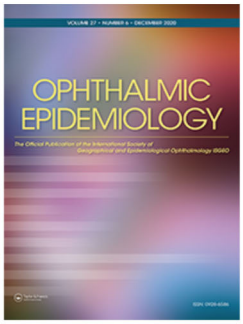

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Symmetry of Disease in Retinopathy of Prematurity in the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study

Lisa Y. Lin[a], Anne K. Jensen[a], Graham E. Quinn[a,b], Alyssa Spiller[a], Lauren A. Tomlinson[a], Gui-Shuang Ying[b], and Gil Binenbaumon behalf of the Postnatal Growth and Retinopathy of Prematurity Study Group[a,b*]

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ABSTRACT

Purpose: To determine the symmetry of retinopathy of prematurity (ROP) between fellow eyes in a broad-risk cohort.

Methods: A retrospective cohort study, the Postnatal Growth and ROP (G-ROP) Study, of 7483 infants undergoing ROP examinations conducted at 29 hospitals in the United States and Canada from 2006 to 2012. The main outcomes were the symmetry for the highest stage and the most severe type (1, 2, not 1 or 2, no ROP) of ROP and disease course of the fellow eye when only one eye developed type 1.

Results: 93% of infants had eyes symmetric for the highest stage and 94% for type. Among 459 infants who developed type 1, 379 (82.6%) did so in both eyes simultaneously and were treated bilaterally; 44 (10%) were treated for type 1 in one eye and type 2 in the fellow eye; and 36 (8%) were treated unilaterally initially, of which 6 fellow eyes developed type 1 and were treated (4 within 2 weeks, all within 4 weeks); 5 developed type 2 and regressed; and 25 developed ROP less than type 1 or 2, which was treated in 13 cases and regressed spontaneously in 12 cases.

Conclusions: ROP was highly symmetric between eyes with respect to the presence and severity of disease in a large, broad-risk cohort representative of infants undergoing ROP screening. When type 1 develops in one eye and type 2 in the fellow eye, the risk of progression to type 1 in the fellow eye appears very low if it has not occurred within 4 weeks.

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Retinopathy of prematurity (ROP) is a disease of the developing retinal vasculature in premature infants and a leading cause of childhood blindness worldwide.[1] Infants at risk are currently identified based on birth weight (BW) and gestational age (GA) criteria and require serial dilated fundus examinations to detect disease that requires treatment. Follow-up intervals for subsequent screening examinations are determined based on the most severe ROP present in either eye of the infant using a classification defined by zone and stage of disease and presence or absence of plus disease.

Previous studies have reported a high correlation of ROP severity between eyes among high-risk infants.[2,3] In the Cryotherapy for Retinopathy (CRYO-ROP) study, infants with BWs less than 1251 g had high inter-eye correlation (75.0% to 94.2%) for the worst acute-phase ROP observed (defined as no ROP, less than pre-threshold ROP, pre-threshold ROP, or threshold ROP). They also found a high correlation for the zone of ROP and the presence of plus disease.[2] Subsequently, a high correlation of ROP between eyes was found in the Telemedicine Approaches to Evaluating of Acute-Phase ROP (e-ROP) study.[3] In this study, masked non-physician readers evaluated digital retinal images to determine the presence of "referral warranted disease" (defined as the presence of stage 3 or above, plus disease, or zone I ROP). They found 85% agreement between eyes for referral-warranted ROP and 73% agreement between eyes for ROP severity (defined as no ROP, mild ROP, type 2 ROP, or type 1 ROP). These findings in high-risk cohorts help substantiate our current understanding that the pathogenesis of ROP is largely driven by systemic factors[4] and provide support for within-subject comparisons when designing clinical trials and other future ROP studies. However, there may be additional useful information to learn from studying a cohort that more completely represents the entire spectrum of infants at risk for ROP.

We sought to evaluate inter-eye ROP symmetry in a broad-risk cohort representative of infants undergoing ROP screening examinations. We hypothesized that

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ROP would be highly symmetric for both severity, as defined by worst ROP type according to Early Treatment of Retinopathy of Prematurity (ETROP) criteria,[5] and highest ROP stage. In addition, we evaluated the disease course of fellow eyes when one eye developed severe (ETROP type 1) disease.

Materials and methods

This report is a secondary analysis of data from the first Postnatal Growth and ROP (G-ROP) study, a multicenter, retrospective cohort study of infants undergoing ROP screening examinations between 2006 and 2012 at 29 hospitals in the United States and Canada.[6,7] Institutional review board approval and waiver of consent were obtained at all study hospitals, and the study was conducted in compliance with the Declaration of Helsinki.

The general G-ROP study design is described below. Additional detailed methods and the primary study results are available in prior publications.[6,7] Briefly, the G-ROP study's primary aim was to develop a postnatal weight gain ROP predictive model, which took the form of modified screening criteria. Infants were enrolled in the study if they underwent ROP screening and had known BW, GA, and sufficient postnatal weight measurements before 36 weeks of postmenstrual age (PMA). All babies undergoing examinations were eligible, regardless of BW or GA at birth. Infants were examined by experienced pediatric ophthalmologists or retina specialists, following local institutional protocols for the timing of first and subsequent examinations until retinal vascular maturity or disease regression. BW, GA, and PMA at each examination; International Classification of Retinopathy of Prematurity (ICROP) classification at each examination (including stage, zone, and presence of plus or pre-plus disease); PMA and type of all treatments; and extensive medical and demographic information were collected.

The primary outcome for this secondary analysis was inter-eye symmetry of ROP severity, considered both as the highest stage and the worst ETROP pre-threshold type, ranging from most to least severe as type 1 ROP, type 2 ROP, ROP present but not severe enough to be type 1 or 2, or no ROP, based on ETROP definitions for type 1 and 2 ROP.[5] Type I is defined as stage 2 or stage 3 in zone II with plus disease; stage 3 in zone I without plus disease; or any stage in zone I with plus disease. Type II is defined as stage 3 in zone II without plus disease; or stage 1 or 2 in zone I without plus disease. The highest stage and worst type were determined prior to treatment if ROP treatment was received. Symmetry was defined as the percentage of infants with the same most severe diagnosis in each eye at any time during the course of eye examinations. In addition, for type 1 ROP, we evaluated the symmetry within 3 days when an infant developed type 1 ROP in either eye. If only one eye developed type 1 ROP, the disease course of the fellow eye was also evaluated.

Results

Of 7483 infants studied, 7032 (94.0%) had symmetric findings for the most severe type of ROP (Table 1): 385 (5.2%) infants had type 1 ROP in both eyes, 355 (4.7%) infants had type 2 ROP in both eyes, 2033 (27.2%) infants had ROP that was less severe than type 1 or 2 disease, and 4259 (56.9%) had no ROP in either eye. Similar results were found for the highest ROP stage, with 6932 (93%) infants reaching the same highest stage in both eyes (Table 2): 4259 (56.9%) infants did not develop ROP in either eye, 1150 (15.4%) infants developed stage 1 in both eyes, 862 (11.5%) infants developed stage 2 in both eyes, 661 (8.8%) developed stage 3 in both eyes, and none had stage 4A or 5 in both eyes.

Of the 459 (6.1%) infants in the cohort that developed type 1 ROP in one or both eyes, 379 (82.6%) infants had type 1 ROP diagnosed in both eyes at the same examination or within 3 days and were treated bilaterally (Figure

Table 1. Inter-eye symmetry for the most severe type of ROP among 7483 infants in the postnatal growth and ROP study.

		Left eye				
		Type 1	Type 2	Not type 1 or type 2	No ROP	Total
Right eye	Type 1	385 (5.1%)	34 (0.5%)	15 (0.2%)	0 (0.0%)	434 (5.9%)
	Type 2	15 (0.2%)	355 (4.7%)	53 (0.7%)	0 (0.0%)	423 (5.7%)
	Not type 1 or type 2	10 (0.1%)	61 (0.8%)	2033 (27.2%)	125 (1.7%)	2229 (29.7%)
	No ROP	0 (0.0%)	3 (0.04%)	135 (1.8%)	4259 (56.9%)	4397 (58.8%)
	Total	410 (5.4%)	453 (6.1%)	2236 (29.9%)	4384 (58.6%)	7483 (100.0%)

Table 2. Inter-eye symmetry for the highest ROP stage among 7483 infants in the postnatal growth and ROP study.

		Left eye						
	Stage	Immature retinal vasculature	1	2	3	4A	5	Total
Right eye	Immature retinal vasculature	4259 (56.9%)	127 (1.7%)	9 (0.1%)	2 (0.03%)	0 (0.0%)	0 (0.0%)	4397 (58.8%)
	1	121 (1.6%)	1150 (15.4%)	74 (1.0%)	6 (0.1%)	0 (0.0%)	0 (0.0%)	1351 (18.1%)
	2	4 (0.1%)	53 (0.7%)	862 (11.5%)	73 (1.0%)	0 (0.0%)	0 (0.0%)	992 (13.3%)
	3	0 (0.0%)	2 (0.03%)	77 (1.0%)	661 (8.8%)	0 (0.0%)	0 (0.0%)	740 (9.9%)
	4A	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.01%)	1 (0.01%)
	5	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.01%)	1 (0.01%)	0 (0.0%)	2 (0.03%)
	Total	4384 (58.6%)	1332 (17.8%)	1022 (13.7%)	743 (9.9%)	1 (0.01%)	1 (0.01%)	7483 (100.0%)

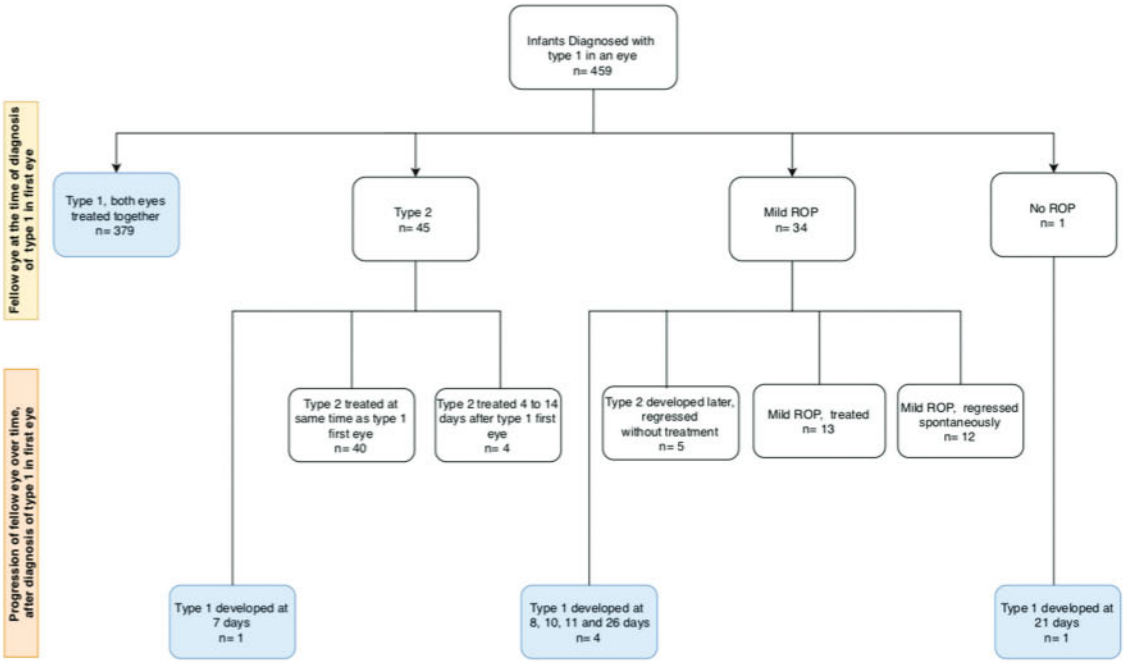

Figure 1. Fellow eye outcomes among 459 infants who had type 1 retinopathy of prematurity (ROP) in at least one eye in the Postnatal Growth and ROP study. "Mild ROP" refers to ROP that was not severe enough to meet the criteria for type 1 or 2 ROP.

1). There were 80 (17.4%) infants with type 1 ROP whose fellow eye did not develop type 1 ROP within 3 days. In a majority of these cases (40 of 80 infants), the fellow eye had type 2 ROP but was treated at the same time as the eye that had type 1 ROP, and an additional four eyes were treated while still type 2 within 4–14 days of the first eye. Therefore, the overall proportion of type 2 eyes that would have progressed to type 1 disease could not be determined. However, the disease course of the 36 remaining untreated fellow eyes with ROP less severe than type 1 was analyzed (1 with type 2 ROP, and 34 with ROP less severe than type 1 or 2, and 1 with no ROP). Six eyes eventually developed type 1 ROP and were treated, four eyes within 11 days, and all eyes within 26 days. Among the remaining 30 eyes, 5 developed type 2 ROP that regressed spontaneously, 13 were treated for ROP less severe than type 1 or 2, and 12 had ROP less than type 1 or 2 that regressed spontaneously. All fellow eyes among the 459 patients who had type 1 ROP in at least one eye eventually developed ROP.

Discussion

In our large, broad-risk cohort representative of all infants undergoing ROP screening examinations, ROP was largely symmetric between eyes with respect to both the presence and severity of the disease. Further, when type 1 ROP developed in only one eye, the risk of progression to type 1 in the fellow eye was low if it had not occurred within 4 weeks. We cannot provide data on progression to type 1 for fellow eyes that had type 2 when the type 1 eye was treated because it was

a common practice to treat the type 2 eye at the same time (40 out of 45 cases) or within 2 weeks even if still type 2 (4 of the remaining 5 cases).

The degree of symmetry found in this study that enrolled all infants undergoing ROP screening examinations is very similar to the correlations noted in the CRYO-ROP study cohort,[2] despite the fact that CRYO-ROP included only infants with BWs less than 1251 g. In contrast, this study included infants with a broader range of BWs from 350 to 4080 g (median BW 1072 g), which is more representative of all infants undergoing ROP examinations.[7] However, compared to our results, relatively lower degrees of inter-eye agreement were found in the e-ROP study, which found only 73% symmetry for the most severe type of ROP and 83% symmetry for the highest stage.[3,8] This discrepancy may be due to differences in methodology for ROP status determination, given very different study goals. In the current study, standard screening examinations were performed by ophthalmologists examining both eyes at the same time and who therefore were aware of the fellow eye diagnosis, possibly creating a slight upward bias in inter-eye correlation. In e-ROP, masked trained non-physician readers evaluated digital retinal images of single eyes in isolation without knowing the ROP status of a matched fellow eye.

One strength of our study was the geographic and racial diversity of the group, which included infants across a broad spectrum of risk for ROP development.[6] However, there are important limitations to consider. We could not provide natural history data for over half of the 80 infants who developed type 1 ROP in only on eye initially because 44 of 45 (97.8%) fellow eyes with type 2 ROP were treated at the same time or within 2 weeks as the type 1 eye. However, this limitation would bias our estimate of the proportion of babies with symmetric type of ROP between eyes downward and therefore would not change our study conclusion that ROP is a highly symmetric disease. Another limitation is related to retrospective medical records data collection. While data were collected from charts by trained and certified data abstractors in a systematic manner and the ophthalmologist examiners were experienced clinicians using ICROP nomenclature, there were no photographs available to allow confirmatory review of the ROP diagnoses. Finally, some degree of intra-observer bias may be present since both eyes were examined by the same person during an individual retinal examination, possibly leading to a higher tendency for symmetric diagnoses. However, we think it is unlikely that such bias could account for the very high degree of symmetry found in this study and in prior studies.

Understanding the correlation of ROP presence and severity between eyes is helpful from both clinical and research perspectives. In the clinical setting, this information may help guide management and treatment decisions, including the determination of the length of follow-up. Furthermore, high rates of symmetry in ROP support future study designs that rely on within-subject controls for ROP treatment trials. Finally, our findings continue to support the current pathophysiologic model for ROP, which heavily weighs systemic factors that also can be used to predict ROP risk. However, further study is needed to identify and describe possible disease-modifying factors that may be present in asymmetric disease.

Conflicts of interest

The authors have no potential conflicts of interest to report.

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