Congenital diaphragmatic hernia in the neonate

Hannah King MB ChB FRCA
Peter D Booker MBBS FRCA MD

The prevalence of congenital diaphragmatic hernia (CDH) ranges between 1:2000 and 1:4000 live births; it accounts for 8% of all major congenital anomalies. Recurrence risk for a subsequent pregnancy is estimated at 2%.[1] Approximately 90% of diaphragmatic defects occur posterolaterally and 80% are left-sided. The severity of the condition varies widely, the degree of pulmonary hypoplasia and pulmonary hypertension largely determining outcome. After recent advances in the care of these patients, several centres are now reporting survival rates >80%. This improved survival is ascribed to increased knowledge of the pathophysiology of the condition and, consequently, better perioperative management.

Aetiology

The aetiology of CDH is unclear in most cases; only 2% occur with a familial association, though various chromosomal abnormalities may be identified in up to 15% of cases. Recent studies have suggested that the region 15q26 is critical for normal diaphragm development. CDH may occur as part of a syndromic genopathy; the most common genetic associations include trisomies 13, 18 and 21. About 40% of patients with CDH have associated major congenital anomalies (Table 1). Patients with major associated anomalies have a much poorer outcome than patients with isolated CDH.[2]

Experimental evidence suggests that pulmonary hypoplasia arises during the embryonic stage of gestation, prior to the development of the fetal diaphragm. One dose of the herbicide nitrofen, when administered to rodents in early pregnancy, consistently induces pulmonary hypoplasia and CDH in a high proportion of their offspring. Studies using this animal model suggest that CDH is attributable to a primary disturbance of pulmonary growth into the pleuroperitoneal canal, and consequent inhibition of growth of the embryonic diaphragm. In this model, both contralateral and ipsilateral lungs are (variably) hypoplastic; ipsilateral lung growth is further impaired at a later stage of gestation by mechanical compression induced by the presence of abdominal organs in the thoracic cavity, interference with fetal breathing movements, and reduction in the secretion of fetal lung fluid.[3]

Table 1 Relative frequency of the main anomalies occurring in infants with congenital diaphragmatic hernia and an associated major anomaly[3]

Cardiac anomalies	**52%**
Ductus arteriosus	
Septal defects	
Atrioventricular valve defects	
Aortic arch hypoplasia	
Musculoskeletal	**20%**
Hypodactyly	
Long bone aplasia	
Talipes	
CNS anomalies	**11%**
Leukomalacia	
Microcephaly	
Cerebral palsy	
Genitourinary	**5%**
Hypospadias	
Renal dysplasia	

Pathophysiology

The affected lung is intrinsically abnormal, all stages of lung development being affected. Lungs from fetuses and children with CDH have underdeveloped airways, abnormal differentiation of type II pneumocytes, and a reduced number of pulmonary arteries per unit lung volume. Intrapulmonary arteries become excessively muscularized during gestation with thickened adventitia and media; moreover, muscularization extends more peripherally. These pulmonary vessels display an abnormal response to vasoactive substances.

Antenatal diagnosis

Routine ultrasound scans of pregnant women in the second trimester have increased the antenatal detection rate of CDH. A recent European study reported a 59% antenatal detection rate; the average gestational age at diagnosis was 24.2 weeks. Typical findings are the

Key points

The aetiology of congenital diaphragmatic hernia is unclear, although 2% is familial and 15% of patients have chromosomal abnormalities.

Experimental evidence suggests that pulmonary hypoplasia is the primary defect in congenital diaphragmatic hernia.

After antenatal diagnosis, cases should be referred to a regional centre for ongoing antenatal care and delivery.

Recent improvements in survival are related to better perioperative management.

Long-term follow-up is essential, owing to ongoing morbidity.

Hannah King MB ChB FRCA
Research Fellow in Paediatric Anaesthesia
University of Liverpool
(Honorary) Consultant Paediatric Anaesthetist
Royal Liverpool Children's Hospital
Eaton Road
Liverpool
L12 2AP

Peter D Booker MBBS FRCA MD
Senior Lecturer in Paediatric Anaesthesia
University of Liverpool
(Honorary) Consultant Paediatric Anaesthetist
Royal Liverpool Children's Hospital
Eaton Road
Liverpool
L12 2AP
Tel: 01512 525223
Fax: 01512 525460
Email: peterdb@liv.ac.uk
(for correspondence)

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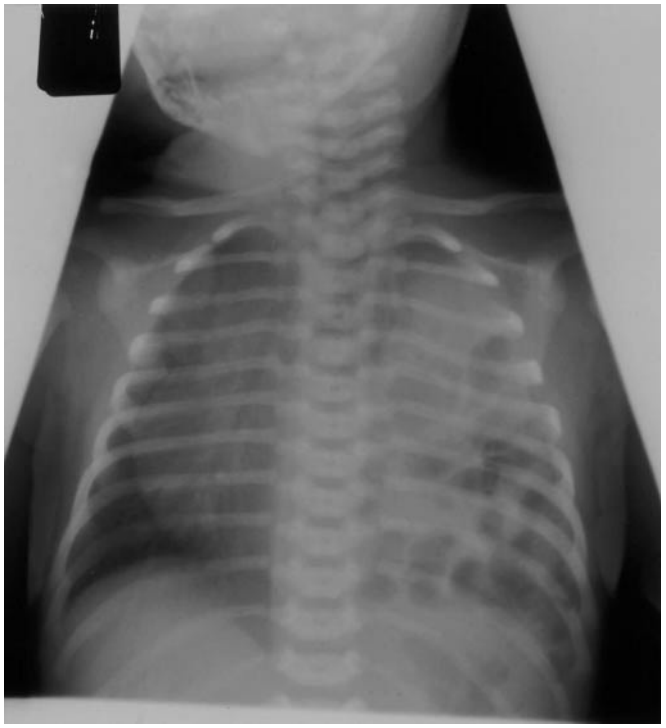

Fig. 1 Typical chest x-ray findings of a left-sided congenital diaphragmatic hernia, showing mediastinal shift and multiple loops of bowel in the left thoracic cavity.

presence of the stomach or loops of bowel within the thoracic cavity—ideally level with the 'four-chamber' view of the fetal heart, along with mediastinal shift away from the side of the lesion. The diagnosis can be missed if the stomach is not in the thorax; right-sided defects are also more difficult to diagnose. Once CDH has been diagnosed, a referral to a tertiary centre should be made for further investigation and prenatal counselling.

Counselling and prognostic indicators

Accurate antenatal counselling requires prognostic indicators of neonatal outcome. Association of CDH with major cardiac or skeletal anomalies is associated with a relatively poor prognosis, so fetal echocardiography in these cases is mandatory. Exclusion of a chromosomal abnormality may require amniocentesis. For isolated CDH, the indices of poor prognosis are less well defined. Most specialized centres will attempt to estimate lung volume using three-dimensional ultrasound or MRI, as the degree of pulmonary hypoplasia largely determines outcome.

Prenatal management

Morphological and biochemical immaturity of the affected lung in patients with CDH suggest that surfactant deficiency may play a role in the pathophysiology of the condition. However, a recently published large-scale controlled study has showed that exogenous surfactant therapy is not associated with a beneficial impact on survival, need for ECMO, or incidence of chronic lung disease in term infants with no other major anomalies.[4]

Similarly, the beneficial effects of prenatal use of corticosteroids for infants with CDH remain unproven. Experimental studies involving CDH animal models have shown that corticosteroids result in accelerated synthesis and release of surfactant and improvement in lung morphology and compliance. Small case series have reported a favourable effect of steroid administration prior to birth in infants with CDH, but the potential benefits of improved lung function may not outweigh the risks to other vital organ development. The results of an ongoing multicentre, randomized, controlled trial by the CDH Study Group that is evaluating the use of betamethasone are awaited with interest.

Fetal surgery for CDH was conceived when postnatal mortality was very high and the aetiology was thought to be attributable solely to compression of the lung by abdominal contents. It was postulated that repair of the hernia antenatally would permit lung growth and result in improved survival. Open fetal surgery with hysterotomy was associated with a high incidence of fetal demise from surgical technical difficulties and preterm labour. Recent innovations involve surgical occlusion of the fetal trachea, which results in gradual distension of the hypoplastic lung with fetal lung fluid. Open tracheal occlusion has been superseded by a fetoscopic approach, with the occlusive balloon being removed just before delivery. However, a recent randomized, controlled trial of tracheal occlusion in fetuses with no liver herniation demonstrated no survival benefit over standard postnatal therapy.[5] Nevertheless, the most severely affected fetuses with liver herniation are a subgroup that may benefit from this *in utero* intervention.

Postnatal resuscitation and stabilization

Routine Caesarean delivery of prenatally diagnosed CDH infants does not confer any benefits over vaginal delivery; hence, the mode of delivery should be decided solely by obstetric considerations. Delivery should be as close to term as possible to maximize pulmonary maturity and in a centre that has the experienced personnel and resources necessary to care for the critically ill neonate. After delivery, aggressive bag and mask ventilation should be avoided to prevent gut distension. The infant should be intubated and ventilated; a large bore nasogastric tube is passed to decompress the intrathoracic bowel. Barotrauma, which will further damage the hypoplastic lung, must be avoided; peak inspiratory pressures should not exceed 25 cm H_2O. $F_{I_{O_2}}$ should be adjusted so that preductal arterial saturations (Sa_{O_2}) are >85%. Once these initial procedures have been performed, the neonate can be transferred to the paediatric intensive care unit (PICU) where arterial and central venous access is established and routine tests, including arterial blood gases and a chest x-ray, are performed (Fig. 1).

Aspects of PICU care

Recent improvements in the survival rate of infants with CDH have been attributed to changes in several aspects of PICU care. Moreover, it has become clear that the timing of surgery *per se* does not affect survival: optimization of clinical parameters before embarking on surgical repair is necessary to ensure the best outcome for the patient.

Mechanical ventilation

Ventilatory support remains the most important aspect of the postnatal management of infants with CDH and recent attention has focused on methods of improving oxygenation while avoiding injury to the hypoplastic lung. In the past, aggressive hyperventilation and the resulting induced alkalosis were used to reverse or eliminate ductal shunting in infants with pulmonary hypertension (PHT). This approach has never been shown to improve outcome; indeed, evidence from postmortem studies suggests that pulmonary barotrauma and damage to the hypoplastic lung may have contributed to the high mortality rate.[6]

In 1985, Wung and colleagues described a ventilatory care strategy in term infants with persistent foetal pulmonary circulation and severe respiratory failure. The aims were to obtain adequate tissue oxygenation and to minimise barotrauma. This was achieved using 'gentle ventilation' with limited inspiratory pressures, permissive hypercapnia, and allowing spontaneous respiration. Ten years later, the same group published a retrospective review of their experience of infants with CDH; they demonstrated an increase in survival and decreased use of extracorporeal membrane oxygenation (ECMO) associated with the use of this respiratory care strategy and delayed surgical repair. Since then, most centres that have achieved high survival rates have followed the same principles: limiting the peak inspiratory pressures to <25 cm H_2O; maintaining a preductal Sa_{o_2} of $>85\%$; and tolerating hypercapnia.

Controversy still exists regarding the use of high-frequency oscillatory ventilation (HFOV) in the management of infants with CDH. HFOV can provide adequate gas exchange when using mean airway pressures no higher than 15 cm H_2O. The technique has been used as both a rescue therapy when conventional ventilation fails and as the primary modality of ventilation. Several small series have shown improved outcome in comparison with historical controls. However, there are no randomized, controlled trials comparing the technique with conventional ventilation in association with permissive hypercapnia. Surgical repair has also been successfully performed while using HFOV.

Certainly, survival in infants with CDH has improved considerably since the avoidance of hyperventilation and barotrauma, whether this 'gentle ventilation' is achieved using conventional ventilation or HFOV.[6]

Management of pulmonary vascular tone

All infants with CDH have an abnormally high pulmonary vascular resistance. An echocardiogram should be carried out to estimate the severity of PHT. The typical findings associated with PHT include flattening of the interventricular septum, tricuspid regurgitation, and a right-to-left or bidirectional shunt at the ductus arteriosus. Right ventricular pressures can be estimated using the tricuspid regurgitation jet. Systemic pulmonary artery pressures, occurring at any time during the perioperative period, are associated with a worse prognosis.

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator that has been shown to improve oxygenation in infants with persistent PHT of the newborn. However, a large randomized, controlled trial of iNO in infants with CDH showed no difference between groups in need for ECMO or survival rate.[7] Nevertheless, infants with elevated right heart pressures may benefit from a therapeutic trial of iNO as it may improve the function of a failing right ventricle. However, its use should be withdrawn if there is not a quantitative reduction in right ventricular pressures on subsequent echocardiographic examination.

Extracorporeal membrane oxygenation

ECMO has been used both as a rescue therapy in those with severe hypoxia after surgical repair and in the stabilisation of infants before and during surgery. Several institutions have reported improvements in survival associated with the use of ECMO, but equally good survival also occurs in centres that do not use ECMO. Long-term morbidity is greater in infants with CDH treated with ECMO compared with: (i) neonates treated with ECMO for other diagnoses; and (ii) those with CDH who did not require ECMO. A Cochrane review on the use of ECMO in newborn infants with potentially reversible respiratory failure concluded that, although infants with CDH showed short-term benefits, the long-term benefits of improved survival without major morbidity were less clear. A recent large UK study showed that infants who had received ECMO for CDH had a significant mortality in the first year of life, and there was long-term physical and neurodevelopmental morbidity in the majority of survivors.[8]

Surgical repair

Surgical repair of CDH was treated as a neonatal emergency up until the 1980s. However, repair of the defect does not result in an improvement in gas exchange, and thoracic compliance and $PaCO_2$ tend to deteriorate in the immediate postoperative period. Most centres now delay surgery for at least 24–48 h after admission, to allow for a period of clinical stabilization and a fall in pulmonary vascular resistance. Surgery may be delayed further if the infant has significant PHT despite appropriate treatment; there is no evidence that timing of surgery affects outcome.[9]

Repair is usually achieved via an abdominal incision with gentle reduction of the abdominal viscera from the thorax. The diaphragmatic defect is either closed by primary repair or, in the case of a large defect, using a prosthetic patch. If there is difficulty closing the abdominal wound because of adverse changes in thoracic compliance, a prosthetic patch may also be incorporated into

the abdominal wall. Minimally invasive surgical repair has been carried out successfully in older children and adults with CDH. However, this approach is not appropriate in the neonate because of a high failure rate and the necessary gas insufflation results in further elevation of the Pa_{CO_2} and aggravation of respiratory acidosis.

Long-term outcome

As improvements in neonatal management result in more marginal infants surviving, long-term follow-up of survivors of CDH is essential and best achieved in a multidisciplinary clinic. Commonly encountered problems include chronic lung disease, gastroesophageal reflux, poor weight gain, neurodevelopmental delays (including hearing problems) and hernia recurrence.

An evaluation of the pulmonary morbidity of 100 survivors showed that the need for ECMO and the presence of a patch repair were predictors of more significant morbidity but that even non-ECMO CDH survivors frequently had ongoing pulmonary morbidity. A study of long-term survivors (mean age 8.15 yr) of mild to moderate CDH, none of whom had significant respiratory symptoms, showed that lung perfusion was impaired in 20% and that 45% had mild to moderate derangement of pulmonary function.[10] All the studied children had normal cardiac function with no evidence of persistent PHT. The authors concluded that, at the present time, we do not know if the functional derangement is attributable to iatrogenic damage occurring during the neonatal period or is a reflection of the severity of the underlying pulmonary disease.

Nutritional problems remain a source of morbidity for survivors of CDH, the presence of a patch repair being a good predictor of severity. Long-term follow-up studies have shown that gastroesophageal reflux occurs in up to 62% of patients, 56% are below the 25th percentile for weight, 32% require a gastrostomy, and 19% require fundoplication. Approximately half the infants that undergo patch repair of their defect will require surgery for re-herniation within 3 yr.

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