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Review

Current concepts on the pathogenesis and etiology of congenital diaphragmatic hernia☆

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ABSTRACT

This review outlines research that has advanced our understanding of the pathogenesis and etiology of congenital diaphragmatic hernia (CDH). The majority of CDH cases involve incomplete formation of the posterolateral portion of the diaphragm, clinically referred to as a Bochdalek hernia. The hole in the diaphragm allows the abdominal viscera to invade the thoracic cavity, thereby impeding normal lung development. As a result, newborns with CDH suffer from a combination of severe pulmonary hypoplasia and pulmonary hypertension. Despite advances in neonatal intensive care, mortality and serious morbidity remain high. Systematic studies using rat and transgenic mouse models in conjunction with analyses of human tissue are providing insights into the embryological origins of the diaphragmatic defect associated with CDH and abnormalities of developmentally regulated signaling cascades.

1. Overview

Congenital diaphragmatic hernia (CDH) is a developmental anomaly occurring in approximately 1 in 2500 live births (Harrison et al., 1994; Stege et al., 2003). Despite having a similar incidence to more readily recongizable diseases such as cystic fibrosis, CDH is not well known outside the realm of neonatology where it is a major clinical concern. A primary characterization of CDH is that the diaphragm fails to form properly during embryogenesis. Normally, the diaphragm develops to form a continuous sheet that completely separates the thoracic and abdominal cavities prior to the major period of internal organ growth. However, in the instance of CDH, a significant proportion of the diaphragm is absent. Posterolateral hernias (referred to as Bochdalek hernias) are the most common hernia type (>80%) with the majority occurring on the left side (85%); less frequently on the right side (13%) or bilateral (2%) (Torfs et al., 1992; Veenma et al., 2012). As a consequence of the abnormal diaphragm openings, the developing abdominal viscera can invade the thoracic cavity, occupying space normally reserved to accommodate the growing lungs (Fig. 1). Further, the loss of a continuous diaphragmatic muscle markedly impairs fetal breathing movements that are necessary for proper stretch-induced lung maturation. As a result, newborns with CDH suffer from a combination of severe pulmonary hypoplasia and pulmonary hypertension (Harrison et al., 1994; Karamanoukian et al., 1995; Wilcox et al., 1996).

Survival rates can vary widely amongst various treatment centers with an overall average of 68% (Tsao and Lally, 2012). However, mortality rates are significantly higher when stillbirths, therapeutic abortions and spontaneous abortions are included (Brownlee et al., 2009; Mah et al., 2009). There is often significant morbidity in survivors that includes bronchopulmonary dysplasia, restrictive and obstructive lung diseases, scoliosis, gastroesophageal reflux, neurodevelopmental deficits, and neurosensorial deafness (Kotecha et al., 2012; Tovar, 2012). In approximately 50% of cases, the diaphragm defect and lung hypoplasia are the only significant anomalies. In remaining cases there are clear non-pulmonary congenital anomalies (e.g. intestinal malrotation, left heart hypoplasia) and in 5–10% of cases there is a chromosomal etiology (e.g. Denys–Drash Syndrome, trisomy 18). Treatment strategies include nitric oxide administration, high frequency oscillatory ventilation, extracorporeal membrane oxygenation, exogenous surfactant administration, fetal trachea occlusion and surgical repair of the diaphragm.

2. Rodent models of CDH

An animal model of CDH arose in the 1970s from toxicological studies showing that the herbicide nitrofen (2,4-dichloro-phenyl-p-nitrophenyl ether), while relatively harmless to adult rodents, caused developmental anomalies in the lungs, hearts, diaphragms and skeletal tissues of fetal rats (Ambrose et al., 1997). Diaphragmatic defects resulting from a single dose of nitrofen administered

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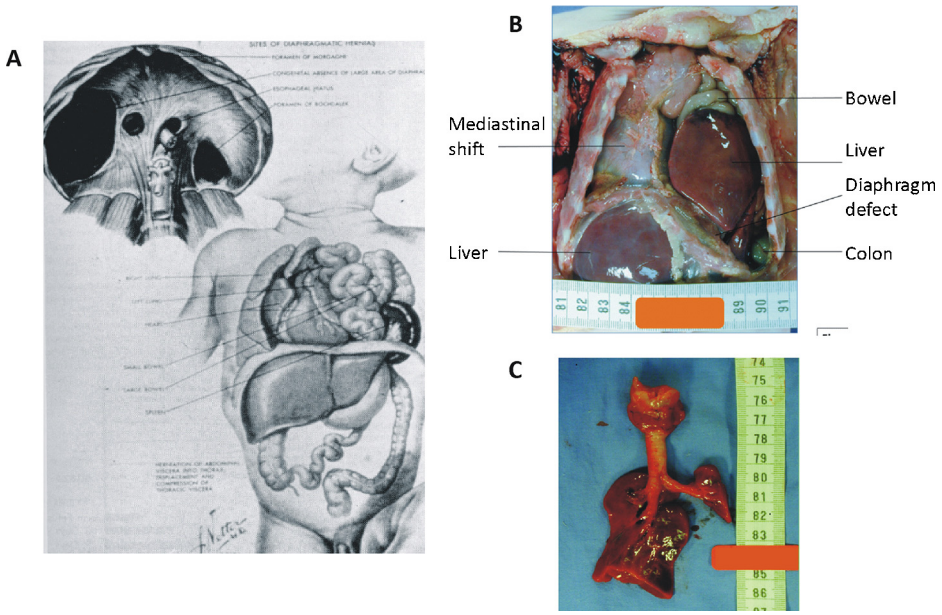

Fig. 1. (A) Drawing showing the general defects associated with congenital diaphragmatic hernia (CDH). Adapted from Skandalakis et al. (1994). (B) Photograph from an autopsy showing the significant invasion of the thoracic cage by abdominal contents through the defective diaphragm tissue (left-sided defect). (C) This results in severe lung hypoplasia of the left lung.
Adapted from Kotecha et al. (2012).

to pregnant rats are remarkably similar to those documented in human Bochdalek CDH, with respect to the size and location of the defect (Fig. 2B). Subsequently, three other CDH-inducing compounds with structural similarities to nitrofen were characterized (Mey et al., 2003; Greer et al., 2000). The timing of administration of all of the CDH-inducing teratogen is critical. Rodents are most susceptible between embryonic day (E9)–12, a developmental window corresponding to gestational weeks 4–6 in humans. Further, if the teratogens are delivered on E8–9 then left-sided defects are more prominent whereas E10–12 administration results in a predominance of right-sided defects. The laterality effects and the reason that left-sided defects are more prominent in human CDH cases are not understood. Presumably, there are slight differences in the timing of developmentally regulated signals in the left versus right side of the primordial diaphragm.

A vitamin A deficient model of CDH has also been characterized. Rats are rendered deficient through-out gestation (~21 day gestation period) except for E8–10 when exogenous retinoic acid maintains heart development and thus viability (Kaiser et al., 2003). As shown in Fig. 2C, this results in the induction of diaphragmatic

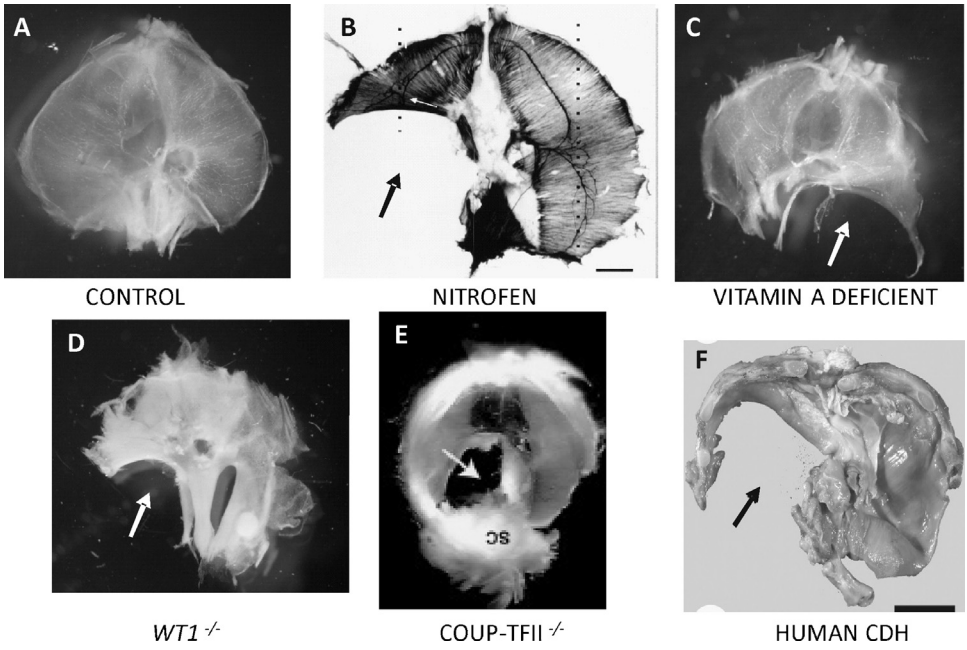

Fig. 2. Photomicrographs of whole diaphragms isolated from a (A) control rat, (B) nitrofen-treated rat, (C) vitamin A deficient rat, (D) *Wt1* null-mutant mouse, (E) COUP-TFII mutant mouse and (F) human CDH case showing representative examples of diaphragm defects (arrows). Diaphragms are oriented such that the top of the image is anterior and the bottom of the image is posterior. Note that the diaphragm defects in all models are consistently located in the posterolateral corner of the diaphragm, consistent with human cases of Bochdalek CDH.