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Pulmonary hypertension in congenital diaphragmatic hernia patients: Prognostic markers and long-term outcomes

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ABSTRACT

Prenatal observed/expected lung–to-head ratio (O/E LHR) by ultrasound correlates with postnatal mortality for congenital diaphragmatic hernia (CDH) patients. The aim of this study is to determine if O/E LHR correlates with pulmonary hypertension (PH) outcomes for CDH patients.

Methods: A single center retrospective chart review was performed for CDH neonates from January 1, 2006, to December 31, 2015, (REB #1000053124) to include prenatal O/E LHR, liver position, first arterial blood gas, repair type, echocardiogram (ECHO), and lung perfusion scan (LPS) results up to 5 years of age.

Results: Of 153 newborns, 123 survived (80.4%), 58 (37.9%) had prenatal O/E LHR, and 42 (27.5%) had postnatal ECHO results. High mortality risk neonates (O/E LHR ≤45%) correlated with higher right ventricular systolic pressure (RVsp) at birth. Generally PH resolved by age 5 years. LPS results did not change over time ($p > 0.05$) regardless of initial PH severity, suggesting that PH resolution did not correlate with increased ipsilateral lung perfusion to offload the right ventricle.

Conclusion: Prenatal prognostic markers correlated with initial PH severity for CDH newborns, but PH resolved over time despite fixed perfusion bias to the lungs. These results suggest favorable PH outcomes for CDH patients who survive beyond infancy.

Type of Study: Retrospective Cohort Study.

Level of Evidence: 3b

Congenital diaphragmatic hernia (CDH) is an anomaly that continues to result in significant mortality and morbidity. Despite recent improvements in perinatal management to improve overall survival, mortality rates persist in the 20% range owing to the irreversible pulmonary hypoplasia that is the hallmark of this condition [1–3]. Using prenatal ultrasound (US) to quantify lung volume of CDH by observed to expected lung-to-head ratio (O/E LHR), we reported that neonatal mortality correlated with O/E LHR [4]. Mortality was greatest for those with O/E LHR <25% but improved for those with O/E LHR ≥25% and ≤45% while no mortality was associated for those cases with O/E LHR >45%. In addition to mortality risk, CDH survivors also experience significant musculoskeletal, neurodevelopmental and nutritional morbidities well into adolescence [5], although these morbidities did not correlate with the same risk stratification markers used for mortality prognostication [6].

Pulmonary hypertension (PH) is a major contributor to the mortality of CDH infants [7,8]. PH results from the increased pulmonary vascular resistance within the hypoplastic lungs of CDH disease. Small caliber and reduced numbers of pulmonary artery branches along with defective angiogenesis of the hypoplastic lungs likely contribute to high pulmonary arterial pressures (PAP) and increased pulmonary vascular resistance [9–12]. Although the right ventricle (RV) initially accommodates the high right-sided pressures through right ventricular hypertrophy (RVH), persistent PH results in RV dilatation and dysfunction, the most severe cases resulting in RV failure [13]. Initial management of PH during postnatal resuscitation involves decreasing RV pressures using pulmonary vasodilators such as inhaled nitric oxide (iNO), sildenafil and prostacyclin [14,15]. Extracorporeal membrane oxygenation (ECMO) is considered a supportive modality to maximally off load the RV in patients with severe PH [16]. Although these treatment modalities

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aid in managing PH in the neonatal period, there is currently no known treatment that can effectively reverse the pulmonary hypoplasia and associated PH in CDH neonates.

Despite the high mortality risk of severe PH among CDH neonates, long-term follow up studies suggest that PH is not a fixed defect. Recent studies using novel lung imaging techniques suggest that PH may improve for CDH survivors despite the persistence of lung perfusion defects of the ipsilateral lung beyond the neonatal period, presumably owing to growth of the contralateral lung [17–19]. Furthermore, there is a paucity of longitudinal data of PH outcomes among CDH survivors and predictors of PH outcomes. The aim of this study is to evaluate the neonatal and long-term outcomes associated with PH in CDH patients and to determine if prenatal and postnatal prognostic markers predict PH neonatal and long-term outcomes.

1. Methods

A retrospective chart review was performed for all neonates with Bochdalek diaphragmatic hernias treated at a single center from January 1, 2006 to December 31, 2015. Patients were excluded if they had Morgagni hernias, bilateral hernias or eventrations or if they presented with Bochdalek hernias beyond the neonatal period. Patients lost to follow up were also excluded. Research Ethics Board approval was obtained (REB#1000053383).

Detailed US assessments of prenatally diagnosed CDH cases were obtained at the Fetal Medicine Unit and independently reviewed by two members of the high risk obstetrics team (G.R. and M.A.A.). The method for obtaining prenatal prognostic parameters including observed/expected lung to head ratio (O/E LHR) by US was previously described [4]. After delivery, CDH newborns were resuscitated at Mount Sinai Hospital and then transferred to our center for postnatal management. All resuscitative measures, including the use of iNO, PGE_1, high frequency oscillatory ventilation (HFOV) and ECMO, were utilized where indicated as previously described [3]. Perinatal data obtained at birth included gestational age, birth weight, first arterial blood gas, Apgar scores, iNO and PGE_1 use, intubation, patch repair and requirement for ECMO support. Liver and stomach position details were obtained from operative notes and neonatal US reports.

Postnatal assessments of PH by echocardiogram (ECHO) were performed at birth, at discharge from hospital and in the CDH Follow Up Clinic as per protocol [5]. Right ventricular systolic pressure (RVsp) was calculated via Bernoulli's equation when tricuspid regurgitation (TR) was present using tricuspid valve jet velocity visualized in two-dimensional ECHO [20,21]. RVsp values were compared with systemic blood pressures to assess the severity of PH at each age range. In the absence of TR to calculate RVsp, PH severity was documented qualitatively by the presence and direction of ductal shunting, septal curvature and right ventricular function. Septal bowing, right to left shunting and right ventricular failure were classified as suprasystemic RVsp, while bidirectional shunting and septal flattening were classified as systemic RVsp.

Lung perfusion scans were performed as a part of the prescribed follow up in the CDH Clinic at 6 months–1 year and 2–5 years age using Technetium (Tc)-99 m macro aggregated albumin (MAA) pulmonary scintigraphy as described [22]. Following intravenous administration of ^{99m}Tc MAA at standard doses [23], planar images in the anterior and posterior projections of the lungs were acquired. Scintigrams acquired were analyzed to quantify regional distribution of each lung and expressed as the percentage of total perfusion.

Multivariate statistical data analyses were performed on nominal and continuous collected data using IBM® SPSS© Statistics version 20. Independent *t*-tests were performed on both RVsp and perfusion difference data comparing means between postnatal prognostic risk groups. Pearson's correlation coefficient test was used to determine trends in RVsp across age periods. Pearson's chi-square and Fisher's exact test were used for binary data. Statistical significance was indicated by two-tailed $p < 0.05$. Outliers in the data, calculated as 1.5 times the interquartile range above and below the third and first quartile, were excluded (n = 6).

2. Results

In total, 153 neonates with Bochdalek hernias (96 males) were treated in the study period, and 30 patients died for a mortality rate of 19.6%. Of the 123 survivors, they were further categorized into two cohorts based on time of CDH diagnosis, whether prenatally or postnatally diagnosed with CDH. Prenatally diagnosed CDH patients were more likely to have left-sided CDH and had greater need for resuscitation compared to postnatally diagnosed CDH infants; prenatally diagnosed CDH infants were more likely to be intubated, had significantly lower Apgar scores at 1 min, lower first arterial blood gas pH and more frequent use of prostaglandin E1 for PH (Table 1).

2.1. Postnatal prognostic markers and PH outcomes for CDH patients

Since postnatal prognostic markers such as the size of diaphragmatic defect as indicated by the need for patch repair [24], liver position [25], and first ABG [26], have been shown to correlate with mortality, these markers were analyzed for correlation with PH severity. The RVsp documented at birth and at discharge for CDH patients with "liver up" did not differ from those without liver herniation but was significantly different beyond 6 months of age ($p < 0.05$, Fig. 1A). Similarly, CDH patients requiring patch repair had significantly higher RVsp compared to those patients who underwent primary repair after the neonatal period ($p < 0.05$, Fig. 1B). For CDH newborns with first ABG pH < 7.25, the RVsp did not differ significantly from those with initial ABG pH > 7.25 except at the age of 6 months–1 year (Fig. 1C). Together, these results indicate that first ABG, liver position and need for patch repair did not distinguish neonatal PH severity but correlated with long-term PH outcomes for CDH survivors.

Table 1
Demographics and prognostic markers for prenatally and postnatally diagnosed CDH survivors.

	Prenatally diagnosed (n = 58)	Postnatally diagnosed (n = 65)	P-value
Gender (M:F)	36:22	41:24	NS
Birth Weight (kg)	3.16 (1.36–4.51)	3.1 (1.18–4.93)	NS
Gestational Age (weeks)	38.4 (33–41)	38.4 (30–42)	NS
Laterality (L:R)	56:2	49:16	<0.001
APGAR 1 min score	5	6 (n = 61)	0.04
APGAR 5 min score	7	8 (n = 60)	NS
1st Arterial Blood Gas pH	7.15	7.24 (n = 56)	<0.001
Patch Repair (%)	44.8	21.5	0.01
Intubated On Admission (%)	67.2	47.7	0.03
ECMO (%)	3.4	6.2	NS
Inhaled nitric oxide use (%)	34.4	28.1	NS
Alprostadil use (%)	34.4	15.4	0.01
Liver Up (%)	32.8	40	NS
Stomach Up (%)	50	20	<0.001
Mediastinal Shift (%)	100	98.5	NS

All values are means for each parameter unless indicated as % in parentheses or listed as a ratio. Birth weight and gestational age are represented as means with ranges in parentheses. APGAR scores are rounded from mean scores. NS: not significant.
Independent *t*-test performed for birth weight, gestational age, Apgar scores, and 1st arterial blood gas pH.
Pearson chi square test and Fisher's exact test (mediastinal shift) used for other parameters.