·Clinical Research·

Spontaneous regression of retinopathy of prematurity: incidence and predictive factors

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Abstract

• AIM: To evaluate the incidence of spontaneous regression of changes in the retina and vitreous in active stage of retinopathy of prematurity(ROP) and identify the possible relative factors during the regression.

• METHODS: This was a retrospective, hospital-based study. The study consisted of 39 premature infants with mild ROP showed spontaneous regression (Group A) and 17 with severe ROP who had been treated before naturally involuting (Group B) from August 2008 through May 2011. Data on gender, single or multiple pregnancy, gestational age, birth weight, weight gain from birth to the sixth week of life, use of oxygen in mechanical ventilation, total duration of oxygen inhalation, surfactant given or not, need for and times of blood transfusion, 1,5,10-min Apgar score, presence of bacterial or fungal or combined infection, hyaline membrane disease (HMD), patent ductus arteriosus (PDA), duration of stay in the neonatal intensive care unit (NICU) and duration of ROP were recorded.

• RESULTS: The incidence of spontaneous regression of ROP with stage 1 was 86.7%, and with stage 2, stage 3 was 57.1%, 5.9%, respectively. With changes in zone Ⅲ regression was detected 100%, in zone Ⅱ 46.2% and in zone Ⅰ 0%. The mean duration of ROP in spontaneous regression group was 5.65±3.14 weeks, lower than that of the treated ROP group (7.34 ±4.33 weeks), but this difference was not statistically significant (P=0.201). GA, 1min Apgar score, 5min Apgar score, duration of NICU stay, postnatal age of initial screening and oxygen therapy longer than 10 days were significant predictive factors for the spontaneous regression of ROP (P<0.05). Retinal hemorrhage was the only independent predictive factor the spontaneous regression of ROP (OR 0.030, 95%CI 0.001-0.775, P=0.035).

• CONCLUSION: This study showed most stage 1 and 2 ROP and changes in zone Ⅲ can spontaneously regression in the end. Retinal hemorrhage is weakly inversely associated with the spontaneous regression.

• KEYWORDS: retinopathy of prematurity; spontaneous regression; incidence; duration of ROP

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INTRODUCTION

Retinopathy of prematurity (ROP) is a multifactorial disease that occurs most frequently in very small and sick infants, which can cause blindness in babies born prematurely. With the increasing survival of premature babies, a "third epidemic" is in the making [1]. However, the incidence of ROP is different in accordance with the different criteria in different countries. The reported incidence of acute ROP varies from 9.8% to 72.7% and the threshold ROP which needs treatment varies from 3.6% to 34.8% [2-8]. In most cases, spontaneous regression of ROP

usually occurs without serious residual in eyes with stages 1, 2 and early stage 3 while blindness or serious visual impairment results from progression to retinal detachment or severe distortion of the posterior retina [1]. Although the early treatment of high-risk prethreshold ROP and threshold ROP can significantly reduce unfavorable outcomes in both primary and secondary (structural) measures [9], the patients who underwent vitrectomy either initially or at a later time have poor postoperative visual acuity even retinal redetachment and poor life-quality in the long run, besides the high care costs [10]. Therefore, there is a need to develop diverse approaches which can prevent ROP blindness extending from policies and practices.

This study aimed to evaluate and report the possibilities and incidence of spontaneous regression of changes in the retina and vitreous in active stage of ROP and identify the possible relative factors during the regression among patients attending a neonatal intensive care unit (NICU) in Guangzhou, China, dividing patients into different groups due to the spontaneous regression of ROP from May 2008 through May 2011.

SUBJECTS AND METHODS

Subjects Totally 957 infants with a birth weight (BW) ＜2 000g or an estimated gestational age (GA) ＜37 weeks were screened for ROP in accordance with the screening criteria proposed by Chinese Medical Association [11]at the NICU of Zhujiang Hospital of Southern Medical University, Guangzhou, China, between May 2008 and May 2011. Approval for the review of hospital charts was obtained from the Department of Scientific Research in Zhujiang Hospital. Confirmed forms were also assigned by the babies' parents or legal guardians before the initial screening.

Methods The sample (n=56) included all preterm infants who were diagnosed as any ROP stage and followed up at least 45 weeks of postmenstrual age or until the retinal fully vascularization or effective stabilization of retinopathy was achieved after treatment. Infants who died or who were lost to follow-up before regression of ROP or documentation of mature peripheral retinal vessels were excluded. If outpatient examinations were missed or delayed more than 2 weeks beyond the scheduled appointment and if the ROP was found to be regressed at the time of the delayed appointment, that patient was considered to be lost to follow-up and was excluded from the study. For the purpose of this study, completely spontaneous regression was defined as the disappearance of all active neovascularization of perfused neovascular shunt with normal vessels to outer zone III without any treatment. The 56 infants were divided into two groups according to the development of ROP. Group A (spontaneous regression ROP group) consisted of 39 patients who were diagnosed with stage 1 or 2 ROP but showed regression; Group B (treated ROP group) comprised 17 patients with which ROP progressed to stage 3 (high-risk prethreshold or threshold ROP, early treatment of ROP) or AP-ROP and received treatment. None of the infants in the study were diagnosed as stage 4 or 5 ROP.

The screening sessions and the follow-up were performed according to Chinese guidelines to detect and treat ROP, which recommended initial ophthalmological examination should be performed between the fourth and sixth weeks of life or from 32 weeks of postmenstrual age and should be repeated weekly or more frequently according to the findings until full vascularization of the peripheral retina is observed or until 45 weeks of postmenstrual age. On each examination, pupils' dilation was done using 0.5% tropicamide at least 30min prior to examination. Topical proparacaine was applied and an eye speculum was inserted. Digital images were taken with the Retinal Camera II (Massie Research Laboratories Inc.) using the 130° ROP lens. Indirect ophthalmoscopy was performed using a 28D lens and secleral depression in necessary. Findings were classified according to the International Classification of Retinopathy of Prematurity[12].

The perinatal variables considered for the study were: gender, single or multiple pregnancy, gestational age at birth, birth weight, weight gain from birth to the sixth week of life, use of oxygen in mechanical ventilation, total duration of oxygen inhalation, surfactant given or not, need for and times of blood transfusion, 1, 5, 10-min Apgar score, presence of common problems of prematurity like bacterial or fungal or combined infection, hyaline membrane disease (HMD) and its severity, patent ductus arteriosus (PDA) and its treatment. Duration of stay in the NICU was also noted. The duration of ROP was also evaluated in all patients who developed ROP, which was calculated for each patient as the time in weeks between the date of the first examination at which any ROP was seen and the date of the first examination at which the ROP was found to have completely regressed.

Statistical Analysis All data was entered into a spreadsheet and analyzed using SPSS for Windows statistical software Version 13.0 (SPSS Inc., Chicago, IL, USA). Clinical characteristics of the two groups were described by mean values and standard deviations. Statistical analysis was

Table 1 Spontaneous regression of ROP in different stage and area

Stage	Zone III	Zone II	Zone I	Incidence(stage)
Stage 1	24 cases R 1case→stage 2→R	2 cases R 1 case→stage 2→R 1 case→stage 2→stage 3→T	1 case→stage 2→stage 3→T	26/30×100%=86.7%
Stage 2	8 cases R 1case(1→stage 2)→R	1 case R 1 case(1→stage 2)→R 1 case(2→stage 3→2)→R 1 case(1→stage 2→3)→T 2 cases (stage 2→3)→T	6 cases→stage 3→T	12/21×100%=57.1%
Stage 3		1 case(2→stage 3→2)→R 1 case(1→stage 2→3)→T 2 cases (stage 2→3) →T 4 cases T	3 cases T 1 case(1→stage 2→3)→T 6 cases (stage 2→3)→T	1/17×100% =5.9%
Incidence (Zone)	33/33×100%=100%	6/13×100%=46.2%	0/10×100%=0%	

R: spontaneous regression; T: treatment.

Table 2 Duration of ROP in the spontaneous regression ROP group (Group A) and Treated ROP group (Group B)

Time(weeks)	Group A	Group B	Significance
Time of initial screening in PMA	34.41±2.22(n=39)	34.30±2.10(n=17)	P=0.788
Time of initial screening in CA	2.94 ±1.89 (n=39)	4.44 ±2.29(n=17)	P=0.014
Time of onset of ROP	35.91±1.84 (n=39)	35.37±1.79(n=17)	P=0.311
Time of ROP regression	41.56 ±3.08(n=39)	42.38±4.65(n=8)	P=0.528
Duration of ROP	5.65±3.14 (n=39)	7.34±4.33(n=8)	P=0.201

ROP: retinopathy of prematurity; PMA: postmenstrual age; CA: chronological age.

performed using the two sample t-test for continuous variables and Fisher's exact test and χ^2 test for categorical variables. A P value of <0.05 was considered statistically significant. The factors that on univariate analysis were found to be statistically different between the groups were then included in a step-wise logistic regression analysis in order to determine the magnitude of association between the related factors and spontaneous regression of ROP. Effect estimates are expressed as odds ratios (OR) with profile likelihood-based on 95% confidence limits.

RESULTS

In our study, there were 56 patients included, who were divided into two groups depending on spontaneous regression or not. There were 30 babies with stage 1 ROP, of which 26 babies (86.7%) were observed spontaneous regression of changes in the retina and vitreous, 2 babies were detected to progress to stage 2 then involuted naturally and 2 were found to progress to severe stage for treatment. In stage 2, 12 infants (57.1%) out of 24 patients including the 2 from stage 1 were found to naturally regress, 9 progressed to stage 3 in which only one regressed completely in stage 3. While, in stage 3, there was only one case (5.9%) from stage 2 spontaneously regressed in the following examinations, the rest 16 patients were treated. Similarly, there were 33 babies with any ROP in zone Ⅲ, which were all completely regressed (100%). In zone Ⅱ, regression in 6 (46.2%) babies of 13 was detected. However, there was no case with natural involution in the three patients with ROP in zone Ⅰ (0%). Table 1 shows the spontaneous regression of ROP in different stage and area.

Table 2 shows a comparison of the two groups for duration of ROP, age of onset and complete regression of ROP, and time of initial screening. The mean duration of ROP in spontaneous regression group (Group A) was 5.65 ±3.14 weeks, which was lower than that of the treated ROP group (7.34 ±4.33 weeks) (Group B), but this difference was not statistically significant (P=0.201). The mean age of onset of ROP was 35.91±1.84 weeks and 35.37±1.79 weeks respectively in group A and B without any significant difference (P= 0.311). Although the average age of complete regression of ROP was slightly lower in group A than in group B, this difference also was not statistically significant (P=0.528). The mean postmenstrual age of initial screening in weeks in the two groups was not different significantly either (P= 0.788). However, the average weeks from birth to initial screening (chronological age) had significant difference (P=0.014).

After univariate analysis, the significant variables for spontaneous regression of ROP were gestational age (GA) (P=0.010), 1 min Apgar score (P=0.009), 5-min Apgar score (P=0.038), duration in NICU (P=0.020), oxygen therapy longer than 10 days (P=0.032) and presence of

Table 3 Univariate analysis for the spontaneous regression of ROP

Variables	Group A	Group B	*P*
GA(weeks)	31.48±2.28 (*n*=39)	29.86 ±1.62 (*n*=17)	[1]0.010
1min Apgar Score	8.10±1.79 (*n*=39)	6.18±2.51 (*n*=17)	[1]0.009
5-min Apgar Score	9.00±1.43 (*n*=39)	7.71±2.22 (*n*=17)	[1]0.038
Duration of NICU stay (days)	50.45±24.38 (*n*=39)	68.5±26.99 (*n*=17)	[1]0.020
Initial screening (CA) (weeks)	2.94±1.89 (*n*=3)	4.44 ±2.29 (*n*=17)	[1]0.014
Oxygen therapy＞10 days			[2]0.032
Retinal hemorrhage			[3]0.002

[1]Two-sample *t*-test; [2]Mann-Whitey *U* test; [3]Chi-Square test.

retinal hemorrhage (P=0.002). The average birth weight (BW) was 1573.08 ±373.31g for group A and 1375.88 ± 314.17g for group B, which was not significantly different (P=0.063). Accordingly, the mean weight gain in the first six weeks of life was 733.39 ±237.97g *vs* 669.29 ±223.18g between group A and B, but this difference was also not statistically significant (P =0.392). The other variables gender, mode of delivery, multiple births, single birth, duration of mechanical ventilation, use of surfactant, indomethacin, erythropoietin, dopamine, blue light, neonatal jaundice, blood transfusion, occurrence of PDA, HMD, septicemia were not considered significant for the spontaneous regression of ROP (P> 0.05). Of the seven predictive factors, only retinal hemorrhage remained in the logistic regression analysis as independent predictive factors (Tables 3, 4).

Table 4 Independent predictive factor for spontaneous regression of ROP after logistic regression

Variable	Beta	OR	95%CI	*P*
Retinal hemorrhage	-3.521	0.030	0.001-0.775	0.035

OR: Odds ratio; CI: Confidence interval.

DISCUSSION

ROP is a contemporary disease, most ROP regresses spontaneously by a process of involution or evolution from a vasoproliferative phase to a fibrotic phase[13]. One of the first signs of stabilization of the acute phase of ROP is the failure of the retinopathy to progress to the next stage [14]. The process of regression occurs largely at the junction of vascular and avascular retinal as retinal vascularization advances peripherally. On serial examinations, the anteroposterior location of retinopathy may change from zone Ⅰ to zone Ⅱ or from zone Ⅱ to zone Ⅲ.The ridge may change in color from salmon pink to white[12].

In our study, in order to record precisely the natural history of ROP, the time of onset was recorded when a demarcation line developed. As regression is a gradual process, it was difficult to be precise about the time it started. The incidence of spontaneous regression of ROP with stage 1 was 86.7%, and with stage 2, stage 3 was 57.1%, 5.9%, respectively. With changes in zone Ⅲ regression was detected in 100%, in zone Ⅱ in 46.2% and in zone Ⅰ in 0%.

The incidence of spontaneous regression of ROP is comparable to other studies[14,15]. Repka *et al*[14] reported that acute-phase ROP began to involute at a mean of 38.6 weeks postmenstrual age. In 90% of patients, the ROP began to involute before 44 weeks of postmenstrual age. Acute ROP that demonstrates involution by moving from zone II to zone III was associated with an unfavorable outcome in 2 (1%) of 200 cases. ROP that was present only in zone III during a child's serial retinal examinations was never associated with the development of a partial or total retinal detachment. Prost [15] studied 168 premature infants with active stages 1-3 and 91 with stages 4-5 ROP during years 1995-2002, they showed that spontaneous regression of changes in the retina and vitreous was observed in 85% of children with stage 1, in 56% in stage 2 and in 25% in stage 3. In stage 3, regression occurred in 35% in stage 3 A, in 18% in 3 B and in 12% in stage 3 C. With changes in zone III regression can be expected in 95%, in zone II in 45% and in zone I in 6%. Spontaneous reattachment of the retina was observed in 27% of children with stage 4A, in 15% with stage 4B and only in 6% in stage 5.

In the natural history of ROP, vascular congestion in the posterior pole was confirmed as an important clinical sign which act as an indictor of the activity of the shunt lesion and indicated whether it was still in an active phase [12]. Similarly, decreased congestion and tortuousity indicated early regression. From the observations made in this study it validates that the disease process in ROP is self-limiting, with a clinically identifiable time of onset and an end stage when the disease process becomes inactive regardless of the stage of ROP previously reached. The mean duration of ROP in the spontaneous regression group was 5.65 ±3.14 weeks. Eliason *et al* [16] reported that the average duration of untreated ROP in white non-Hispanics (8.6±5.4 weeks) and

Hispanics (8.9±7.0 weeks) was not significantly different. However, Hispanic infants showed significantly higher variance in duration than white non-Hispanic infants.

Since the development of ROP is a process, the duration of untreated ROP was not so precise, in our study, the longest duration of ROP in either eye was used for the duration calculations. One possible cause for longer (but not shorter) duration of ROP in some patients could be measurement error induced by missed appointments. If an infant was examined a week or two later than originally scheduled and was found to have regressed ROP at that time, the duration measurement would be artificially lengthened.

The length of the infants' stay in NICU in our study was 50.45±24.38 days *vs* 68.50±26.99 days in group A, B respectively, which had significant difference. Lad *et al*[17] reported that the ROP incidence 15.58% for premature infants with length of stay of more than 28 days from 1997 to 2005 in the United States. The results also conclusively demonstrated the length of stay of more than 28 days as a risk for ROP development in infants. Since prolonged duration of NICU stay was the major risk factors associated with newborn fungal sepsis [18], the shorter the duration of NICU stay, the better predictive for the spontaneous regression of ROP.

Neonatal retinal hemorrhages related to birth trauma are common, benign, and self-limited, other retinal hemorrhages in infancy may signify intracranial aneurysms, accidental or non-accidental injury, and a variety of ocular (*e.g.* Coats' disease, persistent hyperplasia of primary vitreous, ROP, retinal dysplasia, hypertension, myopia) or systemic disease (*e.g.* hematologic or cardiovascular disorders, infection, protein C deficiency) [19]. Retinal hemorrhage due to ROP tend to occur on the surface of the neovascular ridge, which represents an arteriovenous shunt formed by the anastomosis of primitive retinal vessels, meanwhile the vascular fragility also resulting in hemorrhage. Choi *et al* [20] found that most hemorrhages spontaneously resolved without any specific sequelae. In our population, 7 out of 39 in group A with retinal hemorrhage resolved within 13.00±9.54 days (n=3), while 10 out of 17 in group B with retinal hemorrhage resolved within 39.60±21.69 days (n=5). Occurrence of retinal hemorrhage in group A and B was significantly different (χ^2=9.356, P=0.002). Furthermore, presence of retinal hemorrhage was also an inversely predictive factor for the spontaneous regression of ROP.

However, one major limitation of this study is the small number of neonates diagnosed with ROP and smaller sample because of the failure to complete follow-up. It is worth mentioning that our observations are based on data from a single neonatal center and the results can not be accepted without reservations. Another limitation of the study is the difficulty in determining the precise time of ROP regression. Also, the method of calculating ROP duration as the time difference between when ROP was first seen and when ROP was found to be regressed may have resulted in measurements of duration that are artificially increased. The alternative of using the last visit was seen as the endpoint for the duration that calculation would have artificially decreased the duration measurement.

In conclusion, retinopathy of prematurity is a self-limiting disease, most stage 1 and 2 ROP and changes in zone Ⅲ can spontaneously regression in the end. It is worth well knowing the duration of ROP, especially the naturally involution ones can help greatly to choose the optimal initial screening time and limit the times of examination to decrease the discomfort for the infants during the process. The analysis of predictive factors for ROP regression will help to understand the natural history and predict regression in high premature infants. Since ROP may produce serious sequelae of infant blindness, all efforts must be made to prevent the development of advanced ROP. Further study may be useful to quantify these differences and to determine their clinical significance. A better understanding of the natural history of ROP may enable us to assess the effectiveness of medical interventions more accurately, but also to prevent unnecessary treatment in future.

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