influence of the in-utero environment before birth. Below, we suggest that a prenatal 'pre-phase' of ROP sensitizes the developing retina via multiple maternal and fetal inflammatory factors produced in the setting of conditions such as severe pre-eclampsia and/or chorioamnionitis (Fig. 1).

Current therapy

Current therapeutic strategies include tight control of environmental oxygen^{6,7} and laser treatment.⁸ Intravitreal injection of anti-VEGF (Avastin®) is still considered experimental therapy.^{9,10} Although limiting oxygen exposure is non-invasive and apparently effective in reducing ROP risk, some are hesitant to adopt low oxygen strategies due to the lack of long term developmental outcome studies. An impressive reduction of ROP (8 vs 19%) co-occurred with a slight increase in mortality (20 vs 16%) in one recent trial.¹¹ However, it is uncertain whether these two phenomena are causally related and what the long term developmental outcome will be in both groups. Other treatments currently being investigated include those that have the potential to prevent phase I ROP (birth to ≤32 weeks of PMA) as well as those targeting proliferative ROP development in phase II (infants >32–34 weeks of PMA).¹² Therapies such as retinal erythropoietin and serum IGF-1, tight serum glucose control, and omega-3 supplements may decrease phase I ROP. A small observational study has suggested that intravenous fish-oil might reduce ROP risk.¹³ Interventions for phase II ROP include vitamin E supplements, increased thresholds for transfusions in infants with stage III ROP, photopic adaptation, and omega-3 supplements.¹⁴ Given the limited success of these interventions, new therapeutic alternatives should be investigated.

Infection and inflammation as a novel pathogenetic pathway

Whereas immaturity at birth and exposure to supplemental oxygen unquestionably play important etiologic roles in ROP,^{15–17} a novel line of evidence focusing on infection/inflammation is gradually receiving attention.

Retina

It has become evident that the VEGF₁₆₄ isoform leads to leukocyte recruitment in pathologic hypoxia-induced retinal neovascularization.¹⁸ Indeed, oxidative stress, which can be a consequence of inflammation,¹⁹ has been implicated in ROP etiology.²⁰ Moreover, the reduction of pathological retinal angiogenesis by omega-3-polyunsaturated fatty acids may be regulated, in part, through suppression of tumor necrosis factor-alpha (TNF-α),²¹ one of the major pro-inflammatory cytokines. Taken together, these data suggest that inflammatory processes might be part of the retinal neovascularization process, the hallmark of ROP.

Oxidative stress

A delicate balance exists between the production of reactive oxygen species (ROS) and antioxidant defenses. This balance might be disturbed by increased ROS production or inadequate antioxidant defenses. Increased generation of ROS in newborn infants can occur

as a result of many conditions, including hyperoxia, reperfusion, and/or infection. The premature infant has inadequate concentrations of antioxidants at birth, as well as an impaired synthesis of antioxidants in response to hyperoxia and is, therefore, especially susceptible to ROS-induced damage. This can lead to an increased risk for the development of ROS-induced diseases of the newborn, such as ROP.²²

Infection

Low birth weight preterm infants are particularly susceptible to infection, as rates of infection increase with decreasing birth weight and gestational age. Postnatal infection is associated with significant morbidity and neonatal complications, prolonged hospitalization, and death.²³ It has been suggested that exposure of the preterm newborn to infection and inflammatory mediators is associated with an increased risk for ROP. In a large cohort study, infants who developed early onset sepsis had an increased risk for severe ROP.²⁴ In the ELGAN study, the increased risk for ROP was primarily observed in association with late onset neonatal sepsis.²⁵ Multiple other studies support the concept that neonatal sepsis^{26–29} is a risk factor for severe ROP. Fungal infection has also been linked to chorioretinitis and ROP.^{30,31} *Candida* is known to interact with vascular endothelial cells via multiple mechanisms, including release of pro-inflammatory cytokines which injure the developing retinal blood vessels.³² *Candida* sepsis has been independently associated with increased severity of ROP as well as the need for surgical therapy for advanced ROP.³⁰ A systematic review and meta-analysis of eight studies found that systemic fungal infection in very low birth weight infants was significantly associated with ROP and severe ROP.³³

Systemic inflammation

Studies investigating histologic chorioamnionitis as a risk factor for ROP have been inconclusive; an association with ROP is present only in univariate analyses.³⁴ Other studies reveal higher rates of ROP in infants born to mothers with evidence of histologic chorioamnionitis compared to those born to mothers without signs of inflammation.^{35,36} Infants born to mothers with clinical chorioamnionitis as well as maternal leukocytosis have also been reported to be at increased risk of ROP. Maternal systemic inflammation might also contribute to the development of ROP in preterm infants by decreasing levels of IGF-1.³⁷ Low levels of IGF-1 have been associated with an increased risk of ROP and IGF-1 levels vary inversely with the severity of ROP.

At least part of the sepsis-associated risk increase for ROP might be due to circulating products of inflammation. In preterm infants with early onset sepsis, studies suggest there is a relationship between high plasma levels of cytokines IL-6, IL-8, and TNF- α in the first days of life with the later development of ROP requiring treatment.³⁸ Findings from a very large cohort study suggest that levels of circulating proinflammatory cytokines are elevated at multiple time-points after birth in preterm infants who later develop ROP when compared to controls.³⁹

Our own series of epidemiologic studies in three distinct patient populations provides strong support for the hypothesis that prenatal, perinatal, and postnatal systemic inflammation is an additional risk factor for ROP beyond immaturity and/or hyperoxemia.^{6,40,41} First, in trivariate analyses exploring the effects of gestational age <29 weeks, clinical chorioamnionitis (CAM) and neonatal systemic inflammatory response syndrome (SIRS) on ROP occurrence, low gestational age was the most important antecedent; additional individual or joint exposure to SIRS and CAM add appreciably to this risk of progression to high grade disease.⁴⁰ Second, neonatal sepsis, oxygen exposure, and low gestational age are not only independently associated with a significantly increased risk of ROP, but also interact beyond additive and even multiplicative patterns.⁶ Third, while antenatal exposure

to infection or inflammation alone does not appear to convey risk information for severe ROP, their co-occurrence does.⁴¹

A pre-phase of ROP?

Taken together, these data suggest that ROP pathogenesis begins in the prenatal period. Indeed, it might be possible that exposure to intrauterine infection and inflammation contribute to a 'prephase' of ROP, sensitizing the pre-ROP retina for subsequent insults, thereby setting the stage for what is now called phase I and phase II of ROP pathogenesis (Fig. 1).

Maternal pre-eclampsia

This has been associated with an increased risk for severe ROP in preterm infants in some studies,²⁸ whereas others have noted a decreased risk.⁴² Maternal pre-eclampsia appears to have inflammation-like characteristics in the absence of obvious infection.⁴³ Although the exact pathogenesis is still unknown, maternal systemic inflammation in response to pregnancy likely plays a major role in the development of pre-eclampsia as well as in fetal complications such as ROP. Many placental factors such as inflammatory cytokines, corticotropin-releasing hormone, free radical species and activin A are increased in pre-eclampsia.⁴⁴ During placentation, trophoblast cell invasion into the decidua is associated with a massive leukocyte infiltration.⁴⁵ Monocytes and neutrophils bind to syncytiotrophoblast microparticles resulting in increased production of TNF and IL-12 and superoxide radicals, all of which likely contribute to the overall inflammatory response in pre-eclampsia.⁴⁶ The placental ischemia also induces the release of many bioactive factors including VEGF, cytokines, reactive ROS, hypoxia-inducible factors, and matrix metalloproteases (MMPs), leading to further inflammation.⁴⁷ In concert, all of these pre-eclampsia-related factors can alter vascular development and may promote development of ROP.

Pathogenesis of ROP

If infection and inflammation are causally involved in ROP pathogenesis, their effects could be direct, indirect, or both. Systemic inflammation could increase ROP risk by directly affecting retinal angiogenesis. Moreover, inflammation might exert its major effect on ROP incidence and severity by sensitizing the developing retina to O₂-induced changes in growth factor availability and subsequent neovascularization, thereby modifying ROP risk. We consider it likely that the mechanisms are not mutually exclusive.

Direct effect

Infectious organisms and/or their microbial products can stimulate the production of proinflammatory cytokines.²³ The evidence summarized above suggests that increased systemic levels of cytokines are associated with an increased risk for ROP.^{32,38,39} One way in which pro-inflammatory cytokines might exert a direct effect on neovascularization could be via inflammation-regulated VEGF availability.⁴⁸ In this context, we suggest that an anti-inflammatory intervention should reduce oxygen-induced ROP risk in the presence of systemic inflammation, and perhaps even in its absence.

Indirect effect

Newborns with infection are at risk for circulatory and/or respiratory insufficiency with decreased systemic blood pressure, hypoxemia, and pathologic alterations in blood flow.²³ The hypotension and fluctuation of oxygen saturation following sepsis might affect the retinal perfusion and lead to increased retinal ischemia.²⁹ Frequent intermittent hypoxemic

events have been associated with severe ROP requiring laser therapy, independent of gestational age or severity of early systemic illness.⁴⁹

In animal models, the immature retina is very susceptible to hypoxic–ischemic insults. In rats exposed to hypoxia, retinal ganglion cell death was induced, resulting in the development of retinopathy.⁵⁰ Hypoxia alone can stimulate the production of pro-inflammatory cytokines such as TNF- α in the retina, which results in the breakdown of the blood–retinal barrier. Increased expression of TNF- α and IL-1 β is present in the retina of rats for up to three days after hypoxic exposure, inducing retinal ganglion cell death.⁵⁰

Conclusion

Based on current knowledge about ROP etiology and pathogenesis, it seems likely that the O₂/VEGF-related ROP risk is modified by systemic inflammation and cytokine release. The pathogenic mechanisms leading to ROP might begin long before birth. The role for anti-inflammatory drugs to prevent high grade ROP in the presence of systemic inflammation (and possibly even without systemic inflammation) should be investigated.

Practice points

- Known risk factors for ROP include prematurity, hyperoxia after birth (phase I) followed by relative hypoxia (phase II).
- Exposure to perinatal infection/inflammation is associated with an increased risk for ROP.
- Prenatal, perinatal, and postnatal systemic inflammation contribute to a ‘pre-phase’ of ROP, sensitizing the pre-ROP retina for subsequent insults.

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Pathogenetic Phases of Retinopathy of Prematurity

Figure 1.

Proposed multi-phase model of retinopathy of prematurity (ROP) pathogenesis. In the pre-phase, prenatal pro-inflammatory events such as intrauterine infection and pre-eclampsia contribute to fetal inflammation and sensitization to subsequent postnatal insults. In phase I, preterm infants' developing retinas are exposed to hyperoxia relative to in-utero oxygen levels, resulting in retinal vessel growth attenuation. Prenatal exposure to inflammation seems to exacerbate effects of postnatal factors. In phase II, retinal growth leaves part of the retina hypoxic, thereby stimulating intense neovascularization around 32 weeks of postmenstrual age (PMA), which in turn leads to high grade ROP.