ICROP3 UPDATES: REACTIVATION AND REGRESSION



Revisiting the classification has led to significant changes to help you better diagnose, monitor, and treat this condition.

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The committee for the International Classification of Retinopathy of Prematurity, third edition (ICROP3), included 34 international pediatric ophthalmologists and retina specialists who met to revisit the retinopathy of prematurity (ROP) classification.[1] ICROP3 was intended to assist research and clinical trials and provide consensus statements on ROP management but not to provide guidance on management. The main goals of the ICROP3 committee were to address earlier components of the classification that were subjective and open to interpretation; discuss imaging innovations that allow identification and comparison of levels of disease severity; explain the new understanding of ROP pathophysiology with therapies that interfere with VEGF bioactivity and introduce the conditions of regression and reactivation; and recognize patterns of ROP in other regions of the world using the revised classification[1]

Much has changed since the original ICROP in 1984, including the increased use of telemedicine screening and global education on ROP management.[2] In countries that recognized ROP as retrolental fibroplasia in the 1950s,[3] there have been technologic advances in neonatology, oxygen monitoring, and regulation that allow extremely premature infants to survive. In emerging nations, ROP occurs in more developmentally mature infants and can present in a severe and rapidly progressive form.[4,5]

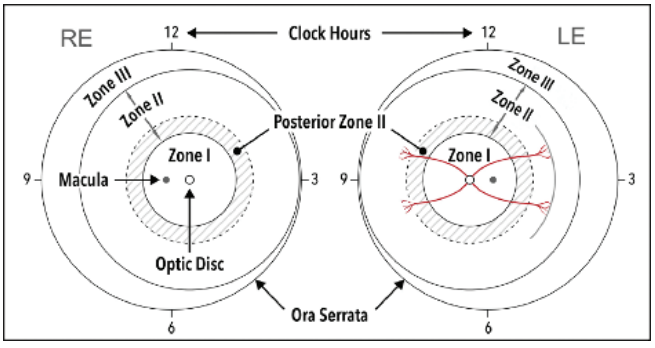

Figure 1. This diagram outlines the different zones evaluated in ROP screening. Reprinted with permission from Chiang MF, et al.[1]

In addition, agents that regulate cell signaling through a VEGF receptor by inhibiting angiogenesis reduce abnormal angiogenesis into the vitreous (stage 3 ROP) and allow angiogenesis to extend retinal vascularization into the periphery toward the ora serrata.[6-10] These processes are included in events of regression, a new term presented in ICROP3.[1] However, reactivation, also described in ICROP3, can occur, especially after anti-VEGF treatment, and this was not commonly seen with laser therapy for ROP in the past.[1]

ZONE, STAGE, PLUS DISEASE

The parameters for describing ROP remain the same: zone, stage, plus disease, and, less often considered for assessing treatment-warranted acute ROP, extent of stage.

Zone defines the retinal area that has been vascularized during development. A zone I fundus is the least vascularized and is associated with the most severe disease. A zone III fundus is the most vascularized. In ICROP3, posterior zone II is a circular area of vascularization centered on the optic nerve with a radius that is approximately 1.5 times the disc–macula distance (Figure 1). The zone II designation is still an estimate because the fovea is not developed in the premature infant.

In addition, zone I secondary to notch was described for eyes with 1 or 2 clock hours of zone I ROP in the horizontal meridian when other clock hours were in zone II (Figure 2).

Incomplete vascularization within a zone was a description before the development of ROP stages. Progressive stage 4 ROP, more common following laser therapy or cryotherapy for threshold ROP in the past, is seen less often with early laser treatment for stage 1 ROP.[11] When progressive stage 4 ROP occurs following laser therapy, the features of concern for a tractional retinal detachment (RD) are vitreous condensation over the ridge or optic nerve, haze, plus disease, or condensation over the ridge to an extent greater than 6 clock hours.[12] These features were distinct from persistent or new stage 3 ROP that warranted laser of skipped areas or antiangiogenic therapy.[12] Exudative RDs can also occur following laser therapy, are associated with a convex

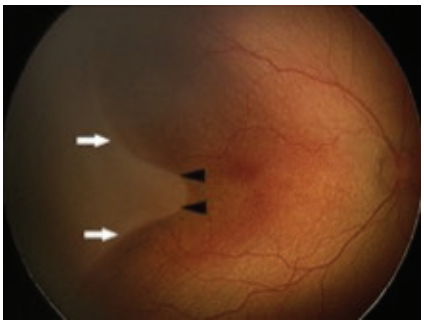

Figure 2. A notch between the vascular arcades (arrows, zone I). Reprinted with permission from Chiang MF, et al.[1]

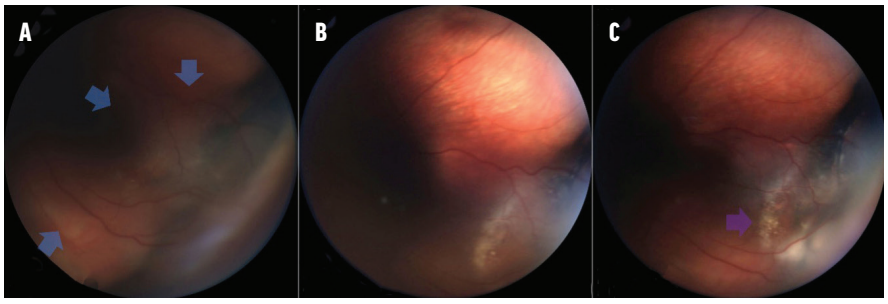

Figure 3. A female infant born at 25 weeks gestational age and 800 g birth weight was treated with laser photocoagulation at 44 4/7 weeks PMA. She presented with progressive stage 4 ROP and an inferotemporal exudative RD (blue arrow) at 55 4/7 PMA (A). During close observation, an improvement in the subretinal fluid occurred (B) with resolution of the RD at 62 3/7 weeks PMA (C). Note the exudation with resolution of subretinal fluid (purple arrow).

appearance, and often resolve with the appearance of exudates (Figure 3). After anti-VEGF therapy, reactivation can occur followed by progressive stage 4 ROP at the previous regressed ridge, at a new reactivated one, and/or at the optic nerve (Figure 4).

Stage 5 ROP was subclassified into 5A having an open funnel, 5B having a closed funnel with a view to the posterior eye, and 5C having a closed funnel with anterior segment involvement, including anterior lens displacement, anterior chamber shallowing, and corneal opacification.

Plus disease, classically described as dilation and tortuosity of the retinal veins and arterioles, now encompasses a spectrum of vascular changes graded by their zone 1 appearance. This acknowledges that clinicians have varying levels of comfort in diagnosing plus disease, although there was strong agreement regarding the normal and severe ends when committee members were asked to grade retinal images.

Aggressive ROP (A-ROP) is rapid development of pathologic neovascularization and severe plus disease without progression through the typical stages. A-ROP expands the earlier aggressive posterior ROP to include aggressive forms that occur in larger preterm infants and extend beyond the posterior retina with more peripheral vascular abnormalities.

REGRESSION

Regression, previously known as *involution* or *resolution*, is the lessening of severity of treatment-warranted ROP and can occur spontaneously (Figure 5) or after treatment but appears to have a more rapid course after anti-VEGF therapy (Figure 6) than laser treatment. Regression in plus disease involves reduction of vascular dilation and tortuosity, although tortuosity may persist or lessen when other conditions, such as cardiac diseases or pulmonary hypertension, are present. Other features of regression include involution of the tunica vasculosa lentis, improved pupillary dilation, media clarity, resolution of intraretinal hemorrhages, and thinning and whitening of the neovascular tissue. An aspect unique to ROP is vascularization into the peripheral avascular retina (VPAR) that can be complete or incomplete. When incomplete, the area devoid of vascularization is called *persistent avascular retina*.

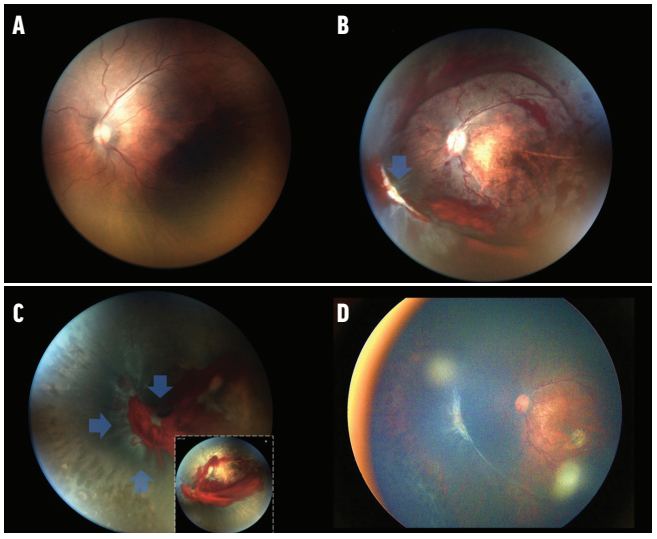

Figure 4. A female infant with a history of intraventricular hemorrhage, born at 26 2/7 weeks gestational age and 610 g birth weight, presented at 35 6/7 weeks PMA with type 1 ROP in the left eye. An injection of 0.25 mg bevacizumab (Avastin, Genentech/Roche) in a volume of 0.01 mL into the vitreous was performed. ROP regression occurred at 40 4/7 weeks (A). Reactivation occurred, and laser photocoagulation was performed to the peripheral avascular retina at 59 6/7 weeks PMA. A vitreous hemorrhage and nasal vitreoretinal tractional RD developed and worsened over the next 7 weeks into progressive stage 4 ROP (B, C; blue arrow). A lens-sparing vitrectomy was performed to segment the nasal vitreoretinal traction. An examination under anesthesia at 83 weeks PMA showed reduced nasal traction and no further extension (D).

REACTIVATION

Reactivation is generally seen following anti-VEGF therapy and may be less commonly appreciated following spontaneous regression. Before anti-VEGF therapy, early stages of ROP could regress, with more peripheral stages developing later as part of the natural history of the disease. Since the adoption of anti-VEGF agents, reactivation can occur much later than in the natural history of ROP. Current recommendations are to monitor infants after anti-VEGF injection until they are 65 weeks postmenstrual age (PMA).[13] Following anti-VEGF therapy, new lines or ridges, dilation, or tortuosity of retinal vasculature, or new extraretinal neovascularization is described by the term *reactivated* at the most anterior ridge. Zone I reactivation can occur with lacy vessels and hemorrhages.

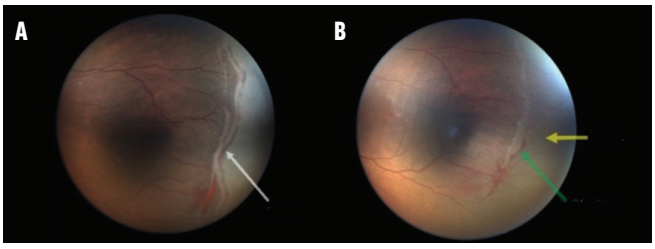

Figure 5. A female infant, born at 22 6/7 weeks gestational age and 660 g birth weight, presented with stage 3, zone II ROP (white arrow) without plus disease at 34 3/7 weeks PMA (A). At 39 5/7 weeks PMA (B), note the regressing ROP (green arrow) and VPAR (yellow arrow).

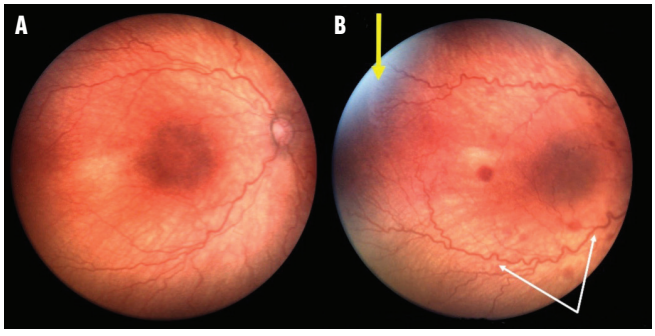

Figure 7. A female infant, born at 24 6/7 weeks gestational age and 555 g birth weight, had regressed ROP at 41 weeks PMA after treatment with 0.25 mg bevacizumab in a volume of 0.01 mL (A). Reactivated ROP occurred at 50 weeks PMA (B) with reactivated stage 2, zone II (yellow arrow) and greater dilation and tortuosity of retinal vasculature (white arrows).

Reactivation does not need to progress through the sequence of stages of acute-phase ROP. Reactivation typically occurs at the site of the original ridge, at the new junction and stage of vascular and avascular retina, or elsewhere in the vascularized retina (Figure 7).

What remains unclear is whether the appearance of angiogenesis at the vascular–avascular junction is the initiation of VPAR or reactivation of extraretinal neovascularization. This is an important consideration for future research because additional treatment with anti-VEGF injections may have detrimental effects on the neural retina or the developing infant from anti-VEGF agents that leak into the circulation.[14,15] Likewise, laser therapy might reduce visual field that would have developed with further VPAR.

ICROP3 also described long-term sequelae such as late tractional, rhegmatogenous, and, rarely, exudative RDs; retinoschisis; persistent avascular retina that may be prone to thinning holes and lattice-like changes; macular anomalies; retinal vascular changes and folds; and glaucoma—some of which are more apparent by fluorescein angiography or OCT.

BETTER GUIDANCE

The ICROP3 provides clearer guidance for future advances in the clinical management of and research on ROP based on advances in technology, pathophysiology, imaging, and an increased incidence of ROP worldwide, especially in emerging countries. ■

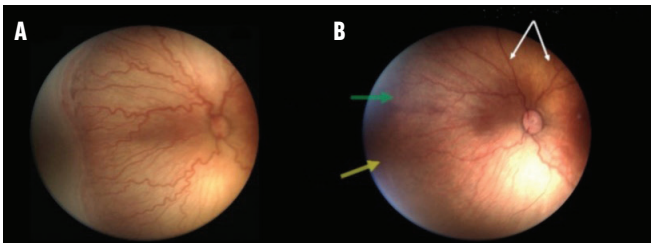

Figure 6. A female infant born at 25 6/7 weeks gestational age and 400 g weight had type 1 ROP with stage 3 disease at 34 4/7 weeks PMA. An intravitreal injection of 0.25 mg bevacizumab in a volume of 0.01 mL was given (A). At 50 weeks PMA (B), there was a faint line representing the regressed ridge (green arrow) and reduced vascular tortuosity and dilation (white arrows). In addition, VPAR occurred (yellow arrow).

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