Do current retinopathy of prematurity screening guidelines miss the early development of pre-threshold type 1 ROP in small for gestational age neonates?

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Abstract

Purpose To investigate whether current UK retinopathy of prematurity (ROP) screening guidelines miss the early development of pre-threshold type 1 ROP in some neonates born small for gestational age (SGA) and consider if the guidelines should be changed.

Methods Data were collected on neonates of ≤ 31 completed weeks gestation and/or birth weight (BW) ≤ 1500 g born over a 37-month period. Babies who did not complete the screening programme in Cambridge and those with other ocular abnormalities were excluded. We compared the time course of ROP progression and the development of the early treatment for ROP pre-threshold ROP in relation to the gestational age and the BW of the babies.

Results A total of 105 neonates were included, 11 (10.5%) were born SGA (less than 9th centile of predicted BW). Of these 11, 2 (18.2%) had pre-threshold ROP at their first screen (median post-natal age (PNA) 6.5 weeks, median postmenstrual age (PMA) 33.5 weeks). No other neonate in this group developed pre-threshold ROP. Of the 94 other neonates, none had pre-threshold ROP at first screen (median PNA 7.1 weeks). Pre-threshold ROP developed in 12 (12.8%) of these babies between 8 and 12 (median 11.5) post-natal weeks, at a PMA of 33–38 (median 35.5) weeks.

Conclusion Current UK ROP screening guidelines recommend first screening at 6–7 post-natal weeks. Our study suggests that pre-threshold type 1 ROP can develop before this especially in SGA babies. We suggest that screening should either start at 4 post-natal weeks in such babies, or be based on PMA rather than PNA, to allow timely laser therapy. *Eye* (2008) 22, 825–829; doi:10.1038/sj.eye.6702728; published online 9 February 2007

Keywords: retinopathy of prematurity; small for gestational age; screening

Introduction

Retinopathy of prematurity (ROP) is a condition affecting the developing retinal vascular system of preterm infants. It remains a significant cause of morbidity among preterm infants. The World Health Organisation's 'Vision 2020 programme'¹ has identified ROP as an important cause of preventable childhood blindness in both high and middle income countries. In USA, ROP remains the second most common cause of childhood blindness.²

Treatment for ROP was shown to be effective in 1988 and since then it has been well established that timely detection and treatment of severe ROP with laser or cryotherapy significantly reduces the risk of poor visual outcome.^{3,4} Previously, treatment was recommended when threshold ROP developed

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Received: 22 September 2006

Accepted in revised form: 22 December 2006

Published online: 9 February 2007

We have no proprietary interests or research funding to declare

(defined as at least 5 continuous or 8 cumulative clock hours of stage 3 ROP in zones 1 or 2 in the presence of plus disease). The Early Treatment for Retinopathy of Prematurity Study (ET-ROP) in 2003 showed that laser treatment at an earlier stage, called pre-threshold type 1 ROP, further reduced the risk of severe visual morbidity. Treatment is now recommended for pre-threshold type 1 disease, defined as: zone 1 ROP of any stage in the presence of plus disease; zone 1, stage 3 disease whether or not plus disease is present, and zone 2 ROP of stage 2 or 3 in the presence of plus disease.⁵

The current UK guidelines set by the Royal College of Ophthalmology and British Association of Perinatal Medicine, recommend screening of all babies born ≤ 31 weeks completed gestational age (GA) and/or birth weight (BW) ≤ 1500 g with the first examination taking place between 6 and 7 weeks post-natal age (PNA).⁶

The team at the neonatal unit at the Rosie Hospital, Cambridge, currently follows the UK screening guidelines and the ET-ROP recommendations by treating infants with pre-threshold type 1 disease. Recently, we noted that one infant had already developed zone 2, stage 3 plus ROP by the time of her first screen and required urgent treatment. Further investigation revealed that this infant was small for gestational age (SGA). The aim of this study was to investigate whether neonates born SGA may develop pre-threshold type 1 ROP earlier than their counterparts. If shown to be the case, should these babies have screening initiated earlier in the post-natal period to pick up pre-threshold type 1 disease and organise timely and effective laser therapy?

Materials and methods

Data were collected retrospectively for neonates admitted during a 37-month period (January 2003 to February 2006) to our level 3 neonatal unit. The unit's database was used to identify all babies born during this period who fitted the UK screening criteria, that is, ≤ 31 completed weeks gestation and/or BW ≤ 1500 g. Data collected included gender, GA at birth (based on date of last menstrual period and scans), and BW. Babies were

considered SGA if their BW was under the 9th centile of that expected.

The following details of the ROP screening were recorded: PNA and postmenstrual age (PMA) at first ROP screen, ROP stage in each eye at first screen, maximum stage of ROP reached, and PNA and PMA at that time. The information was obtained from discharge summaries, case notes, and the dedicated ROP eye examination book. Babies who did not complete screening in Cambridge, who died before screening, and those with other ocular abnormalities were excluded.

Results

One hundred and six babies completed their ROP screening in Cambridge. One baby with abnormal retinal vasculature secondary to Miller–Deiker syndrome was excluded. Of the 105 remaining babies, 11 (10.5%) were SGA; although small, the median GA in this group was almost 2 weeks longer than that in the remainder (Table 1).

Two of these 11 babies (18.2%) developed pre-threshold type 1 ROP and in both of these babies, this was identified at their first ROP screening examination (Table 2). The cases are detailed below.

SGA case 1

This 550 g girl was born at 29 weeks of gestation. She underwent her first screen for ROP at 6 weeks PNA (35 weeks PMA), and was found to have posterior zone 2, stage 3 (2–3 clock hours each eye) ROP with plus disease bilaterally. She underwent laser treatment the same day on the neonatal unit. The ROP regressed in the fortnight following treatment. Her vision was developing normally and there were no significant cicatricial changes at outpatient review 6 months later.

SGA case 2

A 530 g boy born at 26 weeks gestation was first screened at 7 weeks PNA (32 weeks PMA). The infant was noted

Table 1 Demographics of the two groups of infants based on birth weight

	Sex		Gestational age ^a (weeks)			Birth weight (g)		No. of babies reaching ET-ROP threshold ROP (%)
	F (%)	M (%)	Mean	Median	Range	Mean	Range	
SGA (<i>n</i> = 11)	7 (63.6)	4 (36.4)	29.6	31	26–32	936.3	542–1363	2 (18.2)
Non-SGA (<i>n</i> = 94)	58 (61.7)	36 (38.3)	27.2	29	23–32	1169.2	550–2210	12 (12.8)

Abbreviations: ET-ROP, early treatment for retinopathy of prematurity; SGA, small for gestational age.

^aGestational age is the time elapsed between the first day of the last normal menstrual period and the day of delivery.

Table 2 Results at first ROP screen of babies who reached ET-ROP threshold ROP

	Stage 2 + plus disease	Stage 3 ± plus disease	Median PNA ^a at first screen (weeks)	Mean PNA at first screen (weeks)	Median PMA ^b at first screen (weeks)	Mean PMA at first screen (weeks)
SGA (<i>n</i> = 4 eyes of two babies)	2 eyes	2 eyes	6.5 (range 6–7)	6.5	33.5 (range 32–35)	33.5
Non-SGA (<i>n</i> = 24 eyes of 12 babies)	0	0	6 (range 6–7)	6.4	31.4 (range 29–34)	31

Abbreviations: ET-ROP, early treatment for retinopathy of prematurity; SGA, small for gestational age.

^aPNA (postnatal age) is the time elapsed after birth (in weeks).

^bPMA (postmenstrual age) is the time elapsed between the first day of the last menstrual period and birth (gestational age) plus the time elapsed after birth.

Table 3 Analysis of those babies progressing to ET-ROP threshold ROP

	Stage 2 + plus disease	Stage 3 ± plus disease	Median PNA at ETROP threshold ROP (weeks)	Mean PNA at ETROP threshold ROP (weeks)	Median PMA at ETROP threshold ROP (weeks)	Mean PMA at ETROP threshold ROP (weeks)	Mean PMA at laser treatment (weeks)
SGA (<i>n</i> = 4 eyes of two babies)	0	4 eyes	6.5 (range 6–7)	6.5	33.5 (range 32–35)	33.5	35.0
Non-SGA (<i>n</i> = 24 eyes of 12 babies)	9 eyes	15 eyes	11.5 (range 8–12)	10.6	35.5 (range 33–38)	35.7	35.3

Abbreviations: ET-ROP, early treatment for retinopathy of prematurity; SGA, small for gestational age.

to have posterior zone 2, stage 2 ROP with plus disease bilaterally. He received laser treatment within the week and at the time of treatment had early stage 3 with plus disease. The ROP regressed within 2 weeks with no early cicatricial changes and the baby was transferred to his local hospital for follow-up.

Of the 94 infants not considered SGA, none had pre-threshold ROP at his/her first screen (mean PNA 7.1 weeks, median PMA 35 weeks). Twelve babies in this group (12.8%) went on to develop pre-threshold type 1 ROP (Table 2). These babies had a GA range of 23–30 weeks (median 25 weeks) and developed pre-threshold type 1 ROP at 33–38 postmenstrual weeks (median 35.7 weeks) (Table 3).

Pre-threshold type 1 ROP developed at a median 6.5 weeks PNA in the SGA group and a median of 11.5 weeks PNA in the babies >9th weight centile. The median PMA at which pre-threshold type 1 ROP developed was 33.5 weeks in the SGA group and 35.5 weeks in the babies >9th weight centile (Table 3).

Discussion

Of the 105 infants in our study, 10 (9.5%) went on to receive laser treatment for pre-threshold type 1 ROP, a rate comparable to other units.⁷ It has been well documented that babies born SGA have an increased risk of developing severe ROP^{8–10} and this is confirmed in our

small series, with 18.2% of the SGA babies requiring treatment for ROP compared to 12.8% of the others. In addition, however, this study indicates that babies who are SGA may develop pre-threshold type 1 ROP 3–4 weeks earlier in the post-natal period. The two SGA babies that required treatment were found to have stage 2 plus and stage 3 plus at their first screen at 6 and 7 post-natal weeks, respectively. In contrast, the 12 babies not considered SGA who went on to develop pre-threshold ROP, had none or stage 1 ROP at the time of their first screening (median 6 weeks) and developed pre-threshold ROP at a median PNA of 11.5 weeks, well within the screening period.

Fielder *et al*¹¹ have shown that the rate of progression of ROP is governed mostly by PMA rather than PNA, with stage 2 disease developing at a median of 35 weeks PMA and stage 3 developing at 36 weeks PMA. Subhani *et al*¹² have shown that 80% of cases of threshold ROP developing specifically in very low BW babies (<1000 g) occur before 33 weeks PMA. In our series, case 1 had zone 2, stage 3 plus ROP at 35 weeks PMA and case 2 had zone 2, stage 2 plus ROP at 32 weeks PMA. In contrast, the other 12 babies (not considered SGA), who developed stage 2 plus ROP, developed it at a median of 35.5 weeks PMA, suggesting that the ROP disease process progresses more rapidly in some SGA babies. The 5-week difference in post-natal age (6.5 weeks in SGA infants compared to 11.5 weeks in non-SGA infants) at which

pre-threshold disease developed is partly due to the more rapid progression in ROP in these high-risk babies and also due to babies in this group being less premature (median 27.5 weeks gestation compared to median 25 weeks gestation). These facts confirm Fielder's analysis that PMA is more accurate at determining the time at which pre-threshold ROP will occur than PNA.

Factors that may be responsible for the increased risk of severe ROP and the rapidity of its development in SGA babies include chronic uterine hypoxia, abnormal growth factor levels, antioxidant deficiency, and free oxygen radicals *in utero*.^{13,14} Low serum IGF-1 levels in premature infants in the post-natal period are known to increase the risk and severity of ROP.¹⁵ Growth-retarded babies have reduced serum IGF-1 levels *in utero*, so it is not surprising that these babies, if born prematurely, develop severe ROP earlier than non-growth-retarded babies of a similar GA.

The Royal College of Ophthalmologists and British Association of Perinatal Medicine⁶ currently recommends that the first retinal examination should take place between 6 and 7 weeks PNA and that this should capture virtually all babies at risk of severe ROP in the UK.^{16–19} The American Association of Ophthalmologists suggest screening of infants with BW ≤ 1500 g or with GA of ≤ 28 weeks starting at 31–33 weeks PMA or 4–6 weeks PNA.²⁰ The Canadian Ophthalmology Society recommends screening for infants ≤ 30 weeks and/or ≤ 1500 g commencing at 4–6 weeks PNA.²¹ No guideline specifically mentions SGA babies.

Although the baby described in case 2 was treated according to the ET-ROP recommendations at stage 2 with plus disease, it could be argued that the baby described in case 1 would have been treated earlier had the screening been initiated at 4–5 post-natal weeks. It was fortunate in this case that treatment could be instigated rapidly because our unit is a regional ROP treatment centre and there were none of the problems often faced by peripheral units in locating a treatment centre with an available cot and arranging neonatal ambulance transport, which can often delay treatment for several days.

Following the findings of our study, we have now instigated earlier screening starting at 4 weeks PNA for SGA babies, and would estimate this will result in an additional seven screening episodes a year in our busy level 3 neonatal unit. The authors acknowledge that the Royal College of Ophthalmologists guidelines for ROP screening are currently being updated and are likely to lead to screening based on postmenstrual rather than post-natal age. This should enable the identification of early progression to pre-threshold type 1 ROP in this

vulnerable group and facilitate timely treatment to optimise the child's visual outcome.

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