When Babies With ROP Grow Up

Ophthalmologists have long considered retinopathy of prematurity (ROP) to be a strictly neonatal disease. However, a paradigm shift has occurred. Advances in care and treatment of preemies have allowed babies to live longer, and laser ablation and intravitreal anti-VEGF therapy have led to improvements in ocular outcomes. Years later, ophthalmologists are identifying significant late sequelae. Now, ROP is considered a lifelong disease that requires routine follow-up.

"The problem we're seeing, though, is that when these patients get into their teenage years, they move on to adult specialists who may not necessarily be comfortable treating pediatric retinal diseases, including ROP," said Mary Elizabeth Hartnett, MD, at Stanford University in Palo Alto, California. As a result, a large portion of this population may not receive the care they need, she said. "So, all of us—from comprehensive ophthalmologists to retinal surgeons—need to better understand ROP in all of its presentations."

Lifelong Retinopathy: Clinical Features

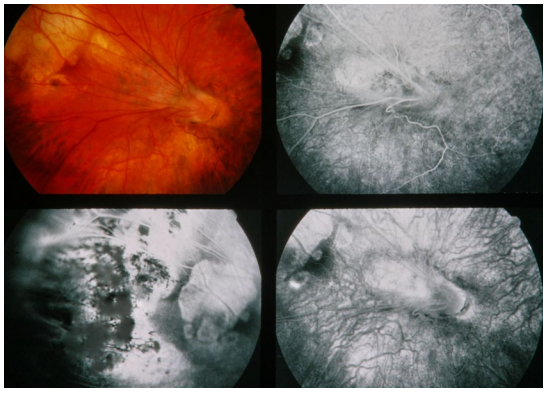
"We used to think of ROP as a disease of prematurity and even sometimes gave parents the impression that their child was safe from ROP once they grew out of the at-risk window," said Peter Campbell, MD, MPH, at Oregon Health & Science University in Portland. "However, as more and more infants survive to adulthood, we're finding that many of them have potentially vision-threatening retinal disease, even without a known history of severe ROP."

Parsing what is abnormal. As is the case with other retinal diseases, sometimes there are no long-term complications, even if the retina looks abnormal, said Dr. Campbell. For example, the retinal vessels might appear a little more dilated and tortuous, the optic nerve might be a little thin, or the anterior segment a bit shallow.

What to look for. On the other hand, patients can develop forms of myopia as well as be at risk for a multitude of late sequelae and sight-threatening conditions regardless of whether they received prior neonatal treatment, said Dr. Hartnett, and the challenge is we don't know which patients will develop future complications from prematurity.

Among the most common long-term complications of the anterior segment are the following:

- increased lens thickness,
- angle-closure and other forms of glaucoma,
- a highly curved cornea,
- early development of cataracts,
- strabismus, and
- amblyopia.



AGING AND ROP. *Fundus photos from a 35-year-old who developed ROP as an infant.*

Posterior segment complications include:

- rhegmatogenous, tractional, and/or exudative retinal detachments,
- retinoschisis,
- retinal folds and tears,
- abnormal foveal development,
- persistent avascular retina, and
- other retinal vascular disorders.

Cortical visual impairment. In addition to structural changes that can interfere with VA, ROP patients can have other neurologic and ophthalmologic manifestations of prematurity as they age, said Dr. Hartnett. "Although it's not completely understood, cortical visual impairment is one of the most common causes of bilateral visual impairment worldwide and affects children born prematurely," she said. This neurological form of visual impairment is a result of damage to the visual processing centers of the brain and, even in seemingly healthy eyes, it can result in photophobia, deficient color vision, and other visual field defects. In addition,

BY MIKE MOTT, INTERVIEWING **PETER CAMPBELL, MD, MPH, KIMBERLY A. DRENSER, MD, PHD,** AND **MARY ELIZABETH HARTNETT, MD.**

some evidence suggests that some abnormalities related to cortical visual impairment may exist at the level of the retina, she said.

"We are still learning a lot about the incidence of sight-threatening disease in this population and what happens as patients age," Dr. Campbell said.

Age-Based Nuances

"We're in an era now where ophthalmologists are seeing adolescents and adults across the three generations of ROP treatment," said Kimberly A. Drenser, MD, PhD, a retina specialist in Royal Oak, Michigan. There are specific nuances to be aware of for each age group that will help ophthalmologists to identify and monitor ex-ROP patients, she said.

The "before" times. Baby Boomers can be distinguished by their age and their past medical care, said Dr. Drenser. These older adults have a completely different presentation from later generations of children who had ROP, she said. Because they were considered miracle babies at the time—born before newer technologies were available—they are aware of and generally disclose their history, so they are fairly easy to identify.

The ablation years. In 2004, laser photocoagulation became the standard of care for type 1 ROP after the Early Treatment for Retinopathy of Prematurity study reported the efficacy of laser ablative therapy in high-risk eyes.[1] Targeting the peripheral avascular retina that incites VEGF production, laser ablation presented several advantages over prior cryotherapies, including precise delivery with less ocular trauma.

Because of the scarring involved in ablative therapy, these eyes are generally easy to identify in adolescents and adults, said Dr. Drenser. "Most ophthalmologists, even if they are not retina specialists, will recognize these laser scars and ask the patient if they were born premature," she said.

And because the therapy has been common practice for almost two decades, ophthalmologists have a general sense of what to expect as children age, said Dr. Drenser. "As the eye elongates and the vitreous changes, these patients tend to have higher levels of myopia and can have some atypical vitreoretinal traction," she said. "But our most recent retrospective analysis has shown that this ablation generation has the least risk of retinal tears and detachment."

The anti-VEGF era. Over the past 10 years, treatment has shifted from laser photocoagulation to intravitreal anti-VEGF injection. Compared with ablation, anti-VEGF treatment is less time-consuming and less technically challenging, and it subjects infants to less stress than the laser procedure, which requires deep sedation or anesthesia, said Dr. Campbell.

Persistent avascular retina. Although anti-VEGF permits some ordered intraretinal vascularization to develop in the peripheral avascular retina, not all the peripheral avascular retina becomes vascularized in all infants. Therefore, patients treated with anti-VEGF agents can be at significant risk of persistent avascular retina as they age, said Dr. Campbell. This thinned, avascular tissue can lead to atrophic retinal holes, lattice degeneration, and retinal tears and detachment.

"This is a critical issue," said Dr. Drenser, "because some studies are showing that up to 90% of kids treated with anti-VEGF are not regrowing and developing normal retinal tissue and will have some degree of avascular retina moving forward." And unlike the ablated population, this anti-VEGF group has an increased risk of morbidity that increases with every year of life because of how the avascular retina weakens and atrophies over the course of time, she said.

As to why incomplete retinal vascularization occurs, more research is needed, said Dr. Campbell. "In the laser era, once you treated a baby, there was no significant avascular retina," he said. "Either you had vascularized retina or you had lasered retina. In the anti-VEGF era though, the disease regresses and you have the opportunity for progressive vascularization, but this is occurring variably in some patients, and we don't know exactly why."

And yet, Dr. Hartnett said, peripheral avascular retina existed in some ROP patients who had regression of disease without laser treatment in the time before anti-VEGF treatment. "Some developed retinal detachments, but we don't know how many with peripheral avascular retina had long-term sequelae. More research is needed," she said.

The untreated. This begs another important question, said Dr. Campbell. How often does nonvascularization occur in "normal" untreated ROP patients who did not previously meet type 1 criteria? "Many times, we've told parents that their baby is no longer at risk of ROP and that they should just follow up with us for strabismus and amblyopia moving forward," he said. "However, there are now several studies suggesting that up to one-third of patients with spontaneously regressed ROP—patients we didn't used to worry about—have potentially clinically significant persistent avascular retina as they age."[2,3]

Anecdotally, Dr. Campbell is seeing more teenagers and young adults from this population present for vitreoretinal care—presumably because, today, more people who were born prematurely are living to adulthood than once was the case. "But we just don't know how common it is to have complications from persistent avascular retina in this population and what to do about it," he said. Many pediatric ophthalmologists and retina specialists are choosing to laser persistent avascular retina as a preventive measure because of just how challenging it is to follow such patients and to reduce any future risk of reactivation, he added.

Anti-VEGF unknowns. There are certainly other unknowns regarding the use of anti-VEGF, said Dr. Hartnett, specifically the effects of intraocular VEGF suppression on the rest of the body. "We do know that anti-VEGF agents cross into the bloodstream and suppress systemic VEGF levels to varying degrees," she said. "We don't yet know how that impacts neuronal health in the retina or leads to clinically significant complications involving other organ systems."

These are hard questions to answer because of many variables, said Dr. Hartnett. For example, she said, the infants who develop ROP tend to be very

small in terms of overall development and are already at a high risk of neural cognitive insufficiency and other complications—which makes it even more difficult to test any effects of anti-VEGF treatment.

Caring for Kids as They Age

Detection difficulties. When ex-ROP patients walk into the clinic, they may not even be aware that they were born prematurely. "It's a perfect storm," said Dr. Drenser, "because many of these children reach prethreshold type 2 ROP but never require treatment, and now they're running around years later with incomplete retinal development." On top of that, a substantial number of kids who were born prematurely develop prethreshold type 1 and are treated with anti-VEGF, she said. But both of these groups are unablated so their eye care team may not recognize them as premature when they enter adulthood.

Thus, general ophthalmologists and adult-only retina specialists need to be on the alert and ready to change treatment course. These eyes are abnormal in subtle ways that place patients at risk if they go unrecognized, said Dr. Drenser.

"For example, a young adult may walk into your office with some peripheral abnormalities or perhaps a detachment," said Dr. Drenser. "But because you don't recognize them as an ex-premature kid, you refer them to an adult vitreoretinal surgeon. It's only then, during surgery, that the specialist sees an anatomy that's extremely different—compared to a typical myopic adult—and one that requires a very different surgery."

Medical mysteries call for histories and imaging. It can take some sleuthing on the physician's part to determine if a patient had ROP as a baby, said Dr. Campbell. That's why all ophthalmic practices should be asking about a history of premature birth as part of the patient intake process.

Ophthalmologists should also set a low threshold when it comes to performing a widefield angiogram or referring a patient to a retina specialist if they have any suspicions. "The pathology in these eyes can be very subtle," said Dr. Campbell. "And without fundus photography, it can be difficult to appreciate avascular retina on clinical examination alone."

Ongoing care. In the end, many patients are going to do well. Children are able to adapt and use other senses, even if they have some visual impairment, said Dr. Hartnett. But because ROP is a lifelong disease, patients should have annual comprehensive eye exams at the very least. And this needs to continue even when children enter adulthood and are responsible for seeking appointments themselves, she said. Also, she notes, adults who had ROP are at increased risk for other ocular conditions including glaucoma.

Until then, parents of these adolescents and young adults need to be educated about the importance of continued care, said Dr. Drenser. Children born prematurely have a lot of doctors' appointments, so it's understandable that parents may forget to follow up with ophthalmology care—but, she said, "because we're seeing more and more relatively young adults with essentially normal visual function develop severe vitreoretinal pathology, we need everyone on board to get these patients seen."

1 Good WV. *Trans Am Ophthalmol Soc.* 2004;102:233-248.
2 Haniff AM et al. *J AAPOS.* 2022;26(1):29-31.
3 Ling XC et al. *Ophthalmol Sci.* Published online Feb. 6, 2023.

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