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Findings in Persistent Retinopathy of Prematurity

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Abstract

BACKGROUND AND OBJECTIVE: To determine whether retinopathy of prematurity (ROP) that persists beyond a postmenstrual age (PMA) of 45 weeks has abnormalities that can be documented by fundus photography or fluorescein angiography (FA).

PATIENTS AND METHODS: Fundus photographs and FAs were reviewed for all premature infants who underwent FA for persistent ROP after 45 weeks PMA.

RESULTS: Of the 487 infants who were screened for ROP, 16 (3.3%) demonstrated ROP beyond 45 weeks. Seven (43.8%) infants received prior treatment with intravitreal bevacizumab (IVB) for Type 1 ROP. FAs were obtained in eight cases; four subjects were previously treated with IVB. Leakage at the vascular-avascular border was demonstrated in seven subjects (87.5%). Shunt vessels, posterior retinal nonperfusion, and absence of the foveal avascular zone was limited to the IVB group.

CONCLUSIONS: There are persistent vascular abnormalities among infants with ROP beyond 45 weeks. Findings that may be missed by RetCam fundus photographs were highlighted with FA.

INTRODUCTION

Retinopathy of prematurity (ROP) is a sight-threatening vasoproliferative disorder characterized by delayed or abnormal retinal vascular maturation among premature infants of low birth weight. With advances in medical care, ROP remains a leading cause of preventable childhood blindness and is increasing as more areas of the world have increased access to neonatal critical care.¹ Fundus photography has received growing attention as a telemedicine tool for remote screening and diagnosis of ROP.² This modality can provide excellent views of Zone I and Zone II. However, visualization of vascular abnormalities in peripheral Zone II and Zone III can be challenging.

Based on data from prior studies, 99% of infants who will develop ROP do so by 46.3 weeks.^{3,4} Thus, it is rare for an infant to reach treatment criteria for peripheral laser ablation as defined by the Early Treatment for Retinopathy of Prematurity (ETROP) study⁵ after a

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postmenstrual age (PMA) of 45 weeks. However, some infants may fail to fully vascularize by 45 weeks and demonstrate areas of persistent Type 2 ROP or halted vascular growth without ROP. The natural history of peripheral nonperfusion with late type 2 ROP is not well-understood and may predispose to several late complications, including vitreous hemorrhage or retinal detachment.^{6,7} Multiple reports of late reactivation after bevacizumab (Avastin; Genentech, South San Francisco, CA) monotherapy have also been described.^{8,9} There are currently no established guidelines on the management of this unique population and no classification system of ROP after intravitreal anti-vascular endothelial growth factor (VEGF) therapy.

In cases where the peripheral retinal vasculature appears uncertain or where there is an atypical vascularization pattern, as is seen after anti-VEGF therapy, fluorescein angiography (FA) may prove to be a helpful additional diagnostic tool.¹⁰ FA has been shown to improve the sensitivity for the diagnosis of stage 3 ROP and may improve visualization of the peripheral vasculature not easily captured by color fundus photography.¹¹ We report a case series to illustrate patient characteristics and vascular findings of infants with peripheral Zone II and Zone III ROP that persists beyond 45 weeks PMA and how FA may aid in the diagnosis of ROP with retinal photography.

PATIENTS AND METHODS

This was a both a retrospective chart review and prospective observational study from a single institution. Both studies were approved by the Institutional Review Board and completed in compliance with the Health Insurance Portability and Accountability Act regulations at the Children's Hospital of Wisconsin. In both studies, ROP screening was performed as per ETROP guidelines by a single examiner at a single center using binocular indirect ophthalmoscopy (BIO) with scleral depression. Additional screening was performed beyond 45 and 50 weeks PMA in cases of persistent ROP and among those treated with bevacizumab.

For the retrospective portion of this study, charts for all patients seen for ROP screening between January 1, 2012, and April 1, 2015, were reviewed. Subjects with 45 weeks PMA or older with avascular retina and ROP without laser photocoagulation therapy were included for analysis. Medical record data for subjects were reviewed for gender, gestational age, birth weight, relevant past medical history, and exam findings by binocular indirect ophthalmoscopy (BIO) with scleral depression. If FA was obtained, the images were reviewed.

For the prospective study, subjects with ROP at 45 weeks PMA or older were identified. Written informed consent was obtained from the parent or legal guardian to be enrolled in the study. The clinical exam findings as visualized by BIO were recorded. Fundus photography was obtained using the RetCam3 digital imaging system (Natus Medical Incorporated, Pleasanton, CA). FA was then obtained with the RetCam using an intravenous injection of 10% fluorescein at a dosage of 7.7 mg/kg followed by a saline flush. Color fundus photographs and fluorescein angiograms were examined by three ophthalmologists.

RESULTS

Of the 487 infants who were screened for ROP between January 1, 2012, and April 1, 2015, 16 (3.3%) infants demonstrated persistent avascular retina with ROP beyond 45 weeks PMA without a history of laser photocoagulation (Table). Findings reported were seen bilaterally within all subjects. Nine of the 16 infants had never met ETROP criteria for treatment. Seven of the 16 infants had previously been treated with a single dose of 0.625 mg bevacizumab in 0.03 mL for Zone I or posterior Zone II ROP with plus disease. The timing of intravitreal bevacizumab (IVB) treatment in these subjects was between 32 weeks and 37 weeks. One of the IVB subjects developed recurrent Type 1 ROP 13 weeks following IVB, at which point peripheral laser ablation was performed. The overall mean (\pm 1SD) gestational age at birth for all subjects with late ROP was 25 weeks \pm 2 weeks (range: 23 weeks to 31 weeks) with a mean birth weight of 666 g \pm 245 g (range: 380 g to 1,291 g). When compared to the group that did not receive treatment, the IVB group had an earlier mean gestational age (23.7 weeks \pm 0.7 weeks vs. 26 weeks \pm 2.1 weeks; $P = .017$), whereas there was no statistically significant difference in the mean birth weights (606 g \pm 70 g vs. 712 g \pm 293 g; $P = .41$).

One (6.25%) of the 16 infants with ROP at 45 weeks PMA or greater had Type 1 ROP with Zone II Stage 3 with plus. Of the remaining patients, three (18.75%) infants were classified as Zone III Stage 2 ROP without plus, seven (43.75%) were classified as Zone III Stage 3 without plus, and five (31.25%) were classified as Zone II Stage 3 without plus.

RetCam color fundus photography captured clear views of Zone I and posterior and mid-Zone II in all subjects. Views of peripheral Zone II and Zone III were limited by peripheral distortion and poor image contrast. In these cases, classification of ROP based on RetCam color fundus photography alone was challenging.

FAs were obtained in eight of the 16 cases (subjects 1–8 in Table). Select images are displayed in Figures 1–4. There were no systemic complications following injection of fluorescein. Of the eight cases, four were previously treated with IVB. Peripheral retinal nonperfusion was identified in all eight cases. Vascular leakage at the junction of the vascular and avascular retina was noted in seven out of the eight subjects. Other findings — including shunt vessels, retinal nonperfusion posterior to the vascular-avascular border, and fine retinal vessels extending through the fovea resulting in an absence of the foveal avascular zone (FAZ) — were limited to the IVB group. Within the IVB group, all subjects demonstrated shunt vessels, three (75%) demonstrated areas of retinal nonperfusion posterior to the brush border, and one infant demonstrated absence of the FAZ. Areas of retinal nonperfusion were most notable in areas adjacent to shunt vessels.

DISCUSSION

We have described a case series of 16 infants with persistent ROP in peripheral Zone II and Zone III beyond a PMA of 45 weeks. Of the 487 infants screened, persistent ROP beyond 45 weeks occurred in 3.3% of the population. By excluding the seven infants previously treated with bevacizumab, only nine (1.8%) treatment-naïve infants demonstrated persistent ROP beyond 45 weeks, suggesting that this is a relatively uncommon occurrence. Although

uncommon, this may be a specific population that may be at an increased risk for late retinal complications warranting further long-term follow-up.

With the increasing access of neonatal intensive care and a shortage of ophthalmologists who screen for ROP, it has become increasingly difficult to provide ROP screening for these at-risk infants. Wide-field digital imaging with the RetCam digital imaging system has gained increasing attention for its potential role in telemedicine and ROP screening.¹² Although high-quality images of Zone I and posterior Zone II can be consistently achieved, imaging the peripheral retina to detect peripheral ROP can be challenging, increasing the risk of underdiagnosis of ROP.¹³ In our study, we found RetCam color fundus photography of peripheral Zone II and Zone III difficult. Views of the periphery were limited by peripheral distortion and poor image contrast, precluding accurate ROP classification based on Ret-Cam color fundus photography alone.

FA has been utilized extensively to evaluate several pediatric vascular disorders, including ROP, Coats' disease, and familial exudative vitreoretinopathy.^{14,15} It has been suggested that FA can improve the sensitivity of diagnosis for stage 3 or worse disease by highlighting the extraretinal vessels and areas of leakage.¹¹ In this study, RetCam photos with FA provided superior visualization of peripheral Zone II and Zone III ROP compared to RetCam color fundus photography. FA-augmented RetCam examination did not uncover areas of occult neovascularization that were not apparent on clinical exam. The presence of leakage at the junction of the vascular and avascular retina was noted in seven out of the eight cases. The one infant without leakage was the eldest infant who was classified as stage 2 ROP by clinical exam at a PMA of 64 weeks. This infant demonstrated only fine vascular arborization in the periphery without evidence of leakage (Figure 1). For telemedicine screening, fundus photography with FA may increase the sensitivity for detecting more peripheral ROP.

Of the 16 cases of late ROP beyond 45 weeks in this series, seven (43.8%) infants had previously been treated with IVB. This finding suggests that IVB therapy can be associated with a further delay in complete retinal vascularization and the persistence of ROP beyond 45 weeks. In the IVB group, FA revealed shunt vessels, areas of nonperfusion posterior to the vascular-avascular border, and an absence of the FAZ (Figures 3 and 4). These findings were unique to the IVB group and have previously been described.¹⁶ The long-term implications of such vascular abnormalities among this population is not well-understood but may predispose to late complications, such as vitreous hemorrhage and retinal detachment. The studies that defined threshold disease as the standard of care requiring treatment were designed before the utilization of anti-VEGF agents for ROP. A study similar to ETROP specifically defining the stages of disease and the threshold for treatment after intravitreal anti-VEGF is needed to reduce the potential risk of late complications and ensure the best anatomic and visual outcomes for these patients.

In this study, FA allowed for the identification of areas of avascularity within vascularized retina among the IVB group. In a report by Lepore et al.,¹⁶ loss of the retinal capillary bed within the vascularized retina was shown to persist for at least 9 months after treatment with IVB in 11 of 12 eyes. One subject in our study had a fine meshwork of retinal vessels

extending through the fovea, resulting in an absence of the FAZ (Figure 3C). In an angiographic study by Henaine-Berra et al., capillaries in the foveal zone underwent involution to form the FAZ in 10 of 16 eyes treated with anti-VEGF therapy.¹⁷ The impact of this delay in foveal maturation is unclear and warrants further investigation. Although FA appears to be a more sensitive modality for evaluating the characteristics of the retinal vasculature in ROP, the role of FA in the screening and diagnosis of ROP has yet to be elucidated and deserves further attention.

The current screening guidelines only describe the location and extent of ROP, but do not go beyond tortuosity and dilation to determine if treatment is warranted. There is currently no clear consensus on the management of persistent avascular retina in ROP that fails to meet ETROP criteria for treatment but persists beyond 45 weeks. Blair et al. estimated the amount of avascular retina in normal children at various postnatal ages by using scleral depression during FA to determine the distance of the vascular termini to the ora serrata. The authors concluded that a distance greater than 2 disc diameters should be considered abnormal.¹⁸ Additional retinal vascular imaging studies will likely help to define a new standard of care following treatment with IVB, in addition to treatment-naïve infants with atypical late ROP.

The most recent screening guidelines as set forth by the American Academy of Pediatrics now recommend screening cessation at 50 weeks, instead of 45 weeks, in the absence of prior Type 1 ROP.¹⁹ In this study, Type 1 ROP did not occur beyond 50 weeks with the exception of one subject that developed recurrent Type 1 ROP at 50 weeks following IVB at 37 weeks. All nine infants in our treatment-naïve group, however, demonstrated persistent Stage 2 or Stage 3 ROP in Zone II or Zone III beyond a PMA of 50 weeks. Although complications from persistent peripheral neovascularization may be rare, we believe these findings highlight the importance of surveillance beyond 50 weeks. Increasing the screening age to 60 weeks is unlikely to capture all of these children since three of our nine treatment-naïve late-ROP infants had persistent Zone III Stage 2 or 3 ROP beyond 60 weeks. It should also be noted that premature infants, even in the absence of ROP, are at an increased risk of a retinal tears or detachment and should thus have more frequent, lifelong monitoring when compared to children not at risk of ROP.²⁰ It is possible that, similar to children with late detachments after anti-VEGF therapy, the persistence of peripheral nonperfusion in this population may further predispose to late retinal complications. Laser photocoagulation treatment may be warranted to prevent late retinal complications.

The limitations of this study include its retrospective design, relatively small sample size and lack of follow-up imaging. Additionally, scleral depression was not utilized during FA, so we were unable to estimate the distance from the vascular termini from the ora serrata.

Overall, this study demonstrates that although uncommon, some infants demonstrate persistent ROP and vascular abnormalities beyond 45 weeks in treatment naïve and IVB-treated infants. This study also emphasizes the utility of FA in identifying peripheral vascular abnormalities not easily appreciated by color fundus photography. This study also highlights the importance of continued surveillance beyond 50 weeks, especially in the context of prior treatment with IVB where the long-term implications are largely unknown and late complications have been demonstrated.^{7,8} Infants with persistent ROP with or

without anti-VEGF treatment may be a special population that could benefit from further study to determine if treatment would be beneficial to anatomic and visual outcomes.

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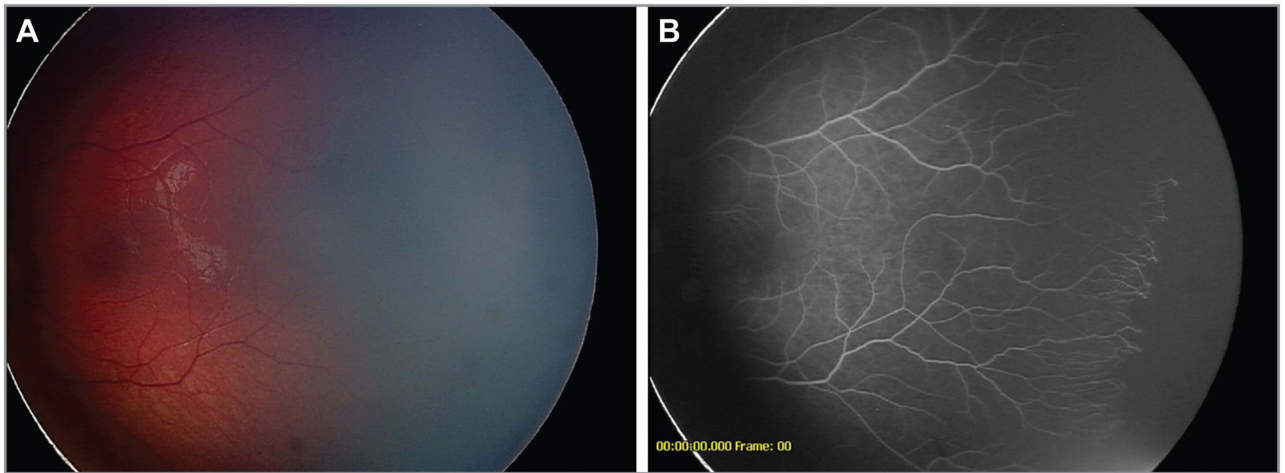
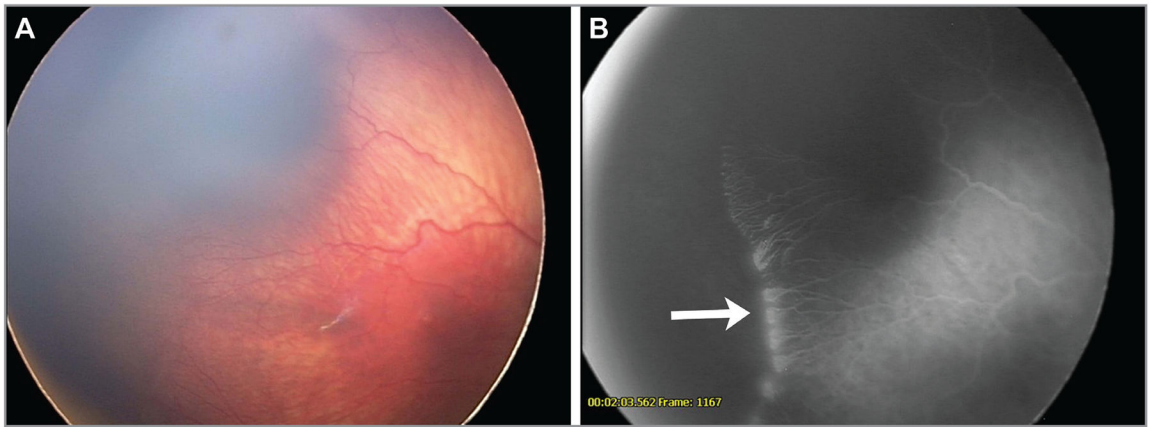


Figure 1.

An ex-31-week infant with Zone III Stage 2 retinopathy of prematurity at a postmenstrual age of 64 weeks. Limited views of the periphery on color fundus photography (A) were enhanced by the addition of fluorescein angiography (B), which revealed persistent avascular retina and fine vascular arborization in the periphery without evidence of leakage.

**Figure 2.**

An ex-23-week infant status post-intravitreal bevacizumab at 35 weeks with recurrent Zone III Stage 3 retinopathy of prematurity at a postmenstrual age of 51 weeks. Zone III is poorly visualized on color fundus photography (A) but clearly identified on fluorescein angiography (B). Late hyperfluorescence (arrow) is seen at the junction of the avascular and vascularized border, consistent with leakage from persistent neovascularization.

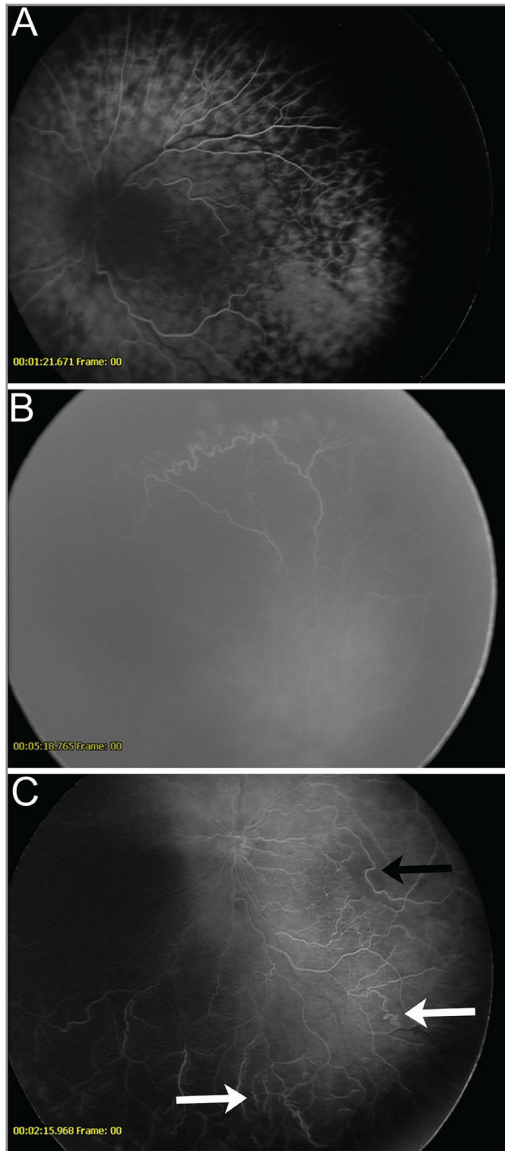


Figure 3.

Ex-24-week infant status post-bevacizumab at 33 weeks with recurrent Zone II retinopathy of prematurity. Fluorescein angiography demonstrates a lobular choroidal filling pattern (A), a circumferential shunt vessel parallel to the junction of the avascular and vascularized retina (B), and a fine vascular network extending through the macula, resulting in the absence of the foveal avascular zone (C). An irregular shunt vessel (black arrow) with adjacent capillary loss is seen within the temporal macula. Irregular branching patterns (white arrows) are seen in the periphery with loss of the adjacent capillary bed.

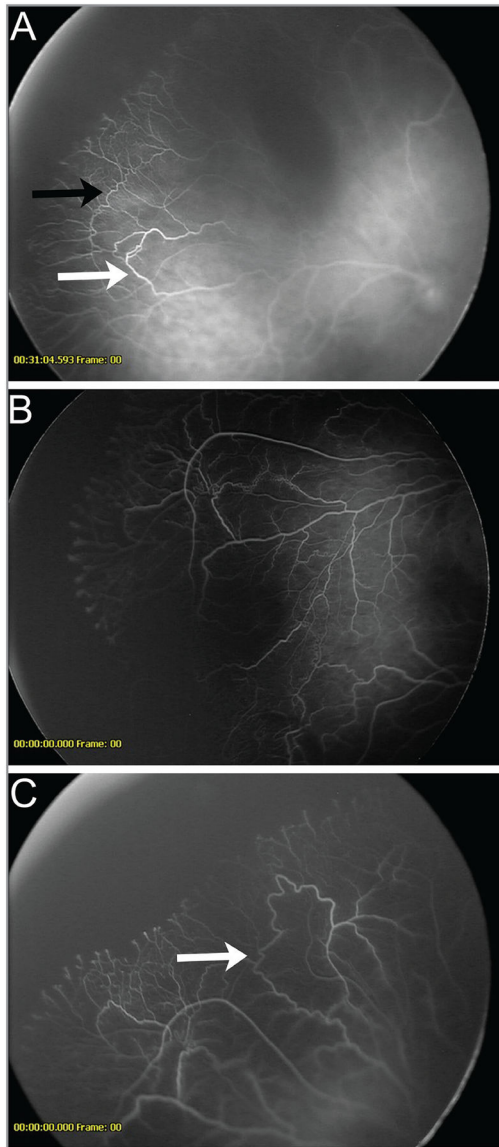


Figure 4.

Fluorescein angiography of an ex-23-week infant status post-intravitreal bevacizumab at 35 weeks with recurrent Zone III retinopathy of prematurity (ROP) at 51 weeks showing a peripheral circumferential shunt vessel (black arrow), in addition to a large peripheral shunt vessel (white arrow). Irregular branching (B) and (C) significant areas of nonperfusion (white arrow) adjacent to a large peripheral shunt vessel are seen in an ex-23-week infant status post-bevacizumab at 35 weeks with recurrent Zone III ROP at 47 weeks.

TABLE

Infants With Retinopathy of Prematurity That Persists Beyond 45 Weeks

Subject	Gestational Age at Birth (Weeks)	Gender	Birth Weight (Grams)	Gestational Age at Time of Imaging (Weeks)	Previously Treated With Bevacizumab
1	26	F	510	53	
2	24	F	720	45	Zone 2 Stage 3 with plus at 33 weeks
3	26	M	1,010	52	
4	26	F	515	51	
5	23	M	583	51	Zone 1 Stage 1 with plus at 35 weeks
6	23	M	590	51	Zone 1 Stage 1 with plus at 35 weeks
7	31	F	1,291	64	
8	24	F	660	47	Zone 1 Stage 3 with plus at 36 weeks
9	24	F	380	63	
10	24	F	480	53	
11	23	F	380	48	Zone 2 Stage 3 with plus at 36 weeks
12	27	M	805	64	
13	24	M	880	46	Zone 1 Stage 3 with plus at 32 weeks
14	25	F	640	54	
15	25	F	780	58	
16	25	F	430	50	Zone 2 Stage 2 with plus at 37 weeks

* Fluorescein angiography was obtained in subjects 1-8.