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Review

Controversies in the management of severe congenital diaphragmatic hernia

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SUMMARY

Despite years of progress in perinatal care, severe congenital diaphragmatic hernia (CDH) remains a clinical challenge. Controversies include almost every facet of clinical care: the definition of severe CDH by prenatal and postnatal criteria, fetal surgical intervention, ventilator management, pulmonary hypertension management, use of extracorporeal membrane oxygenation, surgical considerations, and long-term follow-up. Breakthroughs are likely only possible by sharing of experience, collaboration between institutions and innovative therapies within well-designed multicenter clinical trials.

1. Introduction

The care of the neonate with severe congenital diaphragmatic hernia (CDH) is one of the most challenging, frustrating, and at times rewarding conditions that obstetricians, neonatologists, pediatric surgeons, and other consultants encounter. The disease is widely heterogeneous and therefore many of the studies published which lump the patients together, without stratifying for severity, are misleading. In a disease where all the details matter, and each choice builds upon the next, a successful outcome can become elusive to achieve and difficult to define. The care of the infant with severe CDH is often individualized from center to center. Protocols and guidelines may help establish a baseline of care but adherence can be difficult because of the many passionate and varied opinions. This article will focus on controversies in the care of the infant with severe CDH.

2. Definition of severe CDH

The first challenge in the management of CDH is to accurately define natural history and predict outcome. Several prenatal and postnatal predictors have been suggested to identify the subset of isolated CDH patients that will not survive or will develop severe life-impacting morbidities. Only a few have been confirmed in more than one center. In an era when fetal intervention is considered for the most severely affected cases, the accurate prediction of poor outcome is mandatory for patient selection. Delineating prognostic factors aids caregivers in counseling patients and families in making decisions regarding pregnancy choices and postnatal treatments.

2.1. Prenatal predictors of adverse outcome in isolated CDH

Dr Alexandra Benachi comprehensively reviews the prenatal diagnosis of CDH in this edition of *Seminars*. We focus our discussion on specific markers that define the severe subset of CDH patients. Liver position, determined by ultrasound or magnetic resonance imaging (MRI), is the single most reliable predictor of severity and mortality in CDH and has been validated by multiple centers [1–5]. The presence of liver in the chest associated with a left-sided CDH is indicative of a large defect with early herniation of viscera resulting in severe pulmonary hypoplasia. In our most recent series, mortality with intrathoracic liver position was 65% compared to 7% when the liver was below the diaphragm. It 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 with “liver down” [5]. Other centers further demonstrated that liver herniation also predicted early neonatal morbidity, including need for prosthetic patch repair and prolonged ventilator support [3,6].

For nearly two decades, measures of lung volumes have also been used to predict prognosis in CDH. Initially described by Metkus et al. [7] the lung area to head circumference ratio (LHR) involves an ultrasound measurement of the contralateral lung at the

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level of the four-chamber view of the heart standardized to the head circumference. Though LHR measurements have been validated retrospectively [5,8] and prospectively [9], a number of limitations of LHR have been encountered. First, different methods of LHR measurements (i.e. longest diameter method, anteroposterior diameter method, and tracing method) have been proposed over time, making it difficult to reconcile conflicting results [10]. Second, as with all ultrasonography assessments LHR measurement is observer dependent. Third, LHR may underestimate the actual lung volume in CDH due to compression of the right lung by the mediastinum and herniated viscera in the chest [11]. Fourth, LHR is dependent on gestational age. The lungs grow four times more than the head during pregnancy [12], rendering LHR inadequate for proper evaluation of lung growth at different gestational ages. Finally, improvements in perinatal care are lowering cut-off values of LHR (historically severe CDH defined as LHR <1), and its prognostic value becomes variable and dynamic. In our experience, LHR alone was predictive of survival and need for ECMO, but was not predictive when used in conjunction with liver position or at gestational age <24 weeks [5]. Given the limitation of LHR, recent studies from Europe suggest that the LHR should rather be expressed as function of gestational age [observed (O)/expected (E) LHR]. The O/E LHR can be calculated using a formula specifically developed for this measuring technique and has been validated in 354 fetuses with unilateral isolated CDH in terms of both mortality and morbidity [4,6,12,13].

Parallel to the work being done on ultrasound in the fetus with CDH, research was being conducted on volumetric measurement of the fetal lung by MRI. Whereas the interpretation of the initial data were limited by technical difficulties such as slice thickness, image resolution, etc. [14], more recent studies established and standardized the use of prenatal MRI in evaluating fetal pulmonary hypoplasia. Several investigators found that fetal lung volumes measured by MRI were highly predictive of survival, need for ECMO, complicated neonatal course, and chronic lung disease [15–21]. For isolated left-sided CDH and expectant management, we found that those with an O/E fetal lung volume (O/E FLV) of <25% had 87% mortality rate [20,22]. Mortality significantly decreased for those with O/E FLV of 25–35% (31% mortality) and was the lowest for those with O/E FLV >35% (17% mortality). Nevertheless, many patients with adequate lung volumes for survival, on the basis of gas exchange alone, succumb or have significant morbidity related to the sequelae of unrelenting pulmonary hypertension [23–25]. This raises doubts as to whether prenatal volume assessments will ever provide exact correlation with outcome. What is needed is a more physiologic assessment of pulmonary vascular resistance and/or reactivity. Although the techniques of three-dimensional power Doppler have been applied to evaluate pulmonary vascular anatomy and flow indices later in gestation [26–28], the prognostic value of these new measurements, especially at the gestational ages required for prenatal counseling, must be validated in further studies. Until there is an accurate way to assess the alignment of the pulmonary blood vessels with the alveoli, fetal imaging will be limited in prognostic predictors of postnatal transition.

2.2. Postnatal predictors of adverse outcome in isolated CDH

Similar to the prenatal predictors of disease severity, several postnatal prognostic factors have been investigated with variable results on subsequent validation studies [29–32]. An analysis by The CDH Study Group demonstrated that the size of the defect and the subsequent need of patch repair correlate well with mortality and morbidity [33]. This group also showed that not only did the patients requiring a patch repair have a higher risk of mortality compared to patients undergoing primary repair (21% vs 5%; $P < 0.001$), but that within the group of patients requiring a patch the odds of dying were 14-fold higher (95% CI: 10.35–19.13; $P < 0.001$) than in those with a near absence of the diaphragm compared to the primary repair group. Finally, the need for patch repair was strongly associated with the duration of mechanical ventilation and length of NICU stay [33]. Similar results have been recently published by Brindle et al. [34] demonstrating a 17-fold increase in mortality comparing for CDH patients requiring a patch compared to primary repair. Length of hospitalization, duration of ventilator support, need for ECMO, feeding difficulties, reflux disease, and prolonged oxygen requirement were also significantly higher in the patch group ($P < 0.01$). Defect size and need for patch is likely to be a surrogate for underlying pulmonary hypoplasia. Theoretically a large defect allows evisceration of more abdominal viscera into the chest, resulting in worse compression. Toxicology animal models have supported this hypothesis where timing of the insult contributes to the size of the defect and impacts outcome [35], as well as in the fetal lamb model in which creation of a larger defect earlier in gestation is associated with severe pulmonary hypoplasia [36].

A clinical scoring system has recently been developed using data from the CDH Study Group [32]. The prediction of outcome is based on 5 min Apgar scores, and several other factors including birth weight (measure of prematurity), presence of chromosomal or major cardiac anomaly, and the presence of pulmonary hypertension. Preliminary results suggest that this model was able to reliably identify infants at low risk from those with either moderate or high risk for mortality [32]. The scoring system was brought forth as a way to predict children who need to be transferred to high-volume centers. We strongly argue that all CDH babies should be cared for in high-volume centers. A score that is applied after birth prevents the neonate from receiving the highest level of care from the beginning, in the critical first few minutes and hours of life.

Another postnatal and potentially more important factor than pulmonary hypoplasia is pulmonary hypertension in patients with CDH. Dillon et al. [24] reported no survivors among eight infants with persistent systemic or suprasystemic pulmonary artery pressure at six weeks of age. More recently, Wynn et al. [25] on behalf of the DHREAMS (Diaphragmatic Hernia Research & Exploration; Advancing Molecular Science) study assessed the clinical outcome of 220 patients. The mortality for CDH children with mild pulmonary hypertension, defined by echocardiography, at the time of discharge was 1%, those with moderate 7%, and for those with severe 56% ($P < 0.0001$). As expected, pulmonary hypertension was associated with all factors known to be predictive of dismal outcome: need for patch, need for ECMO, and presence of major associated chromosomal and structural anomalies [25]. Given the impact of pulmonary hypertension on the CDH outcome, it is not surprising that the research focus has shifted towards early identification of pulmonary hypertension and its specific pathophysiological mechanisms. Keller et al. [37] reported on the role of endothelin, a potent vasoconstrictor and smooth muscle cell mitogen, and persistent pulmonary hypertension during the first four weeks of life in CDH patients. They found that endothelin indeed has a potential role in the pathophysiology of severe CDH. They demonstrated that infants with CDH and a poor outcome had higher plasma endothelin levels and more severe PH than infants discharged home. Furthermore, the severity of pulmonary hypertension was associated with endothelin levels [37]. Along those lines, the same group explored the correlation of elevated B-type natriuretic peptide (BNP) plasma levels, an established biomarker of right ventricular pressure overload and pulmonary hypertension. They demonstrated that elevation of BNP levels on day of life 1 is highly predictive of pulmonary hypertension and poor outcome