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Ethnic variations in the incidence and outcome of severe retinopathy of prematurity

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ABSTRACT • RÉSUMÉ

Background: The aim of this study was to assess the incidence and outcome of severe retinopathy of prematurity (ROP) among different ethnic groups in a geographically defined population in the U.K. Severe ROP was defined as any stage 3 or worse disease.

Methods: This was a retrospective study of children born over a 6-year period with a birth weight of 1250 g or less. Threshold ROP was treated with diode laser.

Results: Severe disease developed in 37 out of 355 neonates (10.4%) who underwent ROP screening. The difference in the incidence of severe ROP between infants of Caucasian and South Asian ethnic origin was not statistically significant: 10.2% vs. 10.8% (odds ratio = 1.06; 95% confidence interval: 0.44 to 2.57). This conclusion held after single-variable adjustment for birth weight, gestational age, and score on the Clinical Risk Index for Babies. The incidence of threshold ROP was 3% among infants of both Caucasian and South Asian ethnic origin. There was no significant difference in terms of visual outcome between the Caucasian and South Asian infants.

Interpretation: This study showed no statistical evidence for a difference in the incidence or outcome of severe ROP among infants of South Asian ethnic origin compared with those of Caucasian origin. Although the small numbers in our study mean that a clinically important difference cannot be excluded, it is very unlikely that the 5-fold higher incidence in Asian babies described in the literature is correct for the population from which our subjects were drawn.

Contexte : Évaluation de l'incidence et des séquelles de la rétinopathie du prématuré (RDP) sévère chez divers groupes ethniques d'une population bien délimitée sur le plan géographique au Royaume-Uni. La RDP sévère a été définie comme étant une maladie en stade 3 ou pire.

Méthodes : Étude rétrospective d'enfants nés sur une période de 6 ans et dont le poids est inférieur à 1250 grammes. La RDP au stade seuil a été traitée au laser diode.

Résultats : Sur un total de 355 nouveaux-nés dépistés pour la RDP, 37 (10.4%) ont développé une maladie sévère. L'écart d'incidence de la RDP sévère entre les enfants d'origine ethnique caucasienne et ceux d'origine sud-asiatique n'était pas statistiquement significatif : 10,2 % vs. 10,8 % (rapport de cotes = 1,06 ; intervalle de confiance, 95 % ; 0,44 à 2,57). Cette conclusion est valable après rajustement d'une seule variable pour le poids à la naissance et la durée de la gestation et elle s'évalue selon l'Indice de risque clinique des bébés. L'incidence de la RDP au stade seuil était de 3 % chez les enfants d'origines ethniques caucasienne et sud-asiatique. Il n'y avait pas d'écart significatif en terme de séquelles visuelles entre les enfants caucasiens et sud-asiatiques.

Interprétation : L'étude ne montre pas de statistiques probantes sur l'écart de l'incidence ou des séquelles de la RDP chez les enfants d'origine ethnique sud-asiatique comparativement à ceux d'origine caucasienne. Bien que les « petits nombres » relevés dans notre étude ne signifient pas qu'il faille nécessairement exclure un écart cliniquement important, il est fort improbable que l'incidence 5 fois plus élevée chez les bébés asiatiques décrite dans la littérature s'applique à la population d'où provenaient les sujets.

The CRYO-ROP¹ study showed that cryotherapy for very low birth weight infants (≤ 1250 g) with threshold retinopathy of prematurity (ROP) disease signifi-

cantly reduces the risk of unfavourable structural and functional outcomes. The CRYO-ROP study also highlighted a racial variation in the incidence and severity of

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ROP.² Multiple logistic regression analysis suggested that Caucasian race (in addition to lower birth weight, lower gestational age, and multiple births) was an independent risk factor for the development of threshold ROP. Within the natural history cohort of the CRYO-ROP study, Afro-Caribbean infants had a 65% lower risk of reaching threshold disease as compared with Caucasian infants. With subgroup analysis on patients with any degree of ROP, Afro-Caribbean infants had a 64% lower risk of reaching threshold disease. Suggested reasons for the apparent difference in incidence of severe ROP among Afro-Caribbean vs. Caucasian babies have included differences in medical status at birth, differences in pigmentation of the retina, and differences in socio-economic status.^{3,4} Infants of South Asian origin have heavily pigmented fundi. The incidence of severe ROP among South Asian babies is therefore of interest.

Ng and associates⁵ have published the only previous research regarding the incidence of ROP in a South Asian population. They found the incidence of ROP stage 3 or 4 to be 14.1% in the Asian, 4.2% in the Afro-Caribbean, and 2.7% in the Caucasian groups, and these figures have become established in the literature.

The aim of this study was to assess the incidence and outcome of severe ROP among different ethnic groups, including a large South Asian contingent, in a geographically defined population over a 6-year period. Severe ROP was defined as any stage 3 or worse disease.

METHODS

Ethics approval for our study was obtained from the Leicestershire National Health Care Trust.

This was a retrospective study of all children who had a birth weight of 1250 g or less and were born to mothers who were resident in the county of Leicestershire, U.K., during the study period January 1, 1994, to December 31, 1999, and survived to 42 weeks' postmenstrual age. Cases were identified through the Trent Neonatal Survey (TNS). This survey, established in 1990, is an ongoing study of neonatal intensive care activity in the former Trent Health Region of the U.K. and has been described in previous publications.⁶ The database holds information related to all infants who are of 1500 g birth weight or less and (or) 32 weeks' gestational age or less at

birth, are born to a Trent resident mother, and admitted to a neonatal unit. Data for the TNS are collected by a group of 5 part-time research nurses who visit each neonatal unit on a regular basis and complete a standardized data set for each infant. Information is obtained from the clinical records, discussion with staff, and, when appropriate, personal observation. Since January 1, 1994, the TNS has collected data on the ethnic origin of the newborns included in its database using the following classification: Caucasian, South Asian (India, Pakistan, Sri-Lanka, and Bangladesh), Afro-Caribbean, mixed race, other, and unknown.

All infants with a birth weight of 1250 g or less underwent eye examinations in order to screen for acute ROP. The first eye examinations were carried out when the infants reached a postmenstrual age of 32 weeks. Subsequent examinations were conducted at 2-week intervals until at least 1 examination beyond 40 weeks of postmenstrual age. When stage 3 ROP was imminent or established, the infants were examined more frequently and for a more prolonged period. To ensure that the screening process was complete, appropriate arrangements were made for infants who were due to be transferred to another hospital or discharged home. Prior to eye examination, the pupils were dilated with Cyclomydril eye drops (0.2% cyclopentolate and phenylephrine 1%). Examinations were performed using indirect ophthalmoscopy and a 28 diopter lens, with the aid of an eyelid speculum and scleral indenter. The international classification of ROP was used, and those with threshold or worse disease underwent diode laser treatment to the avascular retina. One of the authors (G. Woodruff) was responsible for all the eye examinations and all laser treatment (except one) in the study period. In his absence, the ophthalmology registrar trained by G. Woodruff would carry out the screening. All infants entered in the ROP screening programme were followed up in the ophthalmology clinic until at least 1 visit past their fifth birthday.

The difference in the incidence of severe ROP between the Caucasian and South Asian groups was quantified by estimated odds ratios (ORs), with 95% confidence intervals (CIs). Logistic regression models were used to obtain ORs adjusted for single variables, but there were insufficient observations to construct more complex multivari-

Table 1—Baseline data and distribution of threshold and severe retinopathy of prematurity (ROP) among screened infants: 1994–1999

Ethnic group	Total no. screened	Birth weight (g) (Median [range])	CRIB (Median [range])	Gestational age at birth (weeks) (Median [range])	Severe ROP (n [%])	Threshold ROP needing laser (n [%])
Caucasian	265 infants, 530 eyes	1030 (420–250)	3 (0–16)	28 (23–36)	27 (10.2) infants, 47 (8.9) eyes	8 (3.0) infants, 5 (2.8) eyes
South Asian	65 infants, 130 eyes	1000 (580–1250)	2 (1–15)	29 (24–38)	7 (10.8) infants, 10 (7.7) eyes	2 (3.1) infants, 4 (3.1) eyes
Other*	25 infants, 50 eyes	1086 (585–1235)	4 (1–16)	28 (24–31)	3 (12.0) infants, 6 (12.0) eyes	0 (0.0) infants, 0 (0.0) eyes

*Combined Afro-Caribbean, Mixed Race, Other, and Unknown ethnic groups.
Note: CRIB, Clinical Risk Index for Babies.

able models. All analyses were completed using the SAS v. 8.2 software (SAS Institute, Cary, N.C.).

RESULTS

In total, 355 neonates were identified who underwent ROP screening, of whom 37 (10.4%) had severe disease. Table 1 presents a summary of characteristics at birth and the incidence of severe and threshold ROP. Data from infants other than those in the Caucasian and South Asian ethnic groups were combined because of the small numbers of observations. The small numbers also meant that all subsequent analyses compared only the Caucasian and South Asian ethnic groups.

There was no statistically significant difference between the Caucasian and South Asian ethnic groups in the incidence of severe or threshold ROP: OR = 1.06 (95% CI: 0.44 to 2.57); $p = 0.89$. After adjustment for birth weight, the estimated OR was 1.04 (95% CI: 0.40 to 2.70), $p = 0.93$, and after adjustment for gestational age at birth the estimated OR was 1.40 (95% CI: 0.54 to 3.56); $p = 0.48$. The Clinical Risk Index for Babies (CRIB)⁷ was used as a measure of neonatal morbidity soon after birth. It is based on 6 parameters: birth weight, gestational age at birth, presence of congenital malformations and maximum base excess, and minimum and maximum appropriate FiO_2 in the first 12 hours of life. After adjustment for CRIB, the estimated OR was 1.32 (95% CI: 0.49 to 3.51), $p = 0.58$.

Table 2 represents the visual acuity outcome at 4–5 years of age. There was no significant difference between the South Asian and Caucasian groups. Table 3 represents the refractive errors in the South Asian and Caucasian groups at 4–5 years of age. Amblyopia was defined as a difference of 2 or more lines in the best corrected visual acuity on the Snellen acuity chart. Consi-

dering all ethnic groups, 27 infants developed severe but prethreshold ROP, not needing laser treatment. In this group there were 2 amblyopic children (both Caucasian), whilst 3 developed strabismus (1 South Asian with infantile esotropia, 1 Caucasian with infantile esotropia, and 1 Caucasian with exotropia). Of the 10 infants with threshold ROP needing laser treatment, 1 South Asian and 2 Caucasian neonates had amblyopia, and 1 South Asian and 1 Caucasian infant had infantile esotropia.

INTERPRETATION

The major source of data on the race and incidence of ROP has been the CRYO-ROP study. Saunders and colleagues⁸ found that the percentage of premature infants with threshold disease in the CRYO-ROP study was more than twice as high for Caucasians as for Afro-Caribbeans (7.4% vs. 3.2%). These results remained highly statistically significant ($p < 0.001$) even after birth weight, gestational age, sex, multiple births, and transport status had been controlled for.

In contrast to the CRYO-ROP study, Arnold and colleagues⁹ provided evidence that increased pigmentation was associated with an increased risk of threshold ROP. They observed that premature infants of native Alaskan descent, who have darker ocular pigmentation than non-native infants, had a higher incidence of threshold ROP than their non-native counterparts.

In our study, no statistically significant difference was found in the incidence of severe ROP between the Caucasian and South Asian groups. This conclusion held after single-variable adjustment for birth weight, gestational age at birth, and CRIB scores.

Ng and associates⁵ published the only previous research comparing the incidence of ROP in South Asian and Caucasian infants. They studied a sample of 505 infants born in the East Midlands of the U.K. (including the county of Leicestershire) with a birth weight of less than or equal to 1700 g during the mid-1980s. They reported the incidence of ROP stage 3 or 4 to be 14.1% in the Asian, 4.2% in the Afro-Caribbean, and 2.7% in the Caucasian groups. The authors could not identify a reason for this observed difference among the ethnic groups. There was no significant difference in gestational age at birth or birth weight between the Asian and Caucasian populations.

Our results show a higher incidence of severe ROP among Caucasian infants and a lower incidence in the South Asian population compared with Ng et al.'s study.⁵ There are several possible contributory factors to the observed differences between the 2 studies. Ng and colleagues screened infants with birth weights up to 1700 g, whereas we included only infants of up to 1250 g birth weight. Clearly the lower birth weight of our infants might account for the observed higher incidence of severe ROP among the Caucasian infants in our study. In our study ethnicity was determined according to a clear clas-

Table 2—Best corrected distance visual acuity (Snellen chart) in eyes with severe retinopathy of prematurity (ROP) in children 4–5 years of age

Best corrected (Snellen) acuity at 4–5 years	Eyes with severe ROP			
	Prethreshold ROP, not lasered		Threshold ROP or worse, lasered	
	Caucasian (n = 32) (%)	South Asian (n = 6) (%)	Caucasian (n = 15) (%)	South Asian (n = 4) (%)
6/6 or better	27 (84)	5 (83)	6 (40)	2 (50)
6/9	3 (9)	1 (17)	5 (33)	1 (25)
6/12	1 (3)	0	3 (20)	1 (25)
6/18	1 (3)	0	0	0
6/24	0	0	1 (7)	0

Table 3—Refractive errors among eyes with severe retinopathy of prematurity (ROP) in children at 4–5 years of age

Best corrected (Snellen) acuity at 4–5 years of age	Eyes with severe ROP			
	Prethreshold ROP, not lasered		Threshold ROP or worse, lasered	
	Caucasian (n = 32)	South Asian (n = 6)	Caucasian (n = 15)	South Asian (n = 4)
Spherical equivalent in diopters (range)	-1 to +5.50	+0.50 to +3.75	-8 to +3	-2 to +1.50
Spherical equivalent in diopters (mean)	+2.50	+3	-2.50	-1

sification protocol by specialist nurses who had been trained in its use. Furthermore, children of mixed ethnicity were grouped separately. In their study, Ng and associates did not clarify the process by which ethnicity was determined. Another possible factor may be the change in the socio-economic status of the Asian population over the 10-year period between the 2 studies. The 2 studies drew patients from similar geographical areas. The different results raise the possibility that an improved standard of living in the Asian population has led to improved maternal health and nutrition, which may in turn affect the morbidity of the child.

Our study did not show statistical evidence for a difference in the incidence of severe ROP among infants of South Asian ethnic origin compared with those of Caucasian origin. The estimated 95% confidence intervals for the OR were wide, so that we cannot exclude a clinically important difference in incidence between these groups. However, our study does provide evidence that it is very unlikely that there is the 5-fold difference, with a preponderance of severe ROP in South Asian babies, currently suggested by the literature. At the very least, this should cause the current view of the relative incidence of severe ROP in these ethnic groups to be questioned.

The authors have no proprietary interest in any aspect of this article.

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