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Mortality and short-term morbidity in infants with exomphalos

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Short running title: Outcomes of infants with exomphalos

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ABSTRACT

Background: Infants with exomphalos major have a high mortality and morbidity. Our aims were to identify predictors of survival regardless of the size of the exomphalos and determine whether infants with exomphalos minor also suffered morbidity.

Methods: Patients were classified as having exomphalos major or minor based on whether the liver was in the exomphalos sac and the size of the abdominal wall defect. The respiratory, gastrointestinal and surgical outcomes of 50 infants with exomphalos, 27 with exomphalos major, were assessed. Receiver operator characteristic curves (ROC) were constructed to identify factors predictive of survival.

Results: No infant with exomphalos minor died; there were seven deaths in the exomphalos major group ($p<0.001$). Infants with exomphalos minor who had chromosomal abnormalities (six had a genetic diagnosis of Beckwith Weidman syndrome) developed severe respiratory distress or chronic respiratory morbidity. Nasogastric feeding at discharge was required in 37% with exomphalos major and 17% with exomphalos minor. A lower gestational age (area under the ROC (AUROC) = 0.814) and birth weight (AUROC 0.797) and longer durations of ventilation (AUROC 0.853) and supplementary oxygen (AUROC 0.810) were predictive of mortality.

Conclusions: Infants with exomphalos regardless of size can suffer chronic morbidity. Mortality is commonest in those with exomphalos major born at lower gestational ages and birth weights.

Key words: death, exomphalos, supplementary oxygen, surgical outcomes, ventilation

INTRODUCTION

Exomphalos is a relatively common congenital abnormality, in one study an incidence of approximately 1 in 4000 to 7000 live births was reported (1). A study from the United States estimated a prevalence of 1.86 (95% confidence intervals [CI] 1.73–1.99) per 10,000 live births (2). Data from six regional congenital anomaly registers in England and Wales between 2005 and 2011 demonstrated that the overall birth prevalence of exomphalos was 3.8 per 10.000 births; 1.4 per 10,000 isolated cases, 1.2 per 10,000 cases with multiple anomalies and 1.2 per 10,000 cases with chromosomal anomalies (3). The one-year survival of live born babies with an isolated exomphalos was 92% compared with 81% in cases with multiple anomalies and 27% in cases with chromosomal abnormalities ($p<0.001$) (3). A previous study from our institution, however, demonstrated that less than 10% of the 445 antenatally diagnosed cases reached operative repair (4).

Fetal exomphalos diameter/abdominal circumference ratio (OD/AC) ≥0.26 has been reported to be associated with increased respiratory, gastrointestinal and surgical morbidities (5). In another study, survival and length of stay differed between live born non-isolated and isolated exomphalos diagnosed by a prenatal ultrasound (6). The outcomes of infants with exomphalos minor, however, have rarely been reported. Our aims were to identify predictors of survival regardless of the size of the exomphalos and determine whether infants with exomphalos minor also suffered morbidity.

MATERIAL AND METHODS

A review was conducted of the outcomes of all infants with an antenatal diagnosis of exomphalos live born between 2004 and 2015 at King's College Hospital (KCH) NHS Foundation Trust. The infants were identified from a neonatal database, the neonatal unit admission book and a surgical database. Exomphalos major was defined as a defect which had more than 50% of the liver in the exomphalos sac and an abdominal wall defect greater than five centimetres in diameter. Infants with smaller defects were diagnosed as having exomphalos minor. None of the infants had cardiac defects reflecting that fetuses were more likely to be terminated if they had exomphalos and other anomalies including cardiac defects. In addition, fetuses with major cardiac anomalies without other anomalies were preferentially delivered at the regional cardiac centre.

Data retrieved from the medical records included birth weight, gestational age at birth, gender and the results of antenatal genetic tests. The duration of mechanical ventilation, mode of ventilation including high frequency oscillatory ventilation (HFOV), duration of supplemental oxygen, need for inhaled nitric oxide (iNO) or postnatal corticosteroids and mortality were also recorded. Infants with bronchopulmonary dysplasia were those diagnosed as having supplementary oxygen dependence beyond 28 days after birth. Postnatal corticosteroids were considered for infants who remained ventilator dependent with high peak inspiratory pressures and inspired oxygen concentrations after two weeks of age. Infants were diagnosed with bronchopulmonary dysplasia if they were oxygen dependent beyond 28days after birth. Details of gastrointestinal outcomes including the time to commence and reach full enteral feeds were documented, as were the length of hospital stay and time to first operative intervention. Infants underwent primary closure, staged closure or delayed closure according to the size of the defect and the infant's

respiratory status, that is, a more conservative approach was undertaken for infants requiring high levels of respiratory support.

Statistical analysis

The data were tested for normality using the Kolmogorov-Smirnov test and found not to be normally distributed. Differences, therefore, were assessed for statistical significance using the Mann-Whitney U test or Chi-square test as appropriate. Receiver operating characteristic curves (ROC) were constructed and the area under the curve (AUROC) calculated to compare the predictive value of factors which differed on univariate analysis at the $p \leq 0.1$ level. Sensitivities and specificities were calculated for factors found to be most predictive. Analysis was performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL).

RESULTS

Fifty infants with exomphalos were live born during the study period, 27 had exomphalos major. There were no significant differences in birthweight (p= 0.073) and gestational age (p=0.129) between those with major or minor abnormalities (Table1). None of the infants in either group had cardiac anomalies. Six infants in the exomphalos minor group had the genetic diagnosis of Beckwith Weidman syndrome and one infant in the exomphalos major group had a minor genetic abnormality with duplication in the short arm of chromosome eight. The time to first surgical intervention occurred later in infants with exomphalos major (four versus two days, p=0.002). Infants with exomphalos major had significantly worse adverse respiratory outcomes with longer median durations of mechanical ventilation (p<0.001) and supplemental oxygen (p<0.001) and a greater need for high frequency oscillatory ventilation (HFOV) (p=0.008) (Table 1). Infants with exomphalos major compared to minor commenced enteral feeds (p=0.004) and achieved

full enteral feeds (p<0.001) at a greater postnatal age (Table 1). In both groups, however, a proportion of infants required nasogastric feeding at discharge, 37% in the exomphalos major and 17% in the exomphalos minor groups. The length of hospital stay was longer in infants with exomphalos major (p<0.001) (Table 1). Infants with exomphalos minor who had chromosomal abnormalities developed severe respiratory distress or chronic respiratory morbidity. No infant with exomphalos minor who did not have chromosomal abnormalities developed severe respiratory distress (as defined by the need for HFOV or iNO) or chronic respiratory morbidity (defined as development of BPD or need for postnatal corticosteroids) (Table 1).

There were seven deaths in the exomphalos major infants and none in those with exomphalos minor (p<0.001). Infants who did not survive were born at an earlier gestational age (p=0.006) and of smaller birth weight (p=0.01) and needed longer durations of mechanical ventilation (p<0.001) and supplementary oxygen (p<0.001) (Table 2). A greater proportion of the non-survivors required nitric oxide (p=0.001), HFOV (p<0.001) and postnatal steroids (p=0.048) (Table 2).

In the overall study group, a gestational age > 35 weeks had an AUROC of 0.814 and a sensitivity of 83% and 72%, a birth weight > 2497gm had an AUROC of 0.797 and a sensitivity of 82% and a specificity of 72% in prediction of survival. Mechanical ventilation >15 days had an AUROC of 0.853 with a sensitivity of 85% and a specificity of 80% and a duration of supplemental oxygen > 40 days had an AUROC of 0.810 with a sensitivity of 72% and a specificity of 85% in prediction of mortality.

DISCUSSION

We have demonstrated that infants with exomphalos born at lower gestational ages and birth weights are at increased risk of mortality. The overall mortality of live born infants with exomphalos in our series was 14%, similar to that reported previously (7). Importantly, we have also demonstrated that infants with exomphalos minor can suffer chronic morbidity as evidenced by the requirement for nasogastric tube feeding at discharge.

Prolonged requirement for mechanical ventilation and supplementary oxygen were also sensitive and specific predictors of survival. This likely reflects infants with exomphalos are at increased risk of pulmonary hypoplasia due to reduced fetal breathing because of poor diaphragmatic function in utero. Indeed, infants with anterior wall defects (AWD) have been shown to have impaired postnatal lung function (8). Infants with AWD studied at median age of five months had significantly lower functional residual capacity (FRC) than healthy age-matched controls (8). Furthermore, children who had had giant exomphalos, when studied at median age of 19.7 months (1-58), had reduced lung volume, increased airway hyper- responsiveness and reduced respiratory system specific compliance (9).

We report a higher incidence of genetic abnormalities in infants with exomphalos minor compared to exomphalos major. This is likely explained by our inclusion of only live born infants and fetuses of pregnancies which were terminated or resulted in intrauterine deaths would be likely to have had multiple congenital abnormalities and/or severe chromosomal abnormalities. Indeed, a previous study from our institution reported that less than 10% of all cases of antenatally diagnosed exomphalos reach an operative stage (4). In 56% of the cases (n=250) there was an abnormal karyotype and from that group there were only two live births (4). In an observational study of 53 patients with

gastroschisis and 43 with exomphalos there were no significant differences in outcomes between those who were and were not diagnosed antenatally (10). The rate of antenatal detection, however, was low (overall 44%) and there was a low rate of chromosomal abnormalities. It has been suggested that despite advances in ultrasound technology, its ability to predict an abnormal karyotype in exomphalos fetuses has not improved (11). In our series of live born infants, only one infant with exomphalos major had a chromosomal abnormality and this was of a minor nature, which likely reflects those with major chromosomal anomalies were detected antenatally and the parents opted for a termination of pregnancy or the infants were stillborn.

Infants with exomphalos major suffered significantly worse respiratory outcomes compared to those with exomphalos minor as evidenced by the longer duration of mechanical ventilation and supplemental oxygen and the requirement for high frequency oscillatory ventilation and/or nitric oxide therapy. Exomphalos minor infants with chromosomal abnormalities, however, suffered severe respiratory distress or chronic respiratory morbidity. Infants with giant exomphalos complicated by pulmonary hypertension have been reported to have increased respiratory support requirements with a longer duration of mechanical ventilation, requirement for tracheotomy and dependence on home oxygen therapy following hospital discharge compared to survivors with no associated pulmonary hypertension (12). In a series of 54 infants with giant exomphalos, 37% had pulmonary hypertension (12). A proportion of infants in our series, more with exomphalos major, required iNO and thus likely had pulmonary hypertension.

We have also demonstrated that infants with exomphalos suffer chronic gastrointestinal problems. The time taken to start and achieve full enteral feeds differed significantly between the two groups, yet, there were no significant differences in birth weight or gestational age between the two groups and none had a cardiac defect. The differences in the time to start and achieve full enteral feeds likely reflects the more severe respiratory abnormalities experienced by the exomphalos major group. Importantly, 37% of the

major group and 17% of the minor group required nasogastric feeding after discharge, parents need to be informed this is a possible outcome. In this study infants had primary closure or a silo fashioned. A recent study of infants with giant exomphalos were treated by negative pressure wound therapy, full feeds were achieved by a postnatal age of 19 days and full closure of the abdominal wall defect by two months of age (13). Whether such an approach would improve better outcomes than current strategies requires testing in a randomized trial.

In conclusion, we have demonstrated that infants with exomphalos born at an earlier gestation and of lower birth weight are more likely to die. In addition, a requirement for prolonged ventilation and supplementary oxygen also predicted mortality, likely reflecting the infants may have had pulmonary hypoplasia. Infants with exomphalos minor did suffer morbidity, these data should be helpful to inform counseling of parents of affected infants.

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Contributor statement:

AG, KA and AH designed the study, SS and IF collected the data, KA and AG analysed the data, KA, SS and AG wrote the manuscript and all authors were involved in writing the manuscript and approved the final version.

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Table 1: Demographics and respiratory and gastrointestinal outcomes according to major or minor status

Data are reported as median (IQR) or n (%)

	Exomphalos major	Exomphalos minor	P value[(1)]	Exomphalos minor without chromosomal abnormalities	P value[(2)]
n	27	23		17	
Birth weight (gm)	2810(2272,3166)	3315 (2587-3517)	0.073	3288 (2344, 4276)	0.072
Gestational age (wks)	38 (36,38)	38 (35.5,38)	0.129	38 (34, 41)	0.072
Genetic abnormality	1 (3.7%)	7 (30.4%)	0.010		
Gender (male)	12 (44.4%)	8 (34.8%)	0.487	(37.5%)	0.582
Duration of mechanical ventilation (days)	13.5 (4,32)	2 (1,3)	0.001	1.5 (1, 10)	<0.001
Duration of Oxygen therapy (days)	23 (5,52)	1(1,3)	< 0.001	1 (0, 17)	<0.001
Intubation at birth	8 (29.6%)	3 (13%)	0.143	0 (0%)	0.014
HFOV	8 (29.6%)	0 (0%)	0.008	0 (0%)	0.012
Nitric oxide	4 (14.8%)	1(4.3%)	0.219	0 (0%)	0.099
BPD at 28 days	9 (33.3%)	2 (8.7%)	0.036	0 (0%)	0.008
Postnatal steroids	2 (7.4%)	1 (4.3%)	0.650	0 (0%)	0.256

(1) Comparison of all exomphalos minor infants to exomphalos major infants
(2) Comparison of exomphalos minor infants without chromosomal abnormalities to exomphalos major infants.

Table 2: Demographics and outcomes according to survival status

Data reported as median (range) or n (%)

	Survived	Not survived	P value
n	43	7	
Gestational age (weeks)	38 (37,39)	33 (33,36)	0.006
Birth weight (gm)	3090 (2628,3463)	1926 (1735,2801)	0.01
Gender (male)	17 (39.5%)	3 (42.9%)	0.590
Duration of mechanical ventilation (days)	4 (1,13)	54 (30,96)	0.002
Duration of supplementary oxygen (days)	3 (1,24)	54 (30,97)	0.004
HFOV	2 (4.7)	6 (85.7)	<0.001
Inhaled nitric oxide	1 (2.3)	4 (57.1)	0.001
BPD	7 (16.3)	4 (57.1)	0.034
Use of Postnatal steroids	1 (2.3)	2 (28.6)	0.048