Original Article

Incidence and Risk Factors for Retinopathy of Prematurity in North of Iran

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Abstract

Purpose: To report the incidence and risk factors for retinopathy of prematurity (ROP) among preterm infants referred to Amiralmomenin Eye Hospital, Rasht, Iran.

Methods: This cross-sectional retrospective study included all preterm infants with birth weight ≤2500 g and/or gestational age ≤36 weeks who had been referred to our facility for ROP screening over a five year period from September 2005 to September 2010. Possible risk factors and findings related to eye examinations were extracted and analyzed.

Results: Among 310 infants, ROP was diagnosed in 64 (20.6%) of referred preterm infants (95% CI: 17.7%-23.5%); these included stage I in 48%, stage 2 in 29%, and stage 3 or higher disease in 23% of subjects. Mean gestational age (GA) and birth weight (BW) in the ROP–affected infants was 30.18 ± 2.28 weeks and 1,422.8 ± 420.8 g, respectively. Low BW, low GA, oxygen therapy, phototherapy, blood transfusion and apnea were risk factors for ROP. After logistic regression analysis, only low GA and low BW were independently associated with the condition.

Conclusion: ROP is a relatively common finding in preterm infants of Guilan Province in the North of Iran. Low BW and low GA were significant risk factors for the disease.

Keywords: Incidence; Infant; Premature; Retinopathy of Prematurity; Risk Factors

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INTRODUCTION

Retinopathy of prematurity (ROP), characterized by abnormal development of retinal vasculature, is an important and preventable cause of childhood blindness.[1] It is estimated that ROP is the cause of 50,000 cases of childhood blindness in the world every year.[2] Introduced in the 1940s as retrolental fibroplasia, ROP presented as an epidemic disease in the 1950s in premature babies in the USA and Western Europe. This epidemic was considered to be caused by unmonitored supplemental oxygen. The second epidemic of ROP was also described in industrialized countries in the 1970s, the cause of which was considered to be higher survival rates in extremely premature babies.[3] According to the available data, there has been an increase in the incidence of ROP in developing countries, which is referred to as the third epidemic.[4] There are several possible reasons for this epidemic such as higher birth rates, especially higher premature birth rates in these countries and compromised neonatal care.[4,5]

A high concentration of supplemental oxygen therapy was previously thought to be the major risk factor for development of ROP.[6-9] However, there are many reports that ROP has been observed in patients without oxygen therapy.[10] Low birth weight (BW) and low gestational age (GA) are well-known risk factors for ROP,[11-18] however several other risk factors have also been implicated such as gender, phototherapy, multiple pregnancy, intraventricular hemorrhage and blood transfusion.[15-18]

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The criteria for ROP screening have been well determined in industrialized countries, but the available data suggests that blindness from ROP varies from region to region.[3] According to many studies performed in various parts of the world, it has been recognized that ROP screening in each region has its own characteristics and a single screening program cannot suit all regions.[4] Iran is one of the countries considered to have a high incidence of ROP;[3] a few studies have addressed the incidence and risk factors of ROP, the most important of which is the study performed by Karkhaneh et al[18] at Farabi Eye Hospital. There is insufficient data regarding ROP in the North of Iran[19] and the current study was designed to determine the incidence and risk factors associated with ROP, and identify infants at risk of the disease in this geographic region.

METHODS

This retrospective cross-sectional study included all infants with BW of 2,500 g or less and/or GA of 36 weeks or less who had been referred to Amiralmomenin Eye Hospital, Rasht, Iran for ROP screening from September 2005 to September 2010.

Data on BW, GA (as determined by either the last menstrual period or ultrasound in the first trimester of pregnancy and confirmed by physical examination of the neonate), gender, multiplicity of gestations, intraventricular hemorrhage, oxygen therapy, mechanical ventilation, respiratory distress, apnea, blood transfusion and phototherapy were collected from the hospital records. The last seven factors were defined as not/any. All infants with fatal systemic anomalies, features suggestive of Norrie disease, media opacity (not related to ROP) precluding fundus visualization, congenital hydrocephalus, cyanotic congenital heart disease, referral later than 10 weeks after birth and loss to follow-up were excluded from the study.

The first examination was performed between 4-6 weeks of age or between 31-33 weeks postmenstrual age. The pupils were dilated by application of tropicamide 0.5% and phenylephrine 1%, and the patients were examined by a retina subspecialist using a binocular indirect ophthalmoscope with 20 D and 30 D lenses. A sterile lid speculum and a scleral depressor were routinely used.

ROP was classified according to the international classification of ROP and follow-up schedules were designed in accordance with suggestions of the American Academy of Pediatrics, American Academy of Ophthalmology and American Association for Pediatric Ophthalmology and Strabismus.[20] Treatment plans were based on recommendations of the Early Treatment of ROP cooperative group.[21]

Data was analyzed by SPSS statistics for windows, Version 18 (Chicago:SPSS Inc.). Univariate analysis was performed with independent *T*-Test and Chi-square Tests. For multivariate analysis, Stepwise logistic regression model was employed to determine the most important risk factors of ROP. *P* values < 0.05 were considered as statistically significant.

RESULTS

During the five-year study period, 345 infants were referred to Rasht Amiralmomenin Hospital. Of these, 14 infants were excluded because of BW more than 2,500 g and/or GA more than 36 weeks. Eleven other infants were excluded because they were referred later than 10 weeks after birth and 10 more were excluded because of incomplete data especially regarding risk factors of ROP. Eventually, 310 infants were enrolled including 140 (45.2%) female and 170 (54.8%) male subjects. Mean BW was 1,727.41 ± 471.05 g and mean GA was 31.88 ± 2.44 weeks.

ROP was observed in 64 (20.6%) infants (95% CI: 17.7%-23.5%), of whom 31 infants (48%) had stage 1, 19 infants (29%) had stage 2, 11 infants (17%) had stage 3, and 3 infants (0.04%) had stage 4 and 5 of the disease. Mean GA of infants with ROP was 30.18 ± 2.28 weeks (range, 25-35 weeks) and mean BW was 1,422.8 ± 420.8 g (range 720-3,000 g). Tables 1 and 2 show the relationship between GA and BW with ROP.

GA of patients with ROP was significantly lower than that of subjects without ROP (independent *T*-test, $P < 0.0001$). A significant difference was also observed between BW of patients with ROP and those without ROP ($P < 0.0001$). The effect of gender, delivery type, multiple pregnancy, intubation and mechanical ventilation, and intraventricular hemorrhage were evaluated by χ^2 test and none of them showed significant relation with development of ROP [Table 3]. However, a significant association was observed between ROP on one hand,

Table 1. Correlation between retinopathy of prematurity (ROP) and birth weight (BW)

BW (g)	Number of infants		Stage (number)			
	Subtotal	With ROP (%)	1	2	3	4-5
≤1.000	17	8 (47.1)	2	4	1	1
1.000-1.250	32	19 (52.4)	6	9	4	0
1.251-1.500	56	13 (23.2)	4	4	4	1
1.501-2.000	114	18 (15.8)	14	1	2	1
>2.000	91	6 (8.6)	5	1	0	0
Total	310	64 (20.6)	31	19	11	3

BW, birth weight; ROP, retinopathy of prematurity; g, gram

Table 2. Correlation between retinopathy of prematurity (ROP)and gestational age (GA)

GA (week)	Number of infants		Stage (number)			
	Subtotal	With ROP (%)	1	2	3	4-5
≤28	32	17 (53.1)	5	7	3	2
29–32	144	37 (25.7)	19	9	8	1
>32	134	10 (7.5)	7	3	0	0
Total	310	64 (20.6)	31	19	11	3

ROP, retinopathy of prematurity; GA, gestational age

and oxygen therapy, phototherapy, respiratory distress, transfusion and neonatal apnea on the other. After logistic regression analysis, only low GA and low BW retained a significant relation with ROP [Table 4].

DISCUSSION

ROP is considered to be a preventable cause of childhood blindness especially if diagnosed and treated at an appropriate time. Iran seems to be one of the countries experiencing the third epidemic of the disease,[3,4,18] therefore it is predicted that the risk of ROP-related blindness in this country is significant. This necessitates acquisition of data about the population at risk.

The current study was conducted at Rasht Amiralmomenin Hospital, Guilan University of Medical Sciences, which is the only tertiary eye hospital in Guilan province, North of Iran. The incidence of ROP in premature infants in our study was 20.6%. In developed countries, the reported incidence of ROP ranges from 19.3% to 25%.[22-24] There is insufficient literature from developing countries as compared to developed countries, probably because ROP has recently emerged as an important cause of childhood blindness. In Iran, reported rates depend on the region of study and vary from 17.5% to 42%.[18,19,25,26] Likewise in India, the incidence of ROP depends on the region of study and ranges from 20% to 47.3%.[27,28]

In the current study the incidence of ROP was lower than that reported in a study from Iran by Karkhaneh et al[18] who reported the condition in 34.5% of infants referred from all over the country to Farabi Eye Hospital and in 25% of infants born in the capital city, Tehran. Table 5 compares the incidence of ROP in our study with studies conducted in other countries and other regions of Iran. Even though, this wide variation in the incidence of ROP can reflect racial and geographical diversity, differences in methodology and selection criteria (including variations in GA and BW) may explain the disparity among these studies.

Comparing the incidence of ROP in industrialized countries during the current decade, the incidence of the disease was higher in our study. The incidence of ROP in infants with BW ≤1,500 g has been reported to be 19% in England,[22] 15% in France[29] and 5.4% in Sweden,[24] but 38% in our study which is comparable to the study by Karkhaneh et al. (40.8%),[18] emphasizing the fact that Iran is now experiencing an epidemic of ROP.

There was a significant correlation between gestational age, birth weight, blood transfusion, respiratory distress,

Table 3. Evaluation of risk factors for neonates with and without ROP

Risk factors	ROP (*n*=64)	No ROP (*n*=246)	*P*
GA (week)	30.18±2.28	32.45±2.26	0.0001
BW (g)	1422.8±420.8	1806.6±451.4	0.0001
Gender			
Female	31	109	0.575
Male	33	137	
Oxygen therapy	63	205	0.002
Mechanical ventilation	7	12	0.08
Respiratory distress	60	202	0.02
Blood transfusion	35	55	0.0001
Multiple births	15	89	0.529
Phototherapy	59	186	0.003
Apnea	26	29	0.0001
Intraventricular hemorrhage	6	19	0.6

ROP, retinopathy of prematurity; GA, gestational age; BW, birth weight; g, gram; n, number

Table 4. Stepwise logistic regression analysis of risk factors for ROP

Potential Risk Factor	*P*
BW ≤1000 g	0.049
1001< BW <1500 g	0.004
GA ≤28 weeks	0.001
29 <GA <32 weeks	0.004

ROP, retinopathy of prematurity; GA, gestational age; BW, birth weight; g, gram

Table 5. Incidence of ROP in our study compared to studies conducted in other countries and other regions of Iran

Authors	Year	Country	BW or GA	Number	ROP (%)
Binkhathlan et al[10]	2007	Arabia	GA <36 weeks or BW <2000 g	174	56
Shah et al[16]	2002	Singapore	BW <1500 g	564	29.2
Karkhaneh et al[17]	2008	Iran (Tehran)	GA <37 weeks	953	34.5
Ebrahim et al[19]	2010	Iran (Babol)	GA <37 weeks	196	19
Ho et al[22]	2005	England	BW <1500 g	187	19.3
Darlow et al[23]	1988	New Zealand	BW <1500	313	21
Larsson and Holmström[24]	2002	Sweden	GA <32 weeks	487	25.5
Naderian et al[25]	2010	Iran (Isfahan)	GA <37 weeks	604	17.5
Bayat-Mokhtari et al[26]	2009	Iran (Shiraz)	BW <1500 g	199	42
Mutlu et al[29]	2006	Turkey	GA <34 weeks	318	37.1
Our study	2011	Iran (Rasht)	GA <36 weeks or BW <2500 g	310	20.6

ROP, retinopathy of prematurity; GA, gestational age; BW, birth weight; g, gram

oxygen therapy and phototherapy with ROP which is consistent with findings of studies performed by Binkhathlan et al,[13] Karkhaneh et al,[18] Mutlu et al[30] and Palmer et al[31]

Multivariate analysis using a logistic regression model, confirmed that only low gestational age and birth weight were significant risk factors for development of ROP. The results of our study are in agreement with previous observations.[13,18,26,30]

We found that oxygen therapy was not an independent risk factor for development of ROP. In agreement with this finding, Palmer et al. reported that oxygen therapy was a non-significant factor for occurrence of ROP. They reported that ROP may also develop in cases who do not receive oxygen therapy.[32] On the other hand, oxygen therapy was an independent risk factor for the development of ROP in many other studies[16,17,32,33] Several studies have shown a significant relationship between the duration of oxygen therapy, oxygen saturation levels, and rapid changes and fluctuations of oxygenation on the development and severity of ROP.[16,17,34-39] Insufficient data on oxygen saturation levels and fluctuations, and duration of oxygen therapy in the current study may partly explain our disagreement with other studies. In our study, mechanical ventilation and respiratory distress were not independent predictors of ROP, which concurs with the report by Murthy et al[33] However, Shah et al reported that ventilatory support was significantly associated with the development of ROP.[17] Differences in the design of these studies may explain the disagreement.

In the current study, risk factors for ROP including phototherapy, blood transfusion, apnea and intraventricular hemorrhage, which are in agreement with previous studies, were not found to be significantly associated with ROP after multivariate regression analysis. Similar to previous studies, risk factors including blood transfusion, phototherapy, apnea and intraventricular hemorrhage, were not found to be significantly associated with ROP.[13-18]

The incidence of ROP in premature infants with BW lower than 1,000 g was low in our study. The number of referred infants with birth weight ≤1,000 g was also relatively small (only 17 cases) which may explain the lower than expected incidence of ROP in this particular subgroup. The low survival rate in infants ≤1,000 g after the 4th post-gestational week in our region is the major factor for the small number of referrals. A study with a larger sample in our province may show the true incidence of ROP in such cases.

Certain limitations pertain to this study. First the study was conducted at a referral eye hospital, so the results may not reflect the true incidence of ROP in the province of Guilan. Second, the nature of this study was retrospective with its own limitations. Third, loss of follow-up due to death of infants with very low gestational age may have affected our results. In addition, sepsis and duration of oxygen therapy as probable risk factors for ROP were not documented in the current study.

In summary, the relatively high incidence of ROP in this study from the North of Iran emphasizes the importance of neonatal screening in this region. The wider range of BW and GA in infants affected with ROP reveals that by application of screening guidelines from industrialized countries in our region, some cases of ROP will be missed; most of these cases are more mature infants with low risk of ROP. Therefore, the screening guidelines seem to require modifications for our region. Since low BW and low GA were the main risk factors for the disease, the best way to reduce the incidence of ROP is better maternal care to prevent premature delivery, and to improve NICU care and monitoring of premature infants during hospitalization.

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