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Incidence Of Retinopathy Of Prematurity In Singapore

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ABSTRACT

The study was done to investigate the incidence and severity of retinopathy of prematurity (ROP) in Singapore over a one-year period. Its relation to factors like birth weight, gestational age are also explored so as to identify high risk groups and provide guidelines for the implementation of a screening programme in Singapore. At the various government restructured hospitals from Dec 1993 to Nov 1994, 34.4% (72 out of 209) of babies, with birth weights less than 1250g or gestational ages less than 32 weeks, developed ROP. The incidence of ROP correlated significantly with low birth weight, early gestational age, multiple births; the severity correlated with low birth weight and multiple births. There was a notably higher proportion of Malays in the study population (premature babies) than all the live births of the same period. From the results, an optimal screening programme should include babies weighing less than 1250g or of gestation earlier than 32 weeks. A first examination at 33 weeks of post-menstrual age is suggested.

Keywords: retinopathy of prematurity, screening programme, low birth weight, early gestational age, multiple births

INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder[1] affecting premature babies. The presence of abnormal vessels and scar tissue can progress on to distortion and traction detachment of the retina, often with exudative features. This can result in loss of vision. In milder forms, affected individuals may develop refractive errors, amblyopia, strabismus, glaucoma, cataracts, corneal changes, retinal and vitreous abnormalities.

The initiating stimulus for ROP is believed to include oxygen[2,3]. Other risk factors[4-6] are low birth weight, early gestational age, ventilator hours, hyper and hypocarbia, hypoxia and acidosis, respiratory distress syndrome, anaemia, exchange transfusions, prolonged parenteral nutrition.

The International Classification of ROP[7,8] is as follows:

1. specifying locations by 3 recognised zones of involvement (Table I)
2. recording the extent by clock hours
3. staging according to the degree of vascular lesions (5 stages) (Table II)

A plus sign is added to the stage number when there is increased dilatation and tortuosity of the retinal vessels, iris vascular engorgement, pupillary rigidity and vitreous haze in the posterior pole. These are ominous prognostic signs.

The traditional term "retrolental fibroplasia" describes the later cicatrical changes. The Reese classification (Table III) is used for these sequelae.

After years of inconclusive studies, retinal ablative treatment was shown by the Multicentre Trial of Cryotherapy for Retinopathy of Prematurity[9-11] to reduce, by approximately one half, the risk of unfavourable retinal outcome from threshold disease. Threshold disease is stage 3 plus ROP with fibrovascular proliferations of more than 5 continuous or 8 cumulative clock hours. Retinal ablation can be done by cryotherapy or laser photocoagulation[12]. In stages 4 and 5, retinal detachment can be treated by vitrectomy or scleral buckling[13]. Other treatment modalities which have been tried, but with conflicting results, include vitamin E supplementation[3], prophylactic surfactant therapy and inositol supplementation to reduce respiratory distress syndrome.[14]

Although ROP cannot be totally prevented, the advent of treatment techniques now allow ophthalmologists to intervene with some hope of preventing blindness. Consequently, screening has become the most vital role of ophthalmologists.

With improvements in neonatal care and increasing survival of very low birth weight babies in the last 20 years, there has been a resurgence of ROP. With this in mind, the present study is undertaken to investigate incidence and severity of ROP in Singapore. Its relation to factors such as birth weight, gestational age, sex, race, multiple birth, are also explored. Screening for ROP has been carried out in Singapore since 1987. No study has been done to

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Table I - Location by zone

The zones are centred on the optic disc but zone 3 is crescentic being widest in the temporal retina and absent nasally.	
Zone 1	extends from the optic disc to twice the disc-foveal distance. (radius of 30°)
Zone 2	extends from the periphery of the nasal retina(ora serrata) in a circle around the anatomic equator. In the temporal retina, in the absence of an anatomical landmark zone 3 cannot be identified precisely. Only known to be entered with certainty when the nasal retina is fully vascularised.
Zone 3	anterior to zone 2, is present temporally, inferiorly, and superiorly, but not in the nasal retina.

Table II - Stages of ROP

Stage	Characteristic		
1	Demarcation line		
2	Ridge		
3	Ridge with extraretinal fibrovascular proliferation		
4	Subtotal retinal detachment		
	a. Extrafoveal		
	b. Involving fovea		
5	Total retinal detachment		
	Funnel:	Anterior	Posterior
		Open	Open
		Narrow	Narrow
		Open	Open
		Narrow	Open

Table III - Cicatrical RLF (Reese 1953)

Stage	
I	Small mass opaque tissue in peripheral without detachment
II	Larger mass opaque tissue in periphery with localis detachment
III	Larger mass in periphery with traction fold to disc
IV	Retrolental tissue covering part of pupil
V	Retrolental tissue covering entire pupillary area

assess the screening criteria in Singapore. As screening is time-consuming, expensive and the long term side-effects of ophthalmoscopic examinations on premature babies are unknown, a screening programme, with an optimal pick- up rate while not unnecessarily exposing children to examinations, should be implemented.

MATERIALS AND METHODS

This is a retrospective study. The sampling frame included the 4 tertiary neonatal units in restructured hospitals, namely Kandang Kerbau Hospital Neonatal Unit I (KKNU 1), Kandang Kerbau Hospital Neonatal Unit 2 (KKNU 2), Singapore General Hospital (SGH) and National University Hospital (NUH). The subjects were babies referred for screening during a one-year period between 1 December 1993 and 30 November 1994.

As all 4 units had screening criteria with slight variations, the inclusion criteria chosen for the study was <32 weeks of gestation age or birth weight <1250g. Babies who were also screened but did not fulfill the inclusion criteria were analysed separately.

Screenings were done by ophthalmologists from Singapore National Eye Centre (SNEC) and NUH via indirect ophthalmoscopy. At the various institutions, the timing of the first screening varied between 6 weeks postnatal and 32 – 34 weeks of post-menstrual age.

The following information were obtained from ROP records or casesheets:

1) identities, 2) date of birth, 3) sex, 4) race, 5) single or multiple birth, 6) birth weight, 7) gestational age, 8) ROP data.

Gestation age, by convention, refers to weeks since last menstrual period. Whenever there was a discrepancy between age due to dates and age due to scores, age due to scores was taken only if the difference was ≥2 weeks. ROP data included the timing and results of screening until one of the following occurred:

- Retina observed to be matured and fully vascularised
- Threshold disease reached and treatment given
- Death of baby

The data was analysed using the SPSS for MS Windows Release 6.0.

RESULTS

A total of 238 children were referred for screening between December 1993 and November 1994. Of these, 29 were excluded as they were either older or heavier than the inclusion criteria. These heavier and less premature babies had oxygen therapy, chronic lung diseases or suspected intrauterine infections. Of these 29, 4 defaulted and were not screened at all. Separate analysis of the remaining 25 babies showed that none developed ROP. In effect, 209 babies entered the study.

Baseline characteristics of the 209 were as follows:

- 90 (43.1%) girls, 119 (56.9%) boys
- 177 (84.7%) single births, 32 (15.3%) multiple births
- 116 (55.5%) Chinese, 23 (11.0%) Indians, 60 (28.7%) Malays, 10 (4.8%) other races
- Mean birth weight was 1096.4g (Range 534–1865g)
- Mean gestational age was 28.8 weeks (Range 23–34)

Incidence of ROP

ROP incidence was designated "+" as long as the infant had some stage of ROP in at least 1 eye on at least 1 occasion. ROP "+" was seen in 72 (34.4%) children.

Severity of ROP

This was taken as the highest stage attained. Stage 1 was seen in 33 (45.8%), stage 2 in 21 (29.2%), stage 3 in 7 (9.7%), threshold in 9 (12.5%), stage 4 in 1 (1.4%), stage 5 in 1 (1.4%). Eight of those with threshold disease underwent cryotherapy whereas 1 was observed and had regression. The infant with stage 4 and the one with stage 5 disease had vitreoretinal surgery.

Stage of ROP at first examination

At first examination, 35 out of the 72 children who ultimately developed ROP, already had ROP–31 with stage 1, 4 with stage 2.

Age when ROP was first diagnosed

When ROP of any stage was first diagnosed, the mean post-menstrual age (corrected age, i.e addition of gestation age and postnatal age) was 35.1 weeks (range 29–42) and the mean postnatal age was 7.7 weeks (range 3–18). Fifty-eight of these babies had stage 1 at onset whereas 11 had stage 2 and 3 had stage 3.

Table IV - Comparison of other studies with present study

Study	England[16] 1988	NZ[17] 1988	Denmark[18] 1990	Sweden[19] 1993	US[20] 1991	S'pore 1995
Number	505	313	201	260	4099	209
Inclusion criteria	≤1700g	<1500g	≤1750g	≤1500g	<1251g	<1250g or <32 weeks
ROP incidence	49%	21%	28%	40%	65.8%	34.4%
Stage 3 and above	4.2%	3.8%	7.0%	20%	18.2%	8.6%

Table V - Screening guidelines

	Screening Criteria			Timing of screening
	birth weight		gestational age	
Holmstrom[19]			<32 weeks	5-6 wks postnatal
Darlow[17]	≤ 1250g	or	<30 weeks	6-9 wks postnatal
Fledelius[23]	< 1750g	or	<32 weeks	
Palmer et al[20]	< 1251g			4-6 wks postnatal
present study's inclusion criteria	< 1250g	or	<32 weeks	32-34 wks post-menstrual 6 wks postnatal
Suggestion	**< 1250g**	**or**	**<32 weeks**	**33 wks postmens**

"wks": weeks; "postmens": post-menstrual age

Age of babies when they developed threshold ROP
At threshold ROP, the mean post-menstrual age was 38.8 weeks (Range 36–41) whereas the mean postnatal age was 12 weeks (Range 9–16). The median post-menstrual age was 39.0 weeks.

Time span from onset of ROP to attainment of threshold severity
This was 3.3 weeks (Range 1–7).

There were statistically significant correlations (chi-squared test) between the incidence of ROP with the following factors:

- low birth weight (p value <0.001)
- early gestation age (p value <0.001)
- multiple birth (p value <0.001)

ROP incidence did not correlate with sex, race (both p values >0.05).

Severity of ROP correlated with

- low birth weight (p value <0.05)
- multiple birth (p value <0.001) but not to gestational age, sex or race (p value >0.05)

While sex distribution of the study population matched that of the live births in Singapore for the same period, there appeared to be a higher proportion of Malays among the study population (the premature babies) when compared to all the live births.

DISCUSSION

Projecting results to a national level

Between November 1993 and end of October 1994, there were 49,563[14] live births in Singapore. Of these, 22,203[44.8%[15]] occurred at government restructured hospitals (namely KKH, SGH and NUH), 54.9% at private hospitals and 0.3% at other locations like residences. Since all at risk babies in the restructured hospitals were referred for screening and captured in this study and 72 were diagnosed to have ROP, the incidence of ROP in this population is 0.32%. If babies born in the private hospitals were included, it is likely that the overall incidence would be less because very premature babies born in private hospitals are normally transferred to the neonatal intensive care units in government restructured hospitals and hence would have been included in the study.

Comparison with previous studies

The present study shows that 34.4% of children with less than 32 weeks of gestation or weighing less than 1250g developed ROP. The results appear to be well within the range of results obtained by 5 other studies (Table IV).

Although the inclusion criteria and examination schedules of the present study are comparable to the American Multicentre Study[20], the incidence of ROP and the incidence of severe disease is much higher in the latter, implying possible population differences or that better neonatal care has evolved since 1991. The lower incidences of ROP and severe disease in New Zealand[17] and Danish[18] studies can be explained by the inclusion of heavier babies who are less at risk of developing ROP. It is interesting to note that despite the inclusion of heavier babies, the Swedish[19] study reported higher incidences of ROP and severe disease when compared to the present study.

The results of mean post-menstrual and mean postnatal ages at onset of ROP are compatible with the Swedish study.[19] The median post-menstrual age at the onset of stage 1 in the study population is very close to that of the American study[20] but the median age for threshold ROP is much higher in the local population.

Consistent with the Swedish[19] and American[20] studies, there are significant inverse correlations between ROP and birth weights and gestational age. However, the study also found a correlation between multiple births and ROP. This could possibly be explained by the fact that children of multiple births tend to be more premature and have lower birth weights. The American study[20], on the other hand, correlated race with ROP. In Singapore, when compared to the live births in Singapore for the same period, there was generally a higher proportion of Malays in those with ROP and those without ROP in the study population, hence there is no correlation between ROP incidence and race.

Screening programmes

Since the 1980s, designs of screening programmes to identify children with threshold disease have been a subject of interest for several groups. Many differing guidelines have emerged (Table V).

Screening criteria
A screening programme for Singapore can be designed based on the results of the present study. Since no baby who did not fulfill the inclusion criteria

of less than 32 weeks of gestation or weighing less than 1250g, had ROP, confining examinations to these limits would have reduced the number of initial ophthalmic examinations by 12% without missing any proliferative retinopathy. The optimal screening strategy represents the best compromise between the chances of timely ROP detection and the unknown side-effects, efforts and cost of diagnostic procedures. Furthermore, the 14 children with gestational ages of 30 weeks or more did not develop ROP stage 3 and above. This means that the gestational age criteria could even be lowered to less than 30 weeks. However, more work involving a larger cohort has to be done to evaluate this proposition further.

Timing of the first examination

Although 35 children already had ROP at first examination, they only had stages 1 or 2; therefore, the existing timing schedules are actually quite adequate. Based on the results of mean ages at onset and at threshold, the ranges in terms of postnatal age were much greater than post-menstrual age. More importantly, Palmer et al[20] showed that the timing of retinal vascular events correlated more closely with post-menstrual age than postnatal age. Hence, timing limits should be applied according to post-menstrual age. The mean post-menstrual age at onset was 35.1 weeks. There was no risk of developing stage 3 ROP before 33 weeks and no risk of developing threshold ROP before 36 weeks. Therefore, the first examination should be timed at 33 weeks of corrected age.

Recommendations for future studies

Further analysis of the recommended screening guidelines has to be done. A long-term follow-up of the 209 babies is also warranted. Of outstanding interest would be their visual outcome, incidence of complications like glaucoma, refractive errors and any other medical complications. In fact, good prospective follow-up of children who have required intensive care should be an integral part of neonatal intensive care.

CONCLUSION

There is more to prematurity and the visual system than ROP; and hopefully as more knowledge about the nature and mechanisms of these associations is gained, the unexpectedly long-running saga of ROP can be brought to a close. In the meantime, the focus of preventive attention should probably shift away from neonatology towards obstetrics and public health, as developing effective methods of avoiding premature delivery and extreme low birth weight can also put the problem to a halt.

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