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ARTICLE

Thymic size at birth in preterm infants with severe respiratory distress syndrome can be used to predict the likelihood of survival: A retrospective cohort study

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Objective. To determine whether the thymic size in preterm infants with severe respiratory distress syndrome (RDS) can be used to predict survival. We also set out to determine which antenatal and postnatal factors have an influence on, or correlation with, thymic size.

Methods. A retrospective study was conducted on 55 consecutive preterm infants who were ventilated for RDS. A chest X-ray (CXR) was taken within the first 24 hours, and the cardiothymic/thoracic ratio (CT/T ratio) calculated. This ratio was then correlated with outcome, as well as antenatal maternal and postnatal factors.

Results. Of the 49 infants included in the study (6 were excluded), 15 died and 34 survived. There was a statistically significant correlation between the CT/T ratio and survival (p=0.029). In those infants above 1 030 g, the CT/T ratio was more significant (p=0.038) than birth weight in predicting survival. The severity of RDS did not influence the CT/T ratio. The only maternal and postnatal factors influencing CT/T ratio were the presence of pre-eclamptic toxaemia (PET) and birth by caesarean section (CS), but these factors did not influence likelihood of survival. Factors found to be not associated with thymic size were antenatal steroid administration, maternal HIV status, clinical chorio-amnionitis, gender, gestational age (small or appropriate weight) and lymphocyte count.

Conclusions. A small thymus measured in the first 24 hours can be used to predict likelihood of survival in infants weighing more than 1 030 g, but not in smaller infants. Prenatal stress associated with PET and indication for CS may cause the thymus to shrink.

The thymus is an important gland that is closely concerned with the development of cell-mediated immunity responses. In the fetus and well newborn, the thymus is proportionally at its largest compared with body weight, and is almost as big as the heart. It continues to grow until puberty, and progressively reduces in size thereafter.[1] Thymic size in neonates is represented by the cardiothymic-thoracic ratio (CT/T) as measured on chest X-ray (CXR).[2-4] There is a constant CT/T ratio in well infants irrespective of gestational age.[2,5]

Thymic size as measured by CT/T ratio in infants with respiratory distress syndrome (RDS) may actually be larger, owing to a decrease in serum cortisol levels in those preterm infants who develop RDS. This could also be explained by the decrease in lung volume that accompanies hyaline membrane disease.[2,3] One study reported a significant relationship between a small thymus and RDS.[6] Although not well documented, thymic involution may be associated with a change in lymphocyte count in the peripheral blood. Lymphocyte count has been correlated with the grade of thymic involution, with mild involution associated with a raised count and severe involution with a decreased count.[7] In neonates, the thymus has been shown to undergo stress-related involution associated with infection,[8] and histological chorio-amnionitis is associated with a small thymus at birth.[4,7] In those with chorio-amnionitis, the more immature the infant, the smaller the corresponding CT/T ratio.[9] There is also a correlation between small CT/T, chorio-amnionitis and bronchopulmonary dysplasia (BPD).[10] Although there is clear evidence that the administration of postnatal corticosteroids decreases radiological thymic size in infants,[3] there has been some debate about whether low-dose antenatal exogenous steroids given to the mother has a thymolytic effect on thymic size.[5,9,11,12] We undertook to investigate whether thymic size in infants diagnosed with RDS is related to survival. In addition, we determined the correlation between the CT/T ratio and the severity of RDS, the first postnatal lymphocyte count, as well

as prenatal and postnatal factors that might have influenced the CT/T ratio.

Method

A retrospective study was conducted on 55 consecutive preterm infants admitted with RDS to the neonatal intensive care unit (NICU) of Tygerberg Hospital over a 3-month period. All infants were ventilated and had surfactant administered. Inclusion criteria were: prematurity (<33 weeks gestation), RDS clinically and radiologically, and a CXR performed within 24 hours of delivery. Exclusion criteria were major cardiac abnormalities, and infants with a CXR that was excessively rotated or the cardiothymic shadow could not be differentiated from that of the lungs owing to severe RDS. Of the 55 infants, 6 were excluded from the study: 3 had insufficient data or parental consent was not taken, one's cardiothymic shadow was completely obscured, one was later considered not to have RDS, and one had Beckwith-Wiedeman syndrome with multiple abnormalities. A total of 49 infants remained. The CXR of each infant was analysed and the CT/T calculated as shown in Fig. 1.[2]

CXRs were twice reviewed on separate days by the principal investigator and a radiologist, both blinded to the infants' names and outcomes . The intra- and inter-observer variabilities were 3.9% and 4.1% respectively. In some instances, where the first CXR was inadequate for technical reasons, the second CXR was used if the infant was still <24 hours old. Severity of RDS was graded (*i*) radiologically (grades I - IV)[13] and (*ii*) in terms of respiratory compromise according to the arterial/alveolar oxygen tension ratio (a/APO_2) (before surfactant treatment). For each child, data about the mother's health and pregnancy-related history, and the child's birth and postnatal course, had been carefully recorded and formed part of a database. The absolute lymphocyte count was obtained at the earliest opportunity.

Ethical consent

Approval of the Institutional Ethics Committee was obtained. Patient anonymity was ensured by uncoupling data from patient names.

Statistical analysis

The relation between the outcome variable CT/T and categorical variables was examined by one-way analysis of variance; the categorical variables were: gender, method of birth, survival, PET, mother's HIV status, prenatal steroid administration, prolonged rupture of membranes and clinical chorio-amnionitis. Correlation coefficients between CT/T and numerical variables were obtained; these variables were birth weight, gestational age, total lymphocyte count and a/APO_2 ratio. Prediction of survival by CT/T and other variables was studied by multiple logistic regression.

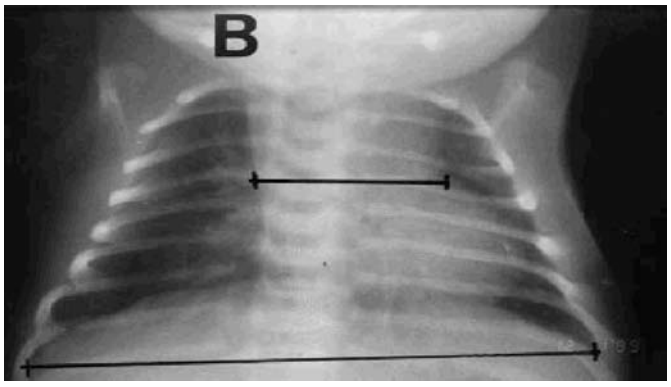

Fig. 1. The CT/T is calculated as a ratio of the cardiothymic shadow at the carina divided by the width of the thorax at the costophrenic angle.

Results

A total of 49 infants were included (21 female, 28 male). Fifteen infants (30.6%) died before day 28. Causes of death were sepsis (7), necrotising enterocolitis (NEC) (2), pulmonary bleed (2), severe RDS (2), pneumothorax (1) and intraventricular haemorrhage (IVH) (1).

The mean of the CT/T ratio of infants who survived differed significantly from the CT/T ratio of the infants who died (p=0.029) (Table I). We found no correlation between the CT/T ratio and a/APO_2 ratio (p=0.736) or the degree of radiologically diagnosed RDS (Table II). A significant association existed between the presence of pre-eclamptic toxaemia (PET), and also the method of delivery and CT/T ratio (Table III). The mean CT/T ratio of infants born to mothers with PET was significantly smaller than those born to mothers who did not have the condition (0.34±0.05 versus 0.38±0.06, p=0.05). Infants delivered by CS had smaller CT/T ratios in comparison with those infants delivered by vaginal route (0.34±0.05 versus 0.38±0.05, p=0.04). However, these two factors did not correlate with outcome in terms of death (p=0.63 for PET; p=0.72 for CS). Of the 16 infants with PET, 13 were delivered by CS performed for fetal distress.

Univariate analysis showed that none of the other factors (i.e. gender, gestational age, antenatal steroid administration, maternal HIV status, clinical chorio-amnionitis or postnatal

TABLE I. ONE-WAY ANOVA COMPARING CT/T AND OUTCOME

Outcome	No.	CT/T (mean (SD))	p-value
Death (15)	15	0.34±0.047	0.029
Alive (34)	34	0.38±0.062	

TABLE II. CT/T RELATED TO THE GRADE OF RDS

Grade of RDS	No.	CT/T (mean (SD))	p-value
Grade I	16	0.34±0.050	0.079
Grade II	21	0.38±0.056	
Grade III	11	0.37±0.070	

One infant excluded owing to grade IV RDS.

Thymus involution at birth is thought to be related to prenatal stress.

TABLE III. RELATIONSHIP BETWEEN CATEGORICAL ANTENATAL AND POSTNATAL VARIABLES AND CT/T RATIO

Variable	No.	CT/T	Variable	No.	CT/T	*p*-value
Male	28	0.37±0.062	Female	21	0.36±0.059	0.413
CS	21	0.34±0.058	NVD	28	0.38±0.059	0.044
PET	16	0.34±0.056	No PET	28	0.38±0.064	0.050
HIV+	8	0.39±0.047	HIV-	32	0.36±0.058	0.527
Steroids	29	0.35±0.063	No steroids	13	0.38±0.057	0.256
Steroids >24 hrs	10	0.34±0.050	No steroids >24hrs	32	0.37±0.064	0.294
PROM	6	0.37±0.053	No PROM	36	0.36±0.061	0.947
Clinical chorio-amnionitis	5	0.40±0.062	No clinical chorio-amnionitis	44	0.36±0.060	0.160
AGA	43	0.36±0.062	SGA	6	0.36±0.054	0.854

PET = pre-eclamptic toxaemia; PROM = premature rupture of membranes; AGA = appropriate size for gestational age; SGA = small size for gestational age.

lymphocyte count (time of collection: 26.4±24.3 hrs)) correlated significantly with CT/T ratio (Tables III, IV). There was, however, a trend for smaller infants to have a lower CT/T ratio (p=0.054) (Table IV). As smaller infants are also at higher risk of dying, we assessed the possible influence of weight on the CT/T and outcome of the infants. Infants were ranked in order of weight and divided into 4 equally sized groups. In the group with the lightest infants, the CT/T ratio was not a significant predictor of outcome. However, it was very significant (p=0.038) in the other 3 groups. The bullets in Fig. 2 represent individual patients plotted at their CT/T values – at 1 if alive, and 0 if dead. With the 0 - 1 ordinate scale, it was possible to plot the fitted logistic regression curve, which shows the probability of survival at CT/T ratio. The fitted curve is horizontal for the weight category ≤1 030 g, while it increases for the weight category above this value. According to the fitted curve, the probability of survival for a CT/T>0.39 is greater than 0.82. This is in accordance with the bullets; all patients with CT/T>0.39 are alive.

TABLE IV. RELATIONSHIP BETWEEN CONTINUOUS POSTNATAL VARIABLES AND CT/T RATIO

Variables	Pearson correlation	*p*-value
Birth weight		
Mean 1 268 g (540 - 1 990 g)	0.227	0.054
Gestational age		
Mean 29.7 weeks (27 - 32)	0.264	0.067
Total lymphocyte count	0.010	0.945
a/APO_2 ratio	0.050	0.736

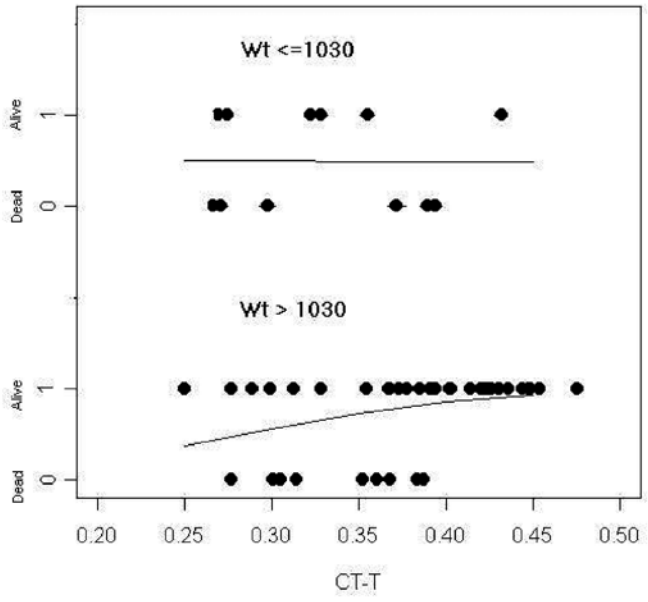

Fig. 2. CT/T values for surviving and dead infants. The fitted logistic regression curve shows the probability of survival at CT-T value.

Discussion

A large thymus measured in the first 24 hours of life can be used to predict the likelihood of survival in infants whose birth weight exceeds 1 030 g. In this weight category, the CT/T ratio was also more significant than weight in predicting survival. We found that the severity of RDS did not influence the CT/T ratio, while prenatal stress due to PET might have caused the thymus to shrink. The average CT/T ratio in the present study of 0.36 was lower than the approximate average of 0.40 quoted in other papers[2,5] but correlated well with the average of infants (without chorio-amnionitis) included in the study by De Felice and co-workers.[9] In the present study, antenatal steroids did not influence thymic size, and neither did maternal HIV status. We also found no correlation between CT/T ratio and the first postnatal absolute lymphocyte count.

At least 53% (8/15) of the infants who died in this study died of infection (sepsis/necrotising enterocolitis). Of the 9 deaths in the >1 030 g weight group, 7 were from infective causes (6 septicaemia and 1 NEC). We postulate that these infants had small CT/T either because they were infected antenatally or had problems in mounting an immune response. We therefore suggest that in those infants >1 030 g with a small CT/T, even greater vigilance must be maintained in terms of looking for and treating infection.

Thymus involution at birth is thought to be related to prenatal stress, and the grade of involution is related to the duration of the illness.[7] Stress involution appears to be mediated by activation of the hypothalamic-pituitary-adrenal axis with glucocorticosteroids causing a thymocytolytic effect with lymphocyte apoptosis in the thymic cortex.[15] We postulate that chronic insufficiency of the placenta due to PET might have caused enough prenatal stress to the fetus to result in thymic involution, which explains the noted difference observed in the present study. These factors, along with other non-PET causes

of fetal distress (the major reason for CS), could also explain the low CT/T ratio among those who were delivered by this route. Our findings are contradictory to those of Chen and co-workers, who found an increased CT/T ratio in preterm infants, with or without RDS, when delivered by CS.[5] However, these infants were older (mean gestation 33.7 weeks) and heavier (mean weight 1 964 g) than ours, and were not as ill. Although one sonographic study linked the size of the thymus to the weight of the infant,[16] a previous study did show that the ratio of CT/T was not affected by gestational age, unless chorio-amnionitis was present.[9] Although we did not have placental histology to determine histological chorio-amnionitis, few of our mothers had clinical chorio-amnionitis.

Conclusion

A CT/T ratio determined within 24 hours after delivery appears to be a useful indicator to help predict survival in preterm infants weighing more than 1 030 g but not in smaller infants. Prenatal stress owing to PET and indications for CS may cause the thymus to shrink.

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