THE **RETINA** PARTNERS

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Case of the Month – January 2021

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A 35-week-old (by post-menstrual age; PMA) infant was referred for evaluation and treatment of retinopathy of prematurity (ROP). The baby was born at 28 weeks gestational age (GA) at a birth weight (BW) of 1100 grams and required supplemental oxygen in the NICU. He had dilated and tortuous posterior pole vessels in 3 quadrants and a ridge with extraretinal neovascularization in posterior Zone 2, consistent with Stage 3 ROP with plus disease in both eyes (Type 1 ROP). The recommendation was made to his parents for treatment. We discussed the options of laser treatment versus intravitreal anti-VEGF therapy versus a combination of both, and after understanding the risks, benefits, and alternatives, the parents elected to proceed with laser.

Clinical Course:

Confluent, ablative laser treatment to the peripheral avascular retina was performed the following day in both eyes. Topical Prednisolone was given for 1 week following laser treatment. The infant was monitored weekly initially thereafter. Within 4 weeks of treatment, the neovascularization had regressed and by 50 weeks PMA the ridge had flattened, the vessels had taken on a more normal caliber and contour, and the retina was attached without fibrosis, traction, folds, or foveal ectopia.

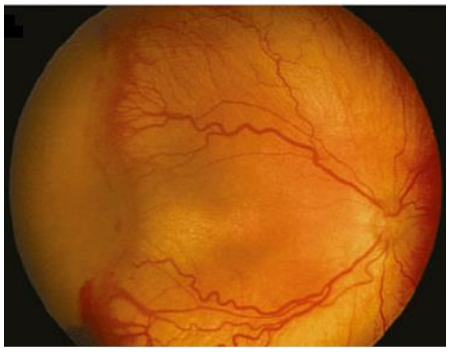

Figure 1: Right eye of a 35-week-old (by PMA) infant with Stage 3 ROP with plus disease in posterior Zone 2. Confluent laser treatment was delivered to the peripheral avascular retina.

Discussion:

Retinopathy of prematurity (ROP) is a disease that affects premature infants born with a young gestational age (GA) and low birth weight (BW). It's the leading cause of lifelong visual disability in developed nations, causing vision loss in approximately 1300 children and severe vision loss in 500 children in the United States each year.

ROP is classified according to the International Classification of ROP system based on the location of retinal involvement (Zones 1-3; Figure 2) and severity of retinopathy (Stages 0-5). The extent of retinal involvement (# of clock-hours), presence or absence of dilated and tortuous vessels in the posterior pole (pre-plus or plus disease), and the pace or tempo of disease progression (aggressive posterior ROP – "APROP") are important considerations in deciding when and how to treat. The stages of ROP are:

Stage 0 - avascular peripheral retina
Stage 1 - thin line at vascular/avascular border
Stage 2 - ridge of tissue with height and width, differentiating it from the demarcation line
Stage 3 - extraretinal fibrovascular proliferation or neovascularization at the ridge
Stage 4A - fovea-sparing retinal detachment
Stage 4B - fovea-involving retinal detachment
Stage 5 - total RD, typically in a funnel

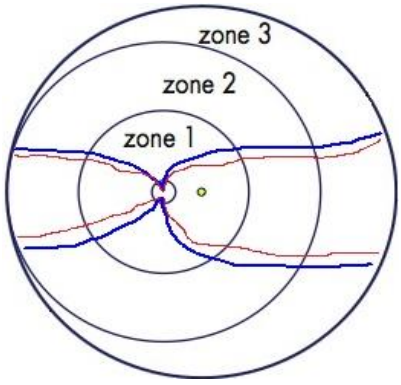

*Figure 2: Zones of ROP. **Zone I** is the area of a circle centered at the optic disc, where the radius is twice the distance from the center of the optic disc to the fovea. **Zone II** is the ring-shaped section of retina surrounding but not including Zone I, where the radius is from the optic disc to the nasal ora serrata. **Zone III** is the remaining crescent-shaped area of peripheral, mostly temporal retina.*

Plus disease - dilated retinal veins and tortuous arteries in the posterior pole (≥ 2 quadrants); retinal vessels increase in caliber due to shunting of peripheral blood through ridge.

Treatment is required for **plus disease** (Figure 3). **Pre-plus** describes mildly dilated and tortuous vessels of insufficient severity for "plus." In the setting of pre-plus disease, the physician may monitor the infant twice weekly, as progression can be rapid. Treatment is required for **Aggressive Posterior ROP (APROP)** which presents early and progresses rapidly to Stages 4 and 5 if untreated. APROP occurs in zone 1 and posterior zone 2 and is characterized by neovascular fronds that lay flat on the retina with no ridge present. **The key to treating ROP is early screening with timely and appropriate treatment** to prevent progression and poor outcomes, such as retinal detachment, retinal dragging or folds, macular ectopia, and retrolental membranes.

The first clinical trial, **CRYO-ROP** (1986), showed that infants with **threshold ROP** (5 contiguous or 8 cumulative clock hours of stage 3 ROP in Zone 1 or stage 3 ROP in Zone 2 with plus disease) treated with peripheral ablative cryotherapy were less likely to have a poor anatomic outcome than infants who were observed (27.2 vs 47.9%; p<0.001). Laser then supplanted cryotherapy as the mainstay of treatment. The Early Treatment of ROP (**ETROP**, 1999) trial showed that earlier laser treatment led to better outcomes for **pre-threshold Type 1 ROP** - **any number of clock hours** of: (A) **Zone 1, any stage, with plus**, (B) **Zone 1, stage 3**, with or without plus, or (C) **Zone 2, stage 2 or 3 with plus**. Unfavorable VA outcomes were reduced from 19.8% (standard treatment) to 14.3% (early treatment; p<0.005) and unfavorable anatomic outcomes were reduced from 15.6% to 9.0%, respectively (p<0.001). Laser treatment has largely remained the gold standard.

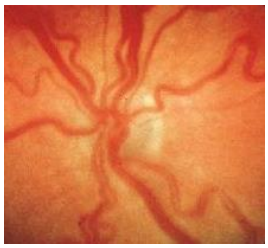

Figure 3: Dilated retinal veins and tortuous arteries consistent with plus disease, requiring prompt diagnosis and treatment.

The **BEAT-ROP** trial (2011) introduced intravitreal anti-VEGF as a treatment for ROP. It showed that for infants with plus disease and stage 3 ROP in Zone 1 or 2, there were fewer recurrences of ROP by 54 weeks PMA in eyes treated with bevacizumab (0.625 mg in 0.025 mL; 4%) compared to laser (22%; p=0.002). Subanalysis showed this significance to hold true for Zone 1 disease (p=0.003), but not for Zone 2 disease (p=0.27). The findings of BEAT-ROP led to a spirited debate (which continues today) on laser vs intravitreal anti-VEGF for ROP. There were some limitations to the trial: the recurrence rate of ROP was unusually high in the laser treatment group (22%, compared to 9% in ETROP), and the ROP recurrence rate cutoff was set at 54 weeks PMA. We now know that laser recurrences typically occur early (within 4 weeks), while intravitreal anti-VEGF recurrences typically occur later (as late as 19 weeks). The **RAINBOW** study subsequently validated the use of ranibizumab 0.2 mg in the treatment of ROP. The **BUTTERFLEYE** study, which is underway, is comparing intravitreal aflibercept to laser for ROP.

There are some potential advantages for anti-VEGF therapy. In infants with active iris NVI that limits pupillary dilation, anti-VEGF can help attain rapid regression of NVI, improved dilation, and the opportunity to deliver appropriate laser treatment. There is also the theoretical opportunity for subsequent vascularization of the peripheral avascular retina for infants treated with intravitreal anti-VEGF for Zone 1 disease. However, it is not yet known how many infants will go on to vascularize to the periphery and how many will require adjunctive laser after anti-VEGF. Nor is it fully known for how long infants treated with anti-VEGF should be monitored. In a retrospective commercial claims database analysis of 298 infants treated between 2011 and 2017 with 2-year follow-up data, there were 235 infants with ROP treated with laser and 63 treated with intravitreal anti-VEGF. Most ocular outcomes were similar, including rates of retinal detachment (p=0.87). There were higher rates of second procedures being performed (both injections and lasers) after intravitreal anti-VEGF injection compared to laser (44% vs 10%; p<0.001). Rates of developmental delay were similar.

Both laser and intravitreal anti-VEGF injections for the treatment of ROP require extensive training. Laser for ROP is one of the most challenging lasers to perform, as there is a very specific definitive area that needs to be treated and skip lesions or missing treatment spots can lead to suboptimal outcomes. Likewise, intravitreal injections in an infant can be challenging, especially if the infant is awake and moving. Special attention should be given to deciding the correct dose of anti-VEGF (significantly lower dose than in adults), injection site, antiseptic protocol, and treatment environment. The best treatment for ROP (especially for Zone 1 with plus) remains a topic of debate. Treatment should be driven by the individual infant's clinical presentation.

Take Home Points: Treatment of Retinopathy of Prematurity

- ROP requires appropriate screening and timely treatment to achieve the best outcomes.
- The mainstay of treatment for several decades has been peripheral, confluent, ablative laser.
- Intravitreal anti-VEGF injections appear effective for Zone 1 ROP, but may alter the disease biology, with late ROP recurrences up to 19 weeks after treatment.

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