Review Article

Retinopathy of Prematurity: A Review

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Abstract

Retinopathy of prematurity is a vaso-proliferative retinal disorder occurring in preterm infants. With the increase in the survival of preterm infants retinopathy of prematurity has become a major cause of childhood blindness worldwide. In this brief review the main aspects of this disease including pathogenesis, classification, epidemiology, screening and treatment are discussed.

Keywords:

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Preterm

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Treatment

Classification

Screening

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Introduction

Severe retinopathy of prematurity (ROP) causes retinal detachment, which results in blindness but milder forms of ROP increase the incidence of ametropia, refractive error; strabismus, and disorders of color discrimination [1-5]. All preterm babies are at risk for ROP, and very low birth-weight is an additional risk factor [6]. Oxygen toxicity and relative hypoxia can both cause the development of ROP [7]. A simple screening test performed within a few weeks after birth by an ophthalmologist can prevent the blindness caused by ROP [8]. In this brief review the main aspects of this disease including pathogenesis, classification, epidemiology, screening, treatment and follow up are discussed.

Mechanism of ROP formation

Retinal vascular development begins before week 12 of gestation from the optic disc towards the retinal periphery [9]. This process is completed a few weeks before the normal time of delivery, but is incomplete in preterm babies causing the development of ROP [9]. The mechanism of ROP formation can be divided to two stages. The primary stage or vaso-constrictive phase is characterized by delayed retinal vascularization caused by higher oxygen levels, while the premature neonate is receiving oxygen supplementation, compared to the oxygen levels experienced in utero [10]. In a premature infant retina is only partially vascularized when this hyperoxia leads to down-regulation of vascular endothelial proliferation and survival factors such as vascular endothelial growth factor (VEGF), leading to incomplete retinal vascular formation [10]. The secondary stage or vaso-proliferative phase begins when metabolically active but poorly vascularized retina, caused by suppression of vessel growth in the primary phase, faces a mismatch between the extent of retinal vascularization and its metabolic needs after the termination of oxygen supplementation [10-14]. This phase involves dilatation of the existing vessels combined with rapid neovascularization and proliferation of new leaky vessels into the vitreous which might lead to sight threatening tractional retinal detachment [12-15].

Classification

The system used for classifying the active ROP is called "The International Classification of Retinopathy of Prematurity (ICROP)". This classification has been used for major clinical trials and to unify the treatment and followup methods. ICROP, which was first developed in 1984 and was subsequently updated in 1987 and 2005, uses several parameters to classify the disease [16,17]. The first parameter is the zone of involvement which includes 3 zones. Zone I radius extends from the optic nerve to twice the distance from the center of the optic nerve to the center of the macula [17]. Zone II extends from the edge of zone I to the nasal ora serrata and zone III represents the remainder of the temporal retina [17]. After determining the zone of involvement the circumferential extent of the disease is described in segments like on the face of a clock [17]. For example, one might report that there is involvement of zone I from 12 to 3 o'clock [17]. The next step in classification is determining the stage of the disease. Stage 1 is characterized by a sharp white demarcation line separating the avascular retina anteriorly from the vascular retina posteriorly [17]. Stage 2 includes a white or pink color ridge

of scar tissue in the region of the demarcation line [17]. Stage 3 is characterized by extraretinal fibrovascular proliferation extending from the ridge into the vitreous [17]. Stage 4 includes subtotal retinal detachment and stage 5 refers to acomplete retinal detachment [17].

Epidemiology of ROP

Globally, it has been estimated that more than 20,000 infants are blinded annually due to retinopathy of prematurity (ROP), and an additional 12,300 develop mild to moderate visual impairment [18,19]. ROP accounts for about 10 % of childhood blindness in developed countries and up to 40 % of blindness in middle and low income countries [2,3]. Data from large studies in countries with well developed neonatal care show a recent decline in the incidence of severe ROP [20]. For Example a 2016 study involving 48,087 preterm infants from population-based networks in Australia, New Zealand, Canada, Finland, Israel, Japan, Spain, Sweden, Switzerland, Italy and the UK, found that the overall incidence of ROP needing treatment declined from 2007 to 2013 [20]. However, with increasing numbers and survival of extremely premature infants, there is likely to be an increasing number of infants affected by ROP worldwide [21-23]. In middle and low income countries where there is often less expert neonatal care, a lack of oxygen saturation monitors and little or no advanced training for neonatologists, ophthalmologists and neonatal nurses, both mild and severe ROPs are seen not only in the smallest infants but also in infants who are more mature compared to the developed countries [24]. Premature infants of up to to 34 weeks gestational age and sometimes more than 1500 g birthweight might develop ROP in countries with developing neonatal care services [24]. In Iran a recent systematic review and meta-analysis was performed including all published studies recording the prevalence of ROP in Iran from their inception until May 2016 [25]. According to this study the overall prevalence of ROP using a random effect model in Iran was 26.1% [25].

Screening for ROP

ROP is a leading cause for childhood blindness globally [1-3]. Screening aims are in time detection and optimal treatment of ROP, thereby reducing the severity and overall burden of the disease [1]. American guidelines given by the American Academy of Pediatrics state that infants with a birth weight ≤ 1500 g or gestational age of ≤ 30 weeks and selected infants with a birth weight between 1500 and 2000 grams or gestational age of more than 30 weeks with an unstable clinical course, should be screened for ROP [26,27]. In many developing economies, larger babies with a birth weight between 1500 grams and 2000 grams may also develop ROP. Hence in countries like Iran, a birth weight ≤ 2000 grams and/or gestational age of ≤ 32 weeks may be used as a cut-off for ROP screening [28]. Bigger babies with a gestational age of 34 to 36 weeks or a birth weight between 1500 and 2000 grams should also be screened if the child has other risk factors for ROP including severe respiratory distress syndrome, anemia, neonatal sepsis, thrombocytopenia, multiple blood transfusions and apnea [27]. If these risk factors are not seriously taken into consideration, affected infants may inadvertently get excluded and hence careful review for risk factors should be taken by the pediatrician [27].

Examination technique

Initial ophthalmological examination in preterm infants should be performed between the 4th and 6th week after birth, using binocular indirect ophthalmoscopy and after pupil dilation, preferably with a 28 D lens and should be repeated according to the findings from baseline examination [1,7]. Prior to examination patients' clinical history including their familial history of ROP, presence of bronchopulmonary dysplasia, history of oxygen-therapy, sepsis, blood transfusions and surfactant therapy should be documented [7]. Mydriatic eye drops routinely used in examinations are a mixture of cyclopentolate and phenylephrine or tropicamide and phenylephrine [1,7].

Treatment methods for ROP

Cryotherapy

Retinal cryotherapy has been a suggested treatment for ROP since 1988 after the Cryotherapy for Retinopathy of Prematurity study conducted in the United States demonstrated a significant reduction in the rate of unfavorable structural changes in treated eyes leading to a 50 % reduction of unfavorable outcomes, including macular dragging and retinal detachment [1, 7, 9,13, 29, 30]. Currently the cryotherapy is not the treatment of choice and its use has dramatically subsided in recent years since it is stressful, requires general anesthesia and can lead to serious complications including conjunctival laceration, vitreous hemorrhage, and constricted visual fields [1,23,29].

Indirect laser photocoagulation

Laser photocoagulation of the peripheral retina utilized indirect delivery system has been frequently to treat ROP in the past few decades [1,31]. In recent years laser photocoagulation has b come the most common ROP treatment. A study from England shows that in 1999, only 1.8 % of babies with ROP were treated with laser, which rose to 11.7 % in 2011 [23]. Laser photocoagulation using infra red diode laser is associated with less morbidity compared to cryotherapy and can be performed by skilled professionals under topical anesthesia in the neonatal unit without transferring the patient to an operating room [1, 9, 23].

Anti-vascular endothelial growth factor drugs

In recent years, anti-vascular endothelial growth factor (VEGF) drugs, which directly block the effects of VEGF, have been used in ROP treatment [1,31]. Successful results with anti-VEGF have been reported, but comparisons of anti-VEGF and laser treatments for ROP are relatively scarce [31]. One of the most serious eye complications of VEGF injection is endophthalmitis, which is rare but devastating [31].

Discussion

Timely screening of ROP is crucial for early management and improved outcomes [9]. Most current screening guidelines use only two most important risk factors including age and birth weight, and not the post-natal factors [26]. However, only about 10 % of the premature babies screened by these methods actually need treatment [26]. Thus there is a need for improvement of the current screening protocols by developing better predictors to reduce the number of ROP screening examinations [26]. It should also be noted that screening criteria and risk factors that are used in one country do not necessarily apply in another country where available perinatal care may not be

comparable [9]. The choice of treatment should be also considered based the cost and availability of the treatment method in a particular country.

Conclusion

Screening for ROP among premature neonates needs to be initiated timely to prevent blindness. There is a need for improvement of the current screening and treatment protocols and tailoring these methods to specific populations to reduce the disease burden.

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Footnotes and Financial Disclosures

Conflict of Interest:

The Authors have no conflict of interest with the subject matter of the present manuscript.