Delayed resolution of retinopathy of prematurity

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PURPOSE To compare the characteristics of infants whose retinopathy of prematurity (ROP) resolves in <50 weeks with those of infants whose ROP resolves in >50 weeks' postmenstrual age (PMA) in order to identify which infants are at risk for delayed resolution and to evaluate whether severe ROP developed after 50 weeks' PMA.

METHODS The medical records of infants screened for ROP from January 2008 to December 2016 at a tertiary care facility were reviewed retrospectively. Infants without follow-up prior to ROP resolution or complete retinal vascularization and those with retinal detachment were excluded. Delayed resolution of ROP was defined as presence of immature retinal vasculature at ≥50 weeks' PMA. The birth characteristics, neonatal complications, and ROP characteristics of infants with and without delayed resolution were compared.

RESULTS A total of 996 infants were included, of whom 136 (13.6%) showed delayed resolution. Increasing severity of ROP (higher stage, lower zone, plus/pre-plus disease) and type 2 ROP was associated with delayed resolution ($P < 0.05$). Other variables associated with delayed resolution included <28 weeks gestational age, ≤3rd percentile birth weight, positive blood culture sepsis, necrotizing enterocolitis, intraventricular hemorrhage, and bronchopulmonary dysplasia ($P < 0.05$). No infants developed type 1 after 50 weeks' PMA. After a prolonged follow-up course consistent with AAP guidelines, a single patient in our study cohort was treated at 81 weeks' PMA for persistent type 2 ROP.

CONCLUSIONS In our cohort, delayed resolution of ROP was more likely in infants with more severe ROP or a complex neonatal course. No patient with delayed resolution developed type 1 ROP after 50 weeks' PMA, supporting AAP guidelines. (J AAPOS 2019;23:90.e1-6)

Ophthalmic screening examinations are instrumental in the identification of retinopathy of prematurity (ROP). Ophthalmic examinations do, however, carry a small risk of adverse effects to the infant, including ocular trauma, apnea, bradycardia, potential systemic effects of dilating eye drops, and nosocomial infection. It is, therefore, essential to minimize the number of screening examinations when possible to limit potential adverse events.[1-3] Additionally, once patients are discharged from the hospital, families take time from work to travel for these examinations at least every 2-4 weeks, adding to the cost of this continued surveillance to the family.

The American Academy of Pediatrics' (AAP) recommends that examinations may be concluded if (1) zone III retinal vascularization is achieved without a previous history of zone I or II ROP; (2) full retinal vascularization is achieved in close proximity to the ora serrata for 360°; (3) there is regression of ROP; or (4) the infant reaches 50 weeks' postmenstrual age (PMA) without prethreshold disease or worse ROP.[4] We investigated the clinical characteristics of infants with persistent ROP or immature retinal vasculature after 50 weeks' PMA. We compared the potential risk factors and neonatal complications of infants whose ROP resolved before 50 weeks PMA and those whose ROP resolved later than 50 weeks' PMA. Our goal was to identify which infants were at risk for delayed resolution of ROP and to determine whether any severe ROP was diagnosed at ≥50 weeks' PMA.

Subjects and Methods

A retrospective cohort study was conducted using records from an ROP registry developed by the Department of Ophthalmology at the University of Colorado. The study was approved by the Colorado Multiple Institutional Review Board. All infants in the registry fulfilled the 2013 screening criteria for ROP: (1) delivered at

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<30 weeks' completed gestation; (2) born with a birth weight of <1,500 g; or (3) an unstable neonatal clinical course as determined by the attending neonatologist.[4] The records of all infants screened for ROP between January 2008 and December 2016 were reviewed retrospectively. Infants who had unresolved ROP and were not lost to follow-up were followed through February 22, 2018, to obtain a date of ROP resolution.

ROP examinations followed standard guidelines[4] and were defined by the International Classification of ROP.[5] ROP examinations were performed by board-certified ophthalmologists who were fellowship-trained in pediatric ophthalmology and have extensive ROP examination experience. Type 1 ROP and type 2 ROP were defined as described in the Early Treatment of Retinopathy of Prematurity study.[6] Low-grade ROP was defined as ROP not meeting the criteria for type 1 or type 2 ROP. We defined severe ROP as type 1 or type 2 ROP. Infants without ROP on examination were defined as having immature retinal vasculature only.

Infants with immature retinal vasculature, low-grade ROP, type 1 ROP, and type 2 ROP were included in the analysis. Resolution of ROP was defined as mature retinal vasculature reaching the ora serrata in untreated infants and resolution of plus disease and vascularization to the border of laser or ora serrata in treated infants on scleral depressed dilated fundus examination. Delay in resolution of ROP was defined as the presence of immature retinal vasculature or any stage of ROP at ≥50 weeks' PMA. In addition to our main variable, type of ROP, other covariates included in the analysis were race/ethnicity, sex, gestational age (GA) at birth, Fenton birth weight percentile defined by the Fenton preterm birth charts,[7] multiple versus singleton births, presence of positive blood culture sepsis, necrotizing enterocolitis, intraventricular hemorrhage, and bronchopulmonary dysplasia. The PMA at time of treatment (laser, bevacizumab injection, or surgical intervention for retinal detachment) was also recorded. Infants without follow-up until complete vascularization of the retina and resolution of ROP (n = 442), those who did not survive prior to resolution of ROP (n = 179), and babies with a retinal detachment (n = 2) were excluded from the analysis. In accordance with contemporary practice, the best estimate of GA was based primarily on clinical assessment at the first maternal prenatal visit and on early ultrasound examination when available.

Statistical Analysis

Descriptive statistics included percentages, means, standard deviations, and medians. Infants identified with delayed resolution of ROP were compared to infants without delayed resolution. Chi-square or Fisher's exact testing for categorical variables and Kolmogorov-Smirnov testing for continuous variables were used to compare the two groups. A P value of <0.05 was considered statically significant. All analyses were performed using SAS software (version 9.4, SAS Institute Inc, Cary, NC).

Results

Records of 996 infants examined for ROP were included in the analysis. Figure 1 demonstrates the distribution of PMA at the time of ROP resolution. Of the 996 infants, 56 (5.6%) developed type 1 ROP; 47 (4.7%), type 2 ROP; 210 (21.1%), low-grade ROP; and 683 (68.6%), immature vasculature only. A total of 136 (13.6%) showed delayed resolution of ROP.

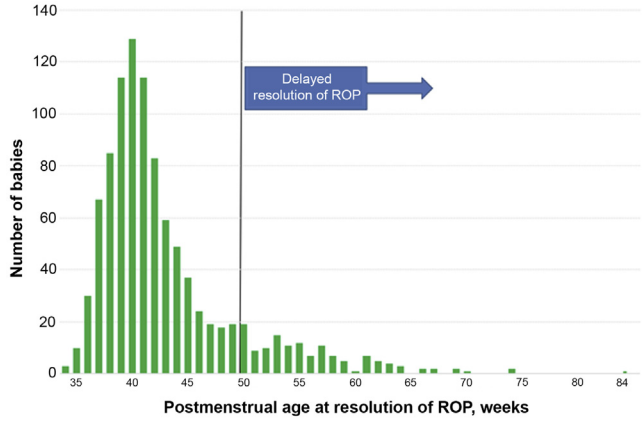

FIG 1. Postmenstrual age at resolution of retinopathy of prematurity (N = 996).

The demographics and birth characteristics are shown in Table 1. There was no difference in rates of delayed resolution of ROP based on race/ethnicity or sex. The median GA at birth was lower in infants with delayed resolution (26.3 ± 1.9 weeks vs 29.1 ± 2.3 weeks). Infants born at <28 weeks' GA were significantly more likely to show delayed resolution. There was a significant inverse relationship between birth weight percentile and delayed ROP resolution with babies born in the 3rd percentile or less, having a delayed resolution rate of 27.1%, almost twice as high as other percentiles. Singleton infants were also more likely to show delayed resolution compared to multiple births ($P < 0.0016$).

Table 2 shows the rate of neonatal complications in infants with delayed ROP resolution versus those without delayed resolution. Infants with positive blood culture sepsis (n = 104, 10.4%) were significantly more likely to have delayed resolution of ROP compared to those without positive blood culture sepsis (36.5% vs 11.0%). Other neonatal complications, including necrotizing enterocolitis, bronchopulmonary dysplasia, and intraventricular hemorrhage, were also significantly associated with delayed resolution of ROP.

ROP characteristics are provided in Table 3. Increasing stage, decreasing zone, and the presence of plus or pre-plus disease were related to delayed resolution. Infants with type 2 ROP more commonly exhibited delayed resolution compared those with immature vasculature, low-grade ROP, or type 1 ROP ($P < 0.0001$).

All infants with type 1 ROP (n = 56) received treatment, either with retinal laser ablation alone (n = 52), with bevacizumab plus laser (n = 2), or with bevacizumab alone (n = 2). The median PMA at time of treatment was 38.4 ± 6.4 weeks (range, 32.4-81 weeks). One infant was treated with laser ablation at 81 weeks for persistent type

Table 1. Demographics and birth characteristics of infants (N = 996)

	Resolved <50 weeks' PMA	Delayed resolution	% Delayed	*P* value[a]
Total	860	136	13.6	
Sex, no. (%)				0.4202
Male	455 (52.9)	77 (56.6)	14.5	
Female	405 (47.1)	59 (43.4)	12.7	
Race/ethnicity, no. (%)				0.4245
White	397 (46.2)	53 (39.0)	11.8	
Hispanic	282 (32.8)	52 (38.2)	15.6	
African American	96 (11.2)	16 (11.8)	13.5	
Other	85 (9.9)	16 (11.8)	15.8	
GA, weeks				<0.0001
Mean ± SD	29.1 ± 2.3	26.3 ± 1.9	NA	
Median	29.4	26.0		
Gestational age, no. (%)				<0.0001
<28 weeks	243 (28.3)	112 (82.4)	31.6	
28+ weeks	617 (71.7)	24 (17.6)	3.7	
Birth percentile, no. (%)				<0.0430
≤3rd	35 (4.1)	13 (9.6)	27.1	
4th-10th	77 (8.9)	13 (9.6)	14.4	
11th-24th	113 (13.1)	16 (11.8)	12.4	
25th-75th	485 (56.4)	78 (57.4)	13.8	
>75th	150 (17.4)	16 (11.8)	9.6	
Multiple gestation, no. (%)				<0.0016
Singleton	623 (72.4)	117 (86.0)	15.8	
Twin	209 (24.3)	19 (14.0)	8.3	
Triplet or more	28 (3.3)	0	0.0	

GA, gestational age; *PMA*, postmenstrual age; *SD*, standard deviation.
[a]χ^2 or Fisher exact test for categorical variables and Kolmogorov-Smirnov (nonparametric) test for gestational age as a continuous variable.

Table 2. Neonatal complications in infants with and without delayed resolution of ROP (N = 996)

	Resolved <50 weeks' PMA	Delayed resolution	% Delayed	*P* value[a]
Total	860	136	13.6%	
Positive blood culture sepsis, no. (%)				<0.0001
Yes	66 (7.7)	38 (27.9)	36.5	
No	792 (92.1)	98 (72.1)	11.0	
Missing	2 (0.2)	0	0	
Necrotizing enterocolitis, no. (%)				<0.0001
Yes	61 (7.1)	23 (16.9)	27.4	
No	796 (92.6)	113 (83.1)	12.4	
Missing	3 (0.3)	0	0	
IVH papile score grade, no. (%)				<0.0001
Normal	664 (77.2)	78 (57.4)	10.5	
Grade 1	110 (12.8)	20 (14.7)	15.4	
Grade 2	36 (4.2)	12 (8.8)	25.0	
Grade 3	27 (3.1)	14 (10.3)	34.2	
Grade 4	20 (2.3)	11 (8.1)	35.5	
Missing	3 (0.4)	1 (0.7)	25.0	
BPD, no. (%)				<0.0001
Yes	690 (80.2)	130 (95.6)	15.8	
No	162 (18.8)	6 (4.4)	3.6	
Missing	8 (1.0)	0	0.0	

BPD, bronchopulmonary dysplasia; *IVH*, intraventricular hemorrhage; *PMA*, postmenstrual age; *ROP*, retinopathy of prematurity.
[a]χ^2 or Fisher exact test.

2 ROP. No infant developed type 1 ROP after 50 weeks' PMA.

Four patients in our cohort were treated with bevacizumab injection for type 1 ROP in zone 1 or posterior zone 2. Two of these patients received laser photocoagulation after the injection, one because of unreliable follow-up after hospital discharge and the other because of concern for reactivation at 47 weeks' PMA. The 2 patients that did not receive laser did show a delayed resolution of ROP.

Excluded infants were similar to the study population in terms of sex, single or multiple gestation, and type of ROP for babies who had ROP screening. However, excluded

Table 3. ROP characteristics of infants with and without delayed resolution of ROP (N = 996)

	Resolved <50 weeks' PMA	Delayed resolution	% Delayed	*P* value[a]
Total	860	136	13.6	NA
Highest stage ROP, no. (%)				<0.0001
Immature	667 (77.6)	6 (4.4)	0.9	
Stage 1	66 (7.7)	11 (8.1)	14.3	
Stage 2	80 (9.3)	66 (48.5)	45.2	
Stage 3	38 (4.4)	53 (39.0)	58.2	
Missing	9 (1.0)			
Lowest zone ROP, no. (%)				<0.0001
Fully vascularized	13 (1.5)	1 (0.7)	7.1	
Zone I	2 (0.2)	6 (4.4)	75.0	
Zone II	496 (57.7)	106 (77.9)	17.6	
Zone III	349 (40.6)	23 (16.9)	6.2	
Plus disease present, no. (%)				<0.0001
Yes	31 (3.6)	26 (19.1)	45.6	
No	816 (94.9)	71 (52.2)	8.0	
Pre-plus	10 (1.2)	39 (28.7)	79.6	
Missing	3 (0.3)	0	0	
ROP type, no. (%)				<0.0001
No ROP	677 (78.7)	6 (4.4)	0.9	
Type 1	30 (3.5)	26 (19.1)	46.4	
Type 2	12 (1.4)	35 (25.7)	74.5	
Low	141 (16.4)	69 (50.7)	32.9	

PMA, postmenstrual age; *ROP*, retinopathy of prematurity.
[a]χ^2 or Fisher exact test.

babies differed in race/ethnicity and birth weight percentile. Notably, 61% of babies in the lower percentile were excluded, largely because of death prior to ROP screening. Babies excluded due to loss of follow-up did not differ by birthweight percentile.

Discussion

This is the first study to investigate the incidence of immature retinal vasculature or persistent ROP beyond 50 weeks' PMA and the clinical characteristics of infants with delayed resolution. A significant percentage of infants (13.6%) examined at our institution showed delayed resolution; thus, studying the clinical features of this contemporary cohort is valuable. The 2013 AAP screening guidelines for ROP suggest that ophthalmic examinations for ROP may be discontinued once an infant reaches 50 weeks' PMA; however, many ophthalmologists, including those at our institution, examine patients until full retinal vascularization or regression of ROP is achieved. This may be due to fear of overlooking treatable disease, potential legal implications, or desire to provide reassurance to the patient's family and medical team.

The AAP guidelines are principally based on an analysis performed by Reynolds and colleagues[8] on the data from the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study and the Effects of Light Reduction on Retinopathy of Prematurity (Light-ROP) study. In their study, serious ROP was defined as the presence of four following conditions: (1) prethreshold ROP, (2) threshold ROP, (3) any stage of ROP with plus disease, and (4) stage 3 ROP with plus disease. Their analysis showed that 99% of eyes that developed serious ROP did so by 46.3 weeks' PMA and that prethreshold disease was evident by 45 weeks' PMA in 99% of patients. Given that an eye without prethreshold disease is not at risk for threshold disease, they concluded that termination of screening examinations may occur at 45 weeks' PMA as long as prethreshold or worse ROP is not present.[8] No patient with delayed resolution of ROP in our cohort developed type 1 ROP after 50 weeks' PMA, consistent with the analysis of the CRYO-ROP and Light-ROP data.

Data from the CRYO-ROP study did not include information on the time of full vascularization or regression of ROP. Results of the Light-ROP study showed that 99% of patients with only immature vasculature on all ROP examinations reached full retinal vascularization by 42.6 weeks' PMA. This is consistent with our findings, in that delayed resolution was seen in only 0.9% of infants with only immature retinal vasculature. The time to full vascularization in infants with a history of ROP from the Light-ROP study was not investigated.[8]

Associations between the severity of ROP and lower birth weight, lower GA at birth, and neonatal complications has been well documented in previous studies.[9-12] Therefore, it is not surprising that lower birth weight, lower GA at birth, positive blood culture sepsis, necrotizing enterocolitis, bronchopulmonary dysplasia, and increasing grade of intraventricular hemorrhage were all positively associated with delayed resolution of ROP in our cohort.

Of note, our cohort showed an increased incidence of delayed resolution in singleton versus multiple births.

Previous reports have failed to show a clinically significant difference in the incidence or severity of ROP in singleton versus multiple births.[13,14] Basso and colleagues[15] have shown that infants in multiple births have lower GA-specific mortality during most of the preterm period compared to singletons. They discuss that twinning may induce a stress response that hastens fetal maturation, in turn leading to lower preterm mortality. This reasoning could also explain the reduced incidence of delayed resolution of ROP in our cohort and merits further investigation.

As one may expect, the incidence of delayed resolution of ROP increased as the recorded zone of ROP decreased and stage increased. The presence of plus or pre-plus disease was also positively associated with delayed resolution. Infants with type 2 ROP were more likely than other infants, including those with type 1 ROP, to show delayed resolution. The absence of treatment in high-risk eyes with type 2 ROP is presumed to result in a prolonged course of ROP compared to treated eyes. All patients with type 1 ROP received treatment with retinal laser ablation or bevacizumab and laser, as is standard. Since treatment hastens the regression of ROP, it is not surprising that the duration of ROP and time to complete vascularization was shorter.

Of the 4 infants in our cohort who received anti-VEGF injections, 2 had delayed resolution of ROP, which is not surprising, because anti-VEGF is known to delay retinal vascular maturation and the potential for late reactivation of disease.[16-20] Patients who receive anti-VEGF are followed closely after treatment at our institution (every 1-2 weeks) to monitor for reactivation of ROP until complete resolution. Notably, none of these patients required additional treatment after 50 weeks' PMA. Patients who have ROP treatment with anti-VEGF injections must be monitored until complete vascularization; there have been reports of late reactivation of ROP in these eyes.[16-20]

One infant in our cohort underwent laser photocoagulation at 81 weeks' PMA for persistent type 2 ROP. On examination, this patient showed stable zone 2, stage 3 ROP without plus disease for 10 months prior to treatment on repeat examinations consistent with AAP guidelines. Laser ablation was performed based on the clinical judgment of the treating ophthalmologist because of the increasing difficulty of performing scleral depressed examinations on an awake infant at this age.

Limitations of our study include the variable follow-up of patients once discharged from the hospital, including missed appointments and overdue retinal examinations. In some cases, patients reached 50 weeks' PMA between examinations, making it impossible to determine whether the patient achieved resolution before or after the 50 weeks cut-off. This could have led to a higher recorded incidence of delayed resolution in our study cohort. In addition, there were infants that may have follow-up at other institutions or had good outcomes and did not seek out additional care. The effect of these babies on our rate of delayed resolution is unknown.

A significant percentage of patients in our cohort (13.6%) showed delayed resolution of ROP. Nevertheless, it is important to note that none developed type 1 ROP after 50 weeks' PMA, and only 1 was treated. Although there are no previous studies on delayed resolution of ROP with which to compare our results, it is possible that the incidence of delayed resolution at our institution may be higher than elsewhere because of the higher altitude and larger fluctuations in effective oxygen concentrations if the cannula is misplaced on the infant.[21]

Clinicians may expect infants with more severe ROP or a more complex neonatal course to have delayed resolution of ROP. No patient with delayed resolution of ROP developed type 1 ROP after 50 weeks' PMA, which is consistent with findings from previous studies and in agreement with the AAP guidelines. Our results support the AAP recommendations regarding ending ROP examinations after 50 weeks' PMA. Patients who receive anti-VEGF, however, should continue to be examined until resolution to monitor for late reactivation. Larger studies with extended follow-up are needed to determine whether there are any ophthalmic complications or long-term sequela of delayed ROP resolution later in childhood or adulthood.

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