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Management of prenatally diagnosed congenital diaphragmatic hernia

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SUMMARY

Congenital diaphragmatic hernia (CDH) is a congenital anomaly that presents with a broad spectrum of severity dependent upon components of pulmonary hypoplasia and pulmonary hypertension. While advances in neonatal care have improved the overall survival of CDH in experienced centers, mortality and morbidity remain high in a subset of CDH infants with severe CDH. The most important prenatal predictor of outcome in left-sided CDH is liver position. More precise and reproducible prenatal predictive parameters need to be developed to allow standardization of results between centers and appropriate design of clinical trials in CDH. Thus far, all randomized trials comparing prenatal intervention to standard postnatal therapy have shown no benefit to prenatal intervention. Although recent non-randomized reports of success with balloon tracheal occlusion (and release) are promising, prenatal therapy should not be widely adopted until a well-designed prospective randomized trial demonstrating efficacy is performed. The increased survival and subsequent morbidity of CDH survivors has resulted in the need to provide resources for the long-term follow-up and support of the CDH population.

1. Introduction

Congenital diaphragmatic hernia (CDH) is a developmental defect in the diaphragm that allows abdominal viscera to herniate into the chest. CDH occurs in 1 out of 2200 births. The majority of affected neonates will present in the first few hours of life with respiratory distress that may be mild or so severe as to be incompatible with life. With prenatal diagnosis and advancements in neonatal care, survival has improved but there remains a significant risk of death and complications in infants with severe CDH. Fetal diagnosis of CDH has revolutionized postnatal care by both educating families and preparing the health care teams towards eventual delivery of the CDH patient, but the spectrum of severity in CDH has made standardization of prenatal and postnatal care and patient selection for prenatal intervention persistent challenges.

2. Pathogenesis

CDH is a simple anatomic defect, i.e. an opening in the diaphragm, that leads to devastating physiologic consequences. The pathophysiology of CDH is comprised of both fixed (pulmonary and vascular hypoplasia) and reversible (pulmonary vascular reactivity) components. Because the herniation of abdominal contents through this opening coincides with a critical period of lung development when bronchial and pulmonary artery branching occurs, lung compression by the herniated viscera and bowel results in pulmonary hypoplasia. A lung with severe hypoplasia has fewer branch points and therefore fewer airways, arteries, veins and alveolar structures than a normal lung. This results in fixed increased vascular resistance and decreased surface area for gas exchange.[1,2] Lungs in severe CDH also have markedly abnormal pulmonary vasculature. The peripheral pulmonary arteries are hypermuscular, with a thickened medial muscular layer that extends further distally on the arterioles than normal. This increased muscularity results in increased pulmonary vasoreactivity and clinical lability. As hypoxemia and acidosis stimulate further pulmonary vasospasm, a 'vicious cycle' is initiated with rapid clinical deterioration of the patient and inability to ventilate using conventional techniques.[3]

3. Prenatal diagnosis

Most cases of CDH are diagnosed prenatally. Thoracic lesions that should also be considered when the diagnosis of CDH is made prenatally by ultrasound include diaphragmatic eventration, congenital cystic adenomatoid malformation, bronchopulmonary sequestration, bronchogenic cysts, bronchial atresia, enteric cysts and teratomas. The definitive sonographic diagnosis of fetal CDH relies on the visualization of abdominal organs in the fetal chest. The sonographic hallmark of a left-sided CDH is a fluid-filled

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stomach just behind the left atrium and ventricle in the lower thorax as seen on a transverse view. Other sonographic features that imply the presence of left-sided CDH include the absence of the stomach below the diaphragm, mediastinal shift to the right and a small abdominal circumference. Right-sided CDH is more frequently missed or misdiagnosed because the herniated viscera consists predominantly of the right lobe of the liver which may have similar echogenicity to the lung, or be confused with a solid mass in the chest such as a congenital cystic adenomatoid malformation. The liver can usually be directly visualized in the chest cavity. If there is any doubt, the presence of liver in the chest on either side can be conclusively demonstrated by Doppler examination of the hepatic vasculature and umbilical vein. The appreciation of an elongated intra-abdominal portion of the umbilical vein, an abnormal position and bowing of the portal sinus, and visualization of portal venous and hepatic venous branches above the diaphragmatic ridge are all indicative of intrathoracic herniation of the liver.[4] In addition, on a cross-sectional view, a mid-thoracic or posterior thoracic position of the stomach with tissue visualized anteriorly between the stomach and heart strongly suggests liver in the chest. Finally, magnetic resonance imaging (MRI) is routinely used in many centers and can clearly visualize the extent of liver herniation.

3.1. Prenatal prediction of CDH severity

A complete and accurate assessment of the fetal patient with CDH includes high resolution ultrasound, fetal MRI scan, echocardiography and amniocentesis for fetal karyotype assessment between 20 and 24 weeks of gestation. This allows for maximal information to be obtained from the imaging studies and allows comprehensive non-directive counseling regarding CDH, including the option of elective termination. In order to provide optimal counseling, accurate prenatal prognostication is essential. Much effort has been directed toward identification of poor prognostic indicators in the fetus with CDH, often with conflicting results that are difficult to reconcile.

3.2. Associated anomalies

The fetus with CDH in association with another major anomaly has a very poor prognosis. Although there are recent reports of survivors of CDH associated with congenital heart disease, all of these reports are of patients with a relatively mild CDH and biventricular cardiac anatomy.[5,6] The infant with severe CDH and univentricular CHD has a near 100% mortality and should be offered comfort care. Familial CDH, bilateral CDH, syndromic CDH and CDH associated with specific genetic abnormalities are all associated with very poor outcomes.

3.3. Liver herniation

In addition to patients with associated anomalies, the next clear poor prognostic factor is the presence of liver herniation. This is the single most reliable predictor of severity and mortality in CDH and has been validated by multiple centers.[7–11] The presence of liver in the chest associated with a left-sided CDH indicates a large defect with early herniation of viscera resulting in severe pulmonary hypoplasia. In our most recent series, mortality of patients with liver up was 65% compared to 7% when the liver was below the diaphragm. Liver position was also highly predictive of the need for extracorporeal membrane oxygenation (ECMO) with 80% of liver up patients requiring ECMO compared to 25% of those without liver herniation.[11]

3.4. Measurements of lung volume

Extensive efforts continue to be made to correlate direct or indirect estimates of lung volume with outcome in CDH. This is complicated due to the relatively poor physiologic correlation between pulmonary vascular bed reactivity and lung volume. Thus, it is unlikely that lung volume alone, even if measured precisely, will ever provide exact correlation with outcome. In fact, this has been demonstrated in neonates, where accurate lung volumes derived from postnatal radiographs correlate poorly with clinical status.[12–14] Nevertheless, we feel that lung volume-based prognostication plays an additive role in counseling patients with CDH, although this role needs to be validated at individual fetal treatment centers.

The most frequently cited measurement is the contralateral lung to head ratio or LHR. The controversy surrounding the utility of LHR measurements is representative of the issues related to all lung volume measurements. As originally described at the University of California, San Francisco (UCSF), the right lung area was calculated with the use of a two-dimensional (2-D) perpendicular linear measurement in millimeters. The area equaled the product of the two longest perpendicular linear measurements, with the anterior–posterior (AP) axia parallel to the sternovertebral body axis. The LHR was calculated by a ratio of right lung area (in square millimeters) to head circumference (in millimeters).[15] Since its original description, the LHR has been claimed to be highly reliable as a prognostic indicator by several groups[9,16,17] and of minimal or no value by others.[18,19] Part of this may be explained by lack of standardization of the measurement (for instance, some groups have measured the greatest AP and lateral dimensions of the lung rather than the parameters above) and by clear operator variability, which is related to the volume of cases seen and experience of the sonographer. Another problem is the practice of taking other centers' criteria and applying them out of context to one's own center. The predictive value of the LHR is likely to depend upon the postnatal care provided and survival data for a given center. Given that the postnatal care and survival can vary considerably between centers, it follows that the value of the LHR can only be validated within a center by the generation of data on a particular center's own patient population over time. Finally, over the past two decades, postnatal care has changed markedly for the newborn with CDH. The introduction of delayed repair, permissive hypercapnia (or gentilation), ECMO and a focus on treatment of pulmonary hypertension and cardiac decompensation has impacted on survival in many centers. Thus, LHR as a predictor of mortality becomes a moving target. As mortality improves, LHR becomes less predictive. This has been most evident in single center data from UCSF and CHOP (Children's Hospital of Philadelphia)[11,20] over the years. As our survival has improved, the LHR number that predicts low survival has been moving downward. Currently at CHOP, we do not consider LHR to be independently predictive of survival or need for ECMO. The predictive value of the LHR independent of liver in the chest is not predictive early in gestation (less than 24 weeks), and the additive predictive value when combined with liver in the chest is not statistically significant.[11] Thus, the LHR value in our institution is simply confirmatory of likely severity of a CDH but, in contrast to the past, no longer considered independently predictive of survival or major morbidities.

As LHR is a 2-D estimate of lung size, it is logical to think that perhaps a 3-D lung volume calculation would have higher predictive value. There have been a number of recent reports from several centers utilizing MRI-based volume rendering.[21–27] Modern MRI technology, which allows very rapid scanning and acquisition of closely spaced images, has resulted in the ability to render lung volumes accurately.