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Prediction of bronchopulmonary dysplasia by the chest radiographic thoracic area on day one in infants with exomphalos

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Abstract

Objectives: To determine if infants with exomphalos had abnormal antenatal lung growth as indicated by lower chest radiographic thoracic areas (CRTA) on day one compared to controls and whether the CRTA could predict the development of bronchopulmonary dysplasia (BPD).

Methods: Infants with exomphalos cared for between January 2004 and January 2023 were included. The controls were term, newborn infants ventilated for absent respiratory drive at birth, without lung disease and had no supplemental oxygen requirement by 6 h of age. The radiographs were imported as digital image files by Sectra PACS software (Sectra AB, Linköping, Sweden). Free-hand tracing of the perimeter of the thoracic area was undertaken and the CRTA calculated by the software.

Results: Sixty-four infants with exomphalos and 130 controls were included. Infants with exomphalos had a lower median (IQR) CRTA (1,983 [1,657–2,471] mm²) compared to

controls (2,547 [2,153–2,932] mm², $p < 0.001$). Following multivariable regression analysis, infants with exomphalos had lower CRTAs compared to controls ($p = 0.001$) after adjusting for differences in gestational age and male sex. In the exomphalos group, the CRTAs were lower in those who developed BPD ($n = 14$, 1,530 [1,307–1,941] mm²) compared to those who did not (2,168 [1,865–2,672], $p < 0.001$). Following multivariable regression analysis, the CRTA was associated with BPD development ($p = 0.021$) after adjusting for male sex and gestational age.

Conclusions: Lower CRTAs on day one in the exomphalos infants compared to the controls predicted BPD development.

Keywords: exomphalos; anterior wall defect; lung development; chest radiograph

Introduction

Exomphalos occurs in approximately 1 in 4,000–7,000 live births [1]. Respiratory insufficiency is a significant cause of mortality and morbidity in infants with exomphalos. It is usually ascribed to the increased intraabdominal pressure after surgical closure [2–5]. There is, however, some evidence to suggest that respiratory insufficiency in infants with exomphalos could also be due to impaired antenatal lung growth [6]. Indeed, in one study, daily measurements of functional residual capacity (FRC) in infants with anterior wall defects demonstrated that four of eight infants had FRCs on day one below the reference range and lung volumes were further, but only temporarily impaired by surgical closure of the abdominal wall defects [7]. One study reported stillbirths with exomphalos have small chests [8] and a further study [9] examined the chest radiographs of infants with giant exomphalos and found them to have reduced chest widths and lung areas. In a more recent study, antenatal pulmonary hypoplasia was considered if there was reduced fetal lung:head ratio, reduced fetal chest circumference, reduced total fetal lung volume or low signal in the fetal lung [10].

Lung volumes can be measured using body plethysmography or a dilution technique, but these assessments can

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be difficult to perform in infants and are only available in centres with the necessary expertise. We have previously described how the chest radiographic thoracic area (CRTA) can be used as an alternative and more accessible method to “assess” lung volumes [11]. The CRTA is the measurement of the area of the lungs on a two-dimensional chest radiograph and has been shown to correlate well with the results of the gold standard technique, that is functional residual capacity measurement using helium gas dilution [12]. We have reported normative values of the CRTA method in term infants without respiratory pathology [13] and used the method in infants with congenital diaphragmatic hernia (CDH) to predict survival to discharge from neonatal care [11].

The aims of this study were to determine if, on day one after birth, infants with exomphalos had abnormal antenatal lung growth as indicated by lower CRTAs compared to term-born controls without respiratory pathology and whether the CRTA could predict the development of bronchopulmonary dysplasia (BPD).

Materials and methods

Infants with exomphalos cared for between January 2004 and January 2023 on a tertiary perinatal centre were included in the study. The control group consisted of newborn infants admitted to the neonatal unit due to poor perinatal adaptation or hypoxic ischemic encephalopathy without concomitant respiratory pathology. Those infants were intubated and ventilated for absent respiratory drive at birth and had no supplemental oxygen requirement by 6 h of age. The study was registered with the Clinical Governance Department (number CH159).

The chest radiographs were antero-posterior, obtained in the supine position at end-inspiration and at a standard distance of one m above the infant. Rotated radiographs and radiographs with evidence of a pneumothorax were excluded from the analysis. Rotation was assessed by measuring the distance between the medial edges of the clavicles to the vertebral spinous processes. As some infants with exomphalos were not intubated when the chest radiograph was obtained, whether the infants were intubated or not was also recorded. The radiographs were imported as digital image files by Sectra PACS software (Sectra AB, Linköping, Sweden). The software automatically adjusted for magnification errors. Free-hand tracing of the perimeter of the thoracic area as outlined by the diaphragm and the rib cage was undertaken and the CRTA was calculated by the software. The repeatability of the method has been previously described with an inter- and intra-observer coefficient of repeatability of 1.06 and 1.0 cm² respectively [12]. The chest radiograph with the highest CRTA in the first 24 h after birth for each infant was included in the analysis.

Information from the medical notes

The following data were collected from the medical notes for the infants with exomphalos: full course of antenatal corticosteroids (yes/no), caesarian section (yes/no), gestational age (weeks), birth weight (kg), major or minor exomphalos, presence of chromosomal abnormalities

including Beckwith-Wiedemann syndrome (yes/no), time to full closure (days), number of operations, duration of invasive ventilation (days), bronchopulmonary dysplasia (BPD) defined as oxygen dependency beyond 28 days after birth (yes/no), time to full enteral nutrition (days), length of hospital stay (days), survival to discharge from neonatal care (yes/no) discharge home on supplemental oxygen (yes/no). Exomphalos major was defined as a defect with >50 % of the liver in the exomphalos sac and an abdominal wall defect >5 cm in diameter. Infants with smaller defects were diagnosed as having exomphalos minor [1]. For the control infants, the gestational age, birth weight and sex were recorded.

Statistical analysis

Data were tested for normality using the Shapiro–Wilk and D’Agostino skewness tests and found not to be normally distributed and, therefore, were presented as median and interquartile range. Differences between the infants with exomphalos and control infants were assessed for statistical significance using the Mann–Whitney U test and the χ^2 test. Differences in CRTA between infants with exomphalos and controls was adjusted for sex and gestational age with a multivariable linear regression model with CRTA as the outcome variable and gestational age, sex and a diagnosis of exomphalos as the dependent variables.

The strength of the relationships of the CRTA in the exomphalos group with gestational age, birth weight, duration of ventilation and the length of hospital stay were examined with Spearman’s Rho correlation analysis. The relationship of CRTA with BPD development was examined using a multivariable binary regression model with BPD as the outcome variable, and CRTA, sex and gestational age as the dependent variables. The birth weight was not included in the model due to collinearity with gestational age. Multi-collinearity among the independent variables in the regression analysis was assessed by examination of a correlation matrix for the independent variables.

The statistical analysis was performed using SPSS software, version 27.0 (IBM, Armonk, NY, USA).

Results

In the study period, 69 infants with exomphalos were cared for on the Neonatal Unit. Five of them were excluded as they did not have a chest radiograph in the first day of life (n=2), had rotated X-rays (n=2) or a radiograph which did not include all the lung area (n=1). Sixty-four infants with exomphalos and 130 term control infants were included in the analysis. The demographics, surgical and medical outcomes and CRTA measurements of the infants with exomphalos are presented in Table 1.

The infants with exomphalos had a lower median (IQR) CRTA (1,983 [1,657–2,471] mm²) compared to the controls (2,547 [2,153–2,932] mm², p<0.001). The infants with exomphalos had a lower median (IQR) gestational age (38.1 [35.8–39.0] weeks) and birth weight (3.06 [2.43–3.33] kg) compared to the controls (39.5 [38.0–41.0] weeks and 3.34 [2.98–3.69] kg, p<0.001 for both) and a lower incidence of male sex (42 %) compared to the controls (59 %), p=0.032. Following multivariable regression analysis, the infants with exomphalos

Table 1: Characteristics of the exomphalos study population.

Perinatal	Antenatal steroids	20 (32)
	Caesarian section	45 (71)
	Male sex	27 (42)
	Gestational age, weeks	38.1 (35.8–39.0)
Surgical	Birth weight, kg	3.06 (2.45–3.33)
	Major exomphalos	32 (52)
	Chromosomal abnormalities (8 with Beckwith Wiedman)	13 (21)
	Time to full closure, days	2 (1–5)
	More than one operation	6 (9)
Outcomes	Duration of ventilation, days	3 (1–11)
	Bronchopulmonary dysplasia	14 ()
	Home oxygen	2 (3)
	Time to full enteral feeds, days	13 (10–19)
	Length of hospital stay	15 (12–42)
CRTA	Survival to discharge	56 (88)
	Intubated at measurement	27 (42)
	Right lung CRTA, mm ²	1,169 (955–1,466)
	Left lung CRTA, mm ²	802 (576–1,069)
	Total CRTA, mm ²	1,983 (1,656–2,471)

Data are presented as median (IQR) or n (%).

had a significantly lower CRTA compared to controls ($p=0.001$) after adjusting for differences in gestational age and male sex.

In the exomphalos group, the CRTA was significantly related to gestational age ($r=0.293$, $p=0.019$), birth weight ($r=0.381$, $p=0.002$) and the length of hospital stay ($r=-0.258$, $p=0.040$), but not with the duration of ventilation ($r=-0.088$, $p=0.491$). The median (IQR) CRTA was not significantly different in infants with exomphalos who did (1,898 [1,503–2,380] mm²) or did not have antenatal corticosteroids (2,035 [1,759–2,649] mm², [$p=0.125$]), were born via caesarian section (2,038 [1,657–2,578] mm²) compared to those born vaginally (1,871 [1,641–2,162] mm², [$p=0.330$]), were ventilated at measurement (1,913 [1,585–2,339] mm²) or not (2,069, 1,709–2,498 mm², [$p=0.419$]), had exomphalos major (2,001 [1,594–2,381] mm²) vs. exomphalos minor (1,960 [1,740–2,665] mm² [$p=0.622$]) or in the ones who died (2,188 [1,241–3,198] mm²) vs. the ones who survived (1,948 [1,684–2,434] mm², [$p=0.700$]). The median [IQR] CRTA was higher in male infants with exomphalos (2,265 [1,925–2,742] mm², $n=27$) compared to female infants (1,759 [1,531–2,310] mm², $n=37$, $p=0.003$) and significantly lower in infants with exomphalos who developed BPD (1,530 [1,307–1,941] mm², $n=14$) compared to infants with exomphalos who did not develop BPD (2,168 [1,865–2,672], $n=50$, $p<0.001$). Following multivariable regression analysis with BPD as the outcome variable, the CRTA at birth was significantly associated with the development of BPD ($p=0.021$) after adjusting for male sex and gestational age.

Discussion

We have demonstrated that infants with exomphalos had significantly lower chest radiographic thoracic areas (CRTA) on day one compared to ventilated, term-born controls and that a lower CRTA was significantly associated with development of BPD after adjusting for confounding factors.

We have previously demonstrated a significant correlation between respiratory morbidity (length of supplementary oxygen dependency) in surviving infants and fetal lung volumes obtained by 3D ultrasound who had varying risks for abnormal antenatal lung growth – infants with congenital diaphragmatic hernia or anterior wall defects [14]. Furthermore, fetal lung volumes correlated with postnatal lung volumes assessed by helium gas dilution measurement of FRC. Those results then are in keeping with our current finding of lower CRTAs in the exomphalos infants on day one and that they represent abnormal antenatal lung growth. Primary surgical closure in infants with exomphalos is associated with compromise in lung function [15]. This is most likely related to the surgical return of the herniated viscera into the abdomen and the increase in intra-abdominal pressure that occurs after closure of the abdomen. We report CRTAs measured on day one after birth and before surgery, thus the lower CRTAs compared to the controls reflect reduced antenatal lung growth. Fetuses with exomphalos experience low intra-abdominal pressure *in utero* as their viscera are extra-abdominal. The mechanism for abnormal antenatal lung growth in such fetuses may relate to the decreased radius of the diaphragm curvature which could affect the strength of diaphragm contracture antenatally [16]. Abnormal diaphragmatic function impairs antenatal lung growth [17].

The controls were all ventilated at the time of measurement, but the exomphalos group consisted of ventilated and non-ventilated infants. We do not think this biased our results as there was no significant difference between the CRTAs of the non-ventilated and ventilated infants with exomphalos. Furthermore, it would not be appropriate to perform chest radiographs on non-ventilated babies without respiratory disease for the purposes of developing reference values. The infants with exomphalos had a lower gestational age and birth weight than the term controls as would be expected [1]. We, therefore, adjusted for those factors using multivariable analysis and the CRTAs of the exomphalos infants remained significantly lower than those of the controls.

Our study has strengths and some limitations. We used a chest radiographic thoracic area scoring system which is easy to apply and has been shown to be reproducible.

Although the measurement only gives a two-dimensional assessment of the lungs, the technique's results have been shown to correlate with FRC measurements [12], thus we feel do reflect lung volumes and lung development. Importantly, we were able to compare our results with the results of a large series of controls. The controls were not healthy as evidenced by their need for mechanical ventilation, but this was for absent respiratory drive and not lung disease, so we feel it is an appropriate comparison and enabled us to determine the severity of lung abnormality in the infants with exomphalos. The exomphalos cohort were cared for over a 20 year period and during that time there have been changes in neonatal care. Nevertheless, this enabled us to assess a large number of infants with exomphalos who on average had significantly lower CRTAs. Chest radiographs taken for clinical purposes were used in the analysis and only five were not suitable for analysis, which we feel is a strength of this technique. Not least, there were results from 64 infants that were able to be used, enabling us to make meaningful comparisons with the controls. We defined BPD as oxygen dependency at 28 days rather than the more accepted definition of oxygen dependency at 36 weeks post conceptional age, but that definition is primarily used in prematurely born infants. The majority of the exomphalos infants were born at term and the 28-day definition has been used in a randomized trial of surgical infants with congenital diaphragmatic hernia [18].

We have demonstrated infants with exomphalos had significantly lower chest radiographic thoracic areas than controls on day one and the low CRTAs were significantly associated with development of BPD. We suggest those results reflect that infants with exomphalos have abnormal antenatal lung growth.

Research ethics: Not applicable.

Informed consent: Not applicable.

Author contributions: AG, TD and CH designed the study; MK, ZB, SH and CW collected the data; MK, TD, CH and AG analysed the data, MK wrote the first draft of the manuscript. All authors were involved in the production of the final manuscript and approved it.

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