Management of congenital diaphragmatic hernia

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Abstract
Congenital diaphragmatic hernia (CDH) is associated with high mortality due to lung hypoplasia, pulmonary hypertension and co-existent anomalies. This paper highlights recent progress in the perinatal management of CDH and addresses long term outcome issues for survivors indicating the need for multidisciplinary follow up.

Keywords congenital diaphragmatic hernia; fetal therapies; minimally invasive surgery; outcomes

Introduction

Definition and aetiology
Congenital diaphragmatic hernia (CDH) is a defect in the fetal diaphragm allowing the contents of the abdominal cavity to protrude into the thorax. CDH has an incidence of 1 in 2500 live births in the UK. The birth defect may be associated with other major anomalies and the lesion may become apparent in the fetus, newborn or older child. Some forms of CDH remain asymptomatic and may not present until adulthood.

The majority of defects are sporadic and isolated (70%) with a number of gene mutations identified, e.g. Deletions of 4p, 8q, 15q. Links have been made to environmental factors such as: thalidomide, nitrofen and vitamin A deficiency. CDH may be associated with other chromosomal abnormalities e.g. Fryns’ and Pallister Killian syndromes.

Pathology
The precursors of diaphragm begin development during the 4th week of gestation in the form of the septum transversum and lateral folds of mesenchymal tissue. These partition the abdominal and thoracic compartments with the formation of the pleuropertitoneal membrane occurring by the 8th week. As development continues muscle fibres migrate into this membrane. Failure of these stages of development will result in either a ‘true’ diaphragmatic defect (CDH) or a complete, yet hypoplastatic, diaphragm resulting in a diaphragmatic eventration.

Closure of the right hemidiaphragm occurs before the left, which may account for the higher incidence of left sided diaphragmatic defects (84%). Right diaphragm defects comprise 13% of lesions and 2% are bilateral defects, the remaining cases comprising the rarer variants such as complete diaphragmatic agenesis. The commonest lethal form of CDH is the lesion occurring in the posterolateral aspect of the developing diaphragm notably the Bockdalek hernia with other less common defects e.g. in the anterior-lateral diaphragm notably the Morgagni hernia.

Outcome in CDH remains highly variable with regard to prognosis in comparison to other neonatal surgical conditions, with reported mortality rates varying between 20–60% in centres worldwide. The morbidity and mortality of CDH is traditionally related to the mechanical compression of the herniated viscera on the developing lung leading to pulmonary hypoplasia and pulmonary hypertension. The histological changes seen at post mortem in the underdeveloped ipsilateral lung on the affected side of the defect are also mirrored in the contralateral lung suggesting that what ever insult is responsible for the failure of the diaphragm to develop may also have a global impact on the primordial development of the respiratory system.

Antenatal care (Fetal CDH)

Antenatal diagnosis
Although not always identified in the antenatal period all cases detected prenatally should ideally be referred early to a specialist centre. Antenatal diagnosis allows counselling by a multidisciplinary team (paediatric surgeons, neonatologists and obstetricians) as well as allowing treatment and delivery planning. Antenatal diagnosis has been reported as early as 11th week of gestation, however, in the UK, it is more often diagnosed at the 20 week anomaly scan. Within the wider European region a multicentre study found that 60% of cases of CDH were identified antenatally with a mean gestational age of 24.2 weeks at diagnosis. Recent studies and a systematic review suggest that care in specialist, high volume (more than 5 cases per annum) centres achieve an improved survival rate compared to low volume centres.

Associated anomalies
Antenatal investigations should also attempt to identify any associated anomalies, to permit more accurate counselling, as survival rates in newborns with associated anomalies remains dismal (less than 10%). Amniocentesis is recommended to identify any associated chromosomal anomalies, present in up to 10% of cases, e.g. Trisomies 13,18 & 21, Donnai-Barrow and Fryns syndromes. A thorough sonographic evaluation of the urinary, gastrointestinal and central nervous system should be performed to detect further structural malformations (33%). Echocardiography is utilised to detect cardiac anomalies, present in up to 18% of cases. It may also usefully be deployed to measure pulmonary artery diameters, which have been found to be predictors in some series of postnatal pulmonary hypertension and mortality.

Predicting outcome
Defining antenatal predictors of outcome in CDH has been the subject of intense study over the last few years. Most current
methods rely on indirect techniques, e.g. US/MRI to make an assessment of fetal lung volume. Measurement of the contralateral fetal lung area to head circumference ratio (LHR), using 2D ultrasound (US) imaging, as a predictor of outcome was first proposed by Harrison’s group based at UCSF, San Francisco in the mid 1990’s. LHR gained popularity as a good prognostic marker and led to a randomised clinical trial that guided decision making for fetal intervention in CDH. A systematic review and meta-analysis conducted in 2007 suggested that further refinement with regard to LHR criteria was needed to more accurately predict fetal outcome. More recently LHR measurements have been improved to account for the four fold relative increase of lung area to head circumference that occurs between 12 and 32 weeks in the fetal period. Jani and colleagues (antenatal-CDH registry group) utilising the observed to predicted (O/E) LHR indicated more accurate prognostic scoring in 354 cases of unilateral, isolated CDH.

Aside from determining fetal lung volumes with ultrasound other useful potential markers guiding prognosis antenatally include the presence of liver herniation and the role of fetal MRI lung volumes. Recent studies have shown that fetuses with an increased volume of liver within the thoracic cavity, designated “liver up” cases, are associated with a larger hernia defect, a greater need for prosthetic patch repair and decreased survival.

Fetal intervention
Initial interest in fetal intervention concentrated on open repair of the diaphragmatic defect following maternal hysterotomy. Trials were discontinued due to preterm labour with poor outcome. The dramatic changes seen in lung growth achieved by occluding/plugging the fetal trachea, led to refinements in fetal surgical techniques for CDH. In 2003 Harrison et al, reported a randomised controlled trial of fetal endoscopic tracheal occlusion (FETO) showing equivalent survival to a group of ’high risk’ fetuses managed by conventional postnatal care in specialist CDH centres. This study led to further efforts to improve case selection for fetal intervention using LHR (O/E) entry criteria to identify those with the worse prognosis that may justly benefit from FETO procedures.

Results from recent European programmes using selective entry criteria (O/E LHR less than 27–28% and liver herniation) have found a statistically significant improved survival rate in the FETO treated group in comparison to same severity controls. FETO may therefore have a well defined role in the management of selected, severe fetal cases of CDH. A European randomised trial currently in progress will provide conclusive evidence.

Postnatal care (Newborn management)

Delivery
With an increasing antenatal detection rate of CDH expert opinion regarding the mode of delivery remains a subject of debate. In 2007 the CDH study group interestingly reported a marginal (non significant) survival benefit for elective delivery by caesarean section. Further randomised studies are needed to draw definitive conclusions.

In order to maximise pulmonary development delivery should be planned as near to term (more than 37 weeks) as possible. Delivery should be co-ordinated in specialist centres equipped with full neonatal intensive care facilities with ready access to paediatric surgeons. Elective intubation following birth and ‘gentle’ ventilation (avoiding barotrauma) is recommended. All babies should have a nasogastric tube promptly inserted to avoid gastric distension and vascular access secured to aid delivery of fluids and pharmacological agents. Following stabilisation a full clinical examination is required to exclude associated anomalies. Chest X-ray confirming the diagnosis and echocardiogram is performed to screen for cardiac anomalies.

Postnatal diagnosis – ‘late presenting CDH’
Despite antenatal imaging 40% of patients with CDH remain undetected until after delivery. These cases may present in the immediate newborn period whilst others may remain asymptomatic until later life. Symptoms may include mild respiratory distress or feeding problems. Delayed presentation may occur with small diaphragmatic defects in which there is little or no herniated bowel at birth. Herniation of intestinal viscera as a later dynamic event may follow an episode of increased intra abdominal pressure seen with a respiratory tract infection.

Clinical examination may reveal bowel sounds on chest auscultation. There may be signs of decreased air entry on the affected side and rarely mediastinal shift. Diagnosis is often made on chest X-ray but may require an upper gastrointestinal contrast study for further confirmation.

Stabilisation
‘Gentle’ Ventilation A major advance in the management of CDH in the last 20 years has been the introduction of ‘gentle ventilation’ strategies (permissive hypercapnea) to reduce iatrogenic lung injury from barotrauma. Wung et al, introduced this novel concept characterised by preservation of spontaneous ventilation, permissive levels of hypercapnea (paCO2 60–65mmHg or 9kPa) and avoidance of high inspiratory airway pressures (ideally not exceeding 25 cm H2O) A number of specialist centres are steadily reporting improving outcomes (more than 80% survival) with this approach together with a reduced need for ECMO. High frequency oscillatory ventilation (HFOV) has also been utilised in the perinatal management of CDH both as a ‘rescue therapy’ prior to extracorporeal membrane oxygenation (ECMO) and as a primary ventilatory modality in an attempt to reduce pulmonary barotrauma. There have been several reports of increased CDH survival with HFOV strategies.

Other therapies ECMO has been deployed to treat respiratory failure and pulmonary hypertensive crisis in CDH following failure of conventional therapies. Throughout the 1980’s and early 1990’s ECMO gained momentum in the management of ‘high risk’ newborns with CDH. A UK multicentre randomised controlled trial and a Cochrane review failed to demonstrate significant survival benefits for the use of ECMO in CDH. Currently with the introduction of permissive hypercapnea strategies achieving improved CDH survival there has been a steady decline in the use of ECMO. Many major centres continue to deploy ECMO with variable reported success. Refined entry criteria (ECMO eligibility) may influence outcomes.

Further methods to treat pulmonary hypertension associated with CDH have included the use of inhaled nitric oxide (iNO) and the phospho-diesterase inhibitor sildenafil. A large multicentre randomised controlled trial (NINOS) and a Cochrane review have
Commonly, the development of a pneumothorax or chylothorax is the most Morbidity and benefits of pneumothorax are often achieved using a laparoscopic or thoracoscopic approach. Invasive techniques are described with repair of the diaphragm achieved using a biosynthetic substitute such as Surgisis. More recently, minimally invasive techniques are described with repair of the diaphragm achieved using a laparoscopic or thoracoscopic approach. Benefits include reduced post-operative pain and improved cosmesis. Routine placement of a pleural drain is no longer common practice.

Methods of repair

CDH was once regarded as a surgical emergency with operative repair performed as early as possible after delivery to improve ventilation by reducing the herniated viscera from the thoracic cavity. Currently, it is now accepted that preoperative stabilisation of labile physiology is paramount with delayed surgery scheduled following optimisation of respiratory and cardiac status.

At operation traditionally performed using a subcostal incision the herniated contents are returned to the abdominal cavity and the defect in the diaphragm repaired. In the majority of cases (60–70%) a primary closure can be achieved. In the remaining group a ‘patch’ must be employed to partition the defect. There are a number of different materials available, e.g. Gore-tex, or a biosynthetic substitute — Surgisis. More recently, minimally invasive techniques are described with repair of the diaphragm achieved using a laparoscopic or thoracoscopic approach. Benefits include reduced post-operative pain and improved cosmesis. Routine placement of a pleural drain is no longer common practice.

Morbidity

The development of a pneumothorax or chylothorax is the most common early post-operative complication. A pneumothorax will often present with a sudden deterioration in the cardiac and respiratory parameters of a ventilated patient. Diagnosis of a pneumothorax on a chest X-ray should be made with caution. The lung, on the side of a repaired CDH, will have a degree of hypoplasia and will not fill the hemithorax thereby giving the false impression of a pneumothorax. Post-operative effusions are common, e.g. Chylothorax (28% in some series). The majority of effusions are small and respond to needle thoracocentesis. A recurrent chylothorax may require a pleural drain, orectote and a period of parenteral nutrition.

Compartment syndrome (CS) is rare but must be considered in cases where the volume of herniated abdominal contents returned to the abdomen is large and the diaphragmatic repair is under tension. The risk of developing CS can be minimised by reducing the intra-abdominal pressure. This may be achieved by the use of a diaphragmatic patch and in severe cases an abdominal wall patch.

Overall recurrence rates are approximately 15% in the first two years of life. Risk factors for recurrence include large defect size and the need for a patch. Some long-term studies now report the number of patch repairs requiring revisional surgery at up to 50%.

Outcome and follow up

It remains difficult to accurately report survival data for CDH with rates from 40–80% recorded from different centres. Results from specialist CDH centres show an improvement in survival over recent years, however, population-based studies suggest that this improvement may not include antenatal losses and terminations, the so-called ‘hidden mortality’. With improving survival it is recognised that a corresponding increase in morbidity will be noted in this patient cohort. CDH patients therefore require careful long-term follow up in multidisciplinary clinics as associated morbidity is not solely confined to the respiratory system.

Surgery

Respiratory function

Respiratory function may be impaired as a result of both failure of antenatal development (pulmonary hypoplasia) and postnatal lung injury (secondary to aggressive mechanical ventilation). The prevalence of chronic lung disease (CLD) amongst CDH survivors has been reported to be as high as 50% predominantly affecting ‘high risk’ cases requiring intensive resuscitation and ECMO. CLD and recurrent respiratory infections contribute greatly to the failure to thrive commonly seen in children born with CDH. However, long-term studies have demonstrated that pulmonary function improves as survivors reach adolescence and adulthood.

Gastro oesophageal reflux

The development of GOR is a common problem in CDH survivors, the impact of which is not just limited to feeding difficulties but may exacerbate any respiratory compromise resulting from recurrent aspiration. GOR may be managed with anti-reflux medication but a significant number of CDH survivors will require a fundoplication to manage their symptoms and minimise morbidity.

A Canadian study has reported rates of GOR at 54% in patients having undergone surgery for CDH. A number of theories have been postulated to explain this high prevalence such as defective crura distorting anatomy of the gastroesophageal junction and contributions from a shortened dysmotile oesophagus. Canadian workers found the most significant predictors for the development of GOR were a large defect requiring patch repair or the need for intensive ventilatory support or ECMO.

Neurodevelopmental

Both motor and cognitive deficits are commonly seen in patients with CDH. Long term follow up studies report degrees of neurodevelopmental delay in 30–70% of CDH survivors. A recent North American study looking at survivors in a multidisciplinary clinic at 3 years of life found that 73% of patients had a degree of motor delay (most commonly hypotonia and motor asymmetry), 60% had language problems and 10% had sensory/hearing problems.

It is thought that the neurological morbidity is largely a result of episodes of neonatal hypoxia. Ventilator time and use of ECMO have been found to be statistically significant predictors of future neurological impairment (70% of patients with neurological delay had required ECMO in one study).

Future directions

Steady progress in CDH research has been achieved through better understanding of developmental lung biology including use of experimental CDH models. Genetic studies are steadily helping to identify candidate genes/defective cell signalling. It is still unknown if genetic testing or early intervention will be able to identify high risk cases and whether there is a role for more aggressive ventilation in the most high risk cases.
hoped that through improved knowledge from basic science studies and accumulating clinical experience in managing CDH that we will design and develop better therapies to reduce overall mortality and long term morbidity.

Prenatal intervention in ‘high risk’ CDH with the emergence of FETO may have a defining role in the future with data from a randomised European trial eagerly awaited. Current efforts are energetically focused on identifying the fetus that will most benefit from this procedure. The emerging role of minimally invasive surgery in the treatment of CDH in ‘stable’ newborns and late presenting infants is gaining momentum and may have the potential benefit of reducing early and late morbidity in survivors. Application in ‘high risk’ newborns remains more controversial due to the associated difficulties with ventilation, rising pCO₂ and metabolic acidosis. Advances in anaesthesia and the availability of better instrumentation may allow these techniques to develop a wider role in the future.

Conflict of interest statement

None.

FURTHER READING


Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at term or near term (Cochrane review). Cochrane Database Syst Rev 2001; 4 CD000399.


Practice points

- CDH is a birth defect with high mortality and a wide spectrum of clinical presentation
- The role of fetal intervention (FETO) in ‘high risk’ prenatally diagnosed CDH is currently being evaluated in a European randomised trial
- Outcomes have shown steady improvement through the use of ‘gentle ventilation’ strategies in neonatal units worldwide
- Definitive surgery is scheduled as an elective procedure in the physiologically stable newborn
- Long term follow up studies demonstrate that many patients experience late morbidity indicating a need for multidisciplinary follow up in specialist CDH clinics