

Refractive Errors and Strabismus in Premature Asian Infants with and without Retinopathy of Prematurity

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ABSTRACT

Aim: In Caucasian populations, premature infants with retinopathy of prematurity (ROP) have been reported to have higher risks of developing refractive errors and strabismus. The purpose of this study is to evaluate the rate of these complications in Asian premature infants with and without ROP.

Methods: A retrospective case review of all premature infants referred to the Singapore National Eye Centre for ophthalmology screening. These included all neonates born earlier than 34 weeks gestational age and less than 1500 grams in birth weight. Standardized ophthalmology examinations including cycloplegic refraction and fundus examination at regular intervals were performed to determine the presence of ROP, refractive errors, squints and other ocular abnormalities until the patients were 3 years old.

Results: During 1991 to 1993, a total of 113 neonates were reviewed. Of these, 16 (14.2%) developed ROP. The risk of ROP was higher with lower birth weights and earlier gestational ages. At 1-year follow-up, the rate of myopia was 33.3% in babies with ROP compared to 3.7% in babies with no ROP ($p < 0.001$). The higher rates of myopia in babies with ROP remained with longer follow-up (33.3% and 25% in ROP group versus 3.4% and 3.8% in no ROP group, at 2 and 3 years respectively). There was no difference in rates of astigmatism or hyperopia throughout the 3 years. At 1 year follow-up, the rate of strabismus was 20% in the ROP group compared to 4.9% in the no ROP group ($p = 0.07$). However, this difference in rates of strabismus was not significant at 2 and 3 years of follow-up.

Conclusion: Premature babies with ROP had higher rates of myopia and strabismus than those without ROP. Long-term follow-up of these babies is important for early detection and treatment of these ocular problems.

Keywords: ROP, myopia, astigmatism, strabismus, amblyopia

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INTRODUCTION

Premature infants are at risk of retinopathy of prematurity (ROP), an important potentially blinding condition. ROP has been more prevalent with the advances in obstetric and neonatal care significantly increasing the survival of very low birth weight infants. Its incidence and severity have been shown to be higher in lower birth weight and gestational age infants⁽¹⁾.

Besides retinal complications (such as retinal detachment), infants with ROP have also been reported to have an increased risk of ocular complications such as strabismus and refractive errors⁽²⁻⁴⁾. In Caucasian premature infants with ROP, Robinson and O'Keefe⁽²⁾ showed an increased incidence of strabismus (20% with ROP and 25% without ROP) and myopia (27.5% with ROP and 8.8% without ROP). However, in Asia, the incidence of these ocular complications in premature infants with ROP is not known.

The purpose of this study is to evaluate the type and incidence of ocular morbidity seen in premature infants who developed ROP in Singapore. At the same time, we also evaluated risk factors associated with the development of ROP.

METHODS

A retrospective case review was conducted. The study population consisted of all neonates born earlier than 34 weeks gestational age and less than 1500 grams in birth weight who were referred from the government restructured hospitals between January 1991 to December 1993 to a single paediatric ophthalmologist at Singapore National Eye Centre. All cases were reviewed at 34 weeks gestation or 4 weeks after birth, whichever was later.

Standardized ophthalmic examination was conducted at the initial screening and subsequent follow-up examinations. At the first screening, all patients had topical cyclopentolate 0.5% and phenylephrine 2.5%

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Table I. Characteristics of study population (all premature infants <1500 g birth weight or less than 34 weeks gestations from 1991 to 1993).

| | | ROP N=16 | | No ROP N=97 | | p value |
|-------------------------|-----------|-------------|--------|----------------|--------|---------|
| | | No. | (%) | No. | (%) | |
| Gestational age (weeks) | < 26 | 3 | (18.8) | 1 | (1.0) | p<0.001 |
| | 26-27 | 3 | (18.8) | 1 | (1.0) | |
| | 28-32 | 10 | (62.5) | 74 | (76.3) | |
| | > 32 | 0 | (0.0) | 21 | (21.6) | |
| Birth weight (g) | < 750 | 4 | (25.0) | 2 | (2.1) | p<0.001 |
| | 750-999 | 8 | (50.0) | 13 | (13.4) | |
| | 1000-1499 | 2 | (12.5) | 55 | (56.7) | |
| | ≥1500 | 2 | (12.5) | 27 | (27.8) | |
| Sex | M | 6 | (37.5) | 50 | (51.5) | p=0.42 |
| | F | 10 | (62.5) | 47 | (48.5) | |
| Race | Chinese | 8 | (50.0) | 68 | (70.1) | p=0.44 |
| | Malay | 5 | (31.3) | 20 | (20.6) | |
| | Indian | 2 | (12.5) | 6 | (6.2) | |
| | Other | 1 | (6.3) | 3 | (3.1) | |
| Multiple birth | Yes | 0 | (0.0) | 14 | (14.4) | p=0.21 |
| | No | 16 | (100) | 83 | (85.6) | |

p values: Pearson's Chi-square Test/Fisher's Exact Test used

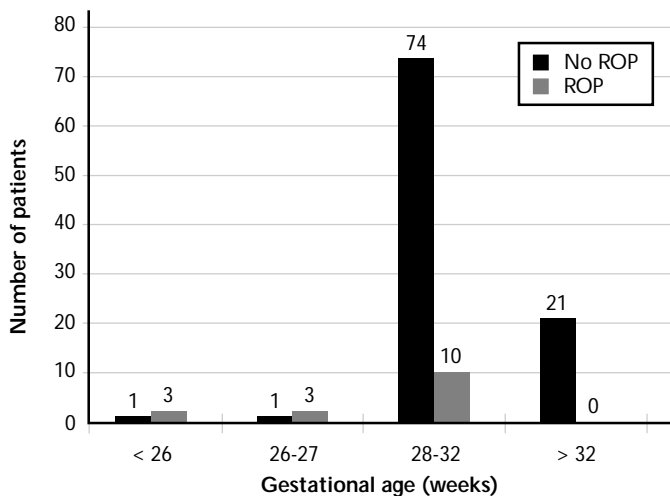


Fig. 1 The distribution of ROP versus gestational age.

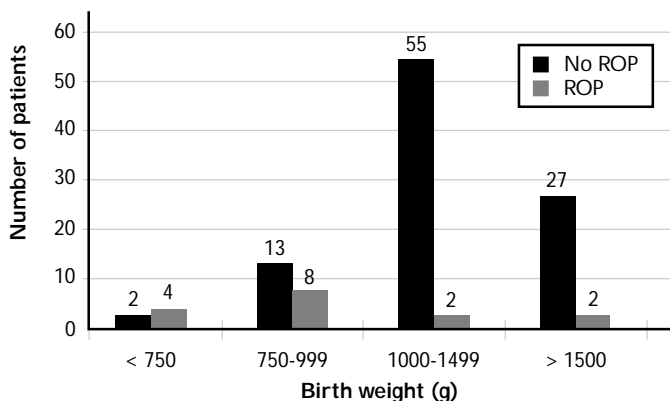


Fig. 2 The distribution of ROP versus birth weight.

instilled half hour before and dilated fundal examination with scleral indentation to detect the presence of ROP performed. All babies continued to be reviewed in the outpatient clinics after being discharged from the neonatal intensive care unit.

Subsequent examinations included visual acuity testing, orthoptic examinations for the presence of a squint, objective cycloplegic refraction and further retinal examination. All babies were routinely reviewed at regular intervals until they were 3 years of age or longer if strabismus or amblyopia developed.

ROP was classified in all our patients according to an international classification⁽⁵⁾. Significant ROP was defined as stage III or IV disease.

The 2 primary ocular morbidity studied were:

1. Refractive errors. Myopia was defined as minus 1.00 dioptres sphere or worse. Hyperopia was defined as plus 3.00 dioptres sphere or worse. Astigmatism was defined as 1.00 dioptres cylinder or worse.
2. Manifest squint, classified as either esotropia or exotropia as detected by the Hirschberg's corneal light reflex test followed by the cover uncover test and measured by the prism and cover test.

RESULTS

A total of 113 babies were reviewed during January 1991 to December 1993 for the presence of ROP. Of these, 56 were males, 57 were females and 67.3% were Chinese, 22.1% Malays, 7.1% were Indians and 3.5% other ethnic races (Table I). This shows a disproportionately larger proportion of Malays in the study population than the racial distribution in Singapore. The average gestational age was 30.2 weeks, ranging from 24 to 34 weeks. The average birth weight was 1297.8 grams, ranging from 600 g to 2180 g.

In all, 16 (14.16%) developed ROP of which only 1 developed stage IV ROP with vitreous haemorrhage and retinal detachment that required surgical intervention. Two had pre-threshold stage III ROP which did not require laser therapy and the rest had early stage I or II disease. The mean duration of follow-up was 2.04 years.

The incidence of ROP in this review of babies who were born less than 1250 g birth weight is 25.0% (13 out of 52), slightly lower than that reported by Leo and Cheong PY⁽⁶⁾. They reported an incidence of 34.4% (72 out of 209) babies with birth weights less than 1250 g or gestational ages less than 32 weeks developing ROP.

The distribution of ROP in this study of premature infants against the gestational age and birth weight is shown in Figs. 1 and 2 respectively. Of the 4 patients

Table II. Refractive errors among the premature infants with and without ROP, numbers (%).

| Refractive errors | Years of follow-up | | | | | | | | |
|---------------------------|--------------------|-----------|---------|-----------------|-----------|---------|-----------------|-----------|---------|
| | 1 year n=81 | | | 2 years n=58 | | | 3 years n=52 | | |
| | ROP | No ROP | P value | ROP | No ROP | P value | ROP | No ROP | P value |
| Myopia ≥1.00 DS | 5 (33.3) | 3 (3.7) | <0.001 | 3 (33.3) | 2 (3.4) | 0.02 | 2 (25.0) | 2 (3.8) | 0.08 |
| Hyperopia >3.00 DS | - | - | - | - | - | - | - | - | - |
| Astigmatism ≥1.00 DC | 4 (26.7) | 11 (13.6) | 0.24 | 4 (44.4) | 14 (24.1) | 0.24 | 6 (75.0) | 19 (36.5) | 0.06 |
| Emmetropia or <3.00 DS | 6 (40.0) | 67 (82.7) | <0.001 | 2 (22.2) | 42 (72.4) | 0.02 | 0 (0) | 31 (59.6) | 0.08 |

with gestational age below 26 weeks (Fig. 1), 3 (75%) developed ROP but none developed significant (stage III or stage IV) ROP. Of the 4 patients with gestational age between 26-28 weeks, 3 (75%) developed ROP and 1 patient (25%) developed significant ROP. Of the 84 patients with gestational age between 28-32 weeks, 10 (12%) developed ROP and 2 (2.3%) developed significant ROP. 21 patients were of gestational age above 32 weeks and none of these developed ROP.

Of the 6 patients with birth weights below 750 g (Fig. 2), 4 patients (67%) developed ROP and 1 (17%) developed significant ROP. Of the 21 patients with birth weights between 750-1000 g, 8 (38%) developed ROP and 2 (10%) developed significant ROP. Of the 57 patients with birth weights between 1000-1500 g, 2 (4%) developed ROP with none developing significant ROP. Of the 29 patients with birth weights above 1500 g, 2 patients (7%) developed ROP and none developed significant ROP.

The refractive errors were evaluated separately in babies with and without ROP. The incidence of myopia was significantly higher in the group with ROP compared to the group without ROP at the 1 and 2-year follow-ups (see Table II and Fig. 3). Five out of 15 (33.3%) of those who had ROP and who were reviewed at the 1-year follow-up developed myopia, 3 out of 9 (33.3%) at 2 years follow-up and 2 out of 8 (25%) when reviewed at 3 years. Whereas 3 out of 81 (3.7%) who did not have ROP were found to have myopia at the 1 year follow-up, 2 out of 58 (3.4%) at 2 years and 2 out of 52 (3.8%) at 3 years follow-up. The incidence of astigmatism was also higher in the ROP group with incidence of 26.7% (4 out of 15), 44.4% (4 out of 9) and 75% (6 out of 8) at the 1, 2 and 3-year follow-up respectively. These figures, though higher than 12.3% (10 out of 81), 24.1% (14 out of 58) and 33.3% (18 out of 54) at the 1, 2 and 3-year follow-up in the group without ROP, were not statistically

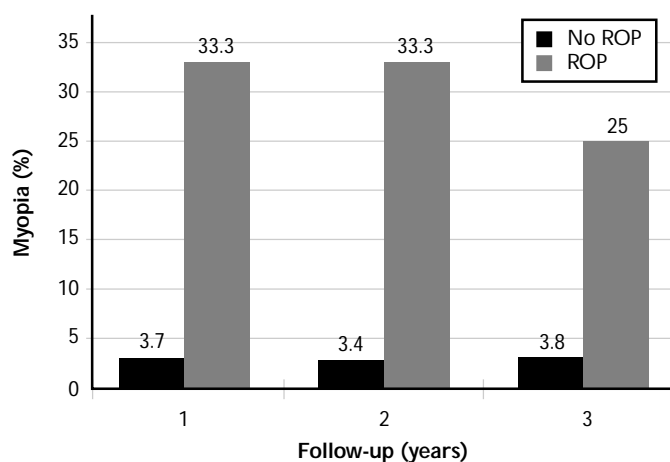


Fig. 3 The incidence of myopia associated with ROP.

significant. No hyperopia of more than +3.00 DS was detected in any of the groups.

The one patient who had stage IV ROP who was born at 26 weeks gestation and birth weight of 735 g had vitreous haemorrhage with retinal detachment. He developed moderately high myopia with cycloplegic refraction of -5.50 sphere/-200 cylinder at 180° axis in the right eye and -9.00 sphere/-1.00 cylinder at 180° axis in the left eye. He was also found to have a right esotropia of 25 prism dioptres at 1, 2 and 3 years of review. He underwent vitrectomy and surgical repair of the retinal detachment.

The incidence of strabismus in the group of babies who had ROP at 1, 2 and 3 year follow-up was 20%, 30% and 25% respectively, as compared to 4.9%, 9.7% and 9.8% in the group of babies who did not develop ROP (see Table III and Fig. 4). These results were again, not statistically significant.

DISCUSSION

A prospective study on 558 children, born at less than 32 weeks gestation, performed by Pennefather et al⁽²⁾, in UK, showed a high incidence of extra-retinal

Table III. Strabismus among the premature infants with and without ROP, numbers (%).

| | Years of follow-up | | | | | | | | |
|----------------|--------------------|-----------|---------|-----------------|-----------|---------|-----------------|-----------|---------|
| | 1 year n=81 | | | 2 years n=58 | | | 3 years n=52 | | |
| | ROP | No ROP | P value | ROP | No ROP | P value | ROP | No ROP | P value |
| Any strabismus | 3 (20.0) | 4 (4.9) | 0.07 | 3 (30.0) | 6 (9.7) | 0.10 | 2 (25.0) | 5 (9.8) | 0.24 |
| Esotropia | 1 (6.7) | 0 (0) | 0.16 | 1 (10.0) | 0 (0) | 0.14 | 1 (12.5) | 0 (0) | 0.14 |
| Exotropia | 2 (13.3) | 4 (4.9) | 0.23 | 2 (20.0) | 6 (9.7) | 0.31 | 1 (12.5) | 5 (9.8) | 1 |
| No strabismus | 12 (80.0) | 77 (95.1) | 0.07 | 7 (70.0) | 56 (90.3) | 0.10 | 6 (75.0) | 46 (90.2) | 0.24 |

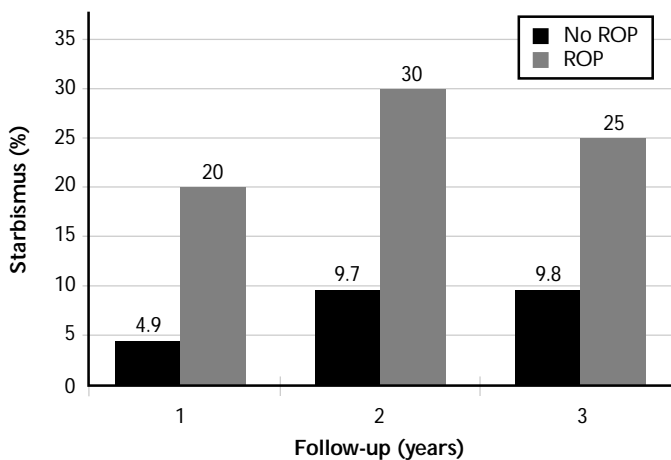


Fig. 4 The incidence of Strabismus associated with ROP.

abnormalities, particularly strabismus (12.5%), cortical visual loss (1.3%), sequelae of retinopathy of prematurity (2.9%), and other significant refractive errors (12.7%). Lue et al⁽⁷⁾ showed that 47.5% of patients with ROP have abnormal chronological change in refraction, most of which are toward myopia. Optotype acuities were significantly poorer among the ROP patients with abnormal than normal refractive courses.

In a recent report of ROP in Singapore hospitals, the incidence of ROP in infants born earlier than 32 weeks gestation and birth weight of less than 1250 grams was 34.4%. The extent of other eye problems in these patients was not reported.

Our prospective study aimed to evaluate the risk factors associated with ROP and the incidence of associated ocular morbidity in particular, refractive errors and strabismus. The disproportionately larger number of Malays as compared to the general population consensus having premature infants and subsequently ROP was noted. This could be attributed to the difference in socioeconomic status of Malays in our country. Other racial, cultural or hereditary risk factors may come into play.

The higher incidence of ROP seen in infants with

earlier gestational ages and lower birth weights shown in this study (Figs. 1 and 2) was not unexpected.

The rate of myopia in children varies from 5% to 18%⁽⁹⁾. The prevalence of myopia in Singapore in kindergarten children is about 10% in 4, 11% in 5 and 12% in 6-year-olds. At the end of 3 years follow-up in our prospective study, we found myopia to be more common in premature babies with ROP than those without ROP as well as in the normal population. The incidence of myopia was significantly higher in the group with ROP compared to the group without ROP at the end of 1 and 2 years follow-up. Four out of 15 (26.7%) of those who had ROP and who were reviewed at the 1-year follow-up developed myopia compared to 3 out of 81 (3.7%) in the non-ROP group ($p=0.00$). Three out of 9 (33.3%) developed myopia in the ROP group at 2 years follow-up compared to 3 out of 58 (5.2%) in the non-ROP group ($p=0.02$). However, myopia development though higher in the ROP group at 3 years follow-up (25%) compared to 2 out of 54 (3.7%) in the non-ROP group, there was no statistical significance ($p=0.08$). This lack of statistical significance is likely to be explained by the high default rate at the end of 3 years follow-up. No regression of myopia was noted in any case of myopia that had developed early and followed-up for 3 years.

The incidence of astigmatism was also higher in the ROP group with incidence of 26.7% (4 out of 15), 55.6% (5 out of 9) and 62.5% (5 out of 8) at the 1, 2 and 3 year follow-up respectively. This figure is high compared to 12.3% (10 out of 81), 24.1% (14 out of 58) and 33.3% (18 out of 54) at the 1, 2 and 3 year follow-up in the group without ROP. However, these differences were not statistically significant, possibly affected by the high default rate of our follow-up by the end of 3 years. No hyperopia of more than +3.00 DS was detected in any of the groups.

Pre-term infants less than 1500 g birth weight or 34 weeks gestation with ROP had higher incidence of ocular misalignment than those without ROP. The incidence of strabismus at 3 years follow-up was 25%

in the ROP group versus 9.8% in the non-ROP group. Exotropia was more common in the ROP group as compared to the non-ROP group (12.5% versus 9.8%) as was esotropia (12.5% in the ROP group versus 0% in non-ROP group) in this study population of pre-term babies at 3 years of follow-up. However these results were not statistically significant. Nonetheless, we do not show the results reported by Schaffer⁽⁸⁾ who found esotropia more common than exotropia in their study of patients with arrested mild ROP.

Although there was only one anecdotal case, which developed stage IV ROP in our study series, it is not surprising to find that this child with the most severe case of ROP developed high myopia (also highest in this series) and strabismus by the first year of follow-up. The cycloplegic refraction was -5.50 sphere/-2.00 cylinder at 180 axis in the right eye and -9.00 sphere/-1.00 cylinder at 180 axis in the left eye. He was also found to have a right esotropia of 25 prism dioptres at 1, 2 and 3 years of review. It thus suggests that increased severity of ROP has a higher risk of developing severe ocular morbidity. He underwent vitrectomy and surgical repair of the retinal detachment but ended with very poor visual prognosis in the eye.

In conclusion, our study shows that premature infants with ROP suffered from an increased risk of ocular morbidity and this included ocular misalignment

and refractive errors. At the end of 3 years of follow-up, manifest squint in particular exotropia, was found to be more common in ROP and, myopia as well as astigmatism occurred more frequently. The increased severity of ROP appears to be associated with an increased incidence and severity of ocular morbidity. Longer follow-up and evaluation of their visual function would be helpful to provide a basis for prognostication and spearhead future developments to help intervene and reduce the ocular morbidity of these premature infants.

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