Neonatal risk factors for retinopathy of prematurity – a population-based study

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ABSTRACT.

Purpose: **The aim of the study was to evaluate possible neonatal risk factors for retinopathy of prematurity (ROP) in a population-based group of preterm, very low birth weight, infants.**

Method: **The main study group included 202 single-born infants with a birth weight of 1500 grams or less. A group of 57 twins were also described. Selected risk factors were extracted from the neonatal records.**

Results: **Univariate analysis revealed an association between ROP and respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), septicaemia, intraventricular bleeding, and the use of ventilator as well as continuous positive airway pressure. In a stepwise logistic regression analysis, however, only gestational age at birth, birth weight and BPD were significantly associated with ROP.**

Conclusion: **Prematurity *per se* remains the strongest risk factor for ROP.**

Key words: retinopathy of prematurity – risk factors – gestational age – birth weight – bronchopulmonary dysplasia.

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A prospective, population-based study of the epidemiology and natural history of retinopathy of prematurity (ROP) was performed in our area during 1988 to 1990 (Holmström et al. 1993). Risk factors for ROP were also studied and a detailed analysis of *maternal* data from antenatal centres and labour rooms was recently published (Holmström et al. 1996). An association of ROP with essential hypertension before pregnancy was found. To supplement the analysis of risk factors for ROP in this population-based group of infants, we added to the study an analysis of *infant-related* risk factors. Further, we included a description of the multiple births, who in previous publications were omitted from analysis, to keep confounding factors to a minimum.

Material and methods

The present study of neonatal risk factors for ROP is based on a population-based, prospective study of the epidemiology of ROP in a well defined geographic area (Holmström et al. 1993). Two hundred and sixty infants with a birth weight of 1500 grams or less and with a survival of at least 8 weeks, were included in that study.

Two hundred and fifty-nine infants – i.e. all the above-mentioned 260 infants, except one for whom no neonatal data could be found – are included in the present study (Table 1). The infant who was not included weighed 810 grams, had a gestational age of 26 weeks at birth, developed ROP stage 3 and underwent cryotherapy.

In the original study group, 57 multiple births were included because they fulfilled the criteria of a birth weight of 1500 grams or less and a survival of at least 8 weeks. Of these, 34 came from

Table 1. Gestational age, birth weight and sex of the study population.

		Gestational age (complete weeks)		Birth weight (g)		Sex (n)	
	n	Mean	Range	Mean	Range	Female	Male
Total premature group	259	29	24–35	1159	648–1500	134	125
Single births	202	28.9	24–35	1139	648–1490	106	96
Multiple births	57	29.4	26–35	1228	839–1500	28	29
Dropout group	33	31.7	27–36	1318	1000–1500	18	15

Table 2. Major neonatal diagnoses and treatments.

Respiratory distress syndrome (RDS)	Ventilator
Bronchopulmonary dysplasia (BPD)	Continuous positive airway pressure (CPAP)
Apnea	Oxygen by mask
Pneumothorax	Exchange transfusion
Pneumonia	Phototherapy
Septicemia	
Intraventricular bleeding	
Patent ductus arteriosus	
Hyperbilirubinemia	
Hypoglycemia	

complete twin sets, while a further 17 had a sibling who weighed more than 1500 grams or who died within 8 weeks after delivery. There was one complete set of quadruplets. In another set of quadruplets two infants weighed more than 1500 grams.

Thus, 202 single-born infants (259 less 57) constitute the main study group, of whom 106 were female and 96 male.

There was a dropout group of 35 infants. Twenty-one of those were excluded because the first examination was performed too late, – i.e. after term, or because the last examination was performed too early, i.e. before term. Fourteen infants were not referred from the neonatologists; they were identified with the help of the Swedish National Board of Health and Welfare. The dropout group has been clinically described, although we have no information on ROP in these infants. When looking at the neonatal data, we found that 2 of the 35 infants were stillborn and should not have been included in the dropout group from the outset.

In the present study, we chose 15 diagnoses and treatments considered as possible risk factors for ROP, either on basis of previous studies or because they appear relevant for fetal metabolism and circulation (Table 2). Factors known to be recorded only with irregularity by the neonatologists were omitted from analysis.

Bronchopulmonary dysplasia (BPD) was diagnosed according to Northway et al. (1967), – i.e. infants treated with ventilator and having a characteristic picture on x-ray.

Statistical methods

For continuous data, the unpaired t-test was used when the distributions were normal and the Mann-Whitney test when the distributions were not normal.

Initially, associations between potential risk factors and ROP were assessed using the chi-square test or Fisher's exact test. Considering the multivariate structure of the data, we found that a stepwise, forward, logistic regression analysis was necessary to determine the most important predicting factors (Hosmer et al. 1989).

Results

ROP was seen in 81 (40.1%) of the 202 single-born infants in the main study group. Of these, 40 (19.8%) had mild ROP (18 stage 1, 22 stage 2) and 41 (20.3%) had severe ROP (36 stage 3, five stage 4). There was no correlation between gender and ROP. As shown in the previous, prospective, population-based study (Holmström et al. 1993), the ges-

Table 3. Variables showing a significant relation with ROP ($p<0.05$).

	ROP (n=81)		No ROP (n=121)				95% CI of Odds Ratio	
	n	%	n	%	p	Odds Ratio	Lower bound	Upper bound
Respiratory distress syndrome (RDS)	33	(40.7)	31	(25.6)	$p<0.05$	2	1.09	3.65
Bronchopulmonary dysplasia (BPD)	18	(22.2)	2	(1.7)	$p<0.001$	17	3.82	75.64
Septicemia	17	(21)	11	(9.1)	$p<0.05$	2.66	1.17	6.02
Intraventricular bleeding	17	(21)	9	(7.4)	$p<0.01$	3.31	1.39	7.85
Ventilator	28	(34.6)	15	(12.4)	$p<0.001$	3.73	1.84	7.58
Continuous positive airway pressure	33	(40.7)	33	(27.3)	$p<0.05$	1.83	1.01	3.33

Table 4. Results of the stepwise multiple logistic regression analysis of neonatal variables associated with ROP.

Risk Factor	Log Odds Ratio (b)	Standard Error of b	Odds Ratio	95% CI of Odds Ratio	
				Lower bound	Upper bound
Gestational age at birth	−0.304	0.091	1.36[1)]	1.14	1.62
BPD	2.303	0.796	10.0	2.08	48.1
Birth weight	−0.0019	0.00084	1.20[2)]	1.02	1.42
Constant	10.26				

[1)] Odds ratio for a decrease of 1 week in gestational age.
[2)] Odds ratio for a reduction of 100 g in birth weight.

tational age was significantly lower in the ROP group (27.7 weeks), than in the no ROP group (29.8 weeks) ($p<0.001$). Correspondingly, the two groups had mean birth weights of 1031 g and 1211 g, respectively ($p<0.001$). Obviously, the more immature the infant, the higher the risk of ROP.

Univariate analysis of the association between ROP and a given diagnosis or treatment was performed. Variables showing a significant difference ($p<0.05$) between the ROP and no ROP groups are presented in Table 3.

A stepwise logistic regression analysis of the significant findings from the univariate analysis was then performed. The relation of the log odds of the gestational age and the birth weight to ROP was linear, and it was therefore decided to include them as continuous variables in the regression analysis (Hosmer et al. 1989). Gestational age at birth, BPD and birth weight were associated with ROP (Table 4). The odds ratio was calculated for a decrease of one week of gestation and for a reduction of 100 grams in birth weight.

ROP was seen in 23 (40.4%) of the 57 multiple births. Severe ROP was seen in 10 (17.5%) of the multiple births (versus 20.3% in single-born). No significant differences with regard to neonatal diagnosis and treatment were seen among the multiple births, as compared to the main study group.

Five sets of twins with a difference of at least two stages of ROP (a difference regarded as clinically significant), were separately analysed. There was no correlation between birth weight and ROP. In four of the five sets, however, the sickest infant had the highest stage of ROP.

In the dropout group of 33 children, the mean birth weight was higher than in the total group of 259 infants (1318 versus 1159 grams) and the infants had a higher mean gestational age at birth (31.7 versus 29 weeks). Twenty-two of the infants were single births and 11 were multiple births.

A further analysis of the single-born infants in the dropout group showed that they, on the whole, were less immature and less sick than the infants in the main study group. No single-born infant in the dropout group had a diagnosis of bronchopulmonary dysplasia, patent ductus arteriosus or intraventricular hemorrhage. Sepsis was seen less often (4.5% versus 13.9%) and only 4.5% in the dropout group required treatment with a ventilator, against 21.3% in the main study group.

Discussion

The etiology of ROP remains obscure, and is thought to be multifactorial (Majima 1977, Bossi et al. 1984, Purohit et al. 1985, Hammer et al. 1986, Darlow et al. 1992, Schaffer et al. 1993, Gallo et al. 1993). Immaturity *per se* seems to be the most important risk factor (Majima 1977, Bossi et al. 1984, Darlow et al. 1992, Schaffer et al. 1993). Oxygen supply also seems to be related to the development of ROP (Lucey & Dangman 1984), but since hyperoxia (Patz et al. 1952, Kinsey et al. 1977), fluctuations of oxygen (Gallo et al. 1993, Lucey 1988, Saito et al. 1993) as well as hypoxia (Ashton & Henkind 1965, Johnson et al. 1978, Lucey et al. 1981) have been associated with the condition, the pathogenetic role of oxygen, as related to modern neonatology principles, remains enigmatic.

The infants belonging to the dropout group presented with fewer potential neonatal risk factors for ROP, in terms of degree of prematurity and general health, than the single-born infants in the main study group. The consequence of the composition of the dropout group is that, if anything, the frequence of ROP is overestimated in the study.

The single-born infants formed the main study group, but in a group of multiple births, no difference from the single born was found with respect to relevant diagnoses and treatments in the neonatal period. Sets of multiple births with significantly different stages of ROP were analysed. Influence of the degree of prematurity and of maternal risk factors, including a possible genetic effect, would then be excluded. In the majority (4/5) of the sets, the sickest infant developed the most severe degree of ROP, which confirms the conception that, apart from prematurity per se, the sickest infants are at highest risk for developing ROP (Biglan et al. 1984, Lucey 1988, Avery & Glass 1988).

In the main study group, the logistic, multiple regression analysis showed that only gestational age at birth, birth weight and BPD were significant risk factors for ROP. An association of *BPD* with ROP has been described previously (Purohit et al. 1985, Biglan et al. 1984, Brown et al. 1990). All the diseases and major treatments used as binary risk factors in our study occur within a few weeks after birth, – i.e. before the onset of ROP. Hence, the variables analysed in the present study usually precede the onset of ROP and therefore may be regarded as predictive risk factors for the development of ROP. Whether BPD is a risk factor in chronological terms or should be regarded as a condition which covariates with ROP is not possible to determine.

ROP was more strongly associated with *gestational age at birth* than with *birth weight* in our analysis (Table 4), which confirms the concept that prematurity *per se* is the main predictive factor for ROP. However, for a given gestational age, infants with the lowest birth weights had the highest risk of developing ROP. This finding corresponds with previous reports by Johnson et al. (1978) and Distefano et al. (1993), who described an association between small for gestational age and ROP.

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