Curr Ophthalmol Rep (2013) 1:213–217
DOI 10.1007/s40135-013-0028-y

PEDIATRIC OPHTHALMOLOGY (S ROBBINS, SECTION EDITOR)

Risk Factors for Retinopathy of Prematurity: Beyond Age, Birth Weight, and Oxygen

Iason S. Mantagos · Deborah K. VanderVeen · Lois E. H. Smith

Published online: 1 October 2013
© Springer Science + Business Media New York 2013

Abstract Retinopathy of prematurity (ROP) remains an important cause of childhood blindness. Improved survival of premature infants has led to more infants being at risk of developing ROP. Advances in basic and clinical research have identified additional risk factors for ROP beyond gestational age, birth weight, and supplemental oxygen. Greater understanding of the pathophysiology of ROP and the risk factors involved will allow more targeted therapeutic approaches.

Keywords Retinopathy of prematurity · Risk factor · Vascular endothelial growth factor · Insulin-like growth factor 1 · Polyunsaturated fatty acids · Erythropoietin

Introduction

Retinopathy of prematurity (ROP) was first described by Terry in 1942 and its association with oxygen exposure was identified soon after [1]. ROP remains an important cause of childhood blindness. Advances in perinatal and neonatal care have led to improved survival of premature infants; therefore, more infants are at risk of developing ROP. ROP accounts for up to 60 % of pediatric blindness and the incidence is 9–60 per 1,000 in some developing countries. This increase in the incidence of ROP with more immature infants surviving has been referred to as the "third epidemic of ROP" [2].

Early gestational age, low birth weight, and supplemental oxygen treatment are well-documented risk factors for developing ROP [3, 4]. Because of this, the current screening criteria published by the American Academy of Pediatrics, the American Academy of Ophthalmology, the American Association for Pediatric Ophthalmology and Strabismus, and the American Association of Certified Orthoptists recommend infants born before 30 weeks of gestation, infants with a birth weight less than 1,500 g, or infants with an unstable clinical course undergo screening for ROP [5].

In addition to the effects of prematurity, low birth weight, and supplemental oxygen use, more risk factors have been identified in the pathogenesis of ROP. The focus of this article is to review the risk factors beyond gestational age, birth weight, and supplemental oxygen use relating to the development of ROP.

I. S. Mantagos (✉) · D. K. VanderVeen · L. E. H. Smith
Department of Ophthalmology, Boston Children's Hospital, 300 Longwood Avenue, Fegan 4, Boston, MA 02115, USA
e-mail: jason.mantagos@childrens.harvard.edu

D. K. VanderVeen
e-mail: deborah.vanderveen@childrens.harvard.edu

L. E. H. Smith
e-mail: lois.smith@childrens.harvard.edu

I. S. Mantagos · D. K. VanderVeen · L. E. H. Smith
Harvard Medical School, Boston, MA, USA

Risk Factors: Beyond Gestational Age, Birth Weight, and Supplemental Oxygen

Vascular Endothelial Growth Factor

The basis of ROP pathogenesis is the disruption of the normal retinal vascularization. ROP occurs in two phases. Phase 1 starts at birth, and is characterized by vaso-obliteration, whereas phase 2 starts after approximately 30–32 weeks of corrected gestational age and is characterized by retinal

neovascularization. During phase 1 ROP, the relative hyperoxia of the ex utero environment along with supplemental oxygen administration leads to downregulation of hypoxia-dependent factors, including vascular endothelial growth factor (VEGF), leading to vaso-obliteration. During phase 2 ROP, the increased metabolic demands of the developing retina coupled with the obliteration of the developing retinal capillaries leads to hypoxia, causing a surge in the levels of hypoxia-dependent factors, which gives rise to abnormal neovascularization. The extent of phase 1 ROP will determine the severity of disease during phase 2 ROP [6–12].

There has been extensive experience with use of VEGF inhibitors in the management of retinal disease secondary to neovascularization, including age-related macular degeneration and diabetic retinopathy [13]. More recently bevacizumab has also been used off-label for the management of ROP, both as a primary form and as a supplemental form of treatment [14–17]. A prospective, multicenter, unmasked, randomized controlled study evaluating the efficacy of intravitreal injection of bevacizumab compared with laser photocoagulation in premature infants with a birth weight less than 1,500 g, less than 30 weeks' gestational age, with stage 3+ ROP in zones 1 and 2 showed a beneficial effect of bevacizumab in the management of stage 3+ ROP in zone 1 [18]. However, this study did not follow the infants for complications and did not address optimal dosing or timing.

Modulation of VEGF levels is likely to be an important component of the treatment of ROP. However, more studies must be done to demonstrate clinical safety and visual acuity outcomes, as well as to evaluate potential ocular and systemic side effects of anti-VEGF [19].

Insulin-Like Growth Factor 1

Insulin-like growth factor 1 (IGF-1) is an important factor for normal angiogenesis and normal fetal growth [20]. Studies in IGF-1 knockout mice indicate that a minimum level of IGF-1 is required for VEGF signal transduction. These mice have poor retinal vessel growth, even though they have normal VEGF levels [21]. Animal studies using the oxygen-induced retinopathy (OIR) mouse model have shown that exogenous administration of IGF-1 receptor antagonists can reduce retinal vasoproliferation [22, 23]. During intrauterine life, IGF-1 is provided by the maternal/placental interface. Following premature birth, VEGF and IGF-1 levels fall, coinciding with phase 1 ROP. During phase 2 ROP, rising VEGF and IGF-1 levels lead to abnormal retinal neovascularization. Low IGF-1 levels during phase 1 ROP are associated with severer phase 2 ROP [23–25]. A clinical trial is currently under way to examine if restoration of IGF-1 levels following premature birth can prevent ROP.

Polyunsaturated Fatty Acids

The predominant retinal polyunsaturated fatty acid (PUFA) is the ω-3 PUFA docosahexaenoic acid (DHA). The role of the ratio of ω-3 PUFA to ω-6 PUFA in angiogenesis is starting to be better understood [26, 27]. With use of the OIR mouse model, pups of mice that had been fed a diet rich in ω-3 PUFA had less abnormal retinal neovascularization [28]. This was also noted in transgenic mice that overexpress the *Caenorhabditis elegans fat-1* gene, which converts ω-6 PUFA to ω-3 PUFA, resulting in elevated tissue levels of ω-3 PUFA [29].

In the developing embryo there is a significant transfer of PUFA from the mother during the third trimester [30]. Thus, infants that are born prematurely have significantly lower plasma levels of PUFA and those levels remain low for at least 4 weeks postnatally if there is no supplementation [31]. Pawlik et al. [32] recently showed that a group of infants born before 32 weeks' gestational age with a birth weight less than 1,250 g that received parenteral nutrition which included DHA from day 1 had more frequent ROP regression and less need for laser treatment than a historic control group that received parenteral nutrition which did not include DHA.

The levels of ω-3 PUFA in the infant seem to be an important factor for developing ROP, and a trial is under way evaluating the parenteral administration of ω-3 PUFA to premature infants.

Erythropoietin

Erythropoietin has also been identified as an important modulator of angiogenesis. Jaquet et al. [33] using endothelial cells derived from human adult myocardial tissue demonstrated the same angiogenic potential of recombinant human erythropoietin as VEGF using an in vitro assay. In the OIR mouse model, exogenous erythropoietin administration during phase 1 has been found to prevent vaso-obliteration [34], while erythropoietin inhibition during phase 2 using small interfering RNA can prevent neovascularization [35]. Recombinant human erythropoietin administration for the treatment of anemia of prematurity has been identified as an independent risk factor for the development of ROP and treatment-warranted ROP [36]. Exogenous recombinant human erythropoietin may be a risk factor for ROP, and in the future manipulation of erythropoietin levels could have a role in the treatment of ROP.

Postnatal Weight Gain

The relationship between poor postnatal growth, weight gain, and low serum IGF-1 levels has been well documented. As mentioned previously, there is also a strong association

between low IGF-1 levels and the severity of ROP [24, 25]. More recent studies have shown that poor postnatal growth in the first weeks of life is associated with later development of ROP [37, 38]. In addition to low postnatal IGF-1 levels, poor postnatal growth is multifactorial, including poor nutrition, low birth weight standard deviation score, number of days on a ventilator, oxygen supplementation at concentrations above 40 %, insulin and corticosteroid treatment, and low white blood cell counts [39].

The weight, insulin-like growth factor, neonatal ROP (WINROP) algorithm was developed on the basis of weekly postnatal weight and serum IGF-1 measurements, but has been modified to reflect postnatal weight gain and gestational age at birth without IGF-1 measurements to be independent of blood sampling. It detects slowing of the rise of an infant's weight gain (which reflects IGF-1 levels) and identifies infants at risk of developing treatment-warranted ROP [38, 40, 41].

Early Glucose Levels

The relationship between early postnatal hyperglycemia and the later development of ROP has been established [42–44]. Kaempf et al. [45] showed elevated blood glucose levels during the first 29 days of life and insulin use for the management of hyperglycemia were associated with the development of stage 3 and stage 4 ROP. Vanhaesebrouck et al. [46] demonstrated that premature infants with average daily glucose levels greater than 6.0 mmol/L during the first week of life were more likely to develop ROP. The exact pathophysiology of how hyperglycemia relates to the development of ROP is unknown. It is possible that hyperglycemia is an indicator of stress, immaturity, and illness, all of which are known risk factors for ROP [47]. We know that IGF-1 counteracts insulin resistance [48], and that IGF-1 levels are reduced following premature birth [24]. Since insulin resistance can lead to hyperglycemia, it is evident that the relationship between IGF-1, hyperglycemia, and ROP requires further investigation.

Sepsis: Late Bacteremia

The link between neonatal infections and the development of ROP has been known for a long time [49]. More recently, it has been shown that the interaction of sepsis, prematurity, and oxygen exposure may have a synergistic effect [50]. In the same study it was shown that the risk of ROP was higher among infants of higher gestational age. It was theorized that older premature infants could mount a greater inflammatory response to sepsis and that the inflammation contributes to the development of ROP [50, 51]. This is consistent with the ELGAN study, which demonstrated that late (occurring at 2–4 weeks of age) definite bacteremia (culture-proven) and presumed late bacteremia (antibiotics for more than 72 h despite negative blood cultures) were associated with pre-threshold/threshold ROP [52].

Genetic Factors

Variations in the severity and frequency of ROP among different ethnic groups are well documented. The ETROP trial demonstrated a similar incidence of ROP for African American and non-African American infants, but progression to prethreshold ROP was higher for non-African American infants [53]. By comparing the incidence of ROP between monozygotic and dizygotic twin pairs, Bizzarro et al. [54] demonstrated a strong genetic predisposition for ROP after controlling for prematurity and environmental factors.

By evaluation of known genetic mutations in familial exudative retinopathy, because its phenotype is similar to that of ROP, links between specific mutations and ROP have been made. More specifically, mutations in the *NDP* gene have been identified in unrelated patients with severe ROP [55–57]. More recently, Ells et al. [58] showed two novel mutations in the *FZD4* gene that were associated with severe ROP in patients with no signs of familial exudative retinopathy.

Conclusion

It is evident that ROP is a multifactorial disease. The traditional model of prematurity and oxygen use does not completely explain the pathogenesis and variance in the incidence of ROP. recognition of ROP risk factors and better understanding of their interactions will lead to (1) identification of at-risk infants before disease onset, (2) more targeted therapeutic approaches, and (3) reduction of the need for screening of infants that are at low risk of developing ROP, thus reducing this burden on the health care system.

Conflict of Interest Iason S. Mantagos, Deborah K. Vanderveen, and Lois E.H. Smith declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Terry TL. Retrolental fibroplasia in the premature infant: V. Further studies on fibroplastic overgrowth of the persistent tunica vasculosa lentis. Trans Am Ophthalmol Soc. 1944;44:383–96.
2. Hellstrom A, LE Smith, Dammann O. Retinopathy of prematurity. Lancet. 2013;8(5):e64325.
3. Lutty GA, Chan-Ling T, Phelps DL, et al. Proceedings of the third international symposium on retinopathy of prematurity: an update on ROP from the lab to the nursery (November 2003, Anaheim, California). Mol Vis. 2006;12:532–80.

4. Smith LE. Pathogenesis of retinopathy of prematurity. Semin Neonatol. 2003;8:469–73.
5. Fierson WM, et al. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2013;131:189–95.
6. Smith LE. Pathogenesis of retinopathy of prematurity. Semin Neonatol. 2003;8:469–73.
7. Ashton N, Ward B, Serpell G. Effect of oxygen on developing retinal vessels with particular reference to the problem of retrolental fibroplasia. Br J Ophthalmol. 1954;38:397–432.
8. McLeod DS, Brownstein R, Lutty GA. Vaso-obliteration in the canine model of oxygen-induced retinopathy. Invest Ophthalmol Vis Sci. 1996;37:300–11.
9. Smith LE, Wesolowski E, McLellan A, et al. Oxygen-induced retinopathy mouse. Invest Ophthalmol Vis Sci. 1994;35:101–11.
10. Donahue ML, Phelps DL, Watkins RH, et al. Retinal vascular endothelial growth factor (VEGF) mRNA expression is altered in relation to neovascularization in oxygen induced retinopathy. Curr Eye Res. 1996;15:175–84.
11. Stone J, Chan-Ling T, Pe'er J, et al. Roles of vascular endothelial growth factor and astrocyte degeneration in the genesis of retinopathy of prematurity. Invest Ophthalmol Vis Sci. 1996;37:290–9.
12. Miller JW, Adamis AP, Shima DT, et al. Vascular endothelial growth factor/vascular permeability factor is temporally and spatially correlated with ocular angiogenesis in a primate model. Am J Pathol. 1994;145:574–84.
13. Andreoli CM, Miller JW. Anti-vascular endothelial growth factor therapy for ocular neovascular disease. Curr Opin Ophthalmol. 2007;18:502–8.
14. Shah PK, Narendran V, Tawansy KA, et al. Intravitreal bevacizumab (Avastin) for post laser anterior segment ischemia in aggressive posterior retinopathy of prematurity. Indian J Ophthalmol. 2007;55:75–6.
15. Kong L, Mintz-Hittner HA, Penland RL, et al. Intravitreous bevacizumab as anti-vascular endothelial growth factor therapy for retinopathy of prematurity: a morphologic study. Arch Ophthalmol. 2008;126:1161–3.
16. Mintz-Hittner HA, Kuffel RR Jr. Intravitreal injection of bevacizumab (Avastin) for treatment of stage 3 retinopathy of prematurity in zone I or posterior zone II. Retina. 2008;28:831–8.
17. Autrata R, Kejcirova I, Senkova K, Holousova M, Dolezel Z, Borek I. Efficacy of intravitreal pegaptanib as adjunctive treatment for stage 3+ retinopathy of prematurity in zone I and posterior zone II. Eur J Ophthalmol. 2012;22:687–94.
18. Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011;364:603–15.
19. Hard AL, Hellstrom A. On the use of antiangiogenetic medications for retinopathy of prematurity. Acta Paediatr. 2011;100:1063–5.
20. Langford K, Nicolaides K, Miell JP. Maternal and fetal insulin like growth factors and their binding proteins in the second and third trimesters of human pregnancy. Hum Reprod. 1998;13:1389–93.
21. Hellstrom A, Perruzzi C, Ju M, et al. Low IGF-I suppresses VEGF survival signaling in retinal endothelial cells: direct correlation with clinical retinopathy of prematurity. Proc Natl Acad Sci USA. 2001;98:5804–8.
22. Smith LE. Essential role of growth hormone in ischemia induced retinal neovascularization. Science. 1997;276:1706–9.
23. Smith LE, Shen W, Perruzzi C, et al. Regulation of vascular endothelial growth factor-dependent retinal neovascularization by insulin-like growth factor-1 receptor. Nat Med. 1999;5:1390–5.
24. Hellstrom A, Perruzzi C, Ju M, et al. Low IGF-I suppresses VEGF survival signaling in retinal endothelial cells: direct correlation with clinical retinopathy of prematurity. Proc Natl Acad Sci USA. 2001;98:5804–8.
25. Hellstrom A, Engstrom E, Hard AL, et al. Postnatal serum insulin-like growth factor I deficiency is associated with retinopathy of prematurity and other complications of premature birth. Pediatrics. 2003;112:1016–20.
26. Kermorvant-Duchemin E, Sennlaub F, Sirinyan M, et al. Trans-Arachidonic acids generated during nitrative stress induce a thrombospondin-1-dependent microvascular degeneration. Nat Med. 2005;11:1339–45.
27. Fierro IM, Kutok JL, Serhan CN. Novel lipid mediator regulators of endothelial cell proliferation and migration: aspirin-triggered-15R-lipoxin A_4 and lipoxin A_4. J Pharmacol Exp Ther. 2002;300:385–92.
28. Connor KM, SanGiovanni JP, Lofqvist C, et al. Increased dietary intake of ω-3-polyunsaturated fatty acids reduces pathological retinal angiogenesis. Nat Med. 2007;13:868–73.
29. Kang JX, Wang J, Wu L, Kang ZB. Transgenic mice: fat-1 mice convert n-6 to n-3 fatty acids. Nature. 2004;427:504.
30. Crawford MA, Costeloe K, Ghebremeskel K, et al. Are deficits of arachidonic and docosahexaenoic acids responsible for the neural and vascular complications of preterm babies? Am J Clin Nutr. 1997;66:1032S–41S.
31. Martin CR, Dasilva DA, Cluette-Brown JE, et al. Decreased postnatal docosahexaenoic and arachidonic acid blood levels in premature infants are associated with neonatal morbidities. J Pediatr. 2011;159:743–9.e1-e2.
32. Pawlik D, Lauterbach R, Turyk E. Fish-oil fat emulsion supplementation may reduce the risk of severe retinopathy in VLBW infants. Pediatrics. 2011;127:223–8.
33. Jaquet K, Krause K, Tawakol-Khodai M, et al. Erythropoietin and VEGF exhibit equal angiogenic potential. Microvasc Res. 2002;64:326–33.
34. Chen J, Connor KM, Aderman CM, Smith LE. Erythropoietin deficiency decreases vascular stability in mice. J Clin Invest. 2008;118:526–33.
35. Chen J, et al. Suppression of retinal neovascularization by erythropoietin siRNA in a mouse model of proliferative retinopathy. Invest Ophthalmol Vis Sci. 2009;50:1329–35.
36. Suk KK, et al. Human recombinant erythropoietin and the incidence of retinopathy of prematurity: a multiple regression model. J AAPOS. 2008;12:233–8.
37. Lofqvist C, Andersson E, Sigurdsson J, Engstrom E, Hard AL, Niklasson A, et al. Longitudinal postnatal weight and insulin-like growth factor I measurements in the prediction of retinopathy of prematurity. Arch Ophthalmol. 2006;124:1711–8.
38. Hellstrom A, Hard AL, Engstrom E, Niklasson A, Andersson E, Smith L, et al. Early weight gain predicts retinopathy in preterm infants: new, simple, efficient approach to screening. Pediatrics. 2009;123:e638–45.
39. Wikstrand MH, Hard AL, Niklasson A, et al. Maternal and neonatal factors associated with poor early weight gain and later retinopathy of prematurity. Acta Paediatr. 2011;100:1528–33.
40. Lofqvist C, Hansen-Pupp I, Andersson E, et al. Validation of a new retinopathy of prematurity screening method monitoring longitudinal postnatal weight and insulinlike growth factor I. Arch Ophthalmol. 2009;127:622–7.
41. Wu C, Vanderveen DK, Hellstrom A, et al. Longitudinal postnatal weight measurements for the prediction of retinopathy of prematurity. Arch Ophthalmol. 2010;128:443–7.
42. Garg R, Agthe AG, Donohue PK, Lehmann CU. Hyperglycemia and retinopathy of prematurity in very low birth weight infants. J Perinatol. 2003;23:186–94.
43. Ertl T, Gyarmati J, Gaal V, Szabo I. Relationship between hyperglycemia and retinopathy of prematurity in very low birth weight infants. Biol Neonate. 2006;89:56–9.
44. Blanco CL, Baillargeon JG, Morrison RL, Gong AK. Hyperglycemia in extremely low birth weight infants in a predominantly Hispanic population and related morbidities. J Perinatol. 2006;26:737–41.
45. Kaempf JW, Kaempf AJ, Wu Y, et al. Hyperglycemia, insulin and slower growth velocity may increase the risk of retinopathy of prematurity. J Perinatol. 2011;31:251–7.

46. Vanhaesebrouck S, Vanhole C, Theyskens C, et al. Continuous glucose monitoring and retinopathy of prematurity. Eur J Ophthalmol. 2012;22:436–40.
47. Hays SP, Smith EO, Sunehag AL. Hyperglycemia is a risk factor for early death and morbidity in extremely low birth-weight infants. Pediatrics. 2006;118:1811–8.
48. Clemmons DR. Role of insulin-like growth factor in maintaining normal glucose homeostasis. Horm Res. 2004;62(Suppl 1):77–82.
49. Gunn TR, Easdown J, Outerbridge EW, Aranda JV. Risk factors in retrolental fibroplasia. Pediatrics. 1980;65:1096–100.
50. Chen M, Citil A, McCabe F, et al. Infection, oxygen, and immaturity: interacting risk factors for retinopathy of prematurity. Neonatology. 2011;99:125–32.
51. Lee J, Dammann O. Perinatal infection, inflammation, and retinopathy of prematurity. Sem Fetal Neonatal Med. 2012;17:26–9.
52. Tolsma KW, Allred EN, Chen ML, et al. Neonatal bacteremia and retinopathy of prematurity: the ELGAN study. Arch Ophthalmol. 2011;129:1555–63.
53. Good WV, Hardy RJ, Dobson V, et al. Early treatment for retinopathy of prematurity cooperative group. The incidence and course of retinopathy of prematurity: findings from the early treatment for retinopathy of prematurity study. Pediatrics. 2005;116:15–23.
54. Bizzarro MJ, Hussain N, Jonsson B, et al. Genetic susceptibility to retinopathy of prematurity. Pediatrics. 2006;118:1858–63.
55. Shastry BS, Pendergast SD, Hartzer MK, et al. Identification of missense mutations in the Norrie disease gene associated with advanced retinopathy of prematurity. Arch Ophthalmol. 1997; 115:651–5.
56. Hiraoka M, Berinstein DM, Trese MT, et al. Insertion and deletion mutations in the dinucleotide repeat region of the Norrie disease gene in patients with advanced retinopathy of prematurity. J Hum Genet. 2001;46:178–81.
57. Haider MZ, Devarajan LV, Al-Essa M, et al. A C597—>A polymorphism in the Norrie disease gene is associated with advanced retinopathy of prematurity in premature Kuwaiti infants. J Biomed Sci. 2002;9:365–70.
58. Ells A, Guernsey DL, Wallace K, et al. Severe retinopathy of prematurity associated with *FZD4* mutations. Ophthalmic Genet. 2010;31:37–43.