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Retinopathy of prematurity: any difference in risk factors between a high and low risk population?

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PURPOSE. *To document incidence of and risk factors for development of retinopathy of prematurity (ROP) in a population of low birthweight infants (<1500 g).*
METHODS. *The authors registered clinical characteristics (birthweight, gestational age (GA), Clinical Risk Index for Babies (CRIB), Apgar score, respiratory characteristics (intubation, ventilation, respiratory support, supplemental oxygen, oxygenation index), prescription of dopamine, and maximal creatinemia) by retrospective chart review in two consecutive CRIB score-based (<851 g, 851-1350 g) categories. Chi square and Mann-Whitney U tests were used to compare clinical characteristics in both categories and a stepwise logistic regression was done to document independent risk factors for either stage 3 (<851 g) or any grade of ROP (851-1350 g).*
RESULTS. *Incidence of ROP was 65/157 (41%; 76% in <851 g and 22% in 851-1350 g). Incidence of stage 3 ROP was 25/46 (54%) in the <851 g and 4/84 (5%) in the 851-1350 g group. Among other risk factors, maximal creatinemia was a risk factor in the 851-1350 g cohort (p<0.03). In a logistic regression model, only GA (OR 0.42) remained significant in the lowest birthweight category; in the 851-1350 g cohort, GA (OR 0.53) and CRIB score (OR 1.7) were independent risk factors for ROP.*
CONCLUSIONS. *In relatively more mature infants (851-1350 g), the risk to develop ROP is based on GA and on neonatal severity of disease (CRIB score); in the tiniest infants, GA is the most important risk factor. Microangiopathy might explain the association of maximal creatinemia and the risk of developing ROP. (Eur J Ophthalmol 2003; 13: 784-8)*

KEY WORDS. *Retinopathy of prematurity, Risk factor, Clinical Risk Index for Babies (CRIB), Creatinemia*

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INTRODUCTION

The gestational age (GA)-based relative risk to develop retinopathy of prematurity (ROP) in low birthweight infants has a logarithmic or bimodal distribution (1, 2). This distribution probably can be explained by the major impact of immaturity on infants with a GA less than 27 weeks, whereas in more mature infants, ROP likely is the result of a combined effect of preterm birth and neonatal disease severity.

Because treatment to prevent visual impairment in later life depends on early ophthalmologic screening during neonatal stay in infants at risk, additional indicators besides birthweight or GA might be used to further discriminate the relative risk to develop ROP associated with a given birthweight or GA. Such ad-

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ditional indicators most likely are more relevant in a low risk population, because early referral out of the neonatal intensive care unit might be considered in these infants, making ophthalmologic screening more difficult to realize. In addition, variability in impact of different risk factors involved in the development of ROP in high versus low risk populations might provide new insights into differences in underlying pathogenesis. We therefore studied markers of severity of disease in early neonatal life in a population of low birthweight infants (i.e., 1500 g) admitted to a single neonatal intensive care unit over a 2-year period (2000-2001) to document potential differences in risk factors of developing ROP between different birthweight categories.

PATIENTS AND METHODS

A retrospective chart review of low birthweight infants (i.e., <1500 g) admitted to the neonatal intensive care unit, Gasthuisberg, over a 2-year period (2000-2001) was done. Infants needed to be admitted to the unit within 6 hours after birth, to stay in the unit for at least the first week of life, and ophthalmologic screening performed until full retinal vascularization was documented, to be included in this study.

Neonatal characteristics collected in these infants were birthweight, GA, and Apgar score at 1 and 5 minutes. Respiratory characteristics collected were either markers of duration of respiratory disease (day of first extubation, last day of respiratory support, last day of supplemental oxygen) or markers of severity of respiratory disease in the first 72 hours of life (intubation (yes/no), maximal mean airway pressure (MAP) and oxygenation index at maximal MAP (MAP x 100 x fractional oxygen/arterial oxygen (mmHg)). Prescriptive characteristics of dopamine (yes/no, maximal dose in the first week of life, total hours of administration in the first week of life) were recorded as markers of cardiovascular instability. Maximal creatinemia (mg/dl) in the first week of life was registered. Finally, the Clinical Risk Index for Babies (CRIB) score, a disease severity scoring system, was attributed. This score was originally developed to express the relative mortality risk but there are reports on the association of CRIB and long-term morbidity (3-5).

Ophthalmologic screening was performed by indirect funduscopy. First ophthalmologic screening was performed at the postnatal age of 4 weeks and findings were classified according to the International Classification of Retinopathy of Prematurity. In case of normal funduscopy results, a 2-week interval examination was performed until full vascularization. If ROP stage 1 or 2 was diagnosed, the baby was examined on a weekly basis. In case of ROP stage 3, funduscopy was performed twice a week (2). If infants fulfilled Cryo-ROP criteria – i.e., threshold disease (at least five contiguous or eight cumulative clock hours of stage 3 ROP in zone 1 or 2 in the presence of plus disease) – retinal surgery was performed (6).

Incidence, clinical characteristics, and risk factors to develop ROP were studied in survivors in three consecutive birthweight categories (<851 g, 851-1350 g, 1351-1500 g) which were based on the birthweight categories used in the CRIB score (3).

Statistics

Results were reported by median and range or incidence. In the lowest birthweight category (<851 g), clinical characteristics of infants who developed stage 3 were compared to infants who did not develop stage 3 ROP; in the intermediate birthweight category (851-1350 g), clinical characteristics of infants who developed any grade of ROP were compared to infants who did not develop ROP. Chi square or Mann-Whitney U test were used. A p value below 0.05 was considered significant. All significant variables (monovariate analysis) were tested in a stepwise logistic regression model in the different weight categories with either stage 3 ROP (<851 g) or any grade of ROP (851-1350 g) as dependent variable.

RESULTS

Of 186 infants admitted between January 1, 2000, and December 31, 2001, with a birthweight below 1500 g, 157 (84%) survived until discharge. ROP (any stage) was documented in 65 (41%) survivors. Twenty-nine (18%) survivors developed stage 3 ROP. Fifteen infants developed threshold ROP. GA-based risk to develop any retinopathy and stage 3 ROP in this cohort of survivors is shown in Figure 1.

Twenty-five survivors had a birthweight between 1351

and 1500 g. There were no infants who developed ROP in this birthweight category. In the 851-1350 g birthweight category, 84 infants survived, of whom 19 (22%) developed any grade of ROP and 4 developed stage 3 ROP (Tab. I). In the lowest birthweight category (<851 g), 46 infants survived, of whom 35 (76%) developed any grade of ROP and 25 (54%) developed stage 3 ROP (Tab. II).

For each birthweight category, monovariate analysis of neonatal characteristics on relative risk to develop retinopathy was performed (Tab. I and II). In the intermediate birthweight group (851-1350 g), risk factors to develop any grade of retinopathy besides GA and birthweight were Apgar score at 1 and 5 minutes, CRIB score, maximal creatinemia, markers of cardiovascular instability, and markers of severity of respiratory disease (Tab. I). Risk factors to develop stage 3 ROP in the lowest birthweight category (<851 g) were GA, markers of duration of respiratory disease, CRIB score, and markers of cardiovascular instability (Tab. II).

In a stepwise logistic regression model in the intermediate birthweight group (851-1350 g) using any grade of ROP as dependent risk factor, besides GA (OR 0.53, 95% CI 0.37 to 0.77), CRIB score (OR 1.7, 95% CI 1.10 to 2.6) remained an independent risk factor to develop ROP. If birthweight (OR 0.99, 95% CI 0.98-0.99) was considered, the same additional effect of CRIB score (OR 1.6, 95% CI 1.07-2.44) on risk to develop ROP was documented, whereas in the lowest birthweight cohort using stage 3 ROP as dependent risk factor, either birthweight (OR 0.99, 95% CI 0.98-0.99) or GA (OR 0.42, 95%CI 0.24-0.74) was the dominant risk factor to develop stage 3 ROP. We were not able to document any additional independent effect of any of the other available variables in the lowest birthweight group.

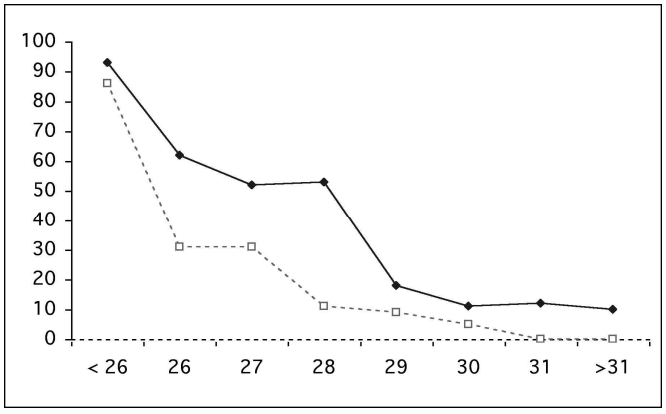

Fig. 1 - *Gestational age-based relative risk (%) to develop any grade of retinopathy (continuous line, black boxes) and stage 3 retinopathy of prematurity (dotted line, white boxes) in this single unit cohort (2000-2001) of survivors with a birthweight below 1500 g (x axis: gestational age).*

TABLE I - CLINICAL CHARACTERISTICS OF INFANTS WITH A BIRTHWEIGHT BETWEEN 851 AND 1350 g

Characteristics	No ROP	ROP	p value
Number	65	19	
GA (weeks)	30 (26-36)	28 (24-32)	0.0003
Birthweight (g)	1230 (895-1350)	980 (866-1340)	0.0004
Apgar score 1 min	7 (1-9)	5 (0-8)	0.040
Apgar score 5 min	8 (4-10)	8 (2-10)	NS
CRIB score	2 (1-7)	3 (1-6)	0.0024
Creatinemia (mg/dl)	1.09 (0.54-1.71)	1.2 (0.86-2.19)	0.030
Dopamine (y/n)	32%	68%	0.01
Maximal dose (µg/kg /min)	0 (0-12)	10 (0-16)	0.0041
Duration administration (hours)	0 (0-112)	14.5 (0-164)	0.01
Intubation (y/n)	58%	94%	0.0075
Maximal OI (0-72 hours)	2.8 (0-21.8)	10.1 (0-19)	0.0009
Duration ventilation (days)	2 (0-33)	9 (0-42)	0.0001
Duration respiratory support (days)	8 (0-52)	34 (0-95)	0.0002
Supplemental oxygen (days)	8 (0-63)	49 (6-144)	0.0000

Clinical characteristics of infants who developed ROP were compared to those of infants who did not develop ROP. Results reported by incidence or median (range)
ROP = Retinopathy of prematurity; GA = Gestational age; CRIB = Clinical Risk Index for Babies; OI = Oxygenation index

TABLE II - CLINICAL CHARACTERISTICS OF INFANTS WITH A BIRTHWEIGHT <851 g

Characteristics	No stage 3 ROP	Stage 3 ROP	p value
Number	21	25	
GA (weeks)	28 (25-33)	26 (24-29)	0.0004
Birthweight (g)	670 (480-845)	680 (400-845)	NS
Apgar score 1 min	7 (1-9)	5 (1-9)	0.042
Apgar score 5 min	8 (6-9)	8 (7-10)	NS
CRIB score	7 (2-10)	9 (2-13)	0.03
Creatinemia (mg/dl)	1.21 (0.78-2.2)	1.21 (0.91-1.71)	NS
Dopamine (y/n)	52%	90%	0.0077
Maximal dose (µg/kg/min)	4 (0-16)	12 (0-12)	0.0012
Duration administration (hours)	4 (0-94)	53 (0-116)	0.0015
Intubation (y/n)	76%	96%	NS
Maximal OI (0-72 hours)	7.3 (0-22.5)	12.8 (0-32.9)	NS
Duration ventilation (days)	7 (0-36)	15 (4-71)	0.044
Duration respiratory support (days)	41 (0-66)	60 (27-93)	0.0024
Supplemental oxygen (days)	46 (0-77)	69 (27-139)	0.019

Clinical characteristics of infants who developed stage 3 ROP were compared to those of infants who did not develop stage 3 ROP. Results reported by incidence or median (range)
ROP = Retinopathy of prematurity; GA = Gestational age; CRIB = Clinical Risk Index for Babies; OI = Oxygenation index

DISCUSSION

Incidence and risk factors to develop ROP were studied in a single-center population of low birthweight infants (<1500 g). Overall incidence of ROP in this cohort is high when compared to American cohorts and is more in line with other European cohorts, most likely to be explained by the impact of racial or genetic factors on the risk to develop ROP (1, 2, 7-10).

Retrospective analysis of risk factors might provide new insights into different mechanisms involved in the pathogenesis of ROP. It is therefore of potential interest that maximal creatinemia in the first week of life in the low risk (851-1350 g) group was a risk factor for ROP. To our knowledge, creatinemia has not yet been described as a risk factor to develop ROP in this birthweight category, although we recently documented the association of renal failure (creatinemia above 1.5 mg/dl) and threshold ROP in a cohort of survivors (n=175) (EpiBel, ≤26 weeks GA) at threshold of viability (11).

The association of increased creatinemia and ROP does not imply a causal association. It is much more likely that both complications are the result of a common underlying etiologic process. Combined renal and retinal microvasculopathy might explain this association in line with the analogous observations in diabetic patients. We therefore believe that this observation further emphasizes the relevance of studying polymorphism of the vascular endothelial growth factor or other growth factors and the associated risk of developing ROP in preterm infants (12-14). This observation should be confirmed by a multicenter, prospective approach, because creatinemia might be just another marker of disease severity in early neonatal life.

Using stepwise logistic regression, CRIB score had no additional impact on the risk of developing ROP in the lowest birthweight category, most likely due to the overall high incidence of ROP in survivors with a birthweight below 851 g. In contrast, CRIB score had an additional independent effect on the risk of developing retinopathy in the intermediate birthweight category and the same results were documented if GA was considered.

Although only based on retrospective data on a relatively limited number of infants in a single unit, these findings are suggestive that immaturity itself had a dominant effect on the risk of developing grade 3 ROP in the tiniest group, whereas prematurity and severity of neonatal disease acted synergistically in the intermediate weight (851-1350 g) group. The observa-

tion of the association of CRIB score and an increased risk of developing ROP in the low risk group might be used to develop a GA-based, disease severity – weighted risk score using markers (GA, CRIB) already available in early neonatal life. Such a risk score might be used to enable caregivers to further refine screening guidelines.

In conclusion, we illustrated that the bimodal distribution of ROP can be explained by an overall high incidence in more immature infants, whereas prematurity and disease severity characteristics seem to act synergistically in less immature infants. The association of maximal creatinemia with development of ROP in a low risk cohort of infants was documented. This association is not causal but creatinemia most likely is an indicator of impaired microperfusion in early neonatal life. These findings might be relevant in the refinement of screening strategies. In addition, these observations might provide new insights into the underlying pathogenesis of this disease. These single-center observations should be tested in a larger, multicenter population using a prospective approach.

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