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Retinopathy of Prematurity in the United Kingdom

Y. K. NG, A. R. FIELDER and M. I. LEVENE
Leicester

Summary
Retinopathy of prematurity (ROP) continues to be a problem for some preterm infants who survive the neonatal period. We review changes which have occurred in the premature infant population and methods of ophthalmological examination since the last survey of ROP in the United Kingdom was conducted between 1951 and 1953. We have analysed data from a retrospective study, and from our current prospective survey of ROP in the East Midlands, to determine the age at onset of acute ROP. The results show that the ophthalmoscopically visible signs of ROP develop over a narrow postmenstrual age range suggesting that acute ROP occurs only after the retina and/or its vasculature have reached a certain stage of development.

Retinopathy of prematurity (ROP), previously called retrolental fibroplasia (RLF), remains a risk for the low birthweight premature infant who survives the neonatal period. Despite considerable research, many aspects of this condition have yet to be clarified. Its pathogenesis is still unknown as are certain aspects of the natural history. Since there have been no clinically-based studies in the United Kingdom for 30 years, neither the incidence nor clinical significance of ROP in this country are known.

We will briefly review the role of oxygen, changes in neonatal care and ophthalmological examination and present preliminary results of our study of ROP in the East Midlands.

The Oxygen question

Studies in the 1950s from this country,[2,4] Australia[3] and the USA[5] showed a relationship between ROP and oxygen treatment. Support for the role of oxygen in the development of ROP was obtained from the experimental work of Ashton.[6] Following this discovery, the use of oxygen in the management of preterm infants was restricted. Curtailing the amount of oxygen given to these infants undoubtedly resulted in a decline in the incidence of ROP.[7] However, during these years of oxygen restriction, the neonatal mortality rate did not continue its previous steady decline.[8,9]

In these early years of oxygen treatment the concentration of oxygen in the inspired air was considered to be the important factor, but later the importance of arterial oxygen tension was realised. Ideally these two should be closely related but in certain clinical conditions, such as the respiratory distress syndrome there may be a considerable disparity: a high inspired oxygen concentration (even 100 per cent) being necessary to achieve a satisfactory arterial tension.

With the development of sophisticated methods of oxygen monitoring, it was anticipated that a decrease in the incidence of ROP would be seen. However, in the 1970s several reports from the USA and Canada were published,[10,11,12] suggesting that ROP was on the increase again, particularly in the very low birthweight group of infants (<1,500 gm).

Correspondence to: A. R. Fielder, FRCS, Department of Ophthalmology, Clinical Sciences Building, Leicester Royal Infirmary, Leicester LE2 7LX.
From: Departments of Ophthalmology and Child Health, Leicester University Medical School, Leicester.

There is no doubt that hyperoxia can lead to ROP but the relationship between oxygen and this condition is more complex than originally thought. Both hyperoxia and hypoxia have been implicated as causative factors,[13] premature infants exposed to high arterial oxygen tensions do not always develop ROP,[14] and it is recognised that ROP can rarely occur in infants who have never received supplemental oxygen.[15,16] Many factors other than oxygen have been implicated in the pathogenesis of ROP and this topic has recently been the subject of a detailed review by Lucey and Dangman.[13] In the present state of knowledge it appears that ROP may not be entirely preventable.

Changes in neonatal care

Since the studies in the 1950s, many changes have occurred in the perinatal management of preterm infants. Firstly, antenatal care has changed, and there is now more active management of mothers at risk of premature delivery. Secondly, there have been many developments in neonatal intensive care techniques, such as in the use of assisted ventilation for the respiratory problems of prematurity. As mentioned previously, blood oxygen monitoring methods have improved and most units caring for the sick newborn infant now use a combination of continuous intra-arterial and/or transcutaneous oxygen monitoring, with intermittent blood gas sampling.

The effect of these changes in care has been a gradual decline in neonatal mortality[17] for all birthweight groups. Consequently there are larger numbers of very low birthweight infants surviving the neonatal period compared with the 1950s.

Retinopathy of Prematurity in the United Kingdom

Early studies, and the more recent reports from the USA, showed an inverse relationship between incidence of ROP and birthweight, i.e. the smallest infants had a higher incidence of ROP.[4,18,19] With the increased survival of this population we might therefore expect to see an overall increase in the incidence of ROP in this country but there have been no papers on ROP in the UK since the 1950s, apart from the paper by Mushin.[20] Therefore we have no recent information on the incidence of either acute or cicatricial ROP except for the figures extracted from registration of blindness and partial sight in children in England.[21]

Ophthalmological examination

Methods of ophthalmological examination in the newborn have changed over the years particularly with the introduction of the indirect ophthalmoscope. The use of this instrument combined with a 28D lens, eyelid speculum and a scleral indentor (for ocular rotation rather than scleral indentation) enables the peripheral retina to be visualised. Thus, it is possible to detect the earliest stages of acute ROP more reliably than was possible previously. Direct comparison between early and more recent reports cannot be made as both methods of examination which we have just described, and diagnostic criteria have changed. The latter was compounded by the lack of a generally accepted clinical classification. In 1984, the International Classification of ROP was agreed and published by a group of paediatric ophthalmologists from all over the world,[22] which will hopefully allow comparisons to be made between the various surveys in different countries.

Retinopathy of Prematurity in the East Midlands

In order to investigate the pathogenesis, treatment and prevention of a condition, an understanding of its natural history is essential. Although the progression of the acute to the cicatricial stages has been well recognised, certain aspects of the natural history of ROP have not received much attention, particularly the time at which acute ROP is first seen. This aspect has been analysed by us retrospectively and is one part of our current prospective study.

Retrospective Study

Since 1981, babies admitted to one of 5 neonatal units in Derby, Leicester and Nottingham have been examined by one of us (ARF) if they have been <1,500 gm birthweight, regardless of whether they were given added oxygen, or if they were over this birth-

weight but had received supplemental oxygen. The pupils were dilated with cyclopentolate 0.5 per cent, 60 minutes and 30 minutes prior to the examination. The infants were then examined using indirect ophthalmoscopy, an eyelid speculum, and a scleral indentor. Examinations commenced at the age of 3 weeks if the infant's clinical condition permitted and were continued weekly whilst the baby remained in the neonatal unit.

Prospective Study

This commenced on July 1, 1985. All babies of birthweight ≤1,700 gms, admitted to these five neonatal units are examined by ARF. The first examination is at 3 weeks of age and continues on a weekly basis whilst the infant is an inpatient and fortnightly following discharge from hospital until a postnatal age of 12 weeks, and thereafter as the clinical condition dictates.

Results

In order that the onset of ROP is determined as precisely as possible, we have analysed the data only of those infants who had at least one normal examination prior to the appearance of ROP. One hundred and forty-three infants satisfied this criterion in the retrospective study and have been reported elsewhere.[23] In the first 6 months of the prospective study, 96 babies have been studied. Fourteen have been lost to follow-up before the age of 12 weeks because of death, transfer to another hospital or failure to attend for outpatient appointments. Forty-six developed acute ROP and 45 infants satisfied the criterion for inclusion in this analysis. The characteristics of both groups and the postnatal age at onset of ROP are summarised in the table.

Table *Postnatal age at onset of ROP*

	Retrospective group (n = 143)	*Prospective group (n = 45)*
Birthweight (gm)		
Range	630–2,700	730–1,700
Median	1,090	1,200
Gestational age (weeks)		
Range	24.5–40.0	25.0–36.0
Median	29	30
Postnatal age at onset of ROP (days)		
Range	22–85	20–72
Median	45	44

In the retrospective study, infants of <28 weeks gestation had a median postnatal age at onset of ROP of 51 days compared with 40 days for infants of ≥28 weeks gestation. This difference was significant ($p<0.0001$, Mann-Whitney). Similarly, when grouped according to birthweight, infants <1,000 gm developed ROP at a median postnatal age of 48 days, compared with infants ≥1,000 gm who had a median age at onset of 40 days ($p<0.0001$, Mann-Whitney). Overall, there is a significant correlation between birthweight and gestational age with the postnatal age at onset. As yet, the numbers in the prospective study are insufficient to be grouped in this way.

Allowing for the degree of prematurity of the infant, we determined the postmenstrual age at which each infant developed ROP. Postmenstrual age is the sum of the gestational age at birth and postnatal age at which ROP was first seen. The infants in the retrospective analysis developed ROP at postmenstrual ages which ranged from 30.8 to 44.5 weeks and 121 (86 per cent) exhibited the first signs of ROP between 32.5 and 38.5 weeks. Of the 45 infants in the prospective survey, 41 (91 per cent) developed ROP between 31 and 41 weeks postmenstrual age, the range for the whole group being 30.7 to 44.1 weeks.

Discussion

Although the assessment of gestational age cannot be precise[24] and as ophthalmological examination is difficult and only performed once a week, the results presented should not be taken too literally, but they do indicate the time when acute ROP first appears as closely as possible under the circumstances. They also confirm our clinical impression that the more premature infant tends to develop ROP later than the larger less premature infant. This agrees with earlier work.[25,4] However, when the degree of prematurity is taken into account, it appears that acute ROP in all infants develops over a narrow range of postmenstrual age. Flynn, considering the optimum time for examination, observed this

in his group of study infants but did not comment on this particular aspect.[26]

Although the pathogenesis of ROP is still unknown, it is generally accepted that it is a disease that affects the developing retinal vasculature. It is known that its occurrence is related to gestational age and perinatal events[13] and the severity of the disease is also affected by these factors. It might therefore be expected that the less mature, smaller, sicker infant would develop ROP at an earlier postnatal age than the more mature, well, preterm infant. Our findings confirm that this is not the case and show that acute ROP seems to develop over a similar time span whatever the gestational age of the infant.

Our results indicate that a certain stage of development, probably at retinal level, has to be reached before the ROP response can occur. This was first suggested by Kinsey.[5] Alberman has highlighted the problems of patient selection in the premature population by using either criteria for admission to neonatal intensive care, oxygen requirements, survival or length of stay in hospital.[1] In our retrospective study, it must be recognised that some infants may have developed ROP after leaving the neonatal unit and have escaped detection. For this reason, in the prospective study the infants are examined at least until 12 weeks postnatal age.

As stated, our results show that all infants develop ROP at approximately the same age postmenstrually. Although both gestational age and birthweight are highly positively correlated, birthweight may exhibit a large scatter for a given gestational age. Thus gestational age rather than birthweight may be a more appropriate parameter for the study of this condition.

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