Retinopathy of Prematurity: Do We Still Have a Problem?

The Charles L. Schepens Lecture

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Objective: To assess the present-day prevalence of retinopathy of prematurity (ROP) worldwide.

Methods: A search of the literature was conducted to better define the worldwide experience with ROP. An interview was also conducted with 2 schools for the blind, Overbrook in Philadelphia, Pennsylvania, and Perkins in Watertown, Massachusetts. The study also is based on personal experience with ROP over the last 49 years.

Results: Worldwide, the prevalence of ROP is on the rise in developing countries, and some of those ROP-affected premature infants are heavier than 1500 g. In western countries, extremely low-birth-weight infants (<1000 g) are also surviving. Currently, the Overbrook School for the Blind has 11 of 55 children between the ages of 3 and 5 years with ROP (20%). The Perkins School has 34 of 200 children from birth to age 3 years with ROP (17%). During 2009, 47 babies had laser treatment for ROP in the neonatal intensive care unit of Jefferson Medical College by physicians from Wills Eye Hospital. Twenty-four infants had been identified in a screening of 591 patients (4.1%). The other 23 had been referred in for treatment. In 2009, we had 187 outpatient visits related to ROP ranging from 6 months to 67 years of age.

Conclusions: Because more and more extreme low-birth-weight infants are surviving in western countries and because of the rising numbers of surviving premature infants in emerging nations, we may be on the verge of an ROP epidemic.

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I AM MOST GRATEFUL TO THE Retina Research Foundation, the Schepens International Society, and Alice McPherson for this magnificent award. Clearly, Charles Schepens was an icon, not only of the 20th century, but for all time in ophthalmology. I was fortunate enough to have a fellowship with him from 1961 to 1962 in Boston at the Massachusetts Eye and Ear Infirmary. During that time, I enjoyed a learning experience like none I had had before. Dr Schepens was a role model for how to care for patients, and the lessons I learned from him have stood me in good stead over the years. His contribution of binocular indirect ophthalmoscopy and his surgical innovations for retinal detachment raised the cure rate for that condition from somewhere between 25% and 40% to close to 90%.

A word, too, about Mrs Schepens. In a conversation I had with her at a party one time, I commented on what a hard worker Dr Schepens was and the long hours that he worked. Her reply was that it is important for a wife to understand that if a man loves what he is doing she should be happy for him.

I might mention, as well, that my initial interest in retinopathy of prematurity (ROP) was stimulated by Dr Schepens. While in Boston, I was fortunate enough to assist him in repairing retinal detachments on patients who had a history and clinical signs of ROP. I was able to carry that interest forward.

WHAT WE KNOW ABOUT ROP

First described by Theodore Terry in 1942, ROP, then known as retrolental fibroplasia, became a major cause of blindness in children in the United States. Actually, the first recognized case was seen in July 1940 by Drs Stewart Clifford, Paul Chandler, and Frederic Verhoeff, who then referred the infant to Dr Terry. Retinopathy of prematurity often resulted from the practice at that time of giving a high percentage of oxygen to low-birth-weight infants. Ultimately, a 40% limit of oxygen was recommended, and the incidence of blindness from ROP decreased. However, many more infants died, and in those infants who survived, the prevalence of cerebral palsy increased.

Today, it is understood that low birth weight and low gestational age are significant contributors to ROP. At present, the condition is more prevalent in the industrialized world but is rising quickly in emerging coun-

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tries. With our better understanding of ROP, one would think that the number of blind infants might be decreasing. However, even extremely low-birth-weight infants (≤1000 g) are now surviving, as well as premature infants of 23 weeks' gestation. Thus, it is probable that we will see even more infants with ROP than in the past.

A WORLDWIDE PROBLEM

According to World Health Organization criteria, there were 1.5 million children worldwide who were blind in 1999. Only a small percentage of cases were due to ROP. Over the last 10 years, however, as indicated earlier, the proportion of blindness as a result of ROP had varied greatly among countries. In ranking blindness from ROP by country, the United States is eighth. Sweden is number 2, and the Eastern European countries of Bulgaria and Lithuania, for example, rank 56 and 67, respectively.

In a personal interview with the Overbrook School for the Blind in Philadelphia, Pennsylvania, I learned that 11 of 55 children between the ages of 3 and 5 years, or roughly 20%, are in the school because of ROP. In a similar interview with the Perkins School for the Blind in Watertown, Massachusetts, 34 of 200 children from birth to age 3 years, or 17%, had ROP. Thus, ROP is still very much with us.

In industrialized countries, some degree of ROP may develop in 72% of infants weighing less than 1000 g at birth, and subsequent blindness can be as high as about 8% to 10%. In general, about 60% of low-birth-weight infants can be expected to develop some degree of ROP.

In our experience at Wills Eye Hospital and Jefferson Medical College, both in Wyndmoor, Pennsylvania, 47 infants had laser treatment for ROP in 2009. Twenty-three of these patients had been referred to us, and 24 were identified in a screening of 591 patients, for a 4.1% incidence.

Studies in Mongolia, Malaysia, and Latin America are detecting more cases of ROP. In Malaysia, for example, examination of 294 children in whom the anatomical site of abnormality could be identified revealed that 20, or about 7%, had ROP. Although the children had impaired vision of varying degrees, 150 children had navigational vision. According to a 2005 report, two-thirds of the 50,000 children known to be blind from ROP worldwide are in Latin America. The numbers may have changed over the last 5 years. However, when the study was done in Lima, Peru, which at that time was a city of 8 million inhabitants, there was only 1 ophthalmologist who single-handedly did ROP screening for the whole city.

The mean premature birth weights of infants in highly developed countries range between 737 and 763 g, and the mean premature birth weights of infants in emerging countries range from 903 to 1527 g. Gestational ages of infants in highly developed countries range from 25.3 to 25.6 weeks, compared with 26.3 to 33.3 weeks in emerging countries.

In addition, larger, more mature infants are developing severe ROP in countries with lower or modest levels of development compared with those in highly developed countries. The reasons for this are probably multifactorial, but unmonitored oxygen is likely a contributing factor. This is similar to what occurred in the 1940s and 1950s when ROP was emerging in the United States. However, in countries such as India and Ethiopia, conditions other than ROP are mainly responsible for blindness.

Finally, the indications for treatment have changed. In the 1980s, 6% of patients with ROP reached the ROP threshold as defined in the Cryotherapy for Retinopathy of Prematurity Study at that time. However, since the Early Treatment for Retinopathy of Prematurity Study results were reported, 9% of patients reached type 1 ROP, the new threshold, requiring earlier intervention than indicated in the Cryotherapy for Retinopathy of Prematurity Study.

A LIFETIME DISEASE

It is important to keep in mind that ROP is a lifetime disease. In 2009, our mid-Atlantic retina practice had 187 visits from patients with ROP, with the patients ranging in age from 6 months to 67 years. The mean age was 28 years, and the median age was 22 years. Only 28 of the 187 visits were for patients younger than 5 years.

Whether treated or untreated in infancy, the retinas in adults who were premature as infants can have a different appearance than in those adults who were full-term infants. For example, dragged retina is a common finding, but less well appreciated is the finding that the mean foveal thickness of the retina in patients with ROP is often greater with loss of the foveal pit than it is in patients who were full-term infants.

Myopia is also prevalent among adults with ROP. In an examination of 43 eyes of adult patients with ROP, 39 (90.7%) were found to be myopic. In a non-ROP population, the prevalence was only 25%. The myopia in adults with ROP is often not axial but, rather, is due to a shorter radius of corneal curvature making for a steeper corner.

Adults with ROP may also develop retinal detachments. For example, we have seen and treated patients in their 40s and 50s for retinal detachment. In April 2008, a 54-year-old woman, who had had a scleral buckle for a rhegmatogenous detachment in her only eye 25 years before,
was seen because of a drop in vision (Figure 1). She had developed a vitreoretinal traction syndrome, which had reduced visual acuity to 20/50 compared with a previous acuity of 20/25. Neither the patient nor I was anxious to operate on this only eye, so we observed it, and by March 2010, the vitreoretinal traction had spontaneously released and visual acuity returned to 20/25 (Figure 2).

Another finding is that many patients with ROP develop cataracts, which are usually nuclear and/or posterior subcapsular. Although there is no scientific evidence to support it, I have been impressed with the number of postcataract eyes that develop a hazy posterior capsule within the first few months postoperatively and the few that have even developed anterior capsular phimosis (Figure 3).

**THE FUTURE**

So, what can we expect as we progress further into the 21st century? Laser therapy has proved extremely effective as treatment for type 1 threshold ROP, with a success rate of 91% to 95% except for some zone 1 eyes.17 Also, bevacizumab (Avastin; Genentech, San Francisco, California), an anti–vascular endothelial growth factor (VEGF) therapy, is now available. It has been demonstrated that when oxygen is increased, the amount of VEGF produced is decreased, and when it is lowered, the VEGF again increases. Because bevacizumab can moderate the amount of VEGF, it is now being used by some as a primary treatment in type 1 ROP. Encouraging results have been reported by Quiroz-Mercado et al18 in Mexico and Mintz-Hittner and Kuffel19 in Texas.

Although the treatment appears to be safe,18-20 it would seem prudent to approach this new therapy with caution. In the early days of retrolental fibroplasia, it was felt that increasing oxygen might help respiratory distress, but, instead, it increased the number of children who became blind from ROP.5 Later, corticosteroids were
used in an attempt to remove premature infants from ventilators earlier, and this led to an increase in cerebral palsy. Referring to the retrolental fibroplasia epidemic in the 1940s and 1950s, William A. Silverman pointed out “that scientific rules of evidence must be satisfied before any new technique in management of premature infants was used in teaching centers.”

For example, the current dosage of bevacizumab for intravitreal injection in ROP is 0.625 mg (0.025 mL), which is half of the dosage used for adults. However, a comparison of vitreous cavity volumes between 2 postmortem eyes from a premature infant and 1 postmortem eye from an adult showed that the volumes of the postmortem eyes from the premature infant were less than one-third that of the postmortem eye from the adult (Figure 4). This raises the question of whether the dosage of bevacizumab could be lowered.

A recent study compared the target range of oxygen saturation of from 85% to 90% with that from 91% to 95% to determine which range of oxygen saturation would most likely minimize retinopathy without adverse effects. The lower range of oxygen saturation (85%-90%) resulted in decreased ROP but increased mortality.

Avery and colleagues have shown that, in patients with diabetic retinopathy, a systemic effect is validated by a response in the fellow eye after bevacizumab injection into the eye that requires treatment. Sears and Sears et al have suggested dose adjustment to match the mean concentration of vitreous VEGF, something with which I agree, and they have also shown that lower oxygen targets at an early gestational age and higher oxygen targets at an older gestational age decrease the incidence and severity of ROP.

Thus, for the present, I personally would consider treatment with bevacizumab in ROP as an adjunct to laser therapy in type 1 eyes that do not react appropriately to laser, in pupils that do not dilate because of iris engorgement, and in tunica vasculosa lentis (Figure 5). But, as Darlow and colleagues point out, a complete understanding of adverse effects is essential before there is widespread implementation of this promising therapy.

In concluding, I would like to paraphrase Francis Church’s response in The New York Sun to Virginia O’Hanlon’s query about Santa Claus. Yes, Virginia, we still have a problem with ROP.

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REFERENCES