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The management of congenital diaphragmatic hernia

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ABSTRACT

Congenital diaphragmatic hernia (CDH) is a structural birth defect that with varying degrees of severity that results in significant neonatal morbidity and mortality. CDH occurs in 1:2,500 live births, and despite the advances in prenatal diagnosis and neonatal intensive care, the mortality and morbidity rate in infants with CDH is significant. In this article, we tried to summarize the main modalities of diagnosis, prognosis and medical treatment in CDH cases, found in specialty literature.

Keywords: congenital diaphragmatic hernia, pregnancy, hemodynamic support, ventilation, ECMO, pulmonary hypertension

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a medical anomaly of the diaphragm that develops during the uterine development of the fetus and is characterized by the herniation of abdominal viscera towards the thoracic cavity. The abdominal contents that herniate can create a mass effect that impedes lung development [1,2]. CDH is a life-threatening congenital anomaly, with an incidence of approximately 1:2,500 live births [1]. The majority of affected neonates present, in the first hours of life, with respiratory distress that may be mild or so severe to be incompatible with life. With the help of prenatal diagnosis and the advancements in neonatal care, survival has improved but there remains a significant risk of death and complications in infants with severe CDH. Antenatal diagnosis of the condition has improved postnatal outcomes. Not only family education regarding the fetal diagnosis of CHD, but advanced prepared medical personnel trained to deliver and assess newborns with this medical condition made an important contribution towards the fetal outcome. There is a constant challenge in making an accurate prenatal and postnatal diagnosis regarding the severity of fetal GHD [2]. Despite advances in both diagnosis and therapy, mortality and long-term morbidity are still high among involved patients, especially when diagnosed early during gestation [3].

METHODS

An extended search has been performed in the databases of PubMed and NCBI to select English articles that were published in medical journals. Articles and publications have been selected taking into consideration the novelty of the information and the year of the publications. Research has been focused on congenital diaphragmatic hernia in the matter of etiopathogenic, prenatal diagnosis and antenatal management. Keywords used in the search strategy included congenital diaphragmatic hernia, pregnancy, hemodynamic support, ventilation, ECMO and pulmonary hypertension.

RESULTS

Etiopathogeny

Congenital diaphragmatic hernia is considered to be a multifactorial disease with an enigmatic eti-

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ology. Although it may occur as a single defect in 50 to 70% of cases, in approximately 30-50% of cases CHD may be part of more complex syndromes that include other structural malformations and chromosomal anomalies [4,5]. Structural defects that are commonly diagnosed include the cardiovascular, central nervous (CNS) and musculoskeletal systems. As regards cardiovascular involvement, most frequently are diagnosed atrial and septal defects, as well as Fallot's tetralogy. Among CNS and musculoskeletal anomalies, hydrocephaly and neural tube defects, respectively limb defects, polydactyly and syndactyly are often associated with CDH [3,6]. As it presented below in Table 1, there are several and various genetic syndromes, as well as structural and chromosomal anomalies that can be associated with GDH [7].

The severity and consequences of congenital diaphragmatic hernia are related to both the extent and the length of time of the abdominal organs herniated into the thoracic cavity. This is closely associated with the normal development of the lungs, with involvement in the anatomy of the lungs, namely parenchyma, airways and circulation, as well as the function of both respiratory and heart systems [8]. The pathophysiology of CDH is comprised of both fixed (vascular and pulmonary hypoplasia) and reversible (pulmonary vascular reactivity) [2]. Alterations of the parenchyma and lung's function include anomalies of the bronchioles with reduced terminal branching, anomalies that often lead to acinar hypoplasia, reduces alveoli number, decreased area for gas exchange, thickening of the alveolar walls and elevated production of interstitial tissue [9].

The association of ventricular hypoplasia to severe left-sided congenital diaphragmatic disease was first described by Siebet et al. 8 deceased infants diagnosed with severe anomalies have been evaluated and it was reported an important reduction of the cardiac mass, as well as other cardiac anomalies, namely left atrium hypoplasia, interventricular and left ventricle septum [10]. In addition, studies report that fetal outcome is particularly associated with the moment of fetal diagnosis. In this regard, Crawford et all. Studied 19 fetuses diagnosed antenatally using ultrasound, before 24 weeks of gestation, with CDH, and they reported a 100% mortality rate when left ventricle hypoplasia is present. In the contrary, when hypoplasia of the left ventricle is diagnosed later during gestation, namely later in the last trimester, the survival rate is considerably increased [12]. Regarding the pathophysiology of the left ventricle hypoplasia, it is believed that the condition appears as a consequence of the visceral herniation into the left part of the thoracic cavity that determines a rotation of the cord, followed by decreased blood flow through the foramen ovale and a constant insufficient filling of the heart left side, as it can be seen in Figure 1 [13].

In addition, left-side hypoplasia may occur as a consequence of combined mechanisms. It may be included abnormal fetal hemodynamics with increased streaming in the ductus venosus and inferior vena cava [14]. Based on extensive research, it has been confirmed the combined pathogeny of left-sided congenital diaphragmatic anomaly. It occurs as a consequence of pulmonary hypertension, hypertrophy, or dysfunction of the right ventricle, but is also related to hypoplasia of the left ventricle and hypertension in the pulmonary venous system. Taking those facts into consideration, it is obvious that those anomalies combined are often unresponsive to common therapies [15].

Prenatal diagnosis

Most cases of congenital diaphragmatic hernia are diagnosed prenatally. We should also consider the thoracic lesions when the diagnosis of CDH is made prenatally by ultrasound: diaphragmatic eventration, bronchopulmonary sequestration, bronchogenic cysts, bronchial atresia, enteric cysts, teratomas. The definitive sonographic organs in the fetal CDH rely on the visualization of abdominal organs in the fetal chest. The sonographic hallmark of the left CDH is a fluid-filled stomach just behind the left atrium and ventricle in the lower thorax as seen on the transverse view. Other sonographic evidence that implies the presence of left CDH includes the absence of the stomach below the diaphragm, medi-

TABLE 1. Genetic syndromes, chromosomal and structural anomalies associated with CDH [7]

Genetic syndromes	Chromosomal Anomalies	Structural Anomalies
Cornelia de Lange syndrome	Trisomy 21	Atrial septal defect
Charge syndrome	Trisomy 13	Ventricular septal defects
Beckwith-Wiedemann syndrome	Trisomy 18	Cardiac
Craniofrontonasal syndrome	Monosomy X	Tetralogy of Fallot
Fryns syndrome	8p23.1 deletion syndrome	Nervous system
Denys-Drash syndrome	Tetrasomy 12 q	Aortic coarctation
Thoracoabdominal syndrome	8q23.1 deletion	Limb reduction defects
Wolf-Hirschhorn syndrome	14p16 deletion 11q23.2 duplications	Polydactyly Syndactyly

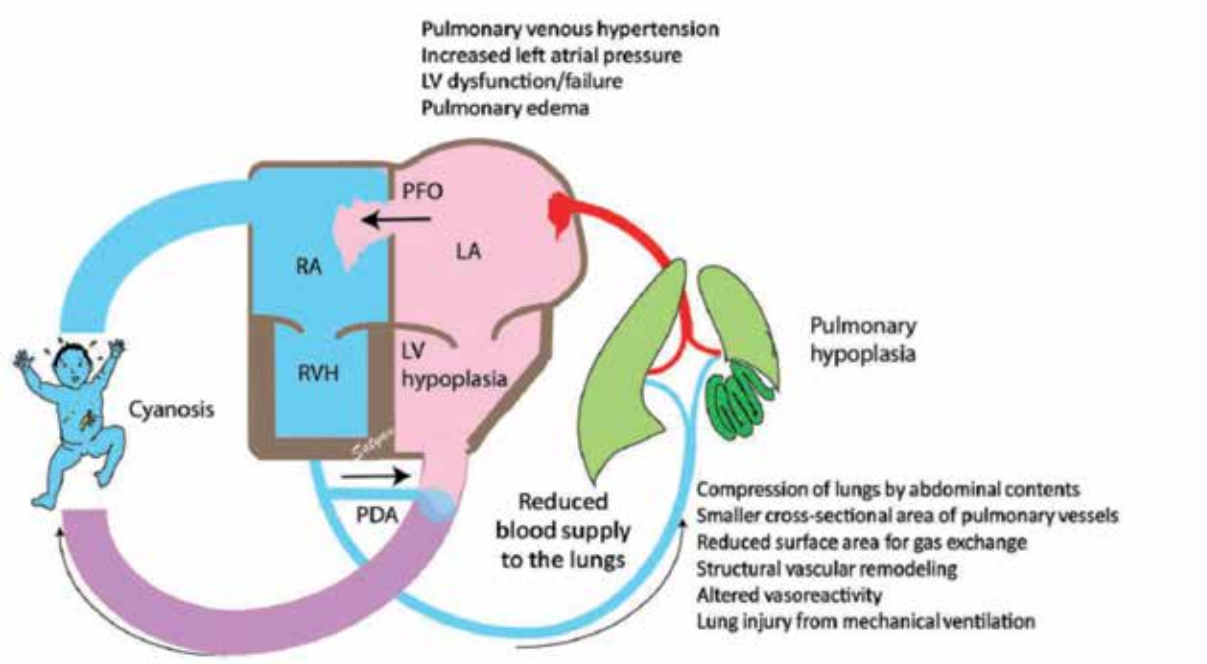

FIGURE 1. Pathophysiology of congenital diaphragmatic congenital hernia. LA- left atrium. LV- left ventricle. PDA- patent ductus arteriosus. PFO patent foramen ovale. RA – right atrium. RVH- right ventricular hypertrophy [13]

astinal shift to the right, and a small abdominal circumference [3,5]. Because of similar echogenicity of the liver and the lungs, right CDH, with the herniation of the right liver lobe into the thorax, is frequently misdiagnosed or mistakenly confused with a solid thoracic mass. The presence of the liver in the chest can be conclusively demonstrated by a doppler examination of the hepatic vasculature and umbilical vein. The MRI is routinely used in many centers and can clearly visualize the extent of liver herniation [2].

Early and prenatal diagnosis is of increased importance in the management of CDH. It is performed using fetal echocardiography for both confirmations of the suspected diagnosis and for the diagnosis of additional cardiac-associated anomalies. Also, family education and determining the fetuses with high-risk complications, may select fetuses for specific interventions and advise patients to address to superior fetal care centers. In addition to left ventricle hypoplasia diagnosis, fetal karyotyping may be helpful to rule out chromosomal abnormalities [4].

Some prenatal predictors have been proposed and refined over the years but the single and most reliable predictor of severity and mortality in CDH is the herniations of the liver. Mortality for patients with liver herniation was 65% compared to 7% when the liver is below the diaphragm. It is extremely important to diagnose liver herniation, because when present, it often requires extracorporeal membrane oxygenation (ECMO) in 80% of fetuses, compared to only 25% when the liver is not involved. Prenatally, several markers that characterize lung volume are useful in evaluating fetal outcomes and required procedures, such as total lung volume, lung-head ratio (LHR), and expected lung-head ratio. The ultrasound measurements can be limited by the differences in maternal body habitus, the position of the fetus, and the difficult distinction between lung and liver tissue [16].

Prognosis of left CDH with liver up correlates with O/E LHR measured at ultrasonographic evaluation:

- Very severe, o/e LHR <15%, survival <5%;
- Severe, o/e LHR 16-25%, survival 20-30 %;
- Moderate, o/e LHR 26-45%, survival 40-60%;
- Mild > 45%, o/e LHR >45%, survival 95% [18].

Besides prenatal measurements, some studies have identified some postnatal clinical factors that are associated with severe illness and/or poor outcomes in CDH. These factors are low Apgar score at birth, initial Ph, highest Pao2, lowest PCO2, or use of mechanical ventilation at 30 days of life. CDH- composite prognostic index (CDH-PCI) is a composite score that encompasses many of these antenatal and postnatal factors: genetic, cardiac, lung and hernia variables and it was found to be predictive not only of the mortality but also of the use of ECMO.

CDH-PI:

- >8 was associated with improved survival (89 % accuracy)
- <6 were treated with ECMO (63 % accuracy)
- <5 received ECMO (75 % accuracy) [17]

Antenatal management

Medical management

Medical therapies aim to improve pulmonary hypoplasia and pulmonary hypertension in the CDH

neonate. Limited evidence exists to support the administration of antenatal corticosteroids in CDH. In a recent, multicenter randomized controlled trial on the antenatal betamethasone effect in CDH mothers at risk for preterm delivery, steroid use was associated with reduced neonatal respiratory morbidity and decreased requirement for substantial respiratory support. Betamethasone was associated with an increased risk of neonatal hypoglycemia, although this appeared to be self-limiting [2].

Other research was made on the effect of exogenous retinoid use on pulmonary hypoplasia in CDH. The potential benefits of this therapy must be weighed against the potential calamitous teratogenic effects of retinoid toxicity. Impaired retinoid signaling has been hypothesized to contribute to CDH pathogenesis. Retinoid therapy remains at a preclinical stage [6].

The most promising antenatal medical intervention for CDH is the use of phosphodiesterase inhibitors (Sildenafil). Sildenafil has demonstrated efficacy in multiple animal models, and now is progressing in clinical applications. The phosphodiesterase inhibitors, unlike corticosteroid or retinoid therapy, have been extensively investigated in maternal-fetal disease, and are widely available in generic and low-cost formulations. A human ex vivo placenta perfusion model suggests that safe maternal dosing of Sildenafil can achieve therapeutic drug concentration in the fetus. A trial, initiated in 2015, sparked the concern regarding potential side effects of prenatal sildenafil therapy. In 2018, it was observed an increased risk of pulmonary hypertension and death in neonates who had received antenatal sildenafil [19].

Interventional

Because of the failed attempts of open fetal surgery, fetal endoscopic tracheal occlusion (FETO) was developed. FETO is performed with a small caliber endoscope and sheath that are inserted into the amniotic cavity through the maternal abdomen and then guided into the fetal trachea via the fetal oral cavity. A small detachable inflatable latex balloon with a one-way valve is inflated below the level of vocal cords using a syringe, which is connected to the balloon via a small-caliber catheter. The occlusion of the trachea is associated with entrapping of the lung fluid into the lung parenchyma and determines lung expansion. A second maneuver is required preceding fetal delivery, in order to remove the inserted balloon [13]. In cases where the removal is urgently needed and is not possible via a fetoscope, the baby may need to be delivered via ex-utero intrapartum treatment (EXIT) procedure to allow for balloon removal while the baby is still on placental support. Balloon removal should be performed under flawless circumstances and several weeks before delivery. It is important because it helps the fetus tolerate the transition to the external environment after delivery, and, it also, it allows type II pneumocytes to develop appropriately. Also, the emergency removal without time for egress of the fluid may complicate postnatal management and ventilation strategies. FETO is not risk-free, it has some potential complications like trichomegaly, tracheomalacia, preterm premature membrane rupture, chorion-amnion separation and preterm delivery [20].

Delivery

After CDH diagnosis, it is advised that routine monitoring has to be performed to assess the severity of the diaphragmatic defect, identify and prevent clinical deterioration and enable delivery planning. There are no evidence-based studies that support planned cesarean section for CDH but the main consensus for CDH delivery in that every effort should be made to deliver at a high-volume specialist center equipped for neonatal stabilization. Perinatal management of CDH neonates plays a crucial determinant of survival in this patient population [3,21].

Ventilation

In CDH newborns with respiratory distress, immediate endotracheal intubations is preferred to bag-valve-mask ventilation, to minimize the risk of intestine insufflation, this risk is diminished by gastric decompression that is achieved by insertion of a nasogastric tube. Judicious sedation is recommended for CDH patients requiring mechanical ventilation. It is not indicated deep sedation unless it is strictly necessary, as a neuromuscular blockage can impair respiratory function, decrease lung compliance, and increase oxygenation indices.

It has been hypothesized that exogenous surfactants can ameliorate respiratory symptoms in CDH infants with pulmonary hypoplasia. Indeed, surfactant deficiency is a recognized feature of pulmonary hypoplasia associated with CDH, but this is thought to be proportional to lung size. Accordingly, the current guidelines do not recommend its use [22].

Hemodynamic support

Hemodynamic instability is commonly encountered in the CDH neonate, continuous monitoring of hemodynamic status should be initiated in the neonatal phase, with an assessment of arterial and venous saturation and echocardiography. Those patients can exhibit decreased cardiac output as a result of increased vascular resistance and ventricular dysfunction. For patients with clinical hypoperfusion, crystalloid therapy and inotropic agents may

be considered, because of the heightened risk of pulmonary edema in this patient population.

Regardless of clinical hemodynamic status, the Canadian CDH Collaborative recommends that all CDH neonates undergo at least two standardized echocardiograms- one baseline assessment within 48 h of birth and the second between 2 and 3 weeks of life. Important prognostic can be inferred from the severity of pulmonary hypertension at 2 weeks of life, including short-term pulmonary morbidity and mortality [23].

ECMO

The primary role of extracorporeal life support in critically ill CDH neonates is as a respiratory and/or circulatory bridge to later surgical repair. Compared to the general neonatal respiratory population requiring ECMO, CDH neonates have the lowest survival rates. Extracorporeal life support organization actually suggests that the survival of CDH patients with ECMO has declined over recent decades. Despite the lack of conclusive evidence, ECMO continues to be offered to CDH patients at specialist centers. It may be considered as a therapeutic option where available, but with full disclosure during prenatal counseling that it carries no established survival benefit [16,17].

Management of pulmonary hypertension

A number of pulmonary vasodilators have been investigated for pulmonary hypertension in CDH. Inhaled nitric oxide is recommended for confirmed systemic pulmonary arterial hypertension with preserved left-ventricular function. When pulmonary hypertension is refractory to inhaled nitric oxide, Sildenafil may be considered as an alternative therapy. Milrinone is indicated where pulmonary hypertension accompanies cardiac dysfunction. To maintain or restore ductus arteriosus patency, prostaglandin E may be used, by reducing right ventricular afterload in patients with pulmonary hypertension and right-ventricular failure [19,21].

Long-term multidisciplinary surveillance

After the surgical repair of CDH, patients need multidisciplinary surveillance because the disease can be associated with neurodevelopmental, gastrointestinal, cardiorespiratory, musculoskeletal and auditory sequelae. As a clinical practice guideline, many institutions refer to the American academy of pediatrics' recommendations for post-discharge follow-up of infants with CDH. The recommendations include several assessments of the newborn, which include radiography of the chest and brain, and evaluation of the gastrointestinal and musculoskeletal systems. In addition, it is recommended to be performed development and auditory clinical evaluation, as well as immunization of the newborns diagnosed with CDH [19].

CONCLUSION

The prediction of neonatal outcomes and morbidity is possible based on prenatal imaging. Ultrasonographic assessment remains heterogeneous and should improve for prenatal treatment because not all CDH fetuses are eligible to receive the prenatal intervention. The management of a neonate with CDH is a complex endeavor that necessitates multidisciplinary management. Over time morbidity has not changed a lot in spite of the new modalities of treatment. The use of FETO, ECMO, corticoids (betamethasone), exogenous retinoids, phosphodiesterase inhibitors, and exogenous surfactants has improved the management of CDH patients, but we must have some well-designed controlled studies to prove significant benefits. Moreover, survivors require multidisciplinary follow-up and research linking antenatal markers for CDH patients with long-term morbidity is still needed.

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