Retinopathy of Prematurity

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Introduction

Retinopathy of prematurity (ROP) is a vaso-proliferative blinding eye disease that affect premature neonates born before 31 weeks of gestation (A full-term pregnancy has a gestation of 38-42 weeks). This disorder is one of the most common causes of visual loss in childhood and can lead to lifelong disability. It remains a serious problem despite striking advances in neonatology.

Epidemiology

The incidence of ROP varies with birth weight but it has been reported to be approximately 50-70% in infants whose weight is less than 1250g at birth. The more premature the infant, the more likely ROP is to develop [1]. Furthermore, an observational study from United Kingdom found that the birth weight of infants from highly developed countries was 737-763g compared with 903-1527g in less-developed countries. Thus, larger and more mature infants seemed to be developing severe retinopathy of prematurity in less-developed nations due to better care in the neonatal intensive care unit in highly developed countries [2].

Pathophysiology

Retinal vasculature begins to develop around 16 weeks of gestation. It grows circumferentially and becomes fully at term. Premature birth results in the slowing of normal retinal vascular maturation. This is due to the exposure of newborn premature infants to hyperoxia which down regulates the production of vascular endothelial growth factor (VEGF). Therefore, blood vessels will be constricted and become obliterated, resulting in delays of normal retinal vascular development. This hyperoxia-vaso-obliteration is known as phase I of ROP (Figure 1). After weaning of oxygen supplementation, a hypoxia driven phase is created due to increased retinal metabolic demand exacerbated by vessel loss from phase I. This hypoxia phase is characterized by an over expression of VEGF resulting in a pathological neovascularization. This hypoxia-neovascularization is known as Phase II of ROP (Figure 1). The severity of ROP is classified as five stages. Stages 1 and 2 are mild and likely to regress spontaneously. In stages 3 and 4 extra retinal neovascularization can become severe enough to cause total retinal detachment (stage 5), which leads to blindness [3,4].

Figure 1: Pathogenesis of Retinopathy of Prematurity.
Risk factors

Although oxygen use and gestational age/birth weight are major risk factors for ROP, other factors reflecting the postnatal changes in the overall health of the baby, such as sepsis, anemia and chronic lung disease are also positively associated with ROP development. Recently postnatal weight gain and insulin-like growth factor 1 (IGF-1) levels, as well as hyperglycemia, were identified as predictors for ROP risk, as important as birth weight and gestational age at birth [5].

Screening and prediction

The current screening guideline of ROP calls for dilated fundus examination by indirect ophthalmoscopy for all premature infants below 30 week gestational age or less than 1500g birth weight with the first examination performed by 31 week postmenstrual age with additional examinations performed repeatedly thereafter to detect late stage of ROP requiring treatment [6].

Prevention and therapy

Prevention: To date, the most effective means to diminish the rates of ROP is to maintain lower level of hemoglobin saturation with oxygen. Other preventive strategies include the early use of antioxidants, notably vitamin E and human Cu/Zn superoxide dismutase (rhSOD) and. However, so far no conclusive positive treatment effect has been shown [7,8]. During the third trimester of pregnancy, a massive transfer of essential fatty acids (ω-3 and ω-6 long-chain polyunsaturated fatty acids) from the mother to the fetus takes place; these essential fatty acids are often not provided after preterm birth. This provides a rational for replacement of these fatty acids in prevention of ROP [9].

Therapy: Cryotherapy was the original mode of treatment (since the 1970s). It involves approximately 50 applications of a freezing probe under direct visualization with cryo applications to the avascular retina. The most common complications include intraocular hemorrhage, conjunctival hematoma, conjunctival laceration, and bradycardia. So far, the standard treatment for ROP is limited to laser photoocoagulation. Although successful, this treatment is invasive and results in loss of peripheral vision. The lack of approved drug treatment for ROP creates a great need for finding new effective therapeutic modalities to treat this devastating disease. Increasing nutrition alone seems to be insufficient to increase IGF-1 to promote postnatal weight gain in the most immature babies [10]. Instead, supplementation with exogenous IGF-1 might improve early postnatal growth and outcome. An IGF-1–IGFBP3 replacement trial (NCT01096784) is now underway, with reduction in the severity of retinopathy of prematurity as the primary endpoint and brain growth and as secondary endpoint. The β blocker propranolol has shown promising data in reducing retinal neovascularization and clinical trials are underway (NCT01239471) and (NCT01079715). Additionally, inositol has been reported to reduce the number of ROP cases and further studies into inositol are underway (NCT00349726, NCT01030575).

A promising future strategy to counter ROP is to use anti-VEGF therapy. Suppression of proliferative retinopathy (phase 2) with injection of anti-VEGF antibody has been reported in many small case-series with bevacizumab treatment. However, a number of issues have to be addressed including, impact on retinal ganglion cell integrity, since VEGF can act as a cytoprotective factor for retinal ganglion cells, systemic effects of bevacizumab, notably on cerebral vasculature [11]. Another method of producing local, ocular anti-VEGF therapy has used gene transfer via an intra vitreal injection of a control vector carrying the appropriate gene.

Future perspectives

Approaches to prevent vaso-obliteration or accelerate normal vascular repair following microvascular degeneration would halt the development of pathological neovascularization. Accordingly, novel vascular repair strategies emerged from advances in regenerative medicine using stem cells, including injection of engineered stem cells into the eye would hasten vascular repair that ultimately improve ROP outcomes [12]. Future safe and nondestructive therapeutic strategies combined with preventive approaches need to be tailored to the individual premature infant’s requirements to achieve maximal levels of cure with minimal ones of side effects.

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