Journal of Pediatric Surgery 50 (2015) 55–59

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Are all pulmonary hypoplasias the same? A comparison of pulmonary outcomes in neonates with congenital diaphragmatic hernia, omphalocele and congenital lung malformation

Adesola C. Akinkuotu [a,b], Fariha Sheikh [a,b], Darrell L. Cass [a,b,c,d], Irving J. Zamora [a,b], Timothy C. Lee [a,b], Christopher I. Cassady [a,e], Amy R. Mehollin-Ray [a,e], Jennifer L. Williams [a,e], Rodrigo Ruano [a,d], Stephen E. Welty [a,c], Oluyinka O. Olutoye [a,b,c,d,*]

[a] Texas Children's Fetal Center, Baylor College of Medicine, Houston, TX
[b] Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX
[c] Department of Pediatrics, Baylor College of Medicine, Houston, TX
[d] Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX
[e] Department of Radiology, Baylor College of Medicine, Houston, TX

ARTICLE INFO

Article history:
Received 24 September 2014
Accepted 6 October 2014

Key words:
Fetus
Lung volumes
CDH
Lung malformation
Omphalocele

ABSTRACT

Introduction: Patients with congenital diaphragmatic hernias (CDH), omphaloceles, and congenital lung malformations (CLM) may have pulmonary hypoplasia and experience respiratory insufficiency. We hypothesize that given equivalent lung volumes, the degree of respiratory insufficiency will be comparable regardless of the etiology.

Methods: Records of all fetuses with CDH, omphalocele, and CLM between January 2000 and June 2013 were reviewed. MRI-based observed-to-expected total fetal lung volumes (O/E-TFLV) were calculated. An analysis of outcomes in patients with O/E-TFLV between 40% and 60%, the most inclusive range, was performed.

Results: 285 patients were evaluated (161, CDH; 24, omphalocele; 100, CLM). Fetuses with CDH had the smallest mean O/E-TFLV. CDH patients were intubated for longer and had a higher incidence of pulmonary hypertension. Fifty-six patients with the three diagnoses had an O/E-TFLV of 40%–60%. The need for ECMO, supplemental oxygen at 30 days of life, and 6-month mortality were similar among groups. CDH patients had a significantly longer duration of intubation and higher incidence of pulmonary hypertension than the other two diagnoses.

Conclusion: Given equivalent lung volumes (40%–60% of expected), CDH patients require more pulmonary support initially than omphalocele and CLM patients. In addition to lung volumes, disease-specific factors, such as pulmonary hypertension in CDH, also contribute to pulmonary morbidity and overall outcome.

Pulmonary hypoplasia is seen in a variety of congenital anomalies including congenital diaphragmatic hernia (CDH), omphalocele and, congenital lung malformation (CLM). CDH, affecting an estimated 1 in 2500 live births, has a reported mortality of 35% to 45% due to pulmonary hypoplasia and pulmonary hypertension [1]. Omphalocele is one of the most common fetal abdominal wall defects and can be associated with pulmonary hypoplasia when the size of the defect is large. CLMs represent a wide spectrum of relatively rare, usually benign, lung malformations that may be associated with pulmonary hypoplasia [2]. Pulmonary hypoplasia is attributed to lung compression from herniated viscera and an intrinsic growth abnormality due to a field defect in CDH; a thoracic deformity and abnormal fetal breathing and diaphragm function in omphalocele [3,4] and compression of the developing lung parenchyma in CLM. In all of these patients, pulmonary hypoplasia leads to worsened respiratory function that threatens survival.

Recent advances in fetal ultrasonography and ultrafast magnetic resonance imaging (MRI) have improved prenatal detection of congenital malformations such as CDH, omphalocele and CLM. MRI in particular has proven to be instrumental in characterizing these conditions [5,6]. Several studies have used MRI-derived lung volume measurements to evaluate the outcomes of fetuses with CDH. These measurements, particularly the observed-to-expected total fetal lung volume (O/E-TFLV) which corrects a measured fetal lung volume for gestational age, have been found to be predictive of mortality and morbidity in patients with CDH and its related pulmonary hypoplasia [7,8]. These measurements help to guide prenatal counseling about neonatal morbidity and mortality as well as eligibility for fetal intervention. Historically, ultrasound-derived measurements have been instrumental in the prenatal diagnosis of omphaloceles to help guide management strategies and predict postnatal outcomes [9]. In CLM, the CCAM (Congenital cystic adenomatoid malformation) volume ratio (CVR) as determined by

* Corresponding author at: Texas Children's Fetal Center, Texas Children's Hospital, 6701 Fannin Suite 1210, Houston, TX 77030. Tel.: +1 832 822 3135; fax: +1 832 825 3141.
E-mail address: oolutoye@bcm.edu (O.O. Olutoye).

http://dx.doi.org/10.1016/j.jpedsurg.2014.10.031
0022-3468/

Table 1
Demographics of all patients with congenital diaphragmatic hernia (CDH), omphalocele and congenital lung malformation (CLM).

Variable	CDH n = 161	Omphalocele n = 24	CLM n = 100	p-value
GA at diagnosis, wk mean ± SD	25.0 ± 6.6	18.7 ± 6.0*	26.0 ± 4.5*#	<0.001
GA at birth, wk mean ± SD	37.5 ± 2.3	35.5 ± 4.3*	38.1 ± 3.0*#	<0.001
Birth weight, g mean ± SD	2906 ± 629	2647 ± 1005	3109 ± 692*	0.015
O/E-TFLV[a], % mean ± SD	35.4 ± 15.4	53.8 ± 20.6*	81.5 ± 20.6*#	<0.001

* $p < 0.05$ vs. CDH.
\# $p < 0.05$ vs. OM.
[a] There were 68 fetuses without prenatal MRI imaging thus, 217 patients (94 CDH, 24 omphalocele and 99 CLM) had measurable lung volumes.

ultrasonography serves as a tool for predicting fetal outcomes, with higher CVRs associated with worse outcomes [2,10].

The utility of prenatal lung volumes in predicting pulmonary outcomes associated with pulmonary hypoplasia in fetuses with CDH has naturally led to its calculation in other anomalies with potential for pulmonary hypoplasia. There are little objective data regarding the utility of prenatal lung volume measurements in predicting pulmonary outcomes in patients with omphaloceles or with CLMs. Therefore, we sought to evaluate pulmonary outcomes of patients with CDH, omphalocele or CLM in relation to calculated fetal lung volumes. We hypothesized that given equivalent lung volumes, the degree of respiratory insufficiency, as defined by: a) length of tracheal intubation, b) need for ECMO and c) need for supplemental oxygen at 30 days of life, would be comparable regardless of the etiology of pulmonary hypoplasia.

1. Patients and methods

This study was approved (H-33693, H-26716 and H-29695) by the Institutional Review Board at the Baylor College of Medicine, Houston, TX, USA.

1.1. Patient population

A retrospective review of patients referred to our multi-disciplinary fetal center with diagnoses of CDH, omphalocele or CLM between January 2000 and June 2013 was performed. Patients with other associated anomalies and pregnancies that ended in intrauterine fetal demise or termination were excluded.

1.2. MRI-derived lung volumes

Fetal lung volumes were obtained by standard volumetric technique using freehand region of interest measurements as previously described [11]. The O/E-TFLV was calculated by dividing the total measured fetal lung volume by the expected fetal lung volume for gestational age as described by Rypens et al. [12]. Lung volumes in fetuses with CLM were measured based on the volume of the residual normal lung.

1.2.1. Data collection

Prenatal data including gestational age at diagnosis and initial fetal MRI imaging; and O/E-TFLV were collected from maternal medical records. Infant records were reviewed for clinical data including gestational age at birth and birth weight. Gestational age at diagnosis, initial MR imaging and birth were determined by last menstrual period if known or the first semester ultrasound. Outcomes that were reviewed included the presence of pulmonary hypertension by echocardiography, treatment of pulmonary hypertension, use of inhaled nitric oxide (iNO), need for extracorporeal membrane oxygenation (ECMO), duration of tracheal intubation, hospital length of stay, need for supplemental oxygen at 30 days of life and mortality at 6 months. Once O/E-TFLV in all three groups was analyzed, a subanalysis of outcomes in patients with O/E-TFLV between 40% and 60%, the most common range of volumes across all three diagnoses, was performed.

1.2.2. Statistical analysis

Results are presented as median with interquartile range for continuous variables unless otherwise noted, and as percentages for categorical variables. Kruskal–Wallis and Mann–Whitney U tests were performed for non-parametric continuous variables. Fisher's Exact test and Chi-square analysis were used for categorical variables. Statistical analysis was performed using IBM SPSS statistical software version 21 (IBM Corporation, Armonk, NY). A p-value of less than 0.05 was considered to be statistically significant.

2. Results

2.1. Demographics

A total of 285 patients met the inclusion criteria for the study. Of these, 161 (56.5%) had CDH, 24 (8.4%) had an omphalocele and 100 (35.1%) had CLM. 68 fetuses did not have prenatal MRI imaging thus, 217 patients (94, CDH; 24, omphalocele; 99, CLM) had measurable lung volumes. Fetuses with omphalocele were diagnosed at an earlier gestational age and were younger at birth compared to those with CLM or CDH (Table 1). Fetuses with CDH had the smallest mean O/E-TFLV (CDH: 35.4 ± 15.4% vs. Omphalocele: 53.8 ± 20.6%vs. CLM: 81.5 ± 20.6%; $p < 0.001$).

2.2. Pulmonary outcomes in all patients

The incidence of pulmonary hypertension (55.9 vs. 8.3 vs. 4.0%; $p < 0.001$) and need for extracorporeal membrane oxygenation (ECMO) (35.4 vs. 0 vs. 0%; $p < 0.001$) were higher in patients with CDH than those with omphalocele or CLM. Patients with CDH were on mechanical ventilation with tracheal intubation for a longer duration than those with omphalocele or CLM (Table 2). Patients with CDH also had significantly longer hospital length of stay compared to those with CLM. Over half of CDH patients (53.2%) required supplemental oxygen at 30 days of life compared to 33.3% of patients with omphalocele and 7.1% with CLM. Mortality at 6 months was lowest in patients with CLM (2.0%) but there was only a statistically significant difference in mortality between patients with CLM and CDH (CDH: 21.1% vs. Omphalocele: 8.3% vs. CLM: 2.0%; $p < 0.001$).