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Congenital diaphragmatic hernia: Defect size correlates with developmental defect

The Congenital Diaphragmatic Hernia Study Group [1]

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Congenital diaphragmatic hernia;
Defect size;
Developmental defect;
Embryology;
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Abstract

Purpose: The aim of our study was to elucidate if the defect size reflects the magnitude of the developmental defect in patients with CDH.

Methods: All patients recorded in the CDH Study Group registry between January 1, 2007, and December 31, 2010, and with defect classification were included in the study. They were divided according to defect size (A–D) and compared for: gestational age (GA), birth weight (BW), number of abnormal organ systems, prevalence of associated anomalies, cardiovascular malformations (CVM), chromosomal anomalies, liver in the chest, and hernia sac.

Results: A total of 1350 of 1778 patients had defect classification: 173 A, 557 B, 438 C, and 182 D. Mortality rate was 0.6%, 5.3%, 22.6%, and 45.6% in group A, B, C, and D, respectively, ($p < 0.0001$; p for trend < 0.0001). GA, BW, prevalence of associated anomalies, particularly CVM, number of abnormal organ systems, and prevalence of sac were significantly different between the groups, with a significant reduction of GA, BW, and prevalence of sac. There was an increase in prevalence of associated anomalies, liver in the chest, and number of abnormal systems as the defect size increased.

Conclusion: Defect size is directly correlated with mortality rate, prevalence of other anomalies (particularly CVM), and number of abnormal systems, and inversely with GA, BW, and prevalence of hernia sac. The defect size may be a marker for the magnitude of developmental abnormality, thereby explaining its relationship with the outcome.

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Congenital diaphragmatic hernia (CDH) is one of the most serious neonatal malformations with a reported incidence of between 1 in 2500 and 1 in 4000 live births [1,2]. Despite advances in neonatal intensive care and new treatment modalities (iNO, gentle ventilation, ECMO, etc.), most multicenter studies still show a survival rate around 65% [3,4]. Pulmonary hypoplasia (PH) with/without pulmonary hypertension, and major associated malformations are thought to be the main causes of a lethal outcome [5]. A recent study from the CDH Study Group showed that the size of the diaphragmatic defect was the major factor influencing the outcome of infants with CDH and that it is the major factor associated with higher mortality rate [6]. In addition, it has also been shown that patch repair, which is a proxy for defect size,

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correlates with higher morbidity at follow-up [7,8]. Although the defect size is supposed to be a marker of degree of PH [6,9], no studies to date have attempted to analyze the correlation between defect size and outcome from a pathogenetic point of view.

The aim of our study was to elucidate if the defect size reflects the magnitude of the embryogenetic developmental defect in patients with CDH.

1. Materials and methods

The CDH Study Group was formed in 1995 to compile data on live born infants with CDH at participating institutions to assess therapies and outcomes. The CDH Study Group consists of tertiary referral centers that voluntarily provide data to a central registry. Data on all infants with CDH who are born at or transferred to a participating center are entered into the database. Data were collected prospectively on all live born patients with CDH from 1995 in participating hospitals and included information on delivery and subsequent hospital care (including surgery when applicable) until death or hospital discharge. The data from the registry forms are entered into a Microsoft (Redmond, WA) Access database and were cross-checked against the original form. Patient demographics, birth information, treatment received and outcome are recorded. The current version of CDH registry (January 2007) attempts to more accurately categorize the severity of disease based on the size of the defect and severity of pulmonary hypertension. Included is a description of the diaphragmatic defect, based on a diagram of the defect, in an attempt to classify each defect based on intraoperative or post-mortem findings. The size of the diaphragmatic defect is determined at the time of repair or at post-mortem examination according to the classification proposed by Tsao and Lally [10]: A to D, where A stands for a small defect which can be repaired primarily and D for diaphragmatic agenesis.

All patients recorded in the CDH Study Group registry between 2007 and 2010 and with defect classification were included in the study. Significant associated anomalies, including chromosomal anomalies, syndromes, and cardiovascular malformations (CVM), were evaluated. Major CVM included hypoplastic left heart syndrome, coarctation of the aorta, and tetralogy of fallot. An isolated ventricular septal defect or atrial septal defect was considered minor. The patients with defect classification were clustered according to the defect size (A–D) and the four groups were compared for the following variables: gestational age (GA), birth weight (BW), prevalence of associated congenital anomalies, prevalence of CVM, prevalence of major CVM, prevalence of chromosomal anomalies, prevalence of liver in the chest (at surgery/post-mortem examination), and prevalence of hernia sac. To define the amplitude of the embryogenetic defect, in each patient, the number of organ systems (cranio-facial, skeletal, muscular, cardiovascular, genitourinary, gastroenterological, and nervous) with one or more abnormalities was recorded and the four groups of patients were compared for the number of abnormal organ systems. Finally, the four groups were compared for mortality rate.

1.1. Statistical analysis

Data were analyzed using GraphPad Prism 5.0 Macintosh Version (GraphPad Software, San Diego, CA, USA, www.graphpad.com). One way ANOVA was used to compare the four groups for continuous variables and χ^2 test was used for categorical variables from the 2×4 tables. Post-test for linear trend for continuous variables and χ^2 test for trend for categorical variables were also used to analyze the changes with the increase of defect size from A to D. Probability values < 0.05 were considered significant and two-sided p values are reported.

2. Results

During the study period 1778 patients were recorded in the registry, from 57 centers (Appendix). The defect was classified in 1350 patients: 173 patients had type A, 557 type B, 438 type C, and 182 type D. Mortality rate was 0.6%, 5.3%, 22.6%, and 45.6% in groups A, B, C, and D, respectively ($p < 0.0001$; p for trend < 0.0001).

Table 1 shows the main findings of the comparison of the four groups. We found a significant difference between the four different groups in gestational age, birth weight, prevalence of associated anomalies, in particular CVM, number of abnormal organ systems, and prevalence of liver herniation and hernia sac. The most common chromosomal anomaly was trisomy 21; the most common syndrome was Fryns syndrome. No difference was found between the four groups in chromosomal anomalies.

As the defect increased in size, patients had a significant reduction of gestational age, birth weight, and prevalence of hernia sac. Conversely, the prevalence of associated anomalies, particularly CVM, the prevalence of liver in the chest, and the number of abnormal systems significantly increased with the increase of defect size.

3. Discussion

To our knowledge this is the first study examining the association between the amplitude of embryological developmental disorder and the size of the defect in CDH patients, using a standard classification of the defect size. We found that the amplitude of the embryopathy, as expressed by the prevalence of associated anomalies and number of abnormal organ systems, is significantly

Table 1 Main findings in the four groups of patients.

	Defect				*p*	*p* (trend)
	A (173 pts)	B (557pts)	C (438 pts)	D (182 pts)		
GA (weeks)	38.10 ± 2.05	37.93 ± 1.89	37.55 ± 2.19	37.25 ± 2.47	0.0002	<0.0001
BW (kg)	3.15 ± 0.61	3.08 ± 0.54	2.97 ± 0.60	2.84 ± 0.61	<0.0001	<0.0001
MLF (%)	24.9	23.7	33.6	41.6	<0.0001	<0.0001
CVM (%)	10.4	13.6	24.2	22.0	<0.0001	<0.0001
Major CVM (%)	3.5	3.4	7.8	12.1	<0.0001	<0.0001
Abn. Systems (#)	1.07 ± 0.35	1.26 ± 0.63	1.37 ± 0.84	1.46 ± 0.92	<0.0001	0.0002
Chr (%)	3.0	1.8	2.6	6.2	0.0719	0.0806
Hernia sac (%)	27.2	23.3	16.9	17.6	0.0014	0.0001
LU	10.3	20.5	49.8	32.2	<0.0001	<0.0001

GA= gestational age; BW= birth weight; MLF= associated anomalies; CVM= cardiovascular malformations; abnormal systems considered: cranio-facial, skeletal, muscular, cardiovascular, genitourinary, gastroenterological, and nervous; Chr = chromosomal anomalies; LU = liver-up in the chest (at surgery). Results are mean ± standard deviation or prevalence.

correlated with the diaphragmatic defect size. Also birth weight and prevalence of hernia sac showed a significant inverse correlation with the defect size, possibly confirming a relationship between defect size and embryopathy. Finally, the defect size was significantly correlated with the prevalence of liver in the chest and mortality rate.

Despite advancement of medical and surgical treatments, the outcome of CDH is still disappointing. Previous reports suggest that the defect size (either expressed as diaphragmatic agenesis or need for patch repair) is associated with a poorer prognosis [4,7,11,12]. A recent study from the CDH Study Group [6] showed that the outcome of infants with CDH correlates with defect size. The odds of dying for patients with diaphragmatic agenesis were 14 times that of patients whose defect allowed primary repair. Patients without agenesis but needing patch repair also had an increased risk of death, with an odds ratio of five. PH is the major determinant of the clinical course of patients with CDH, and both clinical and experimental studies suggest that the degree of PH is associated to the defect size [4,11,13]. Several theories have been proposed to explain the embryopathogenesis of pulmonary hypoplasia in patients with CDH. Keith suggested that PH was a primary defect, which then caused the abnormal development of the diaphragm [14]. This theory was more recently drawn on by Iritani [15], who postulated that primary hypoplastic lung alters the formation of the post-hepatic mesenchymal plate, a mesenchymal structure that appears dorsal to the liver, ventral to the pleuroperitoneal canal, and caudal to the transverse septum and that continues medially to the mesenchyme of the esophagus and laterally to the pleuroperitoneal folds. The abnormal formation of the mesenchimal plate in turn leads to abnormal development of the diaphragm. This hypothesis was subsequently refuted in an FGF10 null-mutant mice model that do not develop lungs, but have normal diaphragm [16]. Another theory proposes that the PH is a secondary event, resulting from compression of the developing lung by prolapsed abdominal organs. The larger the defect, the higher the amount of viscera invading the thorax, the worse the pulmonary development. Allan and Greer [17] suggest that a primary defect occurs in the pleuro-peritoneal folds, a pyramidal shaped tissue that extends medially from the lateral cervical wall to the esophageal mesentery and fuses ventrally with the septum transversum. As a consequence to the defect, abdominal viscera misplacement causes a restricted thoracic space and a secondary lung hypoplasia. Langwieler et al. [13] and Mayer et al. [18], proposed an alternative pathogenetic theory based on reduced thoracic space: a primary defect in the post-hepatic mesenchymal plate induces an abnormal diaphragm, which in turn alters the liver development, causing increased liver volume. The liver herniates into the thorax thereby reducing the available space in the chest for lung development, leading to PH. The degree of PH would be due to the amount of liver herniation which is secondary to the defect size [13,18]. In present series we found that the largest the defect the higher the prevalence of liver in the chest, which is in accordance with the latter pathogenetic theory, although no precise evaluation of the liver volume in the thorax was available. Experimental studies suggest that PH associated with CDH is an event that precedes the development of the diaphragmatic defect. Jesudason et al. [19] found that nitrofen-exposed rat embryos show abnormal lung development before diaphragmatic herniation. Similar findings led Keijzer and coworkers [20] to postulate the dual-hit hypothesis. The first hit affects the mesenchyme of the diaphragm and both lungs and occurs before closure of the diaphragm. The second insult is affecting only the ipsilateral lung and is the result of interference with fetal lung development due to compression. In this view, PH would be part of a global embryopathy and its severity is secondary to the degree of the embryopathy.

In present series of patients with CDH, 375 (27.8%) of 1350 patients had one or more associated congenital

anomalies, and both the prevalence of associated anomalies and the number of abnormal organ systems were related to the defect size. Classically, 30% to 50% of patients with CDH have associated congenital anomalies [21,22]. Molenaar et al. [23] hypothesized that CDH may be part of a more basic disturbance involving many organs and suggested a common pathogenetic link among the malformations clustered in patients with CDH, implying that the cardinal features of CDH are part of a global embryopathy. In support to this hypothesis, several Authors [22,24–28], studying the malformations associated to CDH, both in humans and an animal model of nitrofen-exposed rats, found that the heart and great vessels, the urogenital tract, and the trachea are simultaneously distorted. This wide range of malformations suggests that CDH results from an early disorder involving the diaphragm and other tissues in a widespread embryopathy, not directly related to the diaphragmatic defect, as the anomalies are not constant in all patients. As suggested by experimental and "natural experiment" studies [29–31], the timing and degree of embryonic insult have an influence on the type and number of congenital anomalies. In our series, the higher prevalence of associated anomalies and number of abnormal systems in patients with larger defects suggests a more severe (or earlier) embryonic insult in these patients, leading to larger defects and possibly a more profound PH. This hypothesis is corroborated by the inverse correlation we found between defect size and prevalence of hernia sac. The presence of a hernia sac is classically high in patients with late diagnosis of CDH, which generally have a low prevalence of associated anomalies and a very good prognosis [32,33]. The presence of a sac is regarded as a favorable prognostic factor because it is associated with increased pulmonary volume [34] and may be a marker of a later and less severe embryonic disorder [35].

As shown in earlier studies [6], patients with larger defects have a poorer outcome as compared to those with small defects. In present study, mortality rate significantly and progressively increases from 0.6% to 45.6% from defect A to defect D, respectively. As previously mentioned, also the prevalence of associated anomalies significantly increases from defect A to defect D. In previous studied, the relationship between defect size and associated anomalies showed controversial findings. A study from the CAPSNet database on 182 patients did not demonstrate a relationship between diaphragmatic defect size (in terms of prostethic patch) and other anatomic anomalies, leading to the conclusion that patients that need patch repair have a poorer prognosis independent of other known predictors of mortality [9]. Conversely, Riehle et al. [36] found that associated anomalies were present in 9% of patients with primary repair versus 22% of those requiring a patch (one-tailed $p = 0.042$). Concomitant diagnosis of CDH with other anomalies has been shown to be an indicator of poor prognosis [21,37]. This is particularly true for associated CVM [38,39]. It is possible that the combination of CDH and associated anomalies may portend a poorer outcome due to the combination of pathophysiological aspects of both anomalies. For example, the association of CDH and CVM may lead to superimposed PH, disordered post-natal pulmonary vascular remodeling and abnormal cardiopulmonary physiology. On the other hand, it is possible that the combination of CDH with other anomalies represents the result of a major abnormality in development, leading to a more "fragile" patient who is prone to more complicated clinical course. In this context the association of larger defect, more profound PH, higher prevalence of associated anomalies, and poorer outcome may be regarded as a manifestation of such an abnormal development. In present series, patients with larger defects also had lower gestational age and birth weight, further contributing to their poorer outcome.

The CDH Registry was formed to allow collection and analysis of data on presentation, treatment, and outcome of CDH from a large number of centers. Registries have proven to be a good way of collecting data on rare conditions and of mitigating institutional bias in patient selection and treatment. As with any data from registries, there are caveats to their interpretation. The database is observational, and conclusions about therapies should be interpreted cautiously. The data are collected from institutions that differ significantly in their patient recruitment and selection. These differences are important especially when interpreting patients in the nonrepaired category because criteria for "nonsalvageable" patients vary between centers. Many infants with severe cardiac and chromosomal anomalies did not undergo repair making the true impact of these factors difficult to determine. Furthermore, these data only represent outcome to hospital transfer or discharge; both long-term survival and morbidity are likely to be worse. Nonetheless, these data do represent a significant collection of patients with an uncommon disease process.

4. Conclusion

In CDH patients the defect size is correlated with the prevalence of associated anomalies and outcome and may represent a marker of the degree of the underlying embryopathy. Prenatal evidence of signs of larger defects, such as liver herniation, should prompt thorough examination of the fetus to try to detect other congenital anomalies, more frequent in patients with large defect CDH. The prediction of a large defect may help in counseling and identifying, in the future, fetuses/infants most likely to benefit from prenatal treatment and engineered diaphragmatic reconstruction.

Appendix

The centers that contributed to this study.

Alberta Children's Hospital	Calgary	AB	Canada
Arkansas Children's Hospital	Little Rock	AR	
Astrid Lindgren Children's Hospital	Stockholm		Sweden
BC Children's & Women's Health Centre	Vancouver	BC	Canada
Children's Hospital & Research Center Oakland	Oakland	CA	
Children's Hospital Boston	Boston	MA	
Children's Hospital of Akron	Akron	OH	
Children's Hospital of Illinois	Peoria	IL	
Children's Hospital of Los Angeles	Los Angeles	CA	
Children's Hospital of Oklahoma	Oklahoma City	OK	
Children's Hospital of Wisconsin	Milwaukee	WI	
Children's Hospital Omaha	Omaha	NE	
Children's Hospitals and Clinics	Minneapolis	MN	
Children's Memorial Hermann Hospital	Houston	TX	
Children's of Alabama	Birmingham	AL	
Cincinnati Children's Hospital Medical Center	Cincinnati	OH	
Duke University Medical Center	Durham	NC	
Emory University	Atlanta	GA	
Georgia Health Sciences University	Augusta	GA	
Golisano Children's Hospital at Strong	Rochester	NY	
IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico	Milano		Italy
Kosair Children's Hospital	Louisville	KY	
Le Bonheur Children's Medical Center	Memphis	TN	
Legacy Emanuel Children's Hospital	Portland	OR	
Loma Linda University Children's Hospital	Loma Linda	CA	
Lucile Salter Packard Children's Hospital	Palo Alto	CA	
Mattel Children's Hospital at UCLA	Los Angeles	CA	
Miami Valley Hospital	Dayton	OH	
National Center for Child Health and Development	Setagaya-ku	Tokyo	Japan
Ospedale Pediatrico Bambino Gesu	Rome		Italy
Ospedale Riuniti Bergamo	Bergamo		Italy
Osaka University Graduate School of Medicine	Suita	Osaka	Japan
Palmetto Health Richland	Columbia	SC	
Primary Children's Hospital	Salt Lake City	UT	
Radboud University Nijmegen Medical Centre	Nijmegen		The Netherlands
Research Institute at Nationwide Children's Hospital	Columbus	OH	
Royal Children's Hospital	Parkville	Victoria	Australia
Royal Hospital for Sick Children	Glasgow	Yorkhill	Scotland
San Diego Children's Hospital	San Diego	CA	
Sophia Children's Hospital	Rotterdam		The Netherlands
St. Francis Children's Hospital	Tulsa	OK	
St. Joseph's Hospital and Medical Center	Phoenix	AZ	
St. Louis Children's Hospital	St. Louis	MO	
Stollery Children's Hospital	Edmonton	Alberta	Canada
Sydney Children's Hospital	Randwick	NSW	Australia
Texas Children's Hospital	Houston	TX	
The Hospital for Sick Children	Toronto	Ontario	Canada
Universitatsklinikum Mannheim gGmbH	Mannheim		Germany
University of Michigan, C.S. Mott Children's Hospital	Ann Arbor	MI	
University of Nebraska Medical Center	Omaha	NE	
University of Padua	Padua		Italy
University of Texas Medical Branch at Galveston	Galveston	Tx	

(*continued on next page*)

University of Virginia Medical School	Charlottesville	VA	
Vanderbilt Children's Hospital	Nashville	TN	
Vladivostok State Medical University	Vladivostok		Russia
Winnie Palmer Hospital for Women & Babies	Orlando	FL	
Yale New Haven Children's Hospital	New Haven	CT	

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