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Congenital diaphragmatic hernia: pathogenesis, prenatal diagnosis and management — literature review

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ABSTRACT

Congenital diaphragmatic hernia (CDH) is a developmental discontinuity of the diaphragm. It allows abdominal viscera to herniate into the chest and leads to lung hypoplasia. Congenital diaphragmatic hernia is one of the most severe birth defects, with extremely high neonatal mortality. This paper presents a review of the available literature on prenatal diagnosis, management and treatment options for CDH. In selected cases, a prenatal procedure to improve neonatal survival is possible. The authors of this manuscript believe their work might contribute to a better understanding of congenital diaphragmatic hernia and patient selection for the FETO (fetal endoscopic tracheal occlusion) surgery or expectant management.

Key words: congenital diaphragmatic hernia, FETO procedure, tracheal balloon occlusion, lung hypoplasia

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INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a developmental closure defect, resulting in discontinuity of the diaphragm. This allows abdominal viscera to herniate into the chest. CDH occurs in approximately 1 in 3000 live births and results in high neonatal morbidity and mortality [1]. It is also associated with severe pulmonary hypoplasia and pulmonary hypertension. The posterolateral left side of the diaphragm is the most common localization (75–90% of cases), but the defect can be also right-sided (10–15% of cases), or even bilateral (1–2% of cases) [2]. Some authors reported a slightly higher incidence of CDH in male fetuses. CDH prevalence does not appear to be associated with maternal age.

Although diaphragmatic herniation is surgically correctable, *in utero* herniation of the viscera may result in complications, which are often fatal. Since the FETO (fetal endoscopic tracheal occlusion) surgery has become available, adequate patient selection and eligibility for the procedure are of vital importance. The aim of FETO is to minimize pulmonary hypoplasia and reduce mortality. As any other surgical procedure, FETO has some contraindications and may carry the risk of possible adverse side effects.

This paper presents a review of the literature on prenatal diagnosis, embryology, possible pathogenesis and management options for this rare and severe anatomical defect. It may help clinicians to be more confident at diagnosis and particularly when counseling a case with congenital diaphragmatic hernia. It also reviews the indications, risks, and clinical implications of FETO for severe congenital diaphragmatic hernia.

EMBRYOLOGY AND PATHOGENESIS

The diaphragm is derived from the septum transversum, the pleuroperitoneal folds, derivatives from the body wall, the dorsal mesentery, and a pair of pre-muscle masses lying opposite the forth cervical segment of the 9 mm embryo. The septum transversum originates around day 22 at a cervical level, but caudal to the developing heart. In normal conditions, the pleuroperitoneal folds fuse with the septum transversum, the esophageal mesentery and the muscular ingrowth from the body wall invade the folds, forming the muscular part of the diaphragm. Incomplete fusion of any of these components may produce a hernia of Morgagni, a pleuroperitoneal defect, a hiatal hernia, or eventration of the diaphragm. There are several types of diaphragmatic hernia. The most common defect is located in the posterolateral diaphragm (Bochdalek hernia — 95% of cases), while hernias involving the anterior portion of the diaphragm (Morgagni

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hernia) are less frequent. The complete development of the diaphragm should be completed by week 9 and the sealing of the left side occurs a week after the right. The closure of the pleuroperitoneal canal should coincide with resolution of the normal physiological herniation. If a pleuroperitoneal defect persists at 10 weeks of pregnancy, the returning intestines may enter the thoracic cavity, usually on the left side, which is related to the earlier closure of the right pleuroperitoneal opening. Absence of diaphragmatic continuity is always related to abnormal position of the adjacent organs. Bilateral herniation with a significant degree of visceral displacement is the most severe and rare (< 2%). In the left-sided herniation, the stomach is often involved, while the liver is involved when the hernia is on the right; however, the liver may herniate even with left-sided CDH. Both, the right- and the left-sided hernias involve the bowel. Lung development normally occurs at 14–16 weeks of intrauterine life. Interference with normal lung development at this time results in decreased bronchiolar branching and pulmonary hypoplasia, as well as truncation and over-muscularization of the pulmonary arterial tree and pulmonary hypertension. Abnormal development of the lung also results in a dysfunctional surfactant system late in gestation and after birth. Lung hypoplasia and abnormal pulmonary vascular development and function occur on both sides. Vasoconstriction with abnormal pulmonary vasoreactivity also contributes to poor pulmonary blood flow. One of the hypotheses suggests that diminished proliferative capacity in CDH results in a smaller size and lung hypoplasia, whereas diminished apoptosis of the fibroblasts results in an increased thickening of the fibroblastic layer. This leads to developmental abnormalities within pulmonary vasculature, which is the leading cause of CHD-related pulmonary hypertension. The structural and functional defects of the pulmonary tree result in increased vascular resistance and decreased surface area for gas exchange.

Unfortunately, the pathogenesis of CDH remains to be fully elucidated. Several theories have been postulated in cases of non-genetic congenital diaphragmatic hernias. The most likely theory suggests that visceral herniation into the thoracic cavity occurs due to failure of normal closure of the pleuroperitoneal or to environmental triggers which unsettle differentiation of the mesenchymal cells during formation of the diaphragm and other somatic structures [3].

There are also some papers suggesting environmental triggers such as vitamin A deficiency, as well as thalidomide or anticonvulsant exposure among the possible causes [4, 5]. In the 1950s, vitamin A-deficient rats were demonstrated to have CDH [6]. Numerous authors claimed that abnormal retinoid signaling and vitamin A deficiency may be related to the etiology of CDH. Retinoic acid functions as a repressor or co-activator through interactions with other pathways and induces some tissue-specific regulatory molecules. Retinoic acid pathway and link between congenital diaphragmatic hernia has been described in animal models by a number of sources. [7] Also, mycophenolate mofetil (immunosuppressive agent) and allopurinol have both been associated with CDH due to disruption to purine biosynthesis [8].

There is growing evidence that lung abnormalities in CDH are not only related to intrathoracic herniation of the abdominal organs. Pulmonary development may already be affected prior to the development of the diaphragmatic hernia and mechanical compression. The 'double-hit' hypothesis, proposed by Keijzer et al., explains pulmonary hypertension in CDH as a result of two developmental insults: the first one occurring in both lungs before diaphragm development, and the second one affecting only the ipsilateral lung due to interference of the herniated organs with fetal breathing movements [6].

NON-ISOLATED CONGENITAL DIAPHRAGMATIC HERNIA

It is assumed that congenital diaphragmatic hernia usually occurs as an isolated finding, but in 10–30% of the cases there may be an association with chromosomal defects [9]. It may be associated with rare genetic conditions like trisomy 18, tetrasomy 12p (Pallister-Killian syndrome), Fryns syndrome, or isolated structural defects. In cases of complex abnormalities, malformations may occur in all major organ systems. Also, rare genetic syndromes such as Apert, CHARGE, Coffin-Siris, Goltz, Perlman, Swyer, Brachmann-Cornelia De Lange, Goldenhar sequence, Beckwith Wiedemann, Simpson-Golabi-Behmel, Donnai-Barrow, Matthew-Wood, Jarcho-Levin, Fraser, Stickler, Pierre Robin, partial trisomy 5, partial trisomy 20, and polyploidies have also been reported [10]. Selected syndromes associated with congenital diaphragmatic hernia are presented in Table 1. Congenital diaphragmatic hernia may be an isolated structural defect, but it can also be associated with additional anomalies. Structural defects are found in 25–57% of all CDH cases [9], and include congenital heart defects, renal, brain and gastrointestinal abnormalities. The most common list of structural defects associated with CDH and their prevalence are summarized in Table 2.

INHERITANCE

In the vast majority of cases, CDH occurs sporadically, without an identifiable familial link. However, in some cases autosomal recessive, autosomal dominant, and X-linked inheritance patterns have been reported [11]. Sporadic cases occur probably due to *de novo* mutational events in genes for normal diaphragmatic development or reflect polygenic or multifactorial inheritance. The etiology of this defect remains unknown in over 70% of individuals with CDH. As stated above, only a few teratogenic and genetic factors

Table 1. Selected genetic syndromes associated with congenital diaphragmatic hernia

Syndrome	Gene/locus	Phenotype features
Pallister-Killian syndrome	Tetrasomy 12p	CDH, developmental disability, epilepsy, hypotonia, epicanthal folds, flat nose, vision and hearing impairments, congenital heart defects, gastroesophageal reflux, cataracts
Fryns syndrome	Unknown (autosomal recessive inheritance is suggested)	CDH, pulmonary hypoplasia, hypoplasia of the distal phalanges and nails, flat nasal bridge, dysplastic ears, micrognathia, orofacial clefts
Gershoni-Baruch syndrome	Unknown (autosomal recessive inheritance is suggested)	CDH, omphalocele, radial ray malformations
Simpson-Golabi-Behmel	GPC3; Xq26	CDH, macrosomia (prenatal and postnatal), polydactyly, hypoplastic nails, developmental delay
Beckwith-Wiedemann syndrome	IGF2/H19/p57KIP; 11p15.5	CDH, macrosomia, omphalocele, macroglossia, neonatal hypoglycemia
Microphtalmia with linear skin defects	HCCS	CDH, cardiomyopathy, microphtalmia, dermal aplasia
Goltz syndrome	PORCN; Xp22	CDH, focal dermal hypoplasia, dental hypoplasia, syndactyly
Craniofrontonasal syndrome	EFNB1; Xp22	CDH, coronal synostosis, hypertelorism, digital anomalies
PAGOD syndrome	Unknown	CDH, omphalocele, dextrocardia, pulmonary artery hypoplasia
Denys-Drash syndrome	WT1; 11p13	CDH, glomerulopathy, male pseudohermaphroditism

that are known to cause CDH in humans. A brief summary of the etiological factors of congenital diaphragmatic hernia is provided in Table 3 [3].

It is strongly recommended to confirm fetal karyotype with CDH. The estimated recurrence risk of congenital diaphragmatic hernia in future siblings in the absence of a family history is 1–2% after one affected child [12].

DIAGNOSIS

Prenatal diagnosis of CDH is based on an ultrasound scan. In the vast majority of the cases, the abnormality is detected during routine anomaly scan, therefore mean gestational age at diagnosis is about 22–24 weeks [13]. In some cases, CDH may be diagnosed even during the first trimester scan, when the diaphragmatic defect is most likely very large and therefore the prognosis remains poor [14]. The detection rate increases with advancing gestational age and increases if there are associated abnormalities [9]. Usually, the diagnosis is made based on the presence of mediastinal shift and a fluid-filled stomach next to or just behind the heart. In some cases, fetal liver may be herniated into the chest and, appearing as a homogeneous mass in the chest at the level of the heart. Right-sided CDH is much more difficult to diagnose since in ultrasound the liver is similar in appearance to the fetal lung. Color Doppler ultrasound can be helpful in determining liver position by visualization of the ductus venosus and the course of the intrahepatic vessels [15]. In pregnancies with CDH, polyhydramnios may be present due to esophageal compression and if fetal swallowing is impaired. If this is the case, it may increase the risk of premature delivery. In severe cases even hydrops fetalis can occur as a result of mediastinal shift and compression of the great vessels [16].

Magnetic resonance imaging (MRI) allows for an easy assessment of liver herniation. Unlike ultrasound, it is not limited by maternal obesity or oligohydramnios and it provides better soft tissue contrast. Fetal MRI is now commonly used in referral centers for CDH. It has been shown to be effective in confirming the diagnosis and detecting the presence of additional structural defects. Some studies suggested prenatal MRI with lung volume assessment might be more accurate and more descriptive of the outcome.

DIFFERENTIAL DIAGNOSIS

Diaphragmatic eventration refers to the elevation of a thinned and intact diaphragm. The thin and therefore more flexible piece of diaphragm may form a bulge, which contains the abdominal contents displaced into the thorax. A partial elevation of a hemidiaphragm with a normal position of the uninvolved part should suggest the diagnosis, but the thinned membrane is not always detected. Extensive eventrations are extremely difficult to differentiate from congenital hernias at prenatal imaging. Usually, diaphrag-

Table 2. Structural defects associated with CDH (modified from Graham et al. [23])

Body system involved	Type of defects	Estimated frequency
Cardiovascular	Ventricular septal defect	6%
	Atrial septal defect	3%
	Coarctation of aorta	2%
	Hypoplastic left heart syndrome	2%
	Dextrocardia	1%
	Tetralogy of Fallot	1%
	Transposition of the great vessels	1%
	Single ventricle	1%
	Tricuspid atresia	1%
	Pulmonary stenosis	1%
Gastrointestinal	Malrotation	4%
	Imperforate anus	3%
	Absent gallbladder	1%
	Accessory spleen	1%
Urogenital	Renal agenesis	3%
	Cystic kidney	1%
	Absent testes	1%
	Bicornuate uterus	1%
Musculoskeletal	Limb deficiency	5%
	Club foot	4%
	Omphalocele	3%
	Vertebral anomalies	2%
	Arthrogryposis	2%
	Sternal defect	2%
	Abdominal wall defect	1%
	Rib anomalies	1%
	Hip dislocation	1%
	Ectopia cordis	1%
Respiratory	Pulmonary sequestration	1%
	Tracheoeseophageal fistula	1%
Central nervous system	Neural tube defects	3%
	Hydrocephalus	3%
	Ocular hypoplasia	1%
Craniofacial	Cleft lip and/or palate	2%
	Cleft palate	2%

matic eventration is less severe than CDH and sometimes remains symptomless until early childhood. Diaphragmatic agenesis, on the other hand, is considered the most extreme form of CDH. Other thoracic lesions which should be considered in differential diagnosis include congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration, bronchopulmonary foregut malformation, bronchogenic cysts, bronchial atresia, enteric cysts, and

Table 3. Summary of ethological factors of congenital diaphragmatic hernia

Type of factor	Example	Estimated frequency
Environmental	Vitamin A deficiency (animal models) [13]	Rare
Teratogenic drugs	Mycophenylate mofetil Allopurinol Lithium	Rare
Chromosome aberrations	Deletions: 15q26 8p23.1	6%
Single gene mutations	STRA6 GPC3 FOG2	< 10%
Unknown	–	> 70%

Table 4. The most common fetal lung lesions in differential diagnosis of CDH

Type of lesion
Congenital cystic adenomatoid malformation (CCAM)
Bronchopulmonary sequestration
Diaphragmatic eventration
Teratoma
Bronchial atresia
Enteric cysts
Bronchopulmonary foregut malformation

teratomas [9]. Multiple cystic lesions in the chest are more likely to be CCAM than CDH, and a presence of a systemic feeding vessel to a cystic or solid mass is consistent with a bronchopulmonary sequestration. The differential diagnosis may be difficult, however, CDH can be excluded by the presence of normal intraabdominal organs and on the other hand - the diagnosis is certain if intestinal peristalsis is seen within the fetal thorax [9]. The most common lung lesions which need to be excluded in differential diagnosis of CDH are summarized in Table 4.

PROGNOSTIC FACTORS

The prognosis for the survival depends on several factors. If CDH is associated with a chromosomal defect, the long-term prognosis depends on the type of genetic abnormality and coexisting abnormalities (in particular central nervous system and heart defects). Several studies have shown that infants with right-sided CDH have a lower survival rate than those with left-sided lesions (50 vs. 75%) [17]. For the isolated cases of congenital diaphragmatic hernia, the most commonly accepted prognostic parameter is the assessment of the amount of the lung tissue in the fetal chest. It is presented as a lung area to head circumference ratio (LHR).

However, lung volume growth in a developing fetus is different as compared to head growth. To correct for gestational age, LHR may be expressed as a percentage of normal (observed [O]/expected [E]) LHR [18]. Currently, o/e LHR is the most accepted and validated parameter for the estimation of fetal lung size measured by ultrasound. The area of the contralateral lung to the defect is measured, divided by the head circumference and the o/e LHR ratio is calculated [19]. While in normal fetuses LHR increases with gestational age, o/e LHR seems to be constant over the course of pregnancy [20]. One of the predictive prenatal markers of postnatal survival is the absence or presence of liver herniation. Also, the amount of the liver herniated into the chest may be measured by MRI and calculated as herniated-liver-to-thoracic-volume-ratio. Low o/e LHR values combined with liver herniation correspond to increased mortality and early neonatal morbidity [21]. In a group of 329 fetuses with isolated left-sided CDH, Jani et al., observed the rate of postnatal survival to increase from 18% at o/e LHR < 25% to 66 % at o/e LHR 26–45% and 89% at o/e LHR > 45% [22]. The prognosis is more severe in cases of a right-sided defect, liver herniation, low lung area to head circumference ratio (LHR) and low O/E ratio. A large defect is more likely to result in pulmonary hypoplasia and early neonatal death as compared to a small defect. Several predictors for lung hypoplasia and pulmonary hypertension have been described. Some of the predictors assess fetal lung vasculature. The McGoon index (MGI) on ultrasound and the modified McGoon index on MRI are calculated as the sum of the diameters of the right and left pulmonary arteries measured at the bifurcation and divided by the diameter of the aorta. According to some authors, these indices may be useful for predicting neonatal survival and severity of postnatal pulmonary hypertension [23]. Other ultrasound markers are also emerging — such as the position of the fetal stomach in the chest, for example [24]. The intra-abdominal fetal stomach position is associated with a more favorable prognosis, whereas the presence of the stomach within the thorax during the fetal or neonatal period has been shown in multiple studies to correlate with an adverse outcome. Recently, Cordier et al. have confirmed that fetal stomach position was predictive of postnatal survival and the need for patch repair [25]. According to some papers, there might be a strong association between neonatal death, ECMO (extracorporeal membrane oxygenation) requirement and short-term respiratory morbidity, depending on the position of the fetal stomach [24]. According to Russo et al., the need for ECMO may be predicted based on lung size and liver herniation [26].

PRENATAL TREATMENT

Severe and extremely severe diaphragmatic hernias have poor outcomes and the affected patients may be offered fetal endoscopic tracheal occlusion (FETO). The primary goal of FETO is to minimize pulmonary hypoplasia and reduce mortality. Harrison et al. [27], were the first to introduce the concept in animal model by deflation of a previously inflated intra-thoracic balloon. Since its clinical introduction, FETO has been performed for severe cases at 26–28 weeks and for moderate cases at 30–32 weeks of gestation. Tracheal occlusion leads to the accumulation of the lung fluid, which causes increased lung tissue stretch and accelerated growth [28]. On the other hand, it reduces the number of type II pneumocytes and surfactant expression. This is the major rationale for balloon retrieval at 33–34 weeks of gestation [29]. Prenatal balloon removal is also associated with lower morbidity and better survival rate [30]. Jani et al., demonstrated that, in severe CDH, the FETO procedure increased the survival rate from 24.1% to 49.1% [22]. A recently published meta-analysis gathered data from five different studies [31]. Lung-to-head ratio (LHR) of ≤ 1.0 was uniformly used to define severe congenital diaphragmatic hernia and used as an inclusion criterion for FETO. These five studies included a total number of 211 patients — 101 in the control and 110 in the FETO groups. Mean gestation at FETO and at delivery was 28 and 35.6 weeks, respectively. The reported incidence of premature rupture of membranes was 35.3% in the FETO group vs. 27.8% in the control group. Severe pulmonary hypoplasia and pulmonary hypertension were the leading cause of neonatal death in both groups. The meta-analysis revealed that the survival rate was better in the FETO group, with 7-fold greater odds of survival after FETO. The risk of death was 89% in the control group as compared to 50% in the FETO group [31]. Deprest et al., described that premature rupture of membranes, the most common complication of FETO, occurs within three weeks after the procedure in approximately 17% of the cases [18]. Tracheal occlusion may also have some side effects for the fetus and the most common is tracheomegaly, with little or no clinical impact [32]. Following delivery, the surviving neonates still require a diaphragm surgery, often including a prosthetic patch repair.

In most CDH cases, administration of antenatal glucocorticoids may be considered, unless contraindicated. This may decrease morbidity resulting from preterm delivery. Animal studies confirmed improved gas exchange, lung morphology and decreased medial hypertrophy of pulmonary arterioles after administration of antenatal steroids [33].

POSTNATAL TREATMENT

Some newborns with severe CDH may require extracorporeal membrane oxygenation. It consists of the cannulation of both carotid arteries and jugular vein and their connection to the circuit with a membrane gas exchange chamber. It allows oxygen and carbon dioxide exchange

without involving the lungs. ECMO use is typically restricted to infants > 2 kg and gestational age > 34 weeks in the absence of significant intracranial hemorrhage, chromosomal anomalies or other congenital anomalies [34]. There is a not survivable subset of CDH fetuses due to extremely severe pulmonary hypoplasia for whom ECMO may be futile. Some authors reported reduced number of patients treated with this method due to weak evidence of its real benefits in such neonates [35]. Postnatal therapy is complex and includes immediate intubation, small-volume, high-frequency oscillatory ventilation, and intensive pharmacological treatment, including nitric oxide use. A more detailed description of neonatal care is beyond the scope of this paper.

CONCLUSIONS

Congenital diaphragmatic hernia is a complex abnormality. The prognosis remains very poor if the defect is severe and prognostic factors are compound. Mortality and morbidity rates remain high despite modern and intensive care. Also, the genetics of CDH is complex as it might be associated with chromosomal abnormalities or rare genetic syndromes, but the specific inheritance pattern is difficult to establish. Lung hypoplasia and pulmonary hypertension are the most severe neonatal complications. Differing degrees of bilateral pulmonary hypoplasia may explain variation in severity among neonates presenting with respiratory distress and CDH. Prenatal intervention aims at stimulating lung development and this might be achieved by fetal endoscopic tracheal occlusion. In a selected group of newborns with severe CDH extracorporeal membrane oxygenation may be beneficial. Randomized trials and clear guidelines are necessary to establish the true role of an invasive prenatal treatment. The "Tracheal Occlusion To Accelerate Lung growth" trial (www.totaltrial.eu) is an international randomized trial investigating the role of fetal therapy for severe and moderate pulmonary hypoplasia. In the future, also other alternatives to surgical fetal therapy should be explored and studied. The results of this research may offer answers to many questions concerning congenital diaphragmatic hernia.

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