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Retinopathy of prematurity: review of a four-year period

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SUMMARY For a four-year period the development of retinopathy of prematurity (ROP) was determined among neonates considered at risk of acquiring this condition. Fifty-six out of 249 premature infants developed some degree of ROP. Comparison of these infants with a group of 56 controls, admitted to hospital in the same period and matched for sex, birth weight, and gestational age, showed significant differences for sepsis, blood transfusions, and the period of oxygen monitoring in relation to the period of oxygen administration. The most consistent factor associated with the development of ROP was gestational age at the time of birth, though no gestational age group was entirely devoid of ROP. This suggests that screening for ROP should not be restricted to high-risk premature infants only.

During the last decade retinopathy of prematurity (ROP) has often been discussed in clinical paediatric papers.[1,2] Improvements in technology now enable neonatologists to keep alive more neonates of very low birth weight (VLBW) and short gestational age. But although the opportunities for monitoring arterial oxygen tension have also improved, they have not stopped ROP from recurring. Its aetiology remains unknown. We studied the incidence of ROP in a four-year period and evaluated a number of risk factors in its pathogenesis.

Patients and methods

PATIENTS

From 1 April 1977 to 31 March 1981 678 premature neonates were referred to the neonatal intensive care unit of the Wilhelmina Children's Hospital. Eye examinations were performed as soon as the babies' condition permitted them to be transferred from intensive care to the intermediate care ward.

We examined the following children: (a) all those born at a gestational age of under 32 weeks; (b) neonates of 32 and 33 weeks' gestation who had received more than 40% oxygen for longer than one day or who had been artificially ventilated; (c) premature infants of 34 or more weeks' gestation on artificial ventilation or high oxygen concentrations over a longer period.

ROP cases were matched with control patients of the same sex, birth weight, and gestational age admitted to hospital in the same period. If a child with ROP was one of identical twins of which the other one did not develop ROP, the latter served as control (three cases). We thus examined 249 surviving premature infants. ROP was present in 56 (22·8%).

METHODS

Throughout the study period all premature infants receiving any supplemental oxygen were given 10 mg vitamin E/kg body weight on admission and subsequently once a week until the oxygen treatment was discontinued. The oxygen concentration in the inspired air was measured by Hewlett-Packard oxygen meters or set by the oxygen-blenders on the artificial ventilation apparatus (Bourns BP 200).

During the first two years of the study Pao_2 samples were drawn from all indwelling arterial lines at least once every four hours. This was continued during the last two years of the study, during which additional information was gathered by measuring transcutaneous Po_2 ($Ptco_2$) in as many children as long as possible (with a Hellige-Dräger electrode). Every two weeks children were selected for ophthalmic investigation according to the criteria mentioned above. Optimal mydriasis could be obtained in most

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children by giving them tropicamide and phenylephrine HCl 5% alternately every 10 minutes for 1½ hours. After the application of a local anaesthetic a baby-eyelid widener (Heiss) was introduced and indirect monocular ophthalmoscopy performed.

Follow-up investigations were performed as frequently as judged necessary in cases of proliferative ROP (until treatment or regression) or once every two weeks until discharge.

Results

ROP was found in 56 children out of 249 investigated (Table 1). General characteristics and some relevant clinical data of the ROP group and of the 56 non-ROP controls are given in Table 2. Data relating to oxygen administration and monitoring are presented in Table 3.

The ROP stages found in our patients, according to the Patz's modification[3] of Reese *et al.*'s classification (using RLF for retrolental fibroplasia)[4] were: pre-RLF in 23 (41·1%), grade 1 in 23 (41·1%), grade 2 in 7 (12·4%), and grades 3–5 (cicatricial forms leading to blindness) in 3 (5·4%). Fig. 1 shows the distribution of ROP cases in relation to the total of surviving premature infants and clearly points to an increasing risk with decreasing gestational age.

Table 1 *Series of 551 surviving premature infants (out of 678 admissions) from which ROP and control cases have been selected*

	n	*Examined*	*(% of n)*	*ROP*	*(% of examined cases)*
≤32 wks:	169	156	(92·3%)	43	(27·6%)
32–33 wks:	122	73	(39·8%)	8	(11·0%)
≥34 wks:	260	20	(7·7%)	5	(25·0%)

Discussion

The link originally suggested between oxygen and ROP has been challenged, as Silverman stated in 1982,[5] and our study also casts doubt on it. Tables 2 and 3 show that in our ROP and non-ROP groups there are no significant differences between artificial

Table 2 *General characteristics and clinical data of 56 ROP cases and controls*

	ROP	*Non-ROP*
n	56	56
Mean gestational age (wks)	28·7	28·9
Mean birthweight (grs)	1140	1135
Male : female	27 : 29	27 : 29
Artificial ventilation (n)	26	31 NS
Mean duration of ventilation (days)	15·6	14·5 NS
Patent ductus arteriosus	12	15 NS
Bronchopulmonary dysplasia	11	15 NS
Pneumonia	7	5 NS
Sepsis (proved by blood culture(s))	19	8* p<0·05
Exchange transfusion (number of children)	10	3* p=0·06
Mean number of blood transfusions in first two months	6·8	4,7† p<0·005

*χ^2 test.
†Student's *t* test.
NS=not significant.

Table 3 *Data pertaining to oxygen administration and monitoring*

	1 Apr 1977–1 Apr 1979		*1 Apr 1979–1 Apr 1981*	
	ROP	*Non-ROP*	*ROP*	*Non-ROP*
n	20	20	36	36
Mean duration of ≥40% O_2 administration (days)	19	17	14·9	11
Monitoring:				
None	12	8	7	2* p=0·09
arterial	8	12	3	4 NS
arterial + $Ptco_2$	—	—	8	11 NS
$Ptco_2$	—	—	18	19 NS
Mean no. of Pao_2 measurements ≥100 mmHg	2·7	4,3	1·94	3·11 NS
Mean max. Pao_2 (mmHg)	113	108	138	142 NS
Mean no. of $PtCO_2$ measurements ≥100 mmHg	—	—	2,7	4·3 NS
Mean max. $PtCO_2$ (mmHg)	—	—	108	114 NS
Duration of monitoring:				
Duration of suppl. O_2 administered (>40%)	—	—	0·54	1,14† p<0·01

*χ^2 test.
†Student's *t* test.

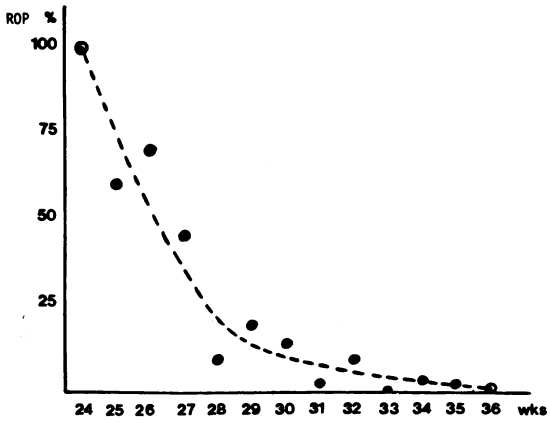

Fig. 1 *Incidence of ROP as a percentage of survival according to gestational age.*

ventilation and its duration, patent ductus arteriosus, bronchopulmonary dysplasia, mean duration of supplementory oxygen administration, and arterial and transcutaneous oxygen monitoring. Table 3 also shows that the introduction of $PtcO_2$ measuring has at least had a beneficial effect with regard to the mean duration of oxygen administration, which has decreased from 19 to 14·9 days in the ROP group and from 17 to 11·0 days in the control group.

That oxygen cannot be eliminated as one of the important factors in ROP may be derived from the fact that a significant difference was found between the study group and the control group in the duration of monitoring. When dividing the duration of monitoring (either arterial and/or transcutaneous) by the number of days supplementary oxygen was administered (≥40%), children from the ROP group were found to have been monitored for a significantly shorter time than those from the non-ROP group (ratios 0·54 and 1·14 respectively, Table 3).

Two other findings from our study may leave the oxygen theory at least partly intact. The first, the difference between exchange transfusions and blood transfusions between the two groups has been observed before[6–8] and widely discussed. The second, although seeming not directly to point to oxygen, is the difference in sepsis incidence. This finding has been reported before[9–12] but has evoked little comment.

It is our impression that the sepsis incidence may relate to the number of blood transfusions required in the neonatal period. In our patient groups there were no significant differences in number of children on artificial ventilation (and its duration) and number of children with arterial lines, which makes it unlikely that the difference in the number of blood transfusions was caused by increased blood sampling. However, increased haemolysis during sepsis periods may offer an explanation. With regard to oxygen radicals, it is now recognised that the oxidative burst which follows the activation of the superoxide generating systems occurs earlier and easier in newborn than in adult neutrophils.[13 14] When this mechanism operates throughout the whole body, and therefore also in the immature tissues and vessels of the eye, a link is established between sepsis with increased ocular toxicity and increased need for blood transfusions. On the basis of this concept we believe other investigators should consider sepsis as a possible risk factor in the development of retinopathy of prematurity.

The incidence of ROP in our patient population is comparable to the incidence mentioned by other authors in recent years.[15 16] The differing figures in different gestational age groups (<32 weeks: 27·6%, 32–33 weeks: 11%, and ≥34 weeks: 25%) may be the result of the selection criteria we used. The increasing risk with decreasing gestational age, probably the most consistently encountered risk factor for ROP in the literature, is also seen in our data (Fig. 1).

However, the finding that among our premature infants no gestational age group is devoid of ROP raises the question of the need for *all* premature infants to be seen by an ophthalmologist. For higher risk groups, in all those centres providing neonatal intensive care, this should be mandatory in our view. For lower risk groups, it seems necessary to define a moment of optimal timing for ROP diagnosis. This would seem to be somewhere between the 5th and 10th week after birth, because those studying children from birth have rarely encountered ROP *for the first time*[10 17] before or after this period.

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