AXIAL LENGTH BIOMETRY IN INFANTS WITH RETINOPATHY OF PREMATURITY

D. E. LAWS[1], R. HASLETT[1], D. ASHBY[2], C. O'BRIEN[1] and D. CLARK[3]
Liverpool

SUMMARY

Ultrasound axial length measurements were obtained on infants under a birthweight of 1500 g or 32 weeks gestation undergoing screening for retinopathy of prematurity (ROP). A total of 496 readings were obtained on 171 infants between 32 and 41 weeks post-conceptual age. Other details recorded were maximum stage of acute ROP, birthweight, gestational age, sex, and biparietal and occipitofrontal head diameters. The relationship of these variables to axial growth of the eye was examined using analysis of covariance with a repeated measures approach. Mean axial length increased from 15.27 mm to 16.65 mm in the left eye during this period. Following adjustment for repeated readings a growth rate of 0.18 mm/week was obtained for both eyes. Male infants were found to have longer axial lengths despite correction for birthweight, gestation and head size ($p<0.0001$ right and left). Higher stages of acute ROP were also associated with shorter axial length ($p<0.05$ for all stages of both eyes) but the rate of growth during the study period did not demonstrate significant differences between stages. Stage 3 infants reaching the threshold for cryotherapy had shorter axial length than stage 3 infants not receiving treatment. The effect of prematurity on the growth of the eye and the significance of these findings with respect to the subsequent development of refractive errors in premature infants are discussed.

Abnormal refractive errors including anisometropia, myopia and astigmatism have been reported by several authors to follow premature birth,[1–7] but the pathophysiology and timing of the changes responsible for these sequelae are incompletely understood. Ultrasonic axial length measurement has been used to try to identify some of the factors responsible for these changes[8–12] but have concentrated on findings from the first year to the end of the second decade. There has been no prospective study starting in the neonatal period, using corrected age and correlating with the stages of retinopathy of prematurity (ROP).

The primary objective of this study was to use ultrasonic biometry to document the axial growth of the eye in the neonatal period of premature infants and identify factors that may relate to later refractive problems. Infants with stage 1 to 3 ROP are compared with a group randomly selected from a previously reported cohort of premature infants who were not observed to develop ROP[13]. Secondary objectives of this study were to confirm and expand on the findings of previous reports of axial length measurement in premature infants. Other variables that may relate to axial growth, such as head size, sex and birthweight, were also examined.

PATIENTS AND METHODS

Infants were enrolled into the study following routine screening for ROP undertaken at the Regional Neonatal Intensive Care, Oxford Street Maternity Hospital, Liverpool. Inclusion criteria were either birthweight under 1500 g or gestation less than 32 weeks. Initial examination was at 6 weeks postnatally and subsequently at 2 weekly intervals until regression was noted or until term. Demographic information was obtained from hospital records. Data obtained from examinations between 32 and 41 weeks post-conceptual age, inclusive, were used for analysis.

Mydriasis was obtained with cyclopentolate 0.5% and phenylephrine 2.5% to both eyes. Immediately before the examination topical oxybuprocaine 0.4% was instilled. A lid speculum was used to gain a maximal view of the retina and indirect ophthalmoscopy performed using a 28 dioptre lens. Indentation was also performed for the full 360°. Oxygen saturation and pulse rate were monitored during the examination. Acute ROP was recorded according to the Committee for the Classification of Retinopathy of Prematurity[14] and infants were later categorised for analysis according to the highest stage

From: [1]Department of Ophthalmology, Royal Liverpool University Hospital; [2]Departments of Statistics and Public Health, University of Liverpool; [3]Department of Ophthalmology, Walton Hospital, Liverpool, UK.

Correspondence to: Mr D. Clark, FRCS, FRCOphth, Department of Ophthalmology, Walton Hospital, Rice Lane, Liverpool L9 1AE, UK.

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reached. Ophthalmic examinations were all undertaken by one observer (D.C.) Ultrasound examination was performed using the Echorule Ultrasonic Biometer (Echorule, Downsview, Ontario, Canada) (sensitivity at 14.5 ± 0.1 mm). The infant was supported in the supine position with the lid speculum *in situ* while the 'A' scan was performed. Care was taken to use the minimum pressure by the probe on the cornea to obtain a reading. Three axial length measurements were recorded at each examination or readings were taken until consistent values were obtained; the mean of these was used for analysis. Where general medical condition precluded prolonged examination fewer readings were accepted. Data were recorded and analysed separately for each eye. Biparietal and occipitofrontal head measurements were taken with slide rule callipers. Data were entered onto the mainframe computer at the University of Liverpool and analysed with statistical package SAS/STAT software (SAS Institute, Cary, NC). Axial length changes between groups were studied using analysis of covariance with corrected age at testing as the covariate; confounding variables were also introduced into the model. A variable number of examinations were performed on different individuals and a repeated measures approach was used to account for this.

RESULTS

One hundred and thirty-four infants with ROP satisfied entry criteria (68 males and 66 females). The control group without ROP contained 25 males and 12 females, making a total of 171 infants in the study. The maximum stage of ROP reached was stage 1 in 57, stage 2 in 37 and stage 3 in 40. The sex distribution for each stage is given in Table I.

Birthweight, gestational age and post-conceptual age at examination were recorded for all infants. The birthweight ranged from 512 to 1900 g (mean 1069 g, SD 310 g) and gestational age ranged from 23 to 32 weeks (mean 27 weeks, SD 2.1 weeks). The male infants' mean birthweight was 1130 g, which was greater than that of the female infants (mean 988 g; $p<0.0001$). Lower gestational age and birthweight were associated with increasing stage of ROP (Table II).

A total of 680 examinations were performed between 32 and 41 weeks post-conceptual age and axial length readings were obtained in 496 (73%) of these: 485 for the right eye and 492 for the left. All infants had at least one satisfactory axial length measurement; however, failure to obtain a reading was more common in smaller infants. Each infant was examined between one and seven times with a mean of 2.9 readings per infant.

The axial length increased in both eyes of all groups with post-conceptual age. Mean axial length increased by 1.38 mm between 32 and 41 weeks post-conceptual age for the left eye (15.27 mm to 16.65 mm). The right eye increased by 1.35 mm over the same period. The mean rate of growth during the study period, taking account of repeated measures on some individuals was 0.18 mm/week for both eyes. Further analysis (including a quadratic term for post-conceptual age) failed to demonstrate non-linearity in the growth rate of either eye (i.e. confirmed linear growth between 32 and 41 weeks post-conceptual age).

Male infants had significantly longer axial lengths for both eyes ($p<0.001$ right, $p<0.001$ left) by a mean of 0.30 mm right and 0.29 mm left. Post-conceptual age, birthweight and individual variation in number of readings were introduced into the analysis but this did not alter the finding of males having longer axial lengths in the right ($p<0.0001$) and left ($p<0.0001$) eyes. Further analysis of infants with each stage of ROP showed this difference was apparent at all stages of ROP. Fig. 1 shows the mean axial length for males and females during the study period for the right eye. The rate of growth for males and females did not differ significantly during the study period although there was a difference in absolute length.

Axial length decreased with increasing stage of ROP (Fig. 2). Further analysis (correcting for the effects of post-conceptual age, birthweight, sex, variable numbers of readings, and biparietal and occipitofrontal head diameter) confirmed the reduction in axial length with increasing stage of ROP ($p<0.05$ right, $p<0.05$ left for all stages). Analysis of the rate of axial growth for each stage during the study period showed a trend towards slower growth in eyes that attained stage 3 ROP than in those with no ROP, but this did not reach significance in either eye.

During the study period 23 of the 40 infants reaching stage 3 ROP also progressed to the threshold for treatment recommended by the Cryotherapy for Retinopathy of Prematurity Cooperative Group.[15] Sixteen infants underwent cryotherapy and 7 underwent diode laser treatment at a mean of 37.3 weeks post-conceptual age. The treated group had significantly shorter axial lengths in both eyes ($p<0.0001$ right, $p<0.0001$ left). This difference remained after adjustment for birthweight, head size, sex post-conceptual age and gestational age, in addition to adjustment for the variable number of readings for each infant. The mean axial length for the treated and non-treated groups at each week of post-conceptual age is shown in Fig. 3, although the numbers of observations are small in the earlier weeks.

The total number of observations with biparietal head measurements was 381, with 380 for occipitofrontal diameter measurement. The correlation coefficient between axial length and these head diameters is given in Table III. The correlation between head size and axial length has been reported previously by Fledelius[8] this is confirmed by our findings and supports the use of these measurements in the analysis where appropriate.

DISCUSSION

The sagittal growth of the eye was linear over the study period. This has previously been reported in our control (stage 0)[13] group and remains consistent for infants with ROP in this study. Pathological study of the globes of human fetuses using micrometer measurements[16] has also demonstrated near-linear growth during this period,

Table I. Maximum stage of acute ROP reached in the right eye

	No. of neonates	
Stage	Male	Female
0	25	12
1	25	32
2	22	15
3	21	19

Table II. Mean gestational age, birthweight and the maximum stage of ROP in the right eye

Stage	Gestation (weeks)	Birthweight (g)
0	29.4 (1.30)	1368 (254)
1	28.4 (1.41)	1154 (253)
2	26.3 (1.46)	928 (197)
3	25.5 (1.56)	815 (186)

Values are the mean (SD)

Table III. Correlation between head diameter and axial length

	Biparietal	Occipitofrontal
Right eye	$r = 0.646$	$r = 0.628$
Left eye	$r = 0.650$	$r = 0.627$

$p<0.0001$ for all groups.

although ultrasound measurements would be expected to give slightly different absolute readings. Linear growth was also recorded using ultrasound axial length readings in premature infants before the development of acute ROP by Tucker *et al.*[17] between 25 and 37 weeks post-conceptual age. These groups found axial growth rates of 0.30 and 0.19 mm/week respectively. This equates to an overall growth rate of 0.18 mm/week in this cohort, but the studies vary in the recording technique and age group examined. Gordon and Donzis[18] measured axial length in a wide age group including 23 premature infants. Detailed comparison with our study is not possible due to the different post-conceptual age groupings, but their axial length of 16.8 mm at 41 weeks is similar to our finding of 16.65 mm for both eyes.

Axial length was inversely related to increasing stage of ROP: the higher the maximum stage of ROP reached, the shorter the axial length. This remained after correction for gestational age, sex, birthweight and head diameters. Hirano *et al.*[12] also looked at the axial growth of the eye in premature and term infants, following them until 1 year, and found shorter axial length in premature infants. However, this is the first report of this finding in the neonatal period using corrected age and direct comparison with the acute stage of ROP.

The progression towards shorter axial lengths with higher stage of ROP was noted in this study before and during the development of acute ROP. This may suggest that acute ROP itself is not causally related to reduced axial length in this age group, although they may share a common aetiology. The close association between ROP and prematurity means that even after correction for other

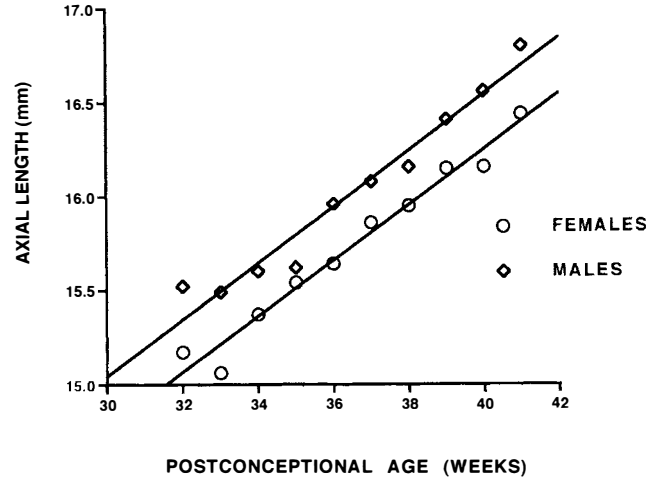

Fig. 1. *Mean axial length for males and females (right eye) with linear regression, demonstrating a similar rate of growth in the two sexes but the consistently shorter eyes of female infants.*

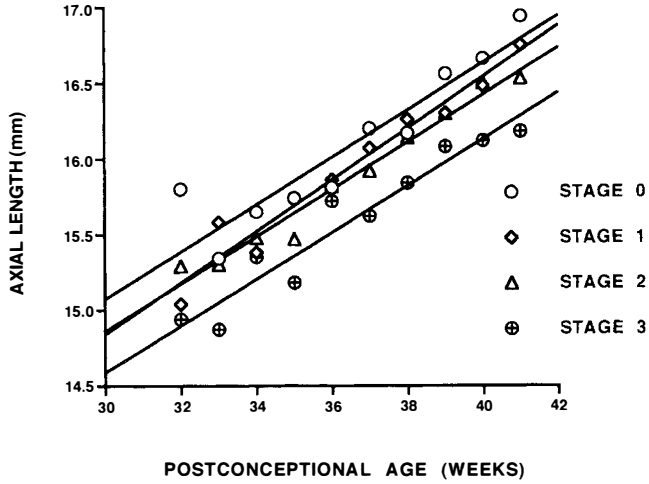

Fig. 2. *Mean axial length and maximum acute stage of ROP (right eye), with linear regression. Axial length was reduced in infants with higher stages of ROP but the rates of growth during the study period did not differ significantly with stage of ROP.*

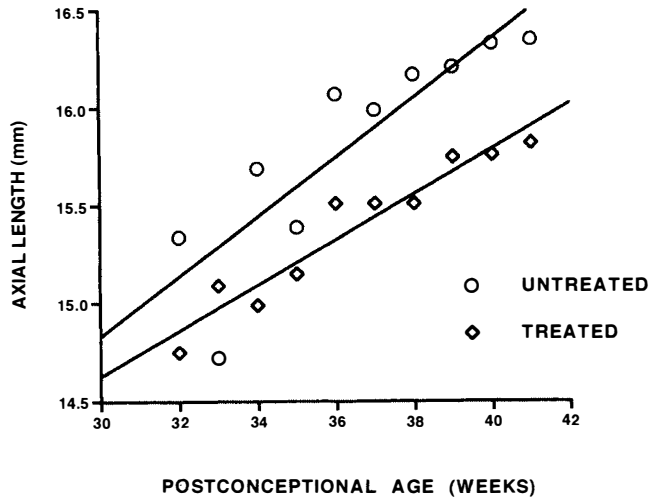

Fig. 3. *Mean axial length in treated and untreated infants with stage 3 ROP. Infants undergoing treatment had shorter axial lengths but were also more premature.*

confounding variables studies of this nature are unable to separate their effects completely. It is not possible to obtain a control group which matches the ROP groups for prematurity, so comment on our findings is limited to association rather than causation. The treated infants with stage 3 ROP had shorter axial lengths than other stage 3 infants but they were also more premature. It would be unethical to randomize treatment to study its effects on ocular growth. Thus future analysis of treatment and refractive outcome would also have to make allowance for the differing degrees of prematurity in the two groups.

Female infants have been noted previously to have shorter axial lengths[10,16] and this was confirmed in this study. Male infants had higher birthweights but the findings remained significant after correction for this and gestational age (Fig. 1) in both eyes.

The later development of myopia in ex-premature infants has been extensively reported.[1–7] Fledelius[19] in a study of keratometry during the second decade found a smaller radius of curvature in ex-premature infants and concluded that low birthweight has a restraining effect on ocular development. Gordon and Donzis[3] in their analysis of the factors responsible for myopia in 5 ex-premature children found that the power of the crystalline lens was significantly greater than in a control group of myopes. Thus the relatively short eye found in this study as early as 33 weeks corrected age in infants who develop higher stages of ROP is likely to be associated with index myopia at a later age. Further axial length biometry readings and refraction are planned on this cohort to investigate this. Study over a longer period may also reveal differences in the rate of growth where this report has shown only absolute differences between groups such as sex, stage of ROP and treatment.

This paper reports linear growth in axial length during the neonatal period in premature infants, and the association of shorter axial length in more premature infants with ROP and female sex.

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Key words: Growth, Refractive error, Retinopathy of prematurity, Ultrasound.

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