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Pathogenesis of Retinopathy of Prematurity: Does Inflammation Play a Role?

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ABSTRACT

Retinopathy of prematurity (ROP) is a disorder of retinal–blood vessel development that is potentially blinding. ROP is the number one cause of blindness in infancy and the second leading cause of childhood blindness in the Unites States. The exact etiology is not completely understood and many factors appear to contribute to the pathogenesis and progression of the disease. These factors may include prematurity, low birth weight, genetic predisposition, oxygen, hypoxia, ischemia, insulin-like growth factor, vascular endothelial growth factor and sepsis. This article reviews the process of retinal development, the pathogenesis of ROP and how oxidative stress, infection and inflammation may contribute this pathogenesis.

Retinopathy of prematurity (ROP) is a disorder of retinal–blood vessel development and is the second leading cause of childhood blindness in the United States behind cortical visual impairment.[1] The National Center for Health Statistics report has listed the incidence of infants born at risk for developing this eye disease (≤32 weeks' gestation) to be at 2% of all live births. In 2008, 84,224 babies were born at or less than 32 weeks' gestation in the United States.[2] The National Eye Institute has estimated that 14,000–16,000 of these infants are affected by some degree of ROP and that 1100–1500 infants in the United States develop ROP that is severe enough to require medical treatment on an annual basis. Of these, 400–600 become legally blind from ROP each year.[3]

Retinopathy of prematurity (ROP) is a potentially blinding disorder caused as abnormal new blood vessels develop in the immature retina. In 1942, an ophthalmologist from Boston named Theodore Terry was the first to recognize a previously undescribed form of blindness in children born prematurely and of low birth weight. He named the condition based on the eye examination finding that showed a white fibrous mass behind the lens which obliterated the retinal vessels—"retrolental fibroplasia."[4] The name was later changed in 1984 by consensus of an international group of pediatric ophthalmologists to retinopathy of prematurity.[5]

Despite efforts to avoid the development of ROP since it was first recognized in the 1940s by Terry, ROP continues to be a challenging problem in the care of premature infants. The exact etiology of ROP is not completely understood and many factors appear to contribute to the pathogenesis and progression of the disease. Prematurity, genetic predisposition, oxygen, hypoxia, ischemia, insulin-like growth factor 1 (IGF-1) and VEGF all have been shown to be important in the development of ROP.[6] Severity of illness, sepsis, acidosis, blood transfusions and light have also been associated with ROP.[7] The degree of prematurity itself remains the most significant risk factor, with the avascular retina of premature babies being at the highest risk.[8,9] High oxygen saturations, oxygen fluctuation and hypoxia are known to significantly contribute to the development of ROP.[8,10–16]

Normal Retinal Development

The vascular supply for the retina consists of two main parts: (1) the choroidal vessels that underlie the retina and (2) the retinal vessels that serve the inner retina. Vascular development for the choroid is complete by 22 weeks of gestation.[17] The choroid provides nutrition through diffusion to the early retina. The choroidal vessels are more permeable and have a high venous partial pressure of oxygen (PaO_2). They lack the ability to autoregulate in response to hyperoxia. Therefore, during times of hyperoxia, PaO_2 levels are raised across the thickness of the retina and the retinal vessels respond by constricting.[7] As the retina matures, there is little change in the choroid blood supply despite the high rate of growth and development in the retinal during mid to late gestation. As a result, the retina requires its own vascular supply for adequate nutrition.[18] Normal retinal vascular development begins at the optic disk at about 16 weeks' gestation through a process of vasculogenesis. Vasculogenesis is the de novo development of vasculature that involves the proliferation, differentiation, and organization of blood vessels from endothelial progenitors—angioblasts.[17] To accomplish vasculogenesis, circulating angioblasts develop early retinal vessels in the region surrounding the optic nerve. Angiogenesis then proceeds to extend the retinal vasculature to the periphery by 36–40 weeks' gestation through formation of new blood vessels from existing vessels.[19,20]

The developing retinal vessels reach only 70% of the distance from the optic disk to the periphery by 27 weeks of gestation.[7] Retinal

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vascular development is ideally accomplished while the fetus is in the uterus in a relatively hypoxic environment where the average PaO_2 is 25–35, which is supported by the infant's fetal hemoglobin and lower metabolic demands.[18]

The retinal vasculature comprises two laminar but interconnected layers: the primary superficial layer and the ganglion cell layer which lies deeper in the retina. The layers are joined by fine capillaries.[21] Vasculogenesis in the retina is believed to be responsible for early vessel formation in the inner plexus but is not responsible for vessel formation in the temporal and peripheral regions of the human retina.[21] The formation of the primary vascular layer in the retina is intimately associated with the development of cells in the nerve fiber/ganglion region known as astrocytes.[22,23] Astrocytes are glial cells that give biochemical support to endothelial cells, sense physiologic hypoxia and express vascular endothelial growth factor (VEGF).[24] VEGF is one of the most important factors in vascular development and is associated with pathologic angiogenesis.[9,20,24] Astrocytes emerge from the optic nerve and migrate just ahead of the developing vascular network.[25] This places them in a position to respond to physiologic levels of hypoxia in the avascular areas of retina.[18,23,26] Astrocytes are present only in retinas in which retinal vasculature forms, and are restricted to the inner layer of retina that allows them to respond to hypoxia of the inner layers by expressing VEGF which is essential to induce the formation of the superficial layer of blood vessels.[23,27] The normal formation of retinal vessels depends on a period of physiologic hypoxia to stimulate the release of VEGF by the astrocytes.[18,26,28,29] Hyperoxia, will inhibit new blood vessel formation by down-regulating VEGF expression by the astrocyte, limiting the hypoxic stimulus.[23,30] This down-regulation may cause a delay in the natural retinal development. When a fetus is delivered prematurely, the normal processes for the developing retinal vascular bed that will nourish the eye are interrupted.

Insulin-like growth factor (IGF-1) is another key factor in retinal development. IGF-1 is hypothesized to regulate retinal neovascularization through control of VEGF activation. Studies have demonstrated a permissive role for IGF-1 in new blood vessel formation as it allows maximum VEGF stimulation of new vessel growth. Low levels of IGF-1 will inhibit vessel growth despite the presence of VEGF.[6,31,32] IGF-1 is supplied to the fetus from the placenta and the amniotic fluid. Premature birth causes IGF-1 levels to fall through loss of the amniotic fluid and placental supply in the fetal environment.[9]

Pathogenesis

When an infant is delivered prematurely, the retinal development must continue in an altered environment, creating the risk for developing ROP. The infant's retina becomes hyperoxic (even in room air) leading to decreased levels of VEGF and for a time, vasculogenesis is halted between the vascular and avascular retina, increasing the risk for developing ROP.[33,34] Additionally, IGF-1 levels fall from in utero levels after birth, due to the loss of IGF-1 which is provided by the placenta and the amniotic fluid.[9] The disease process for the development of ROP is biphasic with an initial phase of vessel growth retardation followed by a second phase of vessel proliferation.[9]

Phase I

The first phase of ROP has been described as the hyperoxia-vasocessation phase.[35] It occurs from birth to postmenstrual age of 30–32 weeks.[11] When a very low birth weight premature infant is born, the infant's immature lung places them at high risk for hypoxemia. The medical response is to provide increased amounts of fraction of inspired oxygen (FIO_2). Under conditions of low retinal metabolic demand this creates relative retinal hyperoxia. Production of VEGF may be inhibited by the high levels of supplemental oxygen the infant may receive in the NICU, which causes cessation of normal retinal growth, and vessel constriction with a potential for vaso-obliteration of new immature vessels. This may cause subsequent death of vascular endothelia cells.[12,30,33,35–38]

In utero, the fetus receives insulin-like growth factor (IGF-1) via the placenta, which ceases at the time of birth. The infant is predisposed to phase 1 ROP due to an inherent lack of normally developed vessels.[19]

After premature birth, IGF-1 is suppressed by poor nutrition, sepsis, and acidosis. Preterm infants with prolonged low serum levels of IGF-1 and slow weight gain, have an increased risk of ROP.[6] A low level of IGF-1 decreases retinal vascular growth by suppressing the VEGF activation necessary for endothelial cell survival.[31] As the infant matures, the non-vascularized retina has increasing metabolic activity leading to tissue hypoxia. This hypoxia promotes increasing levels of VEGF along with increasing IGF-1 to a critical level, which then triggers retinal neovascularization that moves to phase II ROP.[31]

Phase II

The second phase of ROP is the relative hypoxia-revascularization phase. It is characterized by a progressive increase in metabolic activity in the non-vascularized retina resulting in a hypoxia-induced retinal neovascularization. This phase begins around 32–34 weeks' postmenstrual age.[39] Prior to 32 weeks' gestation, the retina is very immature with photoreceptors that are not yet fully functional and the retinal metabolic demand is low.[40] As the retina matures, there is an increased metabolic demand and oxygen consumption, creating a relative retinal hypoxia.[35,41] Hypoxia stimulates the up-regulation of pro-angiogenic growth factors such as vascular endothelial growth factor (VEGF) and erythropoietin, which, in severe cases, leads to uncontrolled vascular growth in the vitreous.[9,11] The changes in retinal tissue oxygenation can be exacerbated by weaning the infant from oxygen therapy and potentially by targeting low oxygen saturation levels. Phase II ROP does not proceed with a gradual transition from avascularized to vascularized retina but rather a demarcated ridge line develops along the retina that separates the central vascularized region of the retinal from the peripheral avascular region. This structure histologically consists of mesenchymal and endothelial cells.[42] Vascular development from this stage may resume without significant disruption, or may progress to significant ROP as seen by an abnormal proliferation of retinal vessels into the vitreous and over the surface of the retina.[43] The new vessel growth is abnormal, producing capillary networks that are fragile, leaky and poorly perfused. These new vessels fail to alleviate tissue hypoxia leading to persistent growth of these abnormal vessels.[44]

Early exposure of the retina to hypoxia and ischemia exacerbate delayed retinal development in premature infants, in part due to low levels of local and systemic growth factors including IGF-1. VEGF production within the retina occurs in response to relative hypoxia but is unable to trigger angiogenesis in the absence of adequate IGF-1. Over time, postnatal levels of IGF-1 recover and reach a critical threshold, and VEGF-induced angiogenesis is triggered, contributing to the occurrence of ROP.[9,44–46]

Classification of ROP

ROP is classified first by the location of the lesion of abnormal vascular development relative to the optic nerve (zone), second by the degree of abnormality (stage), third by the presence or absence of dilated and tortuous posterior pole vessels (plus disease), fourth by the extent of the disease (clock hours) and finally by retinal sequelae as the disease involutes. Severity of disease is based on the zone, stage and presence of plus disease.