6 Aggressive Posterior Retinopathy of Prematurity (APROP)

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Abstract

In this chapter, we will discuss the definition APROP, optimal treatment regimen, and provide example photographs for pattern recognition.

Keywords

Retinopathy of prematurity (ROP) · Aggressive posterior retinopathy of prematurity (APROP) · Plus disease Neovascularization · Oxygen-induced retinopathy Bevacizumab · Laser photocoagulation · International classification of ROP

6.1 What is APROP?

Aggressive Posterior Retinopathy of Prematurity (APROP) is an uncommon form of ROP that can rapidly lead to retinal detachment and blindness if untreated or treated late [1]. *APROP is generally a posterior disease in Zone I or posterior Zone II. APROP displays stage 3 as a flat neovascularization without a detectable fibrotic component. This neovascularization is often invisible with standard techniques. Therefore, APROP is currently defined as prominent plus disease with an ill-defined retinopathy or out of proportion to the observed retinopathy* (Fig. 6.1). This is because APROP does not contain the classic ROP (CROP) fibrotic features, i.e., the stage 1 demarcation line, stage 2 ridge, or fibrotic extraretinal proliferation of stage 3.

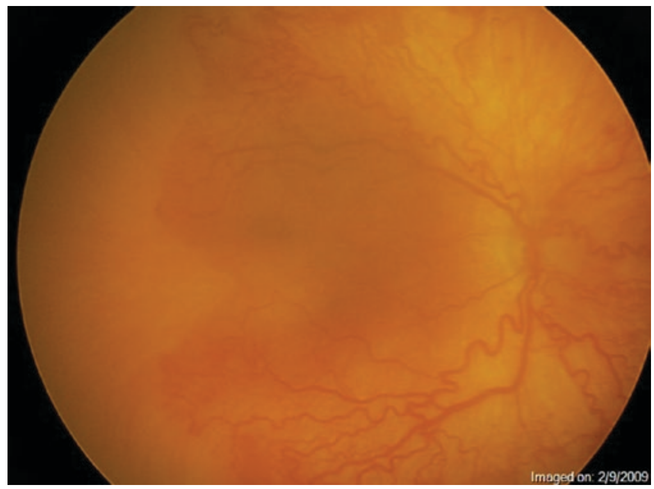

Fig. 6.1 APROP. Note prominent plus disease, out of proportion to perceived retinopathy due to lack of fibrotic elements. However, note the temporal anastomotic vessels and blush from fine neovascularization that obscures the underlying vessels

6.2 Importance of APROP Recognition: Poor Response to Treatment

One factor in the worse outcomes for APROP may be late treatment. Since the neovascularization does not contain fibrotic elements (which provide a sharp contrast to the normally developing retina) it is much harder to recognize. Careful examination with low ambient light and increased magnification (e.g., 20 diopter lens) are critical. If the "naked" neovascularization is missed repeatedly, then the eye may be called immature and given a 2–3 weeks exam interval that is too long and leads to sudden severe disease. The disease will advance to include fibrotic elements which will contract, lead to tractional retinal detachment (TRD), and given the posterior location, rapidly involve most of the

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posterior pole, including the macula. One major contribution of the revised International Classification of ROP [1] definition of APROP was to increase its awareness among ROP screeners. With increased disease recognition treatment has been performed earlier in the disease course. Specifically, in our catchment locale, rates of referral for TRD from untreated APROP declined dramatically after publication of this definition.

Even when treated promptly the failure rates are higher for APROP than for CROP [2–5]. Rates of progression to TRD despite laser photocoagulation range from 20 to 50% [2–4, 6, 7] whereas rates of anatomic failure after laser are generally around 10% [8]. Response to treatment with anti-VEGF or combination treatment of laser photocoagulation and anti-VEGF have been reported to be better, with a failure rate of less than 5% [9]. Since early treatment of APROP and modification of the treatment regime may be helpful in ensuring better outcomes, early recognition of this disease is critical.

6.3 Formal ICROP Definition

ICROP [1, 3] defined APROP as a special form of ROP which we will present below. Prior to the publication of the revised ICROP [1] with its improved photographic documentation of disease examples, this severe posterior ROP was variously termed Rush Disease, Fulminate ROP, Zone I ROP, and in the Japanese literature Type 2 ROP [10, 11]. The term APROP has supplanted this prior terminology in the literature.

ICROP defines APROP as follows: "The characteristic features of this type of ROP are its posterior location, prominence of plus disease, and the ill-defined nature of the retinopathy." Although the descriptors "posterior location" and "prominence of plus disease" may be helpful in distinguishing CROP from APROP, describing it as an "ill-defined retinopathy" is less helpful. Since ETROP criteria for treatment are basically driven by the presence of plus disease, even cases of unrecognized APROP (e.g., posterior plus without CROP demarcation/fibrosis) qualify for treatment. This relatively earlier treatment of APROP that otherwise may not have been recognized until late in the course (i.e., after it evolved to severe fibrosis and TRD) has decreased blindness from APROP. However, as discussed above, the response to conventional treatment of APROP remains worse than CROP. Therefore, identification of APROP may allow modification of the treatment regimen to allow for better outcomes, whether with anti-VEGF, earlier laser treatment, or other strategies. However, the examiner must be able to positively identify APROP, potentially at an earlier timepoint. Stage 3 neovascularization of APROP qualifies for treatment under ETROP guidelines even before the development of plus disease, when in Zone I. We will discuss features that allow positive identification of APROP below.

6.4 Positive Features of APROP

ICROP does further describe some positive features of APROP that are helpful in its identification including: (1) Posterior vessels show increased dilation and tortuosity out of proportion to the peripheral disease; (2) Shunting occurs from posterior to the vascular–avascular junction; (3) Difficulty in distinguishing between arterioles and venules because of the shunting, dilation, and tortuosity; (4) Hemorrhages at the junction between the vascularized and avascular retina; (5). APROP typically is accompanied by circumferential vessels; (6) Lack of progression through CROP stage 1–3; and (7) APROP may appear as a flat network of neovascularization at the deceptively featureless junction between vascularized and non-vascularized retina (Fig. 6.2).

This last feature, in the opinion of the authors, is the most specific finding of APROP: neovascularization without fibrosis. Neovascularization is the purely vascular form of fibrovascular proliferation (stage 3). This differentiates CROP from APROP. Since there are no accompanying fibrotic (i.e., white) elements (which are present in CROP stage 1–3) the vascular–avascular junction appears "featureless." Additionally, there may be a blush of flat neovascular tissue that obscures the underlying retinal vessels (Fig. 6.3).

Additional features that may point to APROP are lack of anterior growth of posterior immature vessels, rapid progression of plus disease, and persistence of tunica vasculosa lentis (Fig. 6.4). Indeed, the inability to achieve sufficient dilation due to tunica is a poor prognostic sign.

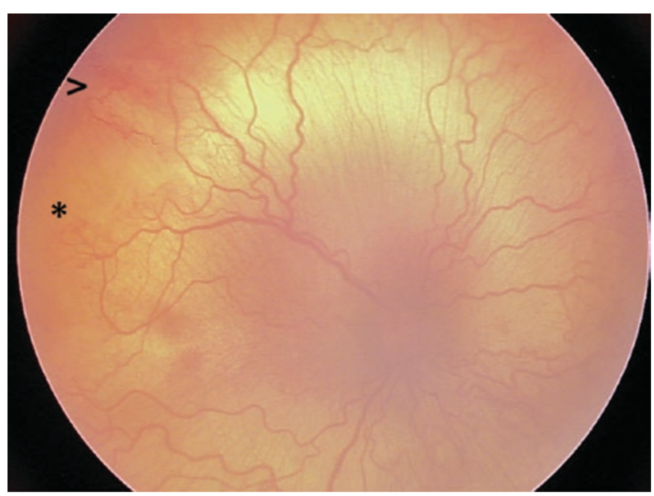

Fig. 6.2 This is an example of APROP. Plus disease is out of proportion to perceived retinopathy. Note the fine, flat network of neovascularization (*) and shunt vessel (>)

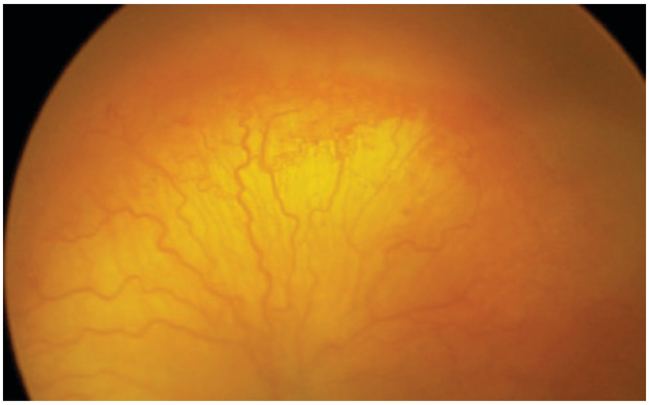

Fig. 6.3 APROP. There is a prominent plus disease despite lack of fibrosis. Note the prominent tangle of naked neovascularization just out of the plane of the retina superiorly that obscures the retinal vessels as they approach the vascular–avascular junction. There is a slight halo superiorly but no corresponding structure (This is a Mach Band due to change in contrast. A Mach band is an illusion of a line at the exaggerated border of two adjoining subtle, yet distinct, shades of a color by triggering edge-detection in the visual system. For further discussion on Mach Band, please see our chapter in Retinopathy of Prematurity: Current Diagnosis and Management by Kychenthal and Dorta [5]

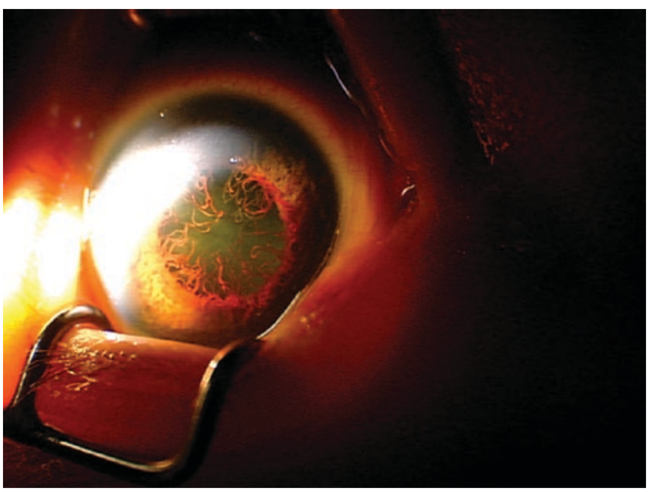

Fig. 6.4 Persistent dilated tunica vasculosa lentis

6.5 Toward Updating the Definition of APROP

The practical objective is to diagnose eyes destined to reach APROP using these positive features that can lead to suspicion of APROP development and thus closer examination even in the absence of plus disease. Strategies during examination to allow detection of difficult to see features such as fine neovascularization include optimizing pupillary dilation, media clarity, magnification (e.g., 20 diopter lens

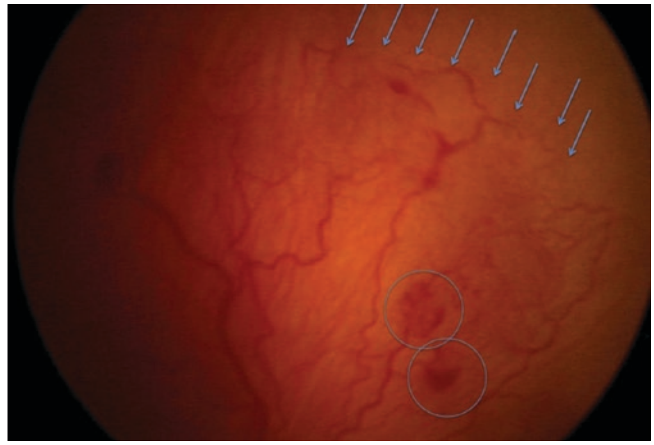

Fig. 6.5 Arrows show terminal vascular shunt, which can be seen in early APROP. Circles demonstrate neovascularization posteriorly

instead of 28), improved focus, glare reduction, and control of movement of the infant's head.

In order to aid in early detection of APROP, we would like to redefine APROP including subclassification of stages, ignoring plus disease for the moment.

Early APROP Vascular shunts. These may be circumferential vessels at the vascular–avascular junction or posterior to the junction (Fig. 6.5). Dilation and tortuosity may be present. This is equivalent to CROP stage 2. Eyes with early APROP but without plus disease need to be monitored closely (at least weekly examination) to allow for timely treatment if progression occurs. If plus disease is present this should be treated, per ETROP criteria.

It is not obvious that a CROP stage 1 equivalent exists in APROP as there is an absence of fibrosis, but this may be the absence of anterior growth of vessels when the vascular–avascular junction is posterior. In practice, this may be difficult to distinguish from simply immature vessels without photographic documentation of lack of anterior growth. Importantly, however, lack of anterior progression should prompt a closer examination schedule, i.e., weekly examination rather than every other week.

Moderate APROP Flat neovascularization, usually in a tangle (Fig. 6.5). This is equivalent to CROP stage 3. This may be associated with (1) annular, C-shaped, or arc-shaped hemorrhages, which may help highlight the otherwise difficult to detect flat neovascular frond without fibrosis (Fig. 6.6); (2) blush of pink/red at vascular termination which is the fine neovascularization (Fig. 6.7); and (3) disappearance of details of retinal vessels as they approach the vascular–avascular junction, since they may be covered by a thin tangle of neovascularization (Fig. 6.8). This is the stage at which the dilation and tortuosity is likely to be out of proportion to the

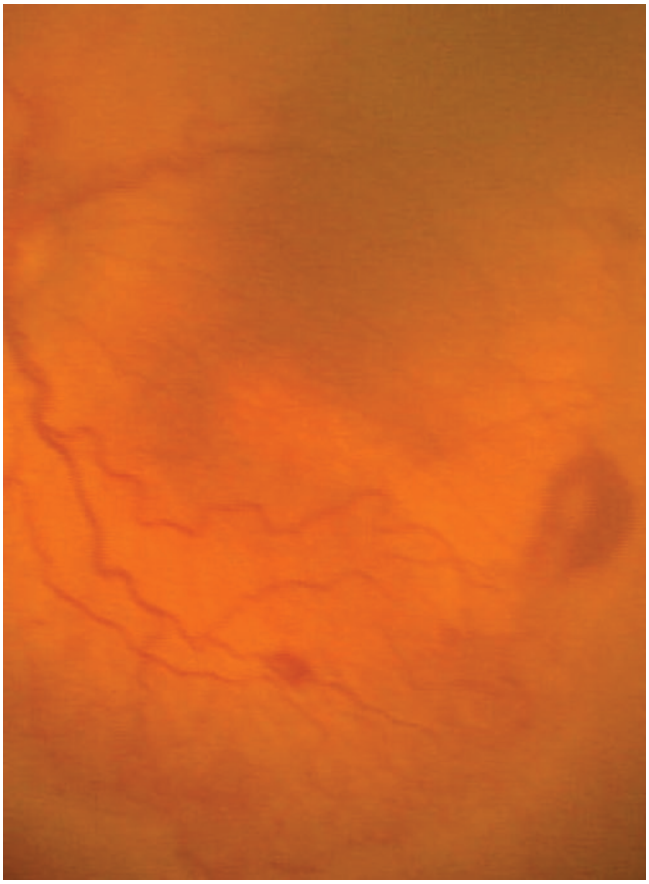

Fig. 6.6 Annular hemorrhage is visible near temporal vascular termination. Extraretinal vessels are likely present in the center

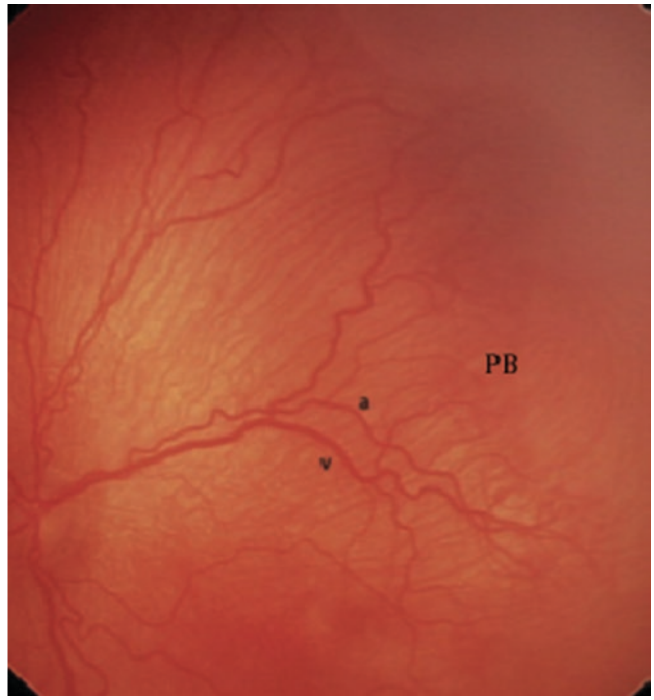

Fig. 6.7 Pink blush (PB) is seen at the vascular termination. This likely represents fine extraretinal vessels. "a" indicates artery and "v" indicates vein

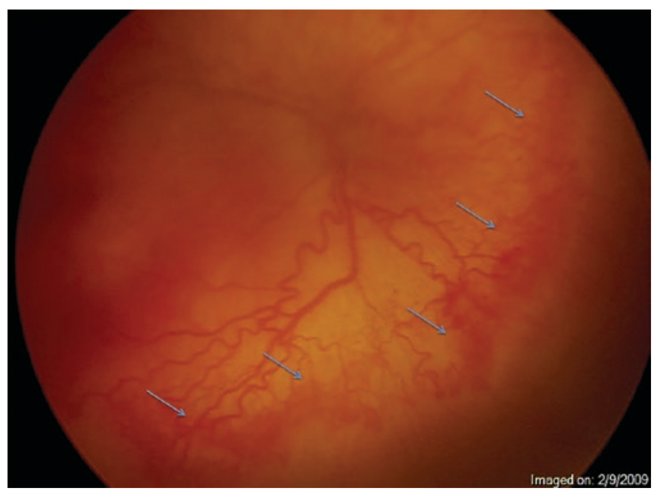

Fig. 6.8 Retina vessels that lose detail or disappear as they approach the avascular retina. They are covered by the blush of "naked" neovascularization. There is no fibrosis present, as would be the case with classic ROP. There is, however, a halo temporally but it has no definitive structure

perceived retinopathy, but this should be the signal to look closer for fine vessels that do explain the dilation and tortuosity. Moderate APROP should be treated. If plus disease is present, then treatment should be done per ETROP recommendation. Similarly, Zone I neovascularization (even without fibrosis since it is stage 3) should be treated even in the absence of plus disease. Moderate APROP in Zone II without plus does not technically meet treatment criteria of ETROP, but treatment should be strongly considered as APROP may progress to late stages quickly.

Late APROP Fibrosis. At first glance, this may look like CROP stage 3 but over time did not progress through the series of conventional stages 1–3 ridges. Instead, the fibrosis developed from the previously "naked" neovascularization, similar to that seen in proliferative diabetic retinopathy. However, once the naked vessels become fibrotic, they frequently contract without treatment (Fig. 6.9). Treatment with anti-VEGF can lead to "crunch" [12]. This "crunch" phenomenon in ROP after anti-VEGF has only been seen by the present authors in the few cases that were sent late for examination and treatment. These eyes have a high rate of progression to tractional retinal detachment with laser as well. With improved awareness and early recognition based on the previous features described, ideally, eyes would not reach this stage.

Very Late APROP Tractional retinal detachment. This is CROP stages 4 and 5. Detachment can occur quickly and

Fig. 6.9 Note the dilation and tortuosity out of proportion to apparent peripheral findings. The central macula has not vascularized. Neovascular tangles are present superotemporally. The fibrotic band demarcated by the arrows is not classic ROP but rather contracted APROP causing localized retinal detachment

should be treated with vitrectomy, although on rare occasions other treatments may be successful, such as scleral buckle [13] or anti-VEGF alone. If the vascularity is quite active, then decreasing anti-VEGF drive before surgery is warranted with anti-VEGF and/or laser. Active vascularity can lead to intraoperative and postoperative bleeding that may complicate surgery and postoperative evaluation.

6.6 Suspected Pathophysiology

The pathophysiologically distinct origin of APROP as opposed to CROP has not been proven but is possibly related to the distinction between vasculogenesis and angiogenesis [14]. In vasculogenesis, retinal vessels form de-novo from mesenchymal cells, whereas in angiogenesis they arise via budding from existing vessels. According to this distinction, CROP forms from the vascular termination where angiogenesis is normally occurring and creates a circumferential ridge. In contradistinction, APROP forms in a more haphazard manner in a posterior location de novo from mesenchymal cells (vasculogenesis). This may explain why foveal formation does not seem to be inhibited by anti-VEGF medications. [15] Alternatively, APROP may be due to extremely high levels of VEGF which cause neovascularization at away from the vascular–avascular junction.

6.7 Special Forms of APROP: Oxygen Induced

This involves obliteration of capillary beds and creates abnormal shunts both at vascular–avascular junction and posterior to it. This occurs in larger babies, usually in less developed nations where oxygen regulation may not be as tight. This, in our view, is not primary APROP but a secondary APROP that results from a later intervention, excessive oxygen or free radical damage. It is probably useful to recognize this pattern for interaction with neonatology about oxygen monitoring. In the literature, this may be called oxygen-induced retinopathy (OIR) or may be labeled as APROP, particularly in areas where it is more common [16]. Reasons that we believe it to be a distinct form of APROP include:

1. It occurs in situations of systemic stress, most commonly the use of unblended, unmonitored, and uncontrolled oxygen supplementation.
2. It occurs among much older infants with a mean gestational age of 28 weeks (median 30 weeks), who often have birth weights above 1250 g.
3. The vascular findings are often well into Zone II, whereas APROP usually is a posterior disease.
4. The angiogram shows a special pattern of an ablative retinopathy with loss of capillary perfusion with retention of larger arterioles and venules which have a looping appearance (Fig. 6.10).

This last pattern indicates vascular damage rather than a primary defect of vascular growth.

6.8 Special Forms of APROP: Recurrence/Reactivation after anti-VEGF

This is an area of interest as descriptors are needed for patterns of ROP reactivation after anti-VEGF. Anterior vascular development may occur and may undergo secondary arrest with shunting and dilated terminal structures (Fig. 6.11). Recurrent extraretinal neovascularization may occur without fibrosis at anterior or posterior locations. Vessels that grow out of the retina at a posterior location seem to do so in areas of prior vascular arrest and extraretinal neovascularization. This seems to recapitulate APROP. Chen et al. describe plus disease as an early sign of reactivation of ROP after anti-VEGF treatment [17]. This again seems to mimic APROP where plus is out of proportion to perceived ROP (Figs. 6.12 and 6.13).

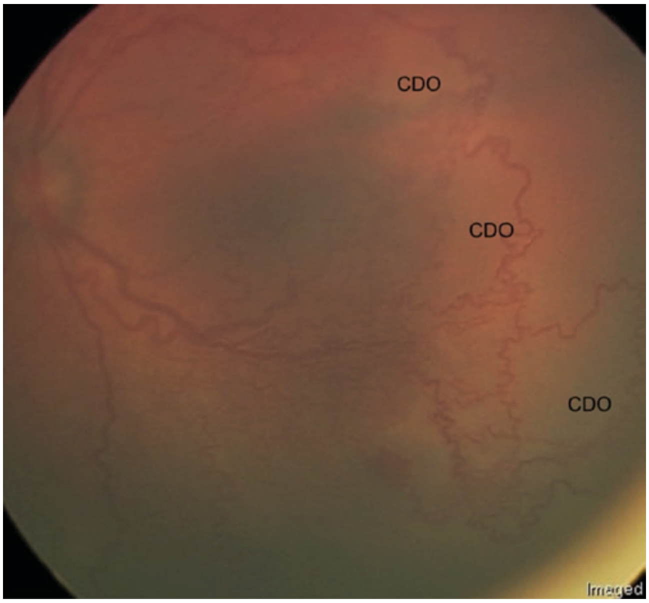

Fig. 6.10 An example of oxygen-induced retinopathy. Large looping vessels are seen surrounding areas of capillary drop out (CDO)

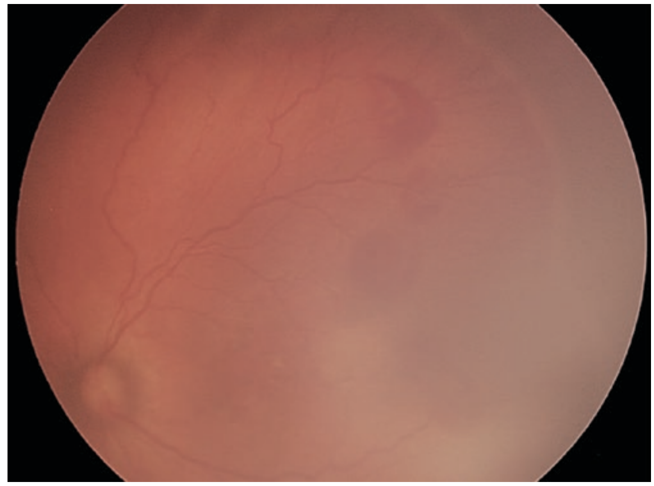

Fig. 6.12 This eye was treated originally with bevacizumab. C-shaped hemorrhages are seen at the area of original neovascularization and a partially fibrotic demarcation ridge is seen temporally at the vascular–avascular junction. The C (or reverse C) shape is due to hemorrhage around a center of extraretinal vessels. In an eye without apparent active ROP, this sign should alert the examiner to the presence of extraretinal neovascularization and possible APROP

Fig. 6.11 The eye was originally treated with bevacizumab and then subsequently was treated with laser to avascular retina after reactivation. Note fine extraretinal vessels at the posterior location of original neovascularization

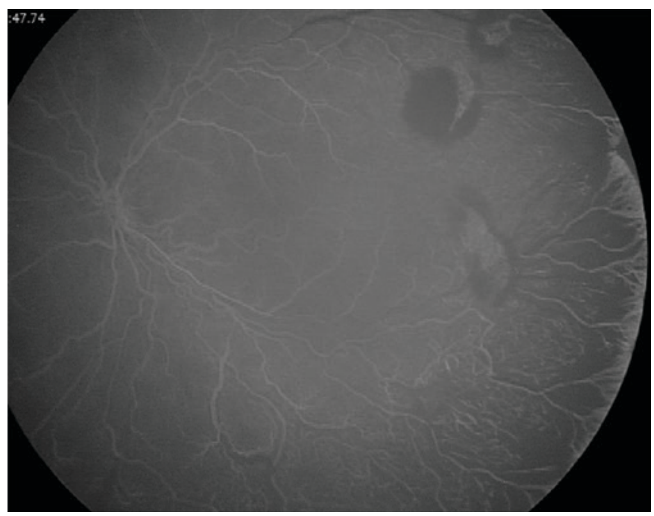

Fig. 6.13 Fluorescein angiography of eye in Fig. 6.12. Perfused vessels are demonstrated at the center of the C-shaped hemorrhages. Capillary dropout is also present, which can be seen in APROP and OIR

6.9 Present State of APROP Detection and Treatment Options

APROP is currently detected by clinical examination looking for the signs described above. If flat extraretinal neovascularization without fibrosis is seen, then APROP is present. Plus disease out of proportion to perceived retinopathy, hemorrhages at the border of the vascular–avascular junction, lack of anterior migration, rapid progression of disease, and persistence of fetal vessels, such as tunica vasculosa lentis and hyaloid artery remnant, should prompt a search for APROP, perhaps switching to increased magnification with 20 diopter lens.

It should be noted that similar to known disagreement among experts in plus disease diagnosis, APROP diagnosis may not be agreed upon using photographs [18, 19]. It is our hope that in the future imaging technology may better standardize this difficult diagnosis.

Fluorescein angiography at the bedside may be helpful in diagnosing APROP. Image processing to increase contrast may be helpful in identifying fine neovascularization [20]. Similarly, OCT and OCTA may help aid its detection, but these need to be demonstrated with further studies [21].

6.10 Treatment of APROP: Laser or Anti-VEGF

There is controversy of the role of anti-VEGF in the treatment of ROP in general and this extends to APROP. The controversy is due to a lack of high-level data comparing treatment options, but in general, there is more agreement that APROP responds poorly to laser and better to anti-VEGF treatment. We will review the rationale and available data for treatment preference.

APROP, like ROP in general, is a disease of nonperfusion, ischemia, proliferation, hemorrhage, and traction retinal detachment. The proliferative retinopathy is driven by VEGF. The essence of effective management is the timely reduction of VEGF. In order to achieve this with laser, treatment must include the entire avascular retina including any avascular zones that are under the neovascularization. Since VEGF is largely produced just anterior to the vascularized retina, posterior skip areas have particularly bad outcomes in all cases of ROP—especially APROP.

Barriers to complete laser photocoagulation include:

1. A persistent pupillary membrane (often called a "persistent tunica vasculosa lentis") that obscures the retina. As discussed above, this is more common in APROP.
2. Limited field of view from iris rigidity and small pupil due to poor dilation and intraoperative constriction.
3. Broad areas of neovascularization may camouflage an underlying area of ischemic retina.
4. Fine neovascularization may be obscured by hazy media.
5. A large area of treatment due to posterior disease may increase the risk of laser complications such as inflammation, exudative detachment, ocular ischemia, and cataract.
6. A longer treatment duration to complete the extensive laser required for APROP and overall more fragile systemic status of infants who are likely to develop APROP may increase the risks of anesthesia. On occasion, these challenges make a complete laser ablation of the avascular retina impossible. Ultimately, incomplete treatments greatly increase the risk of failure and unfavorable outcomes.

Anti-VEGF injection also removes VEGF from the vitreous reservoir immediately whereas laser only stops its production by ischemic retina, allowing already present VEGF to modulate vessels until its vitreal levels decline spontaneously. Another reason for the difficulty treating APROP is that the levels of VEGF in APROP eyes are likely higher than CROP as evidenced by the decreased efficacy of a reduced dose of bevacizumab. Lorenz et al. showed that 0.312 mg bevacizumab induced regression in 100% of Zone II CROP eyes, 80% of Zone I eyes, but only 25% of APROP eyes [22]. It is likely that larger areas of persistent avascular retina found in APROP than CROP after bevacizumab contribute to the likely higher VEGF load [23–25].

In our recent retrospective study [9] of patients treated for APROP at the University of Chicago Comer Children's Hospital, with minimum follow-up to 80 weeks PMA, APROP responded better to bevacizumab than laser photocoagulation. TRD occurred in 1 of 22 eyes with treated with bevacizumab and in 5 of 14 eyes in the laser group ($p = 0.002$). However, reactivation requiring treatment was common in both groups, 9/22 after bevacizumab and 6/14 after laser (NS). The mean gestational age was 24.5 weeks with a mean birth weight of 632 g in the bevacizumab group and 24.7 weeks and 777 g in the laser group. Most eyes in the bevacizumab group did receive treatment completion laser after 60 weeks PMA to reduce the chance of late reactivation of ROP (described below).

In addition to a lower rate of TRD after bevacizumab compared to laser in our recent study, the lower rate of TRD also compares favorably to prior reports of laser treatment for APROP. Drenser [2] reported progression to retinal detachment in 8 of 44 eyes with APROP and Pandya [4] described 3 of 6 eyes with APROP progressing to detachment despite laser. Sanghi reported 17% of APROP eyes progressed to detachment after laser [3]. Gunn reported 2 of 11 APROP eyes progressing to detachment [26]. Ahn et al. found a 15% failure rate of laser for APROP [27]. There are reports of vitrectomy after laser failure for APROP [6].

Most studies comparing the efficacy of bevacizumab to laser for APROP are from outside the United States, and results may be different when infants are larger. Nonetheless, outcomes after bevacizumab are generally more favorable. In a study from Turkey, Gunay reported 0 of 25 APROP eyes progressing to detachment after bevacizumab while 2 of 15 APROP eyes detached after laser [28]. The mean birth weight of infants in the bevacizumab group was 900 g. Nicoara similarly found improved regression of APROP after bevacizumab (94%) versus laser (83%) in a Romanian population with a mean birth weight over 1 kg [29]. Outcomes for the smaller infants treated for APROP in our recent study [9], with a mean birth weight of 632 g in the bevacizumab group, might have been expected to be worse given the lower birth weight. However, the single detachment out of 22 eyes that received initial bevacizumab compares favorably.

With respect to the selection of an anti-VEGF medication, bevacizumab has the most experience worldwide and appears to work well for Type 1 ROP in general and APROP in particular. Ranibizumab use is increasing due to systemic safety concerns (discussed below) but appears to have a higher rate of reactivation, ranging from 26 to 64% for ROP in general, not just APROP [30–37]. Moreover, Chuluunblat found an 18% rate of non-responsiveness [36]. The lack of efficacy may be related to a shorter half-life and therefore early reactivation. Treatment failure for APROP is likely higher. Sukgen and Kocluk [34] found an approximately 50% rate of reactivation of APROP after ranibizumab treatment. Given the lack of concrete data on adverse systemic safety issues, the possibility of blindness due to suboptimal anti-VEGF must be considered. The use of aflibercept [38] and conbercept [39] for ROP have been reported but experience, particularly with APROP, is limited.

With regard to systemic safety concerns regarding anti-VEGF, it is known that the medication reaches systemic circulation and suppresses systemic VEGF and that this effect is longer for bevacizumab than for ranibizumab [40]. The implications of this VEGF suppression, and even optimal levels in preterm neonates [41], are not known. Nonetheless, concerns regarding adverse effects on neurodevelopment continue to limit the use of anti-VEGF, particularly after work by Morin et al. [42]. That data was gathered retrospectively and was unfortunately fraught with bias [43]. The first bias was for the treatment of sicker infants with anti-VEGF, which is demonstrated by SNAP-II scores that measure the severity of systemic illness. The second was for the treatment of infants with more severe ROP with anti-VEGF. Also, 11 patients in the laser arm had mild enough disease to not even meet the usual criteria for treatment. There were no such patients in the bevacizumab arm. The study included infants treated before more wide-spread use of anti-VEGF (after the publication of BEAT-ROP [44]) when bevacizumab was reserved for children not well enough for laser or for salvage treatment. Importantly, both sicker systemic disease and worse ROP are known risk factors for poorer neurodevelopment [45–48]. The study also suffers from significant loss to follow-up of 28% of patients. Among infants that did have sufficient follow-up, nine patients in the laser arm were excluded for inability to perform testing for reasons such as poor cooperation, development delay, blindness, and deafness, whereas only one such patient was excluded from the bevacizumab arm. These patients should have been included as having poor neurodevelopment. Recalculating neurodevelopmental outcomes with the above patients included as having severe delay changes the difference in severe developmental delay to be nonsignificant. Indeed, other studies have failed to find a difference in neurodevelopment between children whose ROP was treated with laser or bevacizumab. [49–52].

To date, no good data exists from unbiased clinical investigations that anti-VEGF causes harmful systemic effects. Given the favorable ocular effect of bevacizumab over laser, and likely ranibizumab, for APROP, the real risk of blindness from retinal detachment must be weighed against the unproven, theoretical risk of neurodevelopment in neonates.

6.11 Reactivation After Anti-VEGF

Due to known late reactivation of ROP after bevacizumab injection [25, 53–57], our standard protocol is to perform fluorescein angiography after 60 weeks PMA to identify and ablate persistent avascular retina with laser. We term this "treatment completion" to emphasize that initial treatment with bevacizumab may have a temporary effect. If these eyes had been treated initially with laser, areas of avascular retina would be considered "skip areas" and these untreated areas would generally be treated to prevent reactivation of disease. The delay in the timing of laser treatment completion reduces anesthesia risk [58, 59] and allows anterior growth of retinal vessels.

We remain vigilant after the use of anti-VEGF because it has a limited blockade effect and a risk of reactivation. Larger areas of persistent avascular retina may explain why APROP is more likely to reactivate than CROP. In a recent study, Mintz-Hittner found 6/6 eyes with APROP reactivated [60]. Dikci et al. found that 5 out of 10 APROP eyes treated with bevacizumab 0.5 mg needed laser to treat recurrence [61]. Our recent study [9] found a 41% reactivation rate for eyes with APROP. The difference in morphology of APROP may point to a meaningful difference in the molecular environment that is related to the increased reactivation rate. Therefore, APROP may behave differently than CROP in the same zone in terms of response to initial treatment and rate of reactivation.

Based on naturally regressed ROP and FEVR, we suspect that reactivation may occur years or even decades later. Therefore, our approach is to treat the acute disease with anti-VEGF and residual peripheral ischemic retina with laser at a later date.

The choice of the term ROP "reactivation" over "recurrence" takes into account several observations. First, bevacizumab binds VEGF to suppress neovascularization but does not prevent its continued production. Second, the pathologic avascular retina is the most essential part of ROP as this retina produces VEGF that drives ROP. Third, treatment that leaves a pathologic ischemic zone of the retina has not cured the ROP and is incomplete. Fourth, pathologic neovascularization after the period of VEGF suppression in the face of ischemia should be expected rather than surprising. Finally, as long as there is pathologic avascular retina the disease is manifestly persistent, and the progression is therefore not a recurrence. The idea of reactivation is that ROP persisted (in a dormant state) and then became active again—progressing to neovascularization or worse, to tractional retinal detachment.

It must be remembered that late retinal detachment can occur up to (and likely past) 3 years of age [25, 53, 54]. Most eyes that received bevacizumab in our recent study [9] as initial treatment for APROP underwent treatment completion fluorescein angiography and laser treatment completion to persistent avascular retina to prevent late retinal detachment. Indeed, the only eye that progressed to detachment in this group did not receive prophylactic late laser and has been described elsewhere [25]. Although we believe bevacizumab to be superior to laser in the treatment of APROP, late prophylactic laser is recommended. Only after this final laser do we consider the treatment complete since it treats the residual avascular area. We expect that the long-term quiescence after late laser prophylaxis will also mimic the outcome of conventional laser treatment. This is consistent with our observations after one decade of anti-VEGF use. However, ROP remains a life-long disease.

References

1. International Committee for the Classification of Retinopathy of, P. The international classification of retinopathy of prematurity revisited. Arch Ophthalmol. 2005;123(7):991–9.
2. Drenser KA, Trese MT, Capone A Jr. Aggressive posterior retinopathy of prematurity. Retina. 2010;30(4 Suppl):S37–40.
3. Sanghi G, et al. Aggressive posterior retinopathy of prematurity: risk factors for retinal detachment despite confluent laser photocoagulation. Am J Ophthalmol. 2013;155(1):159–64. e2
4. Pandya HK, et al. Macular development in aggressive posterior retinopathy of prematurity. Biomed Res Int. 2015;2015:808639.
5. Shapiro MJ, et al. Aggressive posterior retinopathy of prematurity (APROP). In: Andres KB, Paola Dorta S, editors. Retinopathy of prematurity: current diagnosis and management, vol. 1. 1st ed; 2017. p. 49–70.
6. Tereshchenko AV, Belyy YA, Sidorova YA, Trifanenkova IG, Tereshchenkova MS, Yudina YA. Vitrectomy technique in aggressive posterior retinopathy of prematurity. Vestn oftalmol. 2018;134(1):32–7.
7. Early Treatment for Retinopathy of Prematurity Cooperative Group, Good WV, Hardy RJ, Dobson V, Palmer EA, Phelps DL, Tung B, Redford M. Final visual acuity results in the early treatment for retinopathy of prematurity study. Arch Ophthalmol. 2010 Jun;128(6):663–71.
8. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment of retinopathy of prematurity randomized trial. Arch Ophthalmol. 2003;121:1684–94.
9. Blair M, Gonzalez JMG, Snyder L, Schechet S, Greenwald M, Shapiro M, Rodriguez SH. Bevacizumab or laser for aggressive posterior retinopathy of prematurity. Taiwan J Ophthalmol. 2018 Oct-Dec;8(4):243–8.
10. Shah PK, Narendran V, Saravanan VR, Raghuram A, Chattopadhyay A, Kashyap M, Devraj S. Fulminate type of retinopathy of prematurity. Indian J Ophthalmol. 2004 Dec;52(4):319–20.
11. Fetus and Newborn Committee, Canadian Paediatric Society. Retinopathy of prematurity: A systematic review of the literature. Paediatr Child Health. 1998 May;3(3):173–80.
12. Yonekawa Y, Wu WC, Nitulescu CE, Chan RVP, Thanos A, Thomas BJ, Todorich B, Drenser KA, Trese MT, Capone A Jr. Progressive retinal detachment in infants with retinopathy of prematurity treated with intravitreal bevacizumab or ranibizumab. Retina. 2018 Jun;38(6):1079–83.
13. Shah RJ, Garcia-Gonzalez JM, Blair MP, Galasso J, Shapiro MJ. Concurrent scleral buckle and intravitreal bevacizumab for advanced retinopathy of prematurity-related retinal detachment. Retin Cases Brief Rep. 2016 Spring;10(2):183–6.
14. Flynn JT, Chan-Ling T. Retinopathy of prematurity: two distinct mechanisms that underlie zone 1 and zone 2 disease. Am J Ophthalmol. 2006 Jul;142(1):46–59.
15. Garcia Gonzalez JM, et al. Foveal development after use of bevacizumab for aggressive posterior retinopathy of prematurity. Ophthalmic Surg Lasers Imaging Retina. 50(6):e185–7.
16. Martinez-Castellanos MA, Velez-Montoya R, Price K, Henaine-Berra A, García-Aguirre G, Morales-Canton V, Cernichiaro-Espinosa LA. Vascular changes on fluorescein angiography of premature infants with low risk of retinopathy of prematurity after high oxygen exposure. Int J Retina Vitreous. 2017 Jan 16;3:2.
17. Chen TA, Shields RA, Bodnar ZH, Callaway N, Schachar IH, Moshfeghi DM. A spectrum of regression following intravitreal bevacizumab in retinopathy of prematurity. Am J Ophthalmol. 2018;198:63–9.
18. Woo R, Chan RV, Vinekar A, Chiang MF. Aggressive posterior retinopathy of prematurity: a pilot study of quantitative analysis of vascular features. Graefes Arch Clin Exp Ophthalmol. 2015 Feb;253(2):181–7.
19. Shapiro MJ, Blair MP, Garcia-Gonzalez JM. Experts contradict established classification. Graefes Arch Clin Exp Ophthalmol. 2016 Jan;254(1):199.
20. Jayadev C, Vinekar A, Mohanachandra P, Desai S, Suveer A, Mangalesh S, Bauer N, Shetty B. Enhancing image characteristics of retinal images of aggressive posterior retinopathy of prematurity using a novel software, (RetiView). Biomed Res Int. 2015;2015:898197.
21. Vinekar A, Chidambara L, Jayadev C, Sivakumar M, Webers CA, Shetty B. Monitoring neovascularization in aggressive posterior retinopathy of prematurity using optical coherence tomography angiography. J AAPOS. 2016 Jun;20(3):271–4.
22. Lorenz B, et al. Retinal vascular development with 0.312 MG intravitreal bevacizumab to treat severe posterior retinopathy of prematurity: a longitudinal fluorescein angiographic study. Retina. 2017;37(1):97–111.
23. Garcia Gonzalez JM, et al. Prophylactic peripheral laser and fluorescein angiography after bevacizumab for retinopathy of prematurity. Retina. 2017;38(4):764–72.
24. Toy BC, et al. Chronic vascular arrest as a predictor of bevacizumab treatment failure in retinopathy of prematurity. Ophthalmology. 2016;123(10):2166–75.
25. Snyder LL, et al. Very late reactivation of retinopathy of prematurity after monotherapy with intravitreal bevacizumab. Ophthalmic Surg Lasers Imaging Retina. 2016;47(3):280–3.
26. Gunn DJ, Cartwright DW, Gole GA. Prevalence and outcomes of laser treatment of aggressive posterior retinopathy of prematurity. Clin Exp Ophthalmol. 2014;42(5):459–65.
27. Ahn YJ, Hong KE, Yum HR, Lee JH, Kim KS, Youn YA, Park SH. Characteristic clinical features associated with aggressive posterior retinopathy of prematurity. Eye (Lond). 2017 Jun;31(6):924–30.
28. Gunay M, et al. Evaluation of 2-year outcomes following intravitreal bevacizumab (IVB) for aggressive posterior retinopathy of prematurity. Arq Bras Oftalmol. 2015;78(5):300–4.

29. Nicoara SD, et al. Regression rates following the treatment of aggressive posterior retinopathy of prematurity with bevacizumab versus laser: 8-year retrospective analysis. Med Sci Monit. 2016;22:1192–209.
30. Ells AL, Wesolosky JD, Ingram AD, Mitchell PC, Platt AS. Low-dose ranibizumab as primary treatment of posterior type I retinopathy of prematurity. Can J Ophthalmol. 2017 Oct;52(5): 468–74.
31. Huang Q, Zhang Q, Xu Y, Ji X, Fei P, Peng J, Li YA, Zhao P. Asymmetric outcomes of type 1 retinopathy of prematurity after bilateral intravitreal ranibizumab treatment. J Ophthalmol. 2017;2017:1741386.
32. Hu Q, Bai Y, Chen X, Huang L, Chen Y, Li X. Recurrence of retinopathy of prematurity in zone II stage 3+ after ranibizumab treatment: a retrospective study. J Ophthalmol. 2017;2017:5078565.
33. Huang Q, Zhang Q, Fei P, Xu Y, Lyu J, Ji X, Peng J, Li YA, Zhao P. Ranibizumab injection as primary treatment in patients with retinopathy of prematurity: anatomic outcomes and influencing factors. Ophthalmology. 2017 Aug;124(8):1156–64.
34. Sukgen EA, Koçluk Y. The vascularization process after intravitreal ranibizumab injections for aggressive posterior retinopathy of prematurity. Arq Bras Oftalmol. 2017 Jan-Feb;80(1):30–4.
35. Lyu J, Zhang Q, Chen CL, Xu Y, Ji XD, Li JK, Huang QJ, Zhao PQ. Recurrence of retinopathy of prematurity after intravitreal ranibizumab monotherapy: timing and risk factors. Invest Ophthalmol Vis Sci. 2017 Mar 1;58(3):1719–25.
36. Chuluunbat T, Chan RV, Wang NK, Lien R, Chen YP, Chao AN, Chen KJ, Chen TL, Hwang YS, Lai CC, Wu WC. Nonresponse and recurrence of retinopathy of prematurity after intravitreal ranibizumab treatment. Ophthalmic Surg Lasers Imaging Retina. 2016 Dec 1;47(12):1095–105.
37. Zhang G, Yang M, Zeng J, Vakros G, Su K, Chen M, Li H, Tian R, Li N, Tang S, He H, Tan W, Song X, Zhuang R, Shenzhen Screening for Retinopathy of Prematurity Cooperative Group. Comparison of intravitreal injection of ranibizumab versus laser therapy for zone ii treatment-requiring retinopathy of prematurity. Retina. 2017 Apr;37(4):710–7.
38. Vural A, Perente İ, Onur İU, Eriş E, Seymen Z, Hergünsel GO, Salihoğlu Ö, Yiğit FU. Efficacy of intravitreal aflibercept monotherapy in retinopathy of prematurity evaluated by periodic fluorescence angiography and optical coherence tomography. Int Ophthalmol. 2018 Nov 26;39(10):2161–9.
39. Bai Y, Nie H, Wei S, Lu X, Ke X, Ouyang X, Feng S. Efficacy of intravitreal conbercept injection in the treatment of retinopathy of prematurity. Br J Ophthalmol. 2018 Jul 20;103(4):494–8.
40. Wu WC, Shih CP, Lien R, Wang NK, Chen YP, Chao AN, Chen KJ, Chen TL, Hwang YS, Lai CC. Serum vascular endothelial growth factor after bevacizumab or ranibizumab treatment for retinopathy of prematurity. Retina. 2017 Apr;37(4):694–701.
41. Kandasamy Y, Hartley L, Rudd D, Smith R. The association between systemic vascular endothelial growth factor and retinopathy of prematurity in premature infants: a systematic review. Br J Ophthalmol. 2017 Jan;101(1):21–4.
42. Morin J, Luu TM, Superstein R, Ospina LH, Lefebvre F, Simard MN, Shah V, Shah PS, Kelly EN, Canadian Neonatal Network and the Canadian Neonatal Follow-Up Network Investigators. Neurodevelopmental outcomes following bevacizumab injections for retinopathy of prematurity. Pediatrics. 2016 Apr;137(4):e20153218.
43. Blair MP, Shapiro MJ, Ad Hoc Group Concerning Neurodevelopment and antiVEGF. Re: Good: bevacizumab for retinopathy of prematurity: treatment when pathology is embedded in a normally developing vascular system (Ophthalmology. 2016;123:1843-1844). Ophthalmology. 2017 Oct;124(10):e74–5.
44. Mintz-Hittner HA, Kennedy KA, Chuang AZ. BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011 Feb 17;364(7):603–15.
45. Msall ME, Phelps DL, DiGaudio KM, Dobson V, Tung B, McClead RE, Quinn GE, Reynolds JD, Hardy RJ, Palmer EA, Behalf of the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Severity of neonatal retinopathy of prematurity is predictive of neurodevelopmental functional outcome at age 5.5 years. Pediatrics. 2000 Nov;106(5):998–1005.
46. Molloy CS, Anderson PJ, Anderson VA, Doyle LW. The long-term outcome of extremely preterm (<28 weeks' gestational age) infants with and without severe retinopathy of prematurity. J Neuropsychol. 2016 Sep;10(2):276–94.
47. Cooke RW, Foulder-Hughes L, Newsham D, Clarke D. Ophthalmic impairment at 7 years of age in children born very preterm. Arch Dis Child Fetal Neonatal Ed. 2004 May;89(3):F249–53.
48. Beligere N, Perumalswamy V, Tandon M, Mittal A, Floora J, Vijayakumar B, Miller MT. Retinopathy of prematurity and neurodevelopmental disabilities in premature infants. Semin Fetal Neonatal Med. 2015 Oct;20(5):346–53.
49. Lien R, Yu MH, Hsu KH, Liao PJ, Chen YP, Lai CC, Wu WC. Neurodevelopmental outcomes in infants with retinopathy of prematurity and bevacizumab treatment. PLoS One. 2016 Jan 27;11(1):e0148019.
50. Kennedy KA, Mintz-Hittner HA, BEAT-ROP Cooperative Group. Medical and developmental outcomes of bevacizumab versus laser for retinopathy of prematurity. JAAPOS. 2018 Feb;22(1):61–65.e1.
51. Araz-Ersan B, Kir N, Tuncer S, Aydinoglu-Candan O, Yildiz-Inec D, Akdogan B, Ekici B, Demirel A, Ozmen M. Preliminary anatomical and neurodevelopmental outcomes of intravitreal bevacizumab as adjunctive treatment for retinopathy of prematurity. Curr Eye Res. 2015 May;40(6):585–91.
52. Kong L, Dinh KL, Schechet SA, Coats DK, Voigt RG, Demny AB, Steinkuller PG. Comparison of ocular and developmental outcomes in laser-and bevacizumab-treated infants with retinopathy of prematurity. Ophthalmol Res. 3(1):13–22.
53. Hajrasouliha AR, et al. Reactivation of retinopathy of prematurity three years after treatment with bevacizumab. Ophthalmic Surg Lasers Imaging Retina. 2017;48(3):255–9.
54. Hu J, et al. Reactivation of retinopathy of prematurity after bevacizumab injection. Arch Ophthalmol. 2012;130(8):1000–6.
55. Hoang QV, et al. Fluorescein angiography of recurrent retinopathy of prematurity after initial intravitreous bevacizumab treatment. Arch Ophthalmol. 2010;128(8):1080–1.
56. Ittiara S, et al. Exudative retinopathy and detachment: A late reactivation of retinopathy of prematurity after intravitreal bevacizumab. J Am Assoc Pediat Ophthalmol Strab. 17(3):323–5.
57. Patel RD, et al. Significant treatment failure with intravitreous bevacizumab for retinopathy of prematurity. Arch Ophthalmol. 2012;130(6):801–2.
58. Walther-Larsen S, Rasmussen LS. The former preterm infant and risk of post-operative apnoea: recommendations for management. Acta Anaesthesiol Scand. 2006;50(7):888–93.
59. Cote CJ, et al. Postoperative apnea in former preterm infants after inguinal herniorrhaphy. A combined analysis. Anesthesiology. 1995;82(4):809–22.
60. Mintz-Hittner HA, Geloneck MM, Chuang AZ. Clinical management of recurrent retinopathy of prematurity after intravitreal bevacizumab monotherapy. Ophthalmology. 2016;123(9):1845–55.
61. Dikci S, Ceylan OM, Demirel S, Yılmaz T. Which dose of bevacizumab is more effective for the treatment of aggressive posterior retinopathy of prematurity: lower or higher dose? Arq Bras Oftalmol. 2018 Jan-Feb;81(1):12–7.