

## Stage 5 Retinopathy of Prematurity: Then and Now

In this issue of *Retina*, Cusick et al and Lahkanpal et al report their respective experience in the surgical management of total retinal detachment (stage 5) due to retinopathy of prematurity (ROP). The former series represents a panoramic view of a single surgeon's experience over 25 years with a large number of eyes, most of which (78%) had no prior peripheral retinal ablation. The latter series reports the surgical outcome of a smaller number of eyes with progression to retinal detachment despite peripheral retinal ablation. These articles provide an opportunity for reflection on the current status of stage 5 ROP in the United States and around the world.

### Advanced ROP Is Here to Stay

Data from the Early Treatment for Retinopathy of Prematurity Randomized Trial<sup>1</sup> indicate that the incidence of ROP in the United States has been flat over the past 20 years, but severe ROP is more common and occurs in smaller and younger infants. Why has there been no surge in ROP-related morbidity in the United States due to greater severity? Dissemination of information delineating the variable clinical features of the disease,<sup>2-5</sup> refined screening,<sup>6,7</sup> and treatment<sup>8</sup> paradigms based on evidence-based studies, transition to laser from cryopexy for retinal ablation,<sup>9,10</sup> and early lens-sparing vitreous surgery for macula-sparing partial retinal detachment (stage 4A)<sup>11</sup> have mitigated the impact of advanced ROP. However, progression to retinal detachment occurs even with state-of-the-art care: 12% of randomized eyes in the Early Treatment for Retinopathy of Prematurity Study<sup>8</sup> detached before 9 months' corrected age despite timely peripheral ablation. Advanced ROP remains a significant problem in the United States.

---

The authors have no proprietary interests in this article.

Reprint requests: Antonio Capone Jr., MD, 632 Medical Office Building, 3535 West 13 Mile Road, Royal Oak, MI 48073; e-mail: acaponejr@yahoo.com.

Although corneal scarring from measles, vitamin A deficiency, and ophthalmia neonatorum are major causes of blindness in low-income countries, ROP is an important cause in middle-income countries in Latin America, Asia, and eastern Europe.<sup>12</sup> Survival of premature infants in such countries is improving. Our international ophthalmology colleagues are encountering ROP with greater frequency, yet proficiency in ROP diagnosis requires several phases of learning. This gradual accumulation of experience is a right of passage for all who tend to infants at risk for this disease: recognizing the traditional stages, acquiring a sense of disease tempo and how it can vary with zone and systemic status, appreciating the importance and subtleties of plus disease, and gaining familiarity with the unique features of aggressive posterior ROP.

Infants developing ROP requiring treatment in developed countries weigh <1,000 g at birth.<sup>8</sup> Infants with severe ROP in countries with low to moderate levels of development tend to be larger and more mature.<sup>13</sup> Examiners may escape the consequences of poor screening initially, because eyes with poor outcomes are relatively infrequent in larger and older premature infants. The longer one screens, and as survival of extremely premature infants improves, experience with stage 5 ROP invariably increases dramatically. It is for this reason that the World Health Organization "VISION 2020—The Right to Sight" program has identified ROP as one of the prime targets for the control of blindness in children.<sup>14</sup>

### Apples to Apples

The classification system for stage 5 ROP has not changed since the committee for the International Classification of Retinopathy of Prematurity consensus statement in 1987.<sup>3</sup> Stage 5 detachments are funnel shaped and subdivided based on whether the anterior and posterior parts are open or closed. The more open the funnel, the better the surgical prognosis.

Beyond this, however, the International Classification of Retinopathy of Prematurity inadequately addresses the complex and variable anatomy of advanced ROP. Whether an eye is untreated or treated with either cryopexy or laser impacts on both staging and prognosis. Lahkanpal et al note that some eyes diagnosed with stage 5 ROP by preoperative clinical appearance had focal areas of attached peripheral ablated retina. Such eyes, although similar to eyes with stage 5 disease in many ways, actually have funnel-shaped stage 4B detachments. The timing of surgery for stage 5 ROP is based on resolution of neovascular engorgement, and subretinal blood has long been recognized as a critical prognostic feature. A revised classification is needed with adequate descriptive detail necessary for comparative study. Peripheral retinal ablation status, vascular activity, and the presence of subretinal blood are prime candidates for inclusion.

### The Controversy Over Surgery for Stage 5 ROP

The untreated natural history of stage 5 ROP is poor. Spontaneous reattachment is rare, and no light perception blindness is the rule. However, surgery for stage 5 ROP remains controversial. The argument is that the anatomical and visual outcomes are so poor that such interventions are not “worth it.” On these grounds, surgery to repair stage 5 ROP is not performed in the United Kingdom.<sup>15</sup>

Admittedly, stage 5 ROP is a daunting disease. The surgical learning curve is long and steep. The surgery is unforgiving, because a single iatrogenic retinal break often means failure. Complete retinal attachment and restoration of normal posterior pole anatomy are uncommon. Neurologic comorbidity may limit vision even when surgery is successful.

There is tendency to abandon hope, and visual rehabilitation efforts, when visual response is not prompt or because retinal reattachment is incomplete. Visual development after repair is typically slow and limited, with the full effect often not apparent for  $\geq 2$  years.<sup>16</sup> Integration of a team to provide aggressive refractive therapy and visual rehabilitation after surgery is axiomatic. Care for children with stage 5 ROP who have undergone surgery requires high maintenance. The realization that optimizing visual outcome requires much more than surgery is the greatest challenge to a parent’s wherewithal.

How much better than no light perception blindness does outcome need to be for surgery for stage 5 ROP to be considered worthwhile? Poor visual outcome is not invariable, and good visual outcomes are not unheard of.<sup>17–21</sup> However, even low vision is useful for infants as they grow, and visual development occurs

in infants with even minimal retinal reattachment. The ambulatory vision threshold of 5/200 for adults does not seem to apply to children deprived of vision in early infancy, because many ambulate successfully with significantly lower levels of vision. Even children with only light perception vision object emphatically to occlusion.<sup>18</sup> Furthermore, who can presume to know what vision restorative technologies will be available during the lifetime of an infant born today? It is reasonable to expect that more options will await a sighted child than one who does not perceive light.

### The Call for Clinical Trials

Prospective, randomized, controlled clinical trials evaluating the merits of surgery versus observation for stage 5 ROP are an attractive idea. Although selection bias and assessment bias would be minimized, however, uncontrollable variables would mandate an unrealistically large sample size. These include, but are not limited to, the following: birth age and weight, zone and extent of disease at the time of peripheral retinal ablation, timing of peripheral retinal ablation, method of ablation, adequacy of ablation, vascular activity at the time of surgery, postmenstrual age at the time of surgery, detachment configuration (open open, open closed, closed open, or closed closed), surgical technique (with or without scleral buckle, with or without lensectomy, or open-sky or closed vitrectomy), surgeon experience, ocular comorbidities (subretinal hemorrhage, anisometropia, and glaucoma), neurologic comorbidities, postoperative visual rehabilitation initiatives, ethnicity, and the myriad factors that limit follow-up of this study population. Progress in the surgical management of advanced ROP has come from highly specialized single-center case series. Although desirable, large clinical trials are likely to be impractical for this condition.

### Challenges and Future Directions

Every effort must be made using established paradigms—diligent screening, timely laser, and prompt intervention for stage 4A ROP—to interrupt the pathogenetic process of ROP before eyes reach a point of no return and normal vision is unattainable. Unwelcome though it is, stage 5 ROP is here to stay. Surgeons and parents have no choice but to consider the variables pertinent to undertaking surgery for a given infant, in much of the same fashion as is done with surgery for severe ocular trauma, bleb-related endophthalmitis, and other poor prognosis conditions. We look forward to research elucidating the genetic factors modulating the susceptibility to ROP and to development of adjunctive pharmacologic therapies tar-

getting both angioproliferative and cicatricial phases of this condition.

**Key words:** stage 5 retinopathy of prematurity, vitrectomy.

Antonio Capone Jr, MD,  
Michael T. Trese, MD  
Associated Retinal Consultants, P.C.,  
Royal Oak, Michigan

### References

1. 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.
2. Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. *Arch Ophthalmol* 1984;106:471–479.
3. International Committee for the Classification of the Late Stages of Retinopathy of Prematurity. An international classification of retinopathy of prematurity: II. The classification of retinal detachment. *Arch Ophthalmol* 1987;105:906–912.
4. Shaikh S, Capone A Jr, A Schwartz SD, et al. ROP Photographic Screening Trial (Photo-ROP) Study Group. Inadvertent skip areas in treatment of zone 1 retinopathy of prematurity. *Retina* 2003;23:128–131.
5. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol* 2005;123:991–999.
6. Reynolds JD, Dobson V, Quinn GE, et al. CRYO-ROP, LIGHT-ROP Cooperative Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. *Arch Ophthalmol* 2002;120:1470–1476.
7. Section on Ophthalmology, American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2006;117:572–576.
8. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the Early Treatment for Retinopathy of Prematurity Randomized Trial. *Arch Ophthalmol* 2003;121:1684–1694.
9. Ng EY, Connolly BP, McNamara JA, et al. A comparison of laser photocoagulation with cryotherapy for threshold retinopathy of prematurity at 10 years: part 1. Visual function and structural outcome. *Ophthalmology* 2002;109:928–934.
10. Connolly BP, Ng EY, McNamara JA, et al. A comparison of laser photocoagulation with cryotherapy for threshold retinopathy of prematurity at 10 years: part 2. Refractive outcome. *Ophthalmology* 2002;109:936–941.
11. Prenner JL, Capone A Jr, A Trese MT. Visual outcomes after lens-sparing vitrectomy for stage 4A retinopathy of prematurity. *Ophthalmology* 2004;111:2271–2273.
12. Gilbert C, Rahi J, Eckstein M, et al. Retinopathy of prematurity in middle income countries. *Lancet* 1997;350:12–14.
13. Gilbert C, Fielder A, Gordillo L, et al. International NO-ROP Group. Characteristics of infants with severe retinopathy of prematurity in countries with low, moderate, and high levels of development: implications for screening programs. *Pediatrics* 2005;115:e518–e525.
14. Gilbert C, Foster A. Childhood blindness in the context of VISION 2020: the right to sight. *Bull World Health Organ* 2001;79:227–232.
15. Fielder AR. Retinopathy of prematurity. *Community Eye Health Journal* 1997;10:17–19.
16. Katsumi O, Mehta MC, Matsui Y, et al. Development of vision in retinopathy of prematurity. *Arch Ophthalmol* 1991;109:1394–1398.
17. Hirose T, Katsumi O, Mehta MC, Schepens CL. Vision in stage 5 retinopathy of prematurity after retinal reattachment by open-sky vitrectomy. *Arch Ophthalmol* 1993;111:345–349.
18. Seaber JH, Machemer R, Elliott D, et al. Long-term visual results of children after initially successful vitrectomy for stage V retinopathy of prematurity. *Ophthalmology* 1995;102:199–204.
19. Fuchino Y, Hayashi H, Kono T, Ohshima K. Long-term follow up of visual acuity in eyes with stage 5 retinopathy of prematurity after closed vitrectomy. *Am J Ophthalmol* 1995;120:308–316.
20. Mintz-Hittner HA, O'Malley RE, Kretzer FL. Long-term form identification vision after early, closed, lensectomy-vitrectomy for stage 5 retinopathy of prematurity. *Ophthalmology* 1997;104:454–459.
21. Kono T, Oshima K, Fuchino Y. Surgical results and visual outcomes of vitreous surgery for advanced stages of retinopathy of prematurity. *Jpn J Ophthalmol* 2000;44:661–667.