

# Analysis of risk factors for retinopathy of prematurity

Wen-Lin Li, Li He, Xi-Hua Liu, Yu-Mei Wang, Jian-Qing Liu

Department of Ophthalmology, Shenzhen Children's Hospital, Shenzhen 518026, Guangdong Province, China

**Correspondence to:** Wen-Lin Li. Department of Ophthalmology, Shenzhen Children's Hospital, Shenzhen 518026, Guangdong Province, China. Wenlinli6688@126.com

Received: 2011-01-13 Accepted: 2011-11-17

## Abstract

• **AIM:** To analyze the incidence and risk factors for retinopathy of prematurity (ROP).

• **METHODS:** A retrospective analysis was conducted on 568 premature infants from September 2005 to December 2010 with birth weight (BW) equal to or less than 2 500g or a gestational age (GA) at birth of 34 weeks or less. All of the members were examined by indirect binocular ophthalmoscopy.

• **RESULTS:** ROP occurred with an incidence rate of 10.7% among 568 premature infants, and stages 3 and above ROP occurred with an incidence rate of 2.5%. This study showed the infants were more prone to develop ROP with short gestational age, low BW, long time of oxygen inhalation, and severe infants diseases. Twins had a significantly higher rate of ROP (18.3%) than singleton babies (9.8%), ROP were severer in twins than singleton babies .

• **CONCLUSION:** Short GA, low BW, long time of oxygen inhalation, severe infants diseases, and non-singleton babies were the most significant risk factors associated with ROP.

• **KEYWORDS:** retinopathy of prematurity; ROP epidemiology; ROP incidence

DOI:10.3980/j.issn.2222-3959.2011.06.11

Li WL, He L, Liu XH, Wang YM, Liu JQ. Analysis of risk factors for retinopathy of prematurity. *Int J Ophthalmol* 2011;4(6):631-633

## INTRODUCTION

Retinopathy of prematurity (ROP) is a retinal angiopathy, which occurs in premature infants, especially with low birth weight (BW). With the development of the modern Neonatology and the rise of the survival rate among preterm neonates, the incidence of ROP also showed an increased tendency. So, the neonate's quality of life is seriously influenced by the occurrence of ROP.

This study aims to analyze the incidence and the main risk factors for ROP.

## MATERIALS AND METHODS

**Materials** Five hundred and sixty-eight premature infants with gestational age (GA) between 26 and 34 weeks and BW ranged from 962 to 2 500g were screened by indirect binocular ophthalmoscopy from September 2005 to December 2010 in our hospital, and the gender, GA, corrected GA, BW, situation of aspirating oxygen were recorded, whether having neonate's choke, cranial cavity bleeding, anemia and neonate pneumonia.

**Methods** The retinal fundus was examined regularly since infants were 4-6 weeks old and corrected GA was 32 weeks. Thirty minutes before examining, we used Mydrin-P eye drops which contains 5g/L tropicamide and 25g/L pheylephrine to dilate pupils, 5 minutes for one drop per time, a total of 4 times. We examined the posterior and peripheral fundus and the developmental situation of peripheral retinal vessel by indirect binocular ophthalmoscope with 28D lens and scleral depressor. Records were made according to the international classification of ROP. After the first examination, the infants without ROP were examined after 2 weeks, and the babies with stage 1 and 2 ROP were examined every week and the babies with stage 3 or above ROP were examined every day until complete development of peripheral retinal vessel. Threshold ROP patients were treated by photocoagulation. Patients with more severe stages of ROP (stage 4-5) were operated immediately.

**Statistical Analysis** Statistical analysis was performed with SPSS version 15.0 and data were expressed as mean± standard deviation. Analysis of variance (LSD method and  $\chi^2$  test) and  $t$  test were applied for analysis.  $P < 0.05$  was considered statistically significant.

## RESULTS

**Incidence of ROP** Among the examined 568 premature infants, we found that 61 of them (10.7%) achieved ROP in different degrees, in which 28 cases (4.9%) at ROP stage 1, 19 cases (3.4%) at stage 2 of ROP, 10 cases (1.8%) at stage 3 of ROP, 2 cases (0.4%) at stage 4, and 2 cases (0.4%) at stage 5 of ROP. There were 2.5% of the patients over stage 3 of ROP.

## Risk factor for ROP

**ROP Incidence and GA** The younger the GA was, the higher the ROP incidence was ( $P < 0.01$ ). The ROP incidence of the premature infants whose GA was less than 28 weeks was 53.8%, 12.5% for GA 28-32 weeks, and 5.8% for GA 32-34 weeks (Table 1).

**ROP Incidence and BW** The lower the BW was, the higher the ROP's rate was ( $P < 0.05$ ). The ROP incidence of the infants whose BW was 1 000g, was 64.0%, 23.9% for BW 1 000-1 500g; 7.9% for BW 1 501-2 000g, and 2.8% for BW 2 001-2 500g (Table 2).

**ROP Incidence and Postnatal Oxygen Inhalation** Among the premature infants that aspirated oxygen from 48 hours to one week without stopping, the ROP incidence was 10.3%, and over one week, the rate was 15.9%. ROP incidence was closely associated with the time of postnatal oxygen inhalation.

**ROP Incidence and Neonate Diseases** Various kinds of diseases which the prematures suffered from after birth, such as respiratory distress syndrome of newborn, neonatal pneumonia, neonatal anemia, neonatal fetal distress and neonatal hypoxic ischemic encephalopathy maybe make ROP more serious. In present study, the ROP incidence of the infants with neonatal hypoxic ischemic encephalopathy was the highest, which reached 74.9%; the next was the infants with neonatal fetal distress, whose ROP incidence reached 48.7%. The ROP incidences were respectively 35.2%, 28.3%, 18.6% for respiratory distress of newborn, neonatal pneumonia and neonatal anemia.

**ROP Incidence and Fetus Number** The incidence of ROP in twins was higher than that in singletons, which was respectively 18.3%, 9.8% (Table 3).

**Treatment of ROP** Ten cases with ROP stage 3 threshold disease were treated by retinal photocoagulation. Two cases with ROP stage 4 and two cases with stage 5 of ROP were treated by vitreoretinal surgery, twenty-eight cases with ROP stage 1 and nineteen cases with stage 2 were observed 3 months continuously.

## DISCUSSION

Recently, although great progress has been made in ROP diagnosis and treatment, ROP still becomes one of the main diseases which causes childhood blindness [1-3]. In the developed country, ROP accounts for 6% to 18% among causes of blindness in children [4]. In the 1980s, Euro-American's ROP' rates were 10%-34%, and Larsson *et al* [5] reported that the rate of ROP in 392 premature infants was 25.5% in Stockholm, Sweden between 1998 and 2000 years, and in which the rate with stage 3 ROP was 11.7%. With the improving of the infant's serious disease's nursing level, the survival rates of the prematures with low BW steadily raise, which also cause increase in the ROP's rate [6], Li [7] reported about the result of Beijing screening 6 600

**Table 1 ROP's circumstances with different gestational age n(%)**

ROP	≤27 weeks	28-31 weeks	32-34 weeks
Non-ROP	12(46.2)	203(87.5)	292(94.2)
ROP1	5(19.2)	12(5.2)	11(3.5)
ROP2	5(19.2)	9(3.9)	5(1.6)
ROP3	3(11.5)	5(2.2)	2(0.65)
ROP4	0(0.0)	2(0.8)	0(0.0)
ROP5	1(3.8)	1(0.4)	0(0.0)
Total	26(100)	232(100)	310(100)

$P < 0.01$

**Table 2 ROP's circumstances with different birth weight n(%)**

ROP	≤1000g	1001-1500g	1501-2000g	2001-2500g
Non-ROP	9(36.0)	70(76.1)	185(92.0)	243(97.2)
ROP1	8(32.0)	8(8.7)	8(4.0)	4(1.6)
ROP2	4(16.0)	6(6.5)	6(3.0)	3(1.2)
ROP3	3(12.0)	5(5.4)	2(1.0)	0(0.0)
ROP4	1(4.0)	1(1.1)	0(0.0)	0(0.0)
ROP5	0(0.0)	2(2.2)	0(0.0)	0(0.0)
Total	25(100)	92(100)	201(100)	250(100)

$P < 0.05$

**Table 3 ROP incidence of twins and singletons n(%)**

ROP	Singletons	Twins
non- ROP	458 (90.2)	49 (81.7)
ROP1	25 (4.9)	3 (5.0)
ROP2	16 (3.2)	3 (5.0)
ROP3	7 (1.4)	3 (5.0)
ROP4	1 (0.2)	1 (1.7)
ROP5	1 (0.2)	1 (1.7)
Total	508(100)	60(100)

infants between July 2002 and June 2003, and showed that when GA was less than 34 weeks and BW was lower than 2 000g in 109 premature infants, the ROP's rate was 1.7%. However, ROP's rate of 568 premature infants in our investigation was 10.7%. We thought it maybe relate to the rapid development of the modern Neonatology in recent years causing the rise of the survival rate among premature neonates, ROP incidence rates have increased significantly. The real mechanism of ROP is still not clear. Nowadays, people commonly believe that subretinal neovascularization plays an important role in ROP development, and numerous investigations show that ROP is caused by many factors [8,9], including prematurity, low BW, oxygen-therapy, neonates asphyxia, serious infection, cranial cavity bleeding, respiratory distress syndrome, hyperbilirubinemia, but the most essential factor is the infant immaturity. Numerous studies indicated that the lower the GA and BW were, the higher the ROP rate was, as well as the patient's condition is more serious. It is reported that among 194 infants whose BW was lower than 1 500g and GA was less than 32 weeks, the rate of ROP stage 1 and ROP stage 3 was 26.3% and 2.5% respectively in Europe [10] between 1992 and 2000 years. In Brazil, Graziano *et al* [11], in 1997, reported about

102 infants' ROP rate between January 1992 and November 1993, the BW was less than 1500g, the ROP rate was 29.1%; and the BW was <1000g, the rate was 78.5%. The GA was <30 weeks, the ROP rate was 72.7%. Besides, the authors thought that infants with BW<1000g and GA<28 weeks were prone to above ROP stage 3.

The investigation of supplemental therapeutic oxygen for prethreshold ROP (STOP-ROP)<sup>[12]</sup> showed that in infants whose BW was <750g, 750g-900g and 1000g-1250g, their ROP rates were 90.0%, 78.2% and 46.9%, respectively. The ROP rate for GA ≤27 weeks, 28-31 weeks, ≥32 weeks were 83.4%, 55.3% and 29.5%, respectively. For above ROP stage 2, the ROP rate dropped as the BW and GA increased. Our investigation showed that ROP rates were 64.0%, 23.9%, 7.9%, and 2.8%, respectively, for the infants whose BW ≤1000g, 1001-1500g, 1501-2000g, 2001-25000g, and the ROP rate were 53.8%, 12.5%, 5.8%, respectively, for infants whose GA ≤27 weeks, 28-31 weeks, 32-34 weeks.

Unreasonable oxygen therapy also is one of the main risk factor for ROP. Whether aspirating oxygen could bring about ROP or not, which is dependent on the oxygen concentration, time of use, the way of aspirating oxygen, etc. The higher the concentration is, the higher the ROP rate is. In this time of aspirating oxygen at 2-7 days and over 7 days, the incidences of ROP were 10.3% and 15.9%, respectively. There were three infants among which one was at ROP stage 4 and the rest was at ROP stage 5, the time of aspirating oxygen were all over one week. Because our investigation was a retrospective analysis, and the concentration and way of aspirating oxygen were not very detailed, so we didn't summarize and count. The investigation of York *et al*<sup>[13]</sup> showed that the sharper the fluctuation of arterial blood partial pressure of oxygen was, the higher the ROP rate was, and the patients' condition became more and more serious. Besides, dropping suddenly of oxygen concentration was easier to bring about ROP than dropping gradually.

The infant's kinds of risk factors were related closely to ROP. In our study, the ROP rate of the prematures with hypoxic ischemic encephalopathy was 74.9%, ROP rate of the prematures with neonatal fetal distress was 48.7%. For the infants with younger GA maybe have immature development of lung. Meanwhile, they were easier to suffer hypoxic ischemic encephalopathy and neonatal fetal distress etc. So in order to maintain their live, infants must be treated with oxygen therapy. Immature retinal vascular is sensitive to oxygen; the relative high concentration of oxygen can lead to the retinal vascular contraction, blocking; and the retina hypoxia, which brings about vascular growth factor and excites the subretinal neovascularization forming, thereby promotes the occurrence as well as development of ROP.

In present study, the ROP incidence in twins was higher than that in singletons, our results were different from Frilong's. Friling *et al*<sup>[14]</sup> reported that Singletons had a significantly higher rate of advanced ROP (stages II-III) (30.2%) than twins (23.1%). We thought that it maybe relate to the more occurrence rate of the twins with low GA, low BW, neonatal hypoxic ischemic encephalopathy, neonatal fetal distress and asphyxial neonate, but we have no detailed statistics in this regard.

In conclusion, we should highly pay attention to the infant's ocular fundus screening, meanwhile, we also can't ignore these infants with aspirating oxygen too long, suffering kinds of diseases, especially non-singleton. How to reduce the ROP rate and improve the infant's quality of survival have become the most difficult and urgent problem that need to be solved by doctors in neonatology and pediatric ophthalmology in all over the world. With the standardizing of the pediatrics' oxygen therapy and the popularizing of the ROP screening work, the ROP rate will reduce gradually.

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