Retinopathy of prematurity — past, present, and future in this battle against pediatric blindness

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Abstract

Retinopathy of prematurity is a vasoproliferative retinopathy occurring primarily, but not exclusively, in premature infants. The condition is a major cause of pediatric blindness in developed countries. Although acute retinopathy of prematurity regresses spontaneously for more than 90% of infants, a chronic or late proliferative phase follows in some eyes whereby tractional retinal detachments, macula ectopia and scarring, and significant visual loss occur. While retinopathy of prematurity was considered untreatable 10 to 20 years ago, the condition has become controllable in recent years. Cryopexy or laser are useful for arresting progression of ROP to avoid vitreo-retinal complications.

Key words: Retinopathy of prematurity, Cryotherapy, Laser surgery

Introduction

'Retrolental fibroplasia' was first termed by Terry in 1942 to describe the histological findings in some blind babies born prematurely.[1] This was, in fact, what is now known to be end-stage cicatrization from retinopathy of prematurity (ROP).

ROP was rarely seen before the 1940s. The incidence gradually increased in the late 1940s and early 1950s until ROP became the commonest cause of blindness in children in America and some European countries.[2] Retrospectively, it was noticed that premature infants born during this period were placed in incubators and treated with nearly 100% oxygen.[3] When Campbell[4] and Kinsey[5] suggested that ROP might be related to oxygen therapy in premature babies, oxygen use was curtailed resulting in a dramatic decrease in the incidence of ROP. However, this was associated with an increase in mortality and morbidity in the form of severe neurological deficits such as cerebral palsy.[6] Although the subsequent development of oxygen monitoring by arterial blood gas and pulse oximetry has greatly reduced morbidity for premature babies, the improvement of neonatal care has led to the increased survival of prematurely born infants during the past few decades. Consequently, another surge in the rate of ROP has appeared.[3,7]

Definitions

ROP can be defined as a vasoproliferative retinopathy occurring primarily, but not exclusively, in premature infants.[2] During the acute phase, normal vasculogenesis is disrupted. Although acute ROP regress spontaneously for more than 90% of infants, in some eyes, a chronic or late proliferative phase follows whereby tractional retinal detachments, macula ectopia, scarring, and significant visual loss occur.[8] While ROP was considered untreatable 10 to 20 years ago, the condition has become controllable in recent years.[3]

Pathogenesis

Understanding of the pathogenesis of ROP is based on knowledge of the normal development of fetal retinal blood vessels. According to Ashton's theory,[9] which mainly differentiated from those of Michaelson[10] and Cogan,[11] the retinal vascular development begins during the 16th week of gestation. Mesenchymal tissue containing spindle cells, which originate from the primitive hyaloid system, is the

source of the retinal vessels. Mesenchyme grows centrifugally from the optic disc in a wave-like fashion, reaching the nasal ora serrata at the 36th week of gestation and the temporal ora at around term. The vascular precursor grows in the nerve fiber layer. Mesenchymal growth is followed by a capillary meshwork that later remodels to form mature arterioles and veins.

According to Flynn[12] and Kusher et al,[13] the vascular endothelium in ROP could be destroyed by some undefined noxious agents, while the less vulnerable mesenchyme and mature arteries and veins survive and unite via the few remaining vascular channels to form the mesnchymal arteriovenous shunts. Later, the tissues that form the shunt thicken, divide, and differentiate into normal capillary endothelium in cases where ROP regresses. In cases where the membranes proliferate, the primitive cells inside the shunts multiply and break through the internal limiting membrane of the retina, and tractional retinal detachment may ensue.

Incidence and risk factors

ROP is rare in infants with a birth weight of >2000 g. According to the current available evidence, low birth weight and small gestational age are the 2 most important factors associated with ROP. According to several studies, more than 90% of premature babies have some degree of ROP if their birth weight is less than 750 g.[14-16] The rates drop to 75% and 47% for babies weighing 750 to 999 g and 1000 to 1250 g, respectively. The rate of severe ROP (grade 3 or above) development is also related to the birth weight, the rate being 37%, 22%, and 9% for birth weights of less than 750 g, 750 to 999 g and 1000 to 1250 g respectively.[15]

The role of oxygen in the development of ROP has been debated for decades.[17,18] A recent large-scale study into the role of supplemental therapeutic oxygen for prethreshold ROP (STOP-ROP) has invited much attention.[19-21] The study was based on the assumption that retinal neovascularization and later development of tractional retinal detachment is caused by retinal hypoxia. The goal of the study was to determine the efficacy and safety of supplemental therapeutic oxygen for infants with prethreshold ROP in reducing progression to threshold ROP and the need for retinal ablative treatment. Infants with prethreshold ROP and median pulse oximetry of <94% saturation were randomly divided into a conventional treatment group, with pulse oximetry targeted at 89% to 94% saturation, or the supplemental oxygen treatment group, where the pulse oximetry was targeted at 96% to 99% saturation for at least 2 weeks. The treatments were continued until both eyes reached one of the study endpoints of threshold disease requiring retinal ablative treatment, regression of ROP to zone III for 2 consecutive weeks, or full retinal vascularization.

Among the 649 infants enrolled in the study, the rate of progression to threshold ROP in at least 1 eye was not significantly different between the groups (48% in the conventional treatment group versus 41% in the supplemental oxygen group). No significant differences were found in the rates of adverse structural outcomes of retinal detachment or folds (4.4% for conventional treatment versus 4.1% for supplemental oxygen) and macular dragging (3.9% for conventional treatment versus 3.9% for supplemental oxygen). A subgroup analysis suggested a statistically significant benefit of supplemental oxygen for infants who had prethreshold disease without plus disease in the progression to threshold disease (46% [91/196] for conventional treatment versus 32% [63/195] for supplemental oxygen). However, pneumonia, exacerbation of chronic lung disease, or both occurred in more infants in the supplemental oxygen group than in the conventional group (13.2% versus 8.5%). Also, in the supplemental oxygen group, there was an increased need for oxygen, diuretics, and admission to hospital at 3 months of corrected age. The authors thus concluded that no clear beneficial effect of carefully timed supplemental oxygen administration for severe ROP was shown.[19] On the other hand, although the relative risk-benefit of supplemental oxygen for each infant must be individually considered, clinicians need no longer be concerned that supplemental oxygen, at the level used in the study, will exacerbate active prethreshold ROP.[2]

The role of hospital nursery lighting in ROP is another area of debate. Reports supporting[22] and refuting[23,24] the role have been published. The results of a large prospective randomized controlled trial (the LIGHT-ROP study) have recently concluded that a reduction in ambient-light exposure does not alter the incidence of ROP.[25,26]

Surfactant administration in the treatment of neonatal respiratory distress syndrome has also been linked to the development of ROP. Although Repka demonstrated that surfactant administration significantly reduced the incidence and severity of ROP in the extremely low-birth-weight population,[27] other studies have failed to show a similar effect.[28,29] However, surfactant replacement therapy may have a beneficial effect on the development of cicatricial, severe ROP.[30,31] While some researchers have argued that, owing to its effects on improved survival rates, surfactant may produce a larger proportion of infants at risk of developing ROP,[32] others have found that improving survival rates of very premature infants with surfactant administration did not result in an increased number of infants with neurological or ocular impairments.[33-37]

Similarly, controversy exists regarding the possible effects of dexamethasone in increasing the incidence of ROP[38-40] and vitamin E administration as a preventive measure in its progression.[41-44]

ROP has also been found to be associated with neonatal conditions such as respiratory distress syndrome, patent ductus arteriosus, apnea and bradycardia, intracranial hemorrhage sepsis, anemia, and jaundice.[25,45,46] However, mere coexistence or causal relationship between these conditions and ROP cannot easily be confirmed.
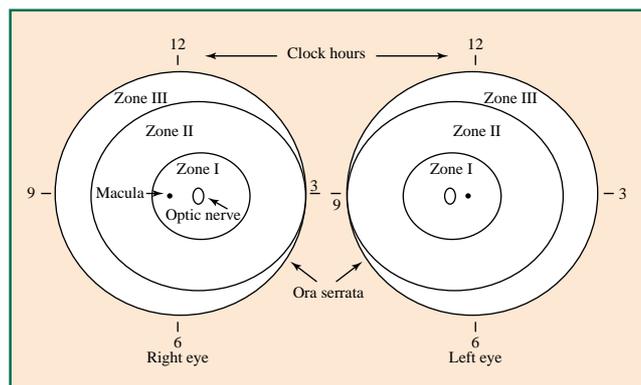
Figure 1. Retinopathy of prematurity zones.

Classification

After decades of confusion and ambiguity resulting from various descriptions by different investigators, the Committee of the International Classification of ROP (ICROP) unified the classification system for ROP in the mid-1980s.[47,48] This is now the most commonly used classification worldwide.

According to the classification, the retina is divided into zones I to III to specify the location of the disease (**Figure 1**). Zone I signifies the most posterior zone, demarcated by a circle centered on the optic nerve, the radius of which is 2-fold the disc-foveal distance. Zone II is a circle centered on the optic nerve, the radius being the distance from the optic nerve to the nasal ora serrata. Zone III is the temporal crescent of peripheral retina not included in zones I and II.

The extent of involvement is described as the number of clock hours. The severity is defined as stages 1 to 5, as follows (**Figures 2 to 6**):
• stage 1 — appearance of a demarcation line between the vascular and avascular retina
• stage 2 — ridge formation, in that the demarcation line develops into an elevation out of the retinal plane
• stage 3 — ridge with fibrovascular proliferation extending off the retina into the vitreous
• stage 4 — subtotal retinal detachment:
  - 4A — extrafoveal
  - 4B — retinal detachment involving the fovea
• stage 5 — total retinal detachment.

Plus disease is described as vessel dilatation and tortuosity in the posterior pole, vitreous haze, iris vascular dilatation, and pupillary rigidity.

Current concepts in the management of retinopathy of prematurity

The Cryotherapy for Retinopathy of Prematurity study

The Cryotherapy for Retinopathy of Prematurity (Cryo-ROP) study was considered a major landmark study in the battle
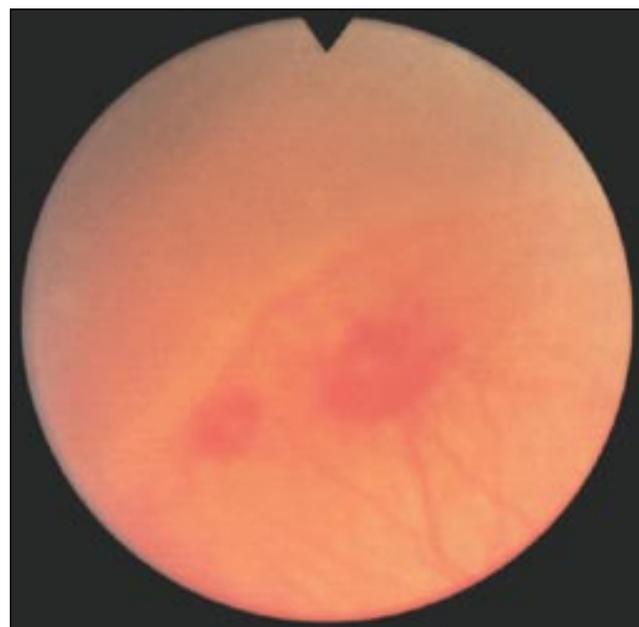

Figure 2. Retinopathy of prematurity stage 1 — demarcation line. The hemorrhages are perinatal and not related to the retinopathy of prematurity. (Reprinted with permission from Dr D. Taylor)
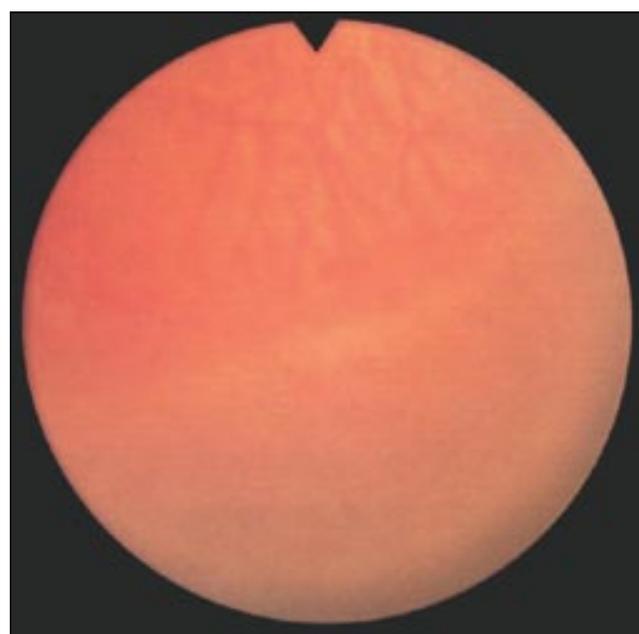

Figure 3. Retinopathy of prematurity stage 2 — ridge projecting forward into the vitreous. (Reprinted with permission from Dr D. Taylor)

against ROP.[49] This was a carefully designed, randomized, prospective trial in which 4099 patients were recruited from 23 centers in the USA during a 2-year period from January 1986 to November 1987.[50-55] All the infants had a birth weight <1251 g, and survived for at least 28 days. Starting from 4 to 6 weeks post-delivery, the patients were examined at least every 2 weeks.

Threshold disease was defined as stage 3 plus ROP in zones I or II involving at least 5 contiguous or 8 interrupted clock-hour sectors of the retina. Prethreshold disease was
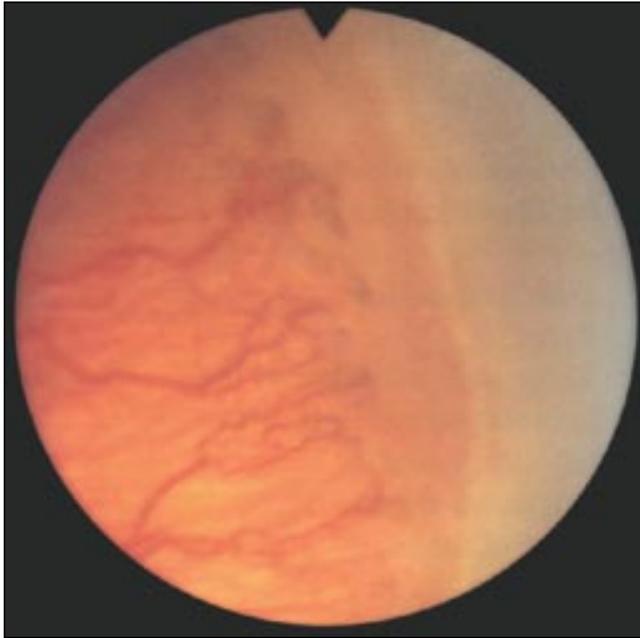
Figure 4. Retinopathy of prematurity stage 3 — ridge with new vessels. (Reprinted with permission from Dr D. Taylor)

Figure 5. Plus disease — marked vascular dilatation and tortuosity in the posterior pole. (Reprinted with permission from Dr D. Taylor)

defined as zone I disease of any stage, zone II stage 2 plus disease, or zone II stage 3 plus disease, but not reaching threshold clock hours, or without plus disease.[50-55] 291 infants developed threshold disease so that the overall incidence of threshold disease was 6%. In 240 infants, both eyes were affected — in these infants, 1 eye was treated and the other eye served as a control. In the other 51 infants, only 1 eye was affected by threshold disease and these patients were randomized to either the treatment or the control group. Treatment was trans-scleral contiguous cryopexy to the peripheral avascular retina using a cryoprobe such as a hammerhead-shaped pediatric probe. Continuous
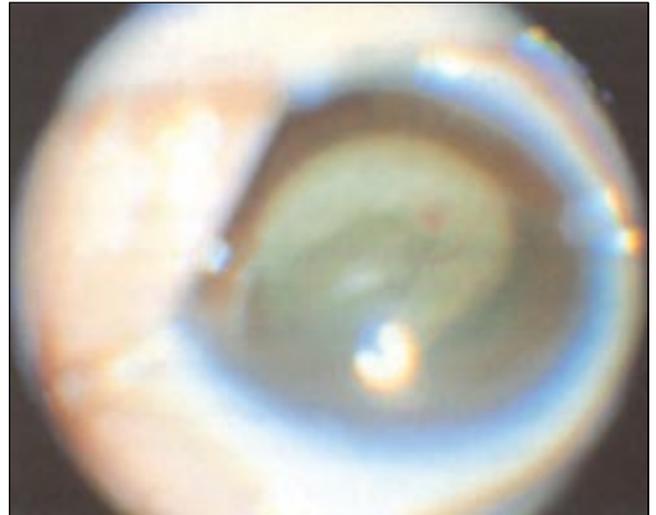

Figure 6. Retinopathy of prematurity stage 5 — funnel-shaped retinal detachment. (Reprinted with permission from Dr D. Taylor)

cryotherapy was performed using direct observation of the fundus, avoiding over-treatment and retreatment.

The initial results indicated that cryopexy could significantly reduce the rate of unfavorable outcomes (defined as retinal detachment, macula folds, or retrolental mass) by approximately 50% at 1 year — 26% of infants in the treated group had unfavorable outcomes compared with 47% in the control group (p < 0.0001).[50-52] At 5.5 years after randomization, the results supported the long-term efficacy of cryotherapy for patients with severe ROP.[54] The rate of unfavorable visual outcomes (20/200 or worse) was 47% in the treated group versus 62% for the control group (p < 0.05). The rate of unfavorable anatomical outcome comparisons also favored treatment (27%) versus no treatment (45%) [p < 0.001]. The study also showed that fewer treated eyes (32%) than control eyes (48%) were blind (p < 0.001). At 10 years post-randomization, the results still favored treatment — 27% versus 48% for anatomical unfavorable outcomes in the treated and untreated groups, respectively, and 44% versus 62%, respectively, for poor visual acuities of 20/200 or worse.[55]

The Cryo-ROP study also examined the natural history of ROP. It was shown that unfavorable functional and structural outcomes were directly correlated with increased posterior involvement and extensiveness of stage 3 plus disease. 'Less-than-threshold' disease had no effect on the development of grating acuity in children aged between 1 and 4.5 years. However prethreshold disease was associated with reduced acuity at both 3.5 and 4.5 years of follow-up.[53,54]

Despite treatment, however, the visual prognosis was still far from ideal for children in both groups. Only 13% of treated eyes and 17% of control eyes had visual acuities 20/40 or better at 5.5 years (p = 0.19).[54] At 10 years, only 25% of treated eyes and 24% of control eyes attained a distant acuity of 20/40 or better (p = 0.63).[55]

Laser photocoagulation

Laser photocoagulation was attempted for ROP as early as 1968.[56] This treatment lost favor in later years due to the difficulty of laser delivery with the early devices. Since the late 1980s, however, laser photocoagulation became increasingly popular as an alternative to cryopexy for the treatment of ROP.[57] When the 5.5-year follow-up results of the Cryo-ROP study were published in 1996,[54] in which the potential to develop good visual acuities of at least 20/40 seemed to be jeopardized in the cryotherapy group (although this tendency was disproved in the 10-year follow up results[55]), enthusiasm for the study of laser for treating ROP further increased.

Laser photocoagulation has been shown in various studies to be as effective as cryotherapy for preventing cicatricial complications of ROP.[57-60] Diode, krypton, and argon lasers were of equal efficacy.[57,58] Transcleral diode laser has been shown to be as effective as transpupillary diode laser.[61] While Hammer et al[58] showed that laser may be more effective than cryotherapy for treating zone I disease, Capone et al's study[59] suggested similar results, in that, of 30 eyes of 17 infants with threshold zone I rush disease, a favorable anatomical outcome was achieved in 83.3% using diode laser photocoagulation compared with 25% in the Cryo-ROP study.

When compared with cryopexy, Connolly et al showed that better visual results could be achieved with laser.[62] Myopia induction may also be less likely with laser than with cryopexy.[63,64] Other possible advantages of photocoagulation over cryopexy include ease of reaching the posterior pole, reduced trauma to the ocular tissues, reduced patient discomfort, reduced need for general anesthesia, and earlier regression of ROP.[60,65]

The recommended techniques of photocoagulation were generally similar to those of cryopexy.[57-61] Laser was applied to the peripheral avascular retina up to, but not including, the ridge. When considering the density of laser applications, it was shown that near confluent burns could achieve a reduced rate of disease progression in eyes with zone II and, to a lesser extent, zone I ROP when compared with laser spots placed 1 to 1.5 burn width apart.[66] However, reported anterior and posterior segment complications include corneal iris burns, multiple posterior synechiae at the pupillary margin, iris atrophy, and hyphema.[2] Transient focal cataract has also been reported, especially where there is persistent tunica vasculosa lentis and argon laser is used.[67] Occasionally, angle closure glaucoma can occur, leading to the need for surgical iridectomies.[68]

Buckling and other vitreo-retinal surgeries

The goal of both cryotherapy and laser photocoagulation is to prevent ROP from reaching stages 4 and 5.[2] Buckling and vitreo-retinal surgeries are needed for patients in whom cryotherapy and laser therapy has failed. The role of scleral buckling procedures in reducing progression from stage 4 to stage 5 ROP was shown in Trese's series, in which anatomical success was achieved in 78% of eyes with stage 4A and 67% with stage 4B disease, with a follow-up period of at least 6 months.[69] Once the ROP has reached stage 5 disease, vitrectomy is needed. Open-sky vitrectomy, in contrast to closed vitrectomy, has been proposed by some researchers to be of benefit for treating total retinal detachment.[70-73] By opening the cornea and removing the lens, the surgeon can directly approach the retrolental membrane. The wide exposure of the operative field permits freedom of movement of the surgical instruments. Dissection of the scar tissue in the vitreous base area is safer and easier than with the closed method.[70] In Hirose et al's series, open-sky vitrectomy resulted in anatomical retinal reattachment for 39.2% of patients and subsequent visual development of stage 5 ROP was shown to occur, although it was limited.[71] Similarly, in Katsumi et al's series, 7.3% of patients attained a visual acuity of 20/200 after the procedures for stage 5 ROP.[72] Although the visual acuities were relatively low, the eyes were still useful to these patients, permitting a certain degree of independence and assimilation into normal life.[2]

However, these procedures are associated with various complications such as cataract, microphthalmos, and glaucoma.[74] Also, once the retina is detached, the overall visual results are poor despite energetic treatment. In Seaber et al's series, form identification was possible for only 5 of 51 eyes after successful total or partial anatomic re-attachment.[75] Moreover, the re-detachment rate is high — only 13 of 51 eyes remained fully attached 61 months after surgery. Similarly, in the follow-up of the Cryo-ROP study, 71 of the 72 patients who underwent lensectomy-vitrectomy had vision of light-perception-only or worse at 5.5 years.[54]

Long-term morbidities

There is no doubt that ROP is a major cause of pediatric blindness in developed countries.[2] Even if premature children are not blinded during the neonatal period, other long-term ophthalmic morbidities remain a challenge for ophthalmologists. The most important morbidities include chronic vitreo-retinal traction, myopia, anisometropia, amblyopia, and strabismus/pseudostrabismus. Vitreo-retinal traction and myopia development have attracted much attention recently (**Figures 7** and **8**).

Vitreo-retinal traction

Since ROP is a 'relatively' new disease entity in ophthalmology, data on the long-term course is still scarce. However, there is an accepted clinical impression that premature birth suggests a higher risk of retinal tear or detachment.[76] Moreover, tractional and rhegmatogenous retinal detachments can occur beyond childhood. These conditions are reported to be especially common in the first and second decades of life. In Tasman's series, the median age for occurrence of rhegmatogenous retinal detachment was 14 years and that for tractional and
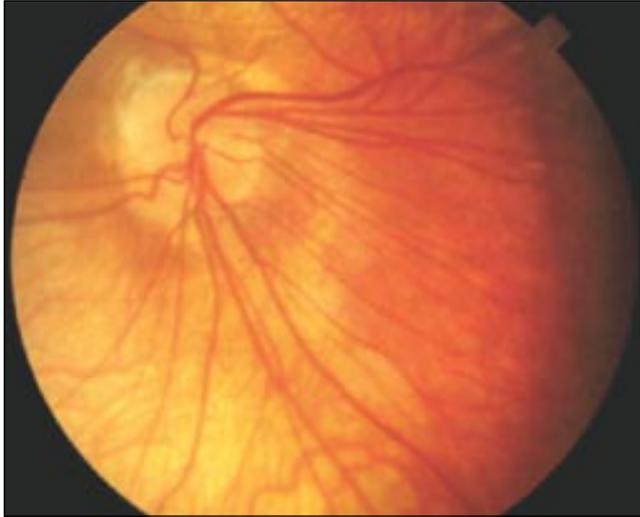
Figure 7. Regressed retinopathy of prematurity with straight-ened and dragged retinal vessels. (Reprinted with permission from Dr D. Taylor)
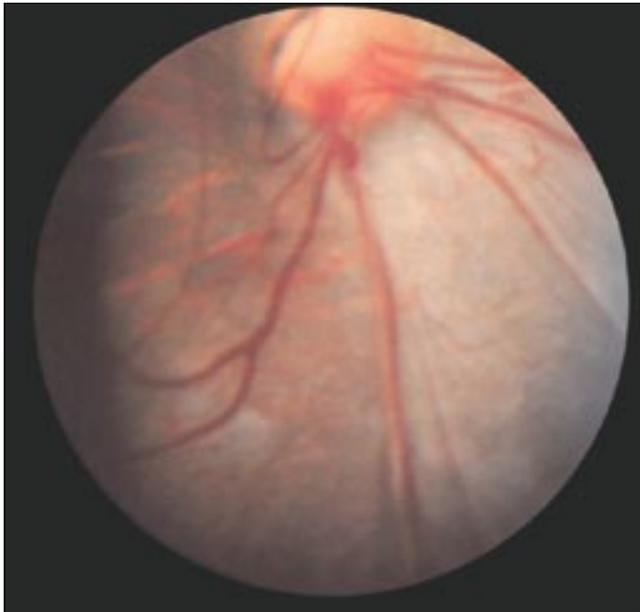

Figure 8. Regressed retinopathy of prematurity with marked nasal dragging of the retinal vessels. (Reprinted with permission from Dr D. Taylor)

exudative retinal detachments was 5.7 years.[77,78] Faris noted that rhegmatogenous retinal detachment tends to occur between the ages of 5 and 15 years.[79] To date, however, no data is available on the rate of occurrence of such long-term complications. Continued follow-up of the Cryo-ROP study group will probably provide information on the need for vigilant monitoring and prospective counseling of patients and their parents.[76]

Myopia development

Correlation between myopia and prematurity has long been observed.[80-83] It has also been shown that low birth weight and increased severity of ROP are strong predictors of myopia and high myopia.[80] For example, in Quinn et al's study, the incidence of myopia (at least -0.25 D) in

premature infants with a birth weight of <1251 g who received no cryopexy treatment was approximately 20% from the ages of 3 months to 5.5 years, while the incidence of high myopia (at least -5 D) was 2% at 3 months, doubling to 4% at 12 months and remaining stable thereafter.[82] The degree of myopia at 3 months predicts the presence of myopia and high myopia at 5.5 years. Similar trends have been observed in other series.[84-86]

The mechanism of myopia development may be different for infants with ROP compared with their healthy counter-parts. Various reports have shown that myopic eyes in infants with ROP usually have steep corneas as well as highly convex and anteriorly displaced lenses.[48-54,87-93] Interestingly, the axial lengths are not particularly long — the higher stages of acute ROP are associated with shorter axial lengths.[89,91-94]

Retinal cryopexy has been implicated as a factor in the production of myopic eyes in various reports.[63-64,83,95-97] How-ever, Quinn et al had the opposite opinion.[98] In their recent analysis, stratification of degree of myopia into different age groups showed that, at 3 months, the distribution was similar between treated and control patients.[98] At ages up to 5.5 years, the incidence of myopia less than -8 D was similar between the 2 groups. Although the incidence of high myopia (at least -8 D) was higher for the treated patients than for the control group (39% versus 29%), this paralleled the reduced proportion of treated than control eyes that were non-refractable (blind). Thus, Quinn con-cluded that, at least in some eyes, cryopexy preserved ocu-lar structures — high myopia developed instead of retinal detachment and inability to refract.[98]

Need for long-term follow-up

As previously mentioned, ROP in the neonatal period can be associated with various long-term morbidities. In a New Zealand population study, it was shown that 79% of children who developed ROP and 60% of at-risk infants who did not develop ROP had some form of visual defect such as high refractive errors, strabismus, or amblyopia.[99] It was recommended that ex-preterm children, especially those in whom ROP developed and either regressed or was treated, should be followed regularly throughout child-hood so that their potential visual problems do not go undetected.[100]

Data of vitreo-retinal complications of adult patients with previous ROP are scarce. As noted by Kaiser et al, among adult patients with a history of premature birth followed up for up to 23 years (median, 6.2 years) 26% (15/108) of asymptomatic patients developed a retinal tear or retinal detachment, 83% of whom had only minimal cicatricial changes from ROP.[76] Although these authors recommended that all premature patients be monitored for a lifetime, explanation of the warning symptoms of retinal detachment and the importance of early ophthalmic consults may be a more practical approach.

Screening for premature infants

Although progressive ROP was once considered an untreatable blinding condition, the results of the Cryo-ROP trial are encouraging.[50-55] Since successful treatment largely depends on timely diagnosis and therefore on a thorough screening strategy,[101] a variety of policies have been adopted by different clinicians. Some infants are screened from their 2nd,[102] 3rd,[103] or 4th[104] week of life, while others are examined for the first time in the 8th[105] or 10th[106] week, at discharge from the hospital or afterwards,[107-108] when their condition was 'sufficiently stable',[109] or when oxygen therapy had been discontinued.[110] While over-screening leads to a waste of resources and systemic upset to infants, under-screening may place the involved infants at risk. The first attempt to determine the 'optimal timing' for detecting ROP was made in 1981 by Palmer, who based his recommendations on retrospective data.[105]

Nowadays, it is generally agreed that infants should be screened for ROP if they weigh <1500 g at birth or are born at ≤31 weeks gestational age.[100] The recommendations from the *Royal College of Ophthalmologists* and the *British Paediatric Association* are that screening should begin at 6 to 7 weeks postnatally and should continue 2-weekly until retinal vessels are seen in zone III.[111] The frequency increases to weekly screening if ROP develops, until it either regresses or reaches threshold level, at which point treatment should be offered. On the other hand, the *American Academy of Paediatrics*, the *American Association for Paediatric Ophthalmology and Strabismus* and the *American Academy of Ophthalmologists* have jointly recommended screening of infants with a birth weight of ≤1500 g or who are born at a gestational age of ≤28 weeks and that screening should begin between 4 and 6 weeks postnatally or 31 to 33 weeks of post-conceptional age, whichever is earlier. Subsequent timing of examinations should be based on the initial findings.[112]

Although the screening protocol may be slightly different in different countries or centers, screening examinations are usually carried out by ophthalmologists with particular expertise in ROP, using indirect ophthalmoscopy and an indenter to visualize the peripheral retina.[84] Timely treatment is now considered the most effective means of blindness prevention for premature infants.

Current status

With the accumulation of knowledge of ROP, more has been learnt. Currently, most ophthalmic experts agree that ROP is a treatable blinding disease that warrants screening. From the economic viewpoint, it has been estimated that up to 350 infants are saved from blindness annually in the USA and US$65 million per year is saved to tax-payers for special education, disability, and lost productivity.[87]

While both cryopexy and laser are useful for arresting progression of ROP, laser might be superior to cryopexy for visual results.[100] Arresting acute ROP aims to avoid vitreo-retinal complications, which usually result in poor visual results despite aggressive treatment.

The future

Despite the recent advances, much room for improvement still exists in the prevention and management of ROP. As previously mentioned, the current treatment for threshold disease as recommended by the Cryo-ROP study only halved the unfavorable anatomical outcomes.[50-54] In addition, when threshold disease was reached and favorable anatomical outcomes were maintained with or without treatment, only <20% of eyes had visual acuity 20/40 or better at 5.5 years.[54] At 10 years, 44% of treated eyes still had unfavorable visual outcomes.[55] Therefore, it seems that the current treatment regimen as designed by the Cryo-ROP study is still far from satisfactory.

Could better visual results be attained with more liberal or earlier treatment? The Early Treatment for ROP (ETROP) study is now underway in the USA.[114] This study will test the hypothesis that earlier treatment for carefully selected infants weighing <1251 g at birth will result in better visual outcome. Intervention will be retinal ablation for a selected group of patients with prethreshold diseases. Prethreshold disease is defined as zone I disease of any stage, stage 2 plus disease at zone II, or <5 contiguous or 8 cumulative clock hours of stage 3 plus disease at zone II. The percentage risk of progression to blindness without treatment is calculated based on various risk factors, including birth weight, gestational age, ethnicity, singleton versus multiple birth status, outborn versus inborn status, severity of ROP, and rate of progression of ROP. When the risk of unfavorable outcome exceeds 15%, the infants will be randomized into treatment or control groups. It is estimated that it will take at least 3 years before the initial results are available.[114]

While ROP progresses to advanced stages despite rigorous intervention for some babies, it spontaneously regresses before the threshold stage for the majority. Genetic factors have been implicated in determining the progression of ROP to advanced stages.[115,116] For example, missense mutations in the Norrie disease gene have been associated with the risk of progression to advanced stages.[115,117] Further studies into the genetic aspect may shed new light on the understanding of ROP.

In future, molecular mechanisms may also play a role in the prevention and management of ROP. Although the precise pathways that regulate apoptosis and retinal vascularization in ocular development remain uncertain, there is considerable evidence that vascular endothelial growth factor (VEGF) is important in the pathogenesis of retinal neovascular diseases. Hypoxia of the peripheral, non-vascularized retina has been shown to increase VEGF expression in experimentally induced retinal neovascularization.[118,119] VEGF receptor protein has been shown to be concentrated in preretinal neovascular growths in a model of ROP.[120] These results

suggest that avenues of research toward therapies using VEGF receptor antagonists might be rewarding.

Conclusion

Prevention of ROP includes adequate prenatal care to minimize premature birth and appropriate systemic intensive care to reduce tissue hyperoxia/hypoxia swings.[121]

The management of ROP begins with a reliable evidence-based screening protocol. All interested parties must cooperate in developing and implementing reliable screening protocols. Timely treatment is essential for halting ROP progression. Future management success will probably rely on discovering new modes of treatment and prevention.[121] There is still a long road ahead for ophthalmologists and neonatologists in this battle against pediatric blindness.

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