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Retinopathy of Prematurity and the Peripheral Retina

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Preservation of visual acuity in advanced, acute phase retinopathy of prematurity (ROP) usually requires retinal ablation (destruction) of peripheral retina. The avascular peripheral retina in ROP likely produces vascular endothelial growth factor (VEGF), which in turn induces pathological angiogenesis at the advancing margin of developing retinal blood vessels. To treat severe ROP, surgeons use a destructive procedure on the peripheral retina to effect regression of neovascularization. The goal is to preserve the macula, which subserves the ability to discriminate fine detail (e.g., read). In fact, without this destructive procedure, the peripheral retina also would be lost because most cases of adverse outcome in advanced ROP result in retinal detachment that involves the entire retina.

What is the effect of destruction of peripheral retina? In the Cryotherapy for Retinopathy of Prematurity Study (CRYO-ROP), peripheral retinal ablation reduced visual fields somewhat, but, surprisingly, not much more than was reduced by the acute phase ROP *per se* (recall that in the CRYO-ROP Study, control eyes did not receive treatment and thus were available for comparison to treated eyes).¹ In other words, peripheral retinal functioning is adversely affected by the ROP disease process. Untreated, control eyes in the CRYO-ROP Study had *advanced* disease, a point of emphasis below.

In 2008, the effect of ROP on peripheral retinal function is more important than ever. Following the CRYO-ROP Study, the National Eye Institute funded a study to evaluate the effect of earlier treatment for ROP at high-risk prethreshold disease (ETROP Study). Advances in neonatal care had led to improved survival rates for more immature infants, but there were concerns about eyes with Zone I disease (very posterior ROP with extensive areas of avascular retina) and about persistent retinal detachment rates for eyes with Zone II advanced disease. Zone I ROP occurs most commonly in the smallest birthweight infants, because retinal vessel development is quite immature. The ETROP Study showed a very significant benefit to earlier treatment at high-risk prethreshold disease.² Surprisingly, approximately 40% of eyes randomized in the ETROP Study had Zone I disease. Reasons for this finding have been discussed,² and while some eyes might have been diagnosed as Zone I when only one clock hour of ROP was present in Zone I (and the other clock hours of disease more anterior), there can be little doubt that Zone I ROP is seen more frequently now than 15 years ago.

There are large numbers of very low birthweight infants with ROP disease that is present for a time in Zone I and regresses without treatment, or is treated in Zone I. In the ETROP Study, there are infants who had Zone I eyes where one eye was treated at prethreshold disease and the fellow, control eye, either treated at conventional threshold disease, or observed as the

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disease simply regressed spontaneously.² The significance of posterior ROP and its effects on visual field and rod (and cone) function is unknown, and is one of the reasons the cohort from the ETROP Study will be followed to age 6 years. At that time, randomized children in the ETROP cohort will have visual fields measured to learn the effects of regressed versus treated posterior disease.

This is one reason why the study reported by Hamilton et al in *The Journal* is so timely.³ These authors report that rod sensitivity is slowed by preterm birth while maturation of responsivity is accelerated. Untreated ROP reduces sensitivity, but treatment for ROP results in reduced sensitivity and responsivity. A likely explanation for this, as discussed by the authors, is that post photoreceptor gain is altered in prematurity with or without ROP, and increased due to extrauterine visual experience. This effect seems to occur even when ROP is mild. On the other hand, conditions which alter the photoreceptor cells themselves will reduce sensitivity. This appears to be the case for ROP and for treated ROP.

The paper has additional significance. The study design included comparisons of full term infants to those who were premature but with no ROP. A nature-nurture experiment emerges wherein the effects of extrauterine time and visual experience can be compared between preterm and term infants. The authors found that extra visual experience influences retinal neuronal behavior. This finding is consistent with other studies where extrauterine experience has been compared between preterm infants and full term matched infants. In a study by Mirabella et al, preterm infants with no other known complications of prematurity (no intraventricular hemorrhage or ROP) showed higher signal amplitudes on steady state visual evoked potentials than did full term infants.⁴ Although Mirabella's study looked at cortical responses, and not simply retinal responses, his group's study has findings similar to the current report. Something about preterm birth influences neuronal development and architecture, both at the level of the retina and the visual cortex.

The peripheral retina, with its population of rod photoreceptor cells, is an accessible area to study effects of preterm birth on neuronal development. Although the findings of this current study are tempered somewhat by the small sample size, the authors have clearly demonstrated that studies of even very small infants are feasible. Future studies should continue to use groups of infants tightly controlled for postconceptual age and other factors. For example, factors such as neonatal jaundice and sex could influence results. Longer follow-up is desirable to learn whether population differences resolve over time. Whether mild ROP will have the same effect on rod functioning as more advanced but untreated ROP should be studied as well.

Meanwhile, effects of preterm birth, and of advanced ROP, on developing retina have assumed an even higher priority, due to changes in demographics of premature infants. Teasing apart the effects of laser treatment versus disease itself becomes particularly important, considering that more infants are now treated with greater amounts of retinal ablation. Visual acuity outcomes in the CRYO-ROP Study, even with preserved structural outcome, were often less than hoped for, indicating that the cone cell population of photoreceptor cells is probably also affected by the disease process or its treatment.⁵ New tools and methods to measure electrophysiological changes are needed. In some areas of the world, inhibitors of growth factors are being evaluated for the management of neovascularization in ROP. We will need to know how these cytokines may also influence other aspects of retina and vision development.

Retinopathy of prematurity is truly a panocular problem. Clinicians understandably emphasize attempting to prevent retinal detachments in this disease, thereby preserving posterior retina and cone cell function. But other effects of ROP on the eye can also be very important, even when the retina structure appears normal. Effects of ROP are not always ophthalmoscopically visible. The authors are to be congratulated for directing our attention to aspects of visual

development that could turn out to be very important to the health and vision status of these very low birthweight infants.

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