Congenital pulmonary lymphangiectasia

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Abstract

Congenital pulmonary lymphangiectasia is a rare condition caused by failure of pulmonary lymphatic vessels to develop normally. It is a known cause of non-immune hydrops fetalis and congenital chylothorax. While it has been recognised in the literature since the 1950s, no standardised treatment has yet emerged and a definitive cause is still unknown. This review seeks to draw together current information on diagnosis, treatment and prognosis, and to recommend that a systemic evaluation of such would provide direction for clinicians in dealing with patients affected by this condition.

Key words

Congenital pulmonary lymphangiectasia, foetal lymphatic development, chylothorax, non-immune hydrops fetalis, pulmonary lymphatics

In 1959, Laurence published an article reporting on 10 cases of stillbirth or neonatal death that showed evidence of dilated pulmonary lymphatic vessels on post-mortem examination. They distinguished this as being a condition distinct and separate from merely being a feature of a generalised lymphatic disorder, and concluded it was likely a congenital disorder due to a developmental defect that resulted in the pulmonary lymphatics maintaining their proportions of approximately 16 weeks gestation. This was the first time the term ‘congenital pulmonary lymphangiectasis’ had been used in a publication. This condition is now generally known as ‘congenital pulmonary lymphangiectasia’ (CPL), but may also still be referred to as congenital pulmonary lymphangiectasis.

In 1970, Noonan et al divided pulmonary lymphangiectasia into three categories: (1) as a feature of a general lymphangiectasis, (2) secondary to a pulmonary venous obstruction, and (3) as a primary developmental disorder. Esther and Barker (2004) proposed defining pulmonary lymphangiectasia as primary or secondary (Figure 1); with primary encompassing developmental abnormalities that are either generalised (part of a general lymphangiectasia involving diverse organ systems), pulmonary (confined to the lungs) or syndromic (associated with unrelated congenital abnormalities); and secondary defining those due to lymphatic or cardiovascular obstruction, or acquired through other means (such as infection). CPL falls within category 3 of Noonan et al’s (1970) classifications, and the primary: pulmonary category of Esther and Barker’s (2004) classification system.

It is now generally postulated that CPL is a result of a failure of the normal regression process of the pulmonary lymphatics, which occurs at approximately 20 weeks of gestation, and it can involve dilation of the subpleural, interlobar, perivascular and peribronchial lymphatic vessels (Bellini et al, 2006; Mele and Sridhar, 2012). Although rare, with studies suggesting that pulmonary lymphangiectasia is present in only 0.5–1% of infants who are stillborn or die in the neonatal period (Esther and Barker, 2004), it is recognised as a cause of both non-immune hydrops fetalis and congenital chylothorax (Dempsey et al, 2005). It can also be a feature in various genetic syndromes, such as Noonan syndrome, Down syndrome and Turner’s syndrome (Lee et al, 2002), and inheritance patterns in non-spontaneous cases include autosomal dominant, autosomal recessive and x-linked (Bellini et al, 2006).

Mutations in specific genes, including forkhead box C2 (FOXC2) and SRY (sex determining region Y) box 18
(SOX18), which are both involved in the development of the lymph vasculature, have been implicated in the causation of pulmonary lymphangiectasia (de Bruyn et al, 2012), and this continues to be an area of research and investigation.

**Diagnosis and investigations**

Table 1 outlines the various diagnostic tests that can be applied to confirm CPL. It may be first detected in the antenatal period through obstetric foetal ultrasound, usually manifesting as hydrops fetalis or polyhydramnios (Esther and Barker, 2004; Dempsey et al, 2005; Bellini et al, 2006). Once CPL is suspected, confirmation can be sought via thoracocentesis, to confirm the presence of chylothorax (Dempsey et al, 2005), or by foetal magnetic resonance imaging (MRI), as proposed by Seed et al (2009). However, the standard criteria for the diagnosis of chylothorax (triglyceride level greater than 110mg per dL) should be treated with caution in the foetus, and also in the neonate not on an enteral feeding regime, due to the potential lack of supply of the chylomicrons required to produce the chyle triglyceride levels (Bellini et al, 2006).

Early presentation of previously undetected CPL can occur within moments of birth, up to several hours afterwards, and is marked by cyanosis, tachypnoea and respiratory distress. Alternatively, an asymptomatic postnatal period can extend for weeks to months, and then present with persistent tachypnoea, cough and wheeze, or with respiratory distress following an acute infection (Esther and Barker, 2004; Delabaere et al, 2008;). Post-birth, high resolution computed tomography (HRCT) may show thickening of the interstitium, ground glass opacity and pleural effusion, and is considered to be one of the most accurate diagnostic tests for CPL (Bellini et al, 2006; Vrielynck et al, 2008; Guillerman and Brody, 2011). Other diagnostic tests include chest X-ray, MRI, lymphangiography, lymphoscintigraphy, thoracocentesis and histological examination (lung biopsy) (Barker et al, 2004; Esther & Barker 2004; Bellini et al, 2008; Gumpeni et al, 2008; Soto-Martinez and Massie, 2009).

### Complications of congenital pulmonary lymphangiectasia (CPL)

As previously mentioned, CPL may present in utero as hydrops fetalis or polyhydramnios. Respectively, these can be caused by impaired venous return due to pleural effusions leading to decreased cardiac output, and increased intrathoracic pressure due to pleural effusions leading to oesophageal obstruction and impaired swallowing (Dempsey et al, 2005). Perinatal mortality rates with primary foetal hydrothorax, such as that which occurs in CPL, have been recorded as ranging from 22% to 53%, with antenatal therapy and delivery post 31 weeks gestation being associated with an improved outcome (Yinon et al, 2008). Hydrothorax is common in CPL and is most often chylothorax, with presentation occurring antenatally, neonatally or in the post-neonatal period (Dempsey et al, 2005; Bellini et al, 2006). Post-birth, untreated chylothorax can lead to malnutrition, weakness, dehydration, metabolic acidosis, respiratory failure and immunological compromise (Gumpeni et al, 2008). Chylopericardium and chylous ascites, along with pulmonary, facial and generalised oedema are also associated with CPL post-birth (Dempsey et al, 2005; Bellini et al, 2006).

For those with CPL who survive the neonatal period, respiratory complications such as recurrent cough and wheeze, sensitivity to respiratory infections and increased respiratory effort, are likely to occur (Barker et al, 2004; Esther and Barker, 2004; Delabaere et al, 2008). Similar to other sufferers of chronic lung disease, CPL patients may also have gastroesophageal reflux and poor growth; although the latter usually resolves and normal growth patterns resume by three years of age (Barker et al, 2004; Esther and Barker, 2004; Bellini et al, 2006).

### Interventions

Early recognition and diagnosis of CPL is essential for maximal effectiveness of any interventions. Relevant interventions focus on maintaining pulmonary

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Possible findings in CPL</th>
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<tbody>
<tr>
<td>Obstetric foetal ultrasound</td>
<td>Hydrops fetalis (including placental enlargement, pericardial effusion, pleural effusion and ascites), polyhydramnios</td>
</tr>
<tr>
<td>Foetal magnetic resonance imagery (MRI)</td>
<td>Lymphatic dilation, pleural effusion, primary cardiovascular defect (in secondary pulmonary lymphangiectasia)</td>
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<tr>
<td>HRCT</td>
<td>Thickening of the interstitium, ground glass opacity, pleural effusion</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Reticulonodular interstitial markings, hyperinflation</td>
</tr>
<tr>
<td>Post-natal MRI</td>
<td>Thickening of the interstitium, pleural effusion, atelectasia</td>
</tr>
<tr>
<td>Lymphangiography</td>
<td>Opacification of pleural lymphatics, formation of extrathoracic lymphatic collateral vessels, presence of lymphatic leaks</td>
</tr>
<tr>
<td>Lymphoscintigraphy</td>
<td>Lymphatic dilation, poor lymphatic clearance rates</td>
</tr>
<tr>
<td>Thoracocentesis</td>
<td>Chylothorax: white, odourless and milky appearance with triglyceride levels &gt; 110mg per dL</td>
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<tr>
<td>Lung biopsy</td>
<td>Lymphatic dilation.</td>
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</table>

**Table 1. Diagnostic tests and possible findings in congenital pulmonary lymphangiectasia (CPL).**
function as optimally as possible, treating and controlling pleural effusions, and maintaining adequate nutrition. Many interventions for CPL may be viewed as mainly supportive, with the goal of allowing the patient sufficient time for the pulmonary development and maturation that will eventually allow them to be weaned from support (Laje et al, 2008).

Follow-up care likely plays an important role in monitoring and treating any further symptoms or chronic conditions that may arise post-recovery and discharge (Mele and Sridhar, 2012).

Table 2 summarises the interventions that may be utilised for CPL.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Description</th>
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<tbody>
<tr>
<td>Mechanical ventilation</td>
<td>High mean airway pressure for maintenance of respiratory function; potentially high frequency oscillatory ventilation and nitric oxide for pulmonary hypertension</td>
</tr>
<tr>
<td>Surfactant</td>
<td>As indicated</td>
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<tr>
<td>Steroids</td>
<td>In cases of premature delivery, to promote lung maturity</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>To treat primary inflammatory conditions</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Long-lasting somatostatin analogue used in treatment of chylothorax</td>
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<tr>
<td>Chest tube</td>
<td>Drainage of pleural effusions</td>
</tr>
<tr>
<td>Thoracocentesis</td>
<td>Drainage of pleural effusions, for diagnostic purposes and relief of respiratory distress</td>
</tr>
<tr>
<td>Pleuroperitoneal shunting</td>
<td>For intractable chylothorax</td>
</tr>
<tr>
<td>Thoracic duct ligation</td>
<td>For intractable chylothorax: indicated after conservative treatment has failed; time frames to intervention vary between authors</td>
</tr>
<tr>
<td>Pleurectomy</td>
<td>For intractable chylothorax</td>
</tr>
<tr>
<td>Pleurodesis</td>
<td>For intractable chylothorax</td>
</tr>
<tr>
<td>Fluid support</td>
<td>Replacement of fluid and electrolytes lost through oedema and pleural effusions</td>
</tr>
<tr>
<td>Medium-chain triglyceride formula</td>
<td>Reduces flow through thoracic duct; may be administered enterally or parenterally</td>
</tr>
<tr>
<td>Protein and vitamin supplementation</td>
<td>For replacement of fat-soluble vitamins and proteins lost through chylothorax</td>
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<tr>
<td>Genetic counselling</td>
<td>Difficult due to rarity and spontaneity of condition.</td>
</tr>
</tbody>
</table>

Respiratory support

Intubation and mechanical ventilation is a frequent requirement in the treatment of CPL. High mean airway pressure is used, with high frequency oscillatory ventilation and nitric oxide potentially indicated in some cases, including those with persistent pulmonary hypertension (Esther and Barker 2004; Dempsey et al, 2005; Bellini et al, 2006; Mele and Sridhar 2012). An increase in intrathoracic pressure due to positive-end expiratory pressure via mechanical ventilation may also help to reduce pleural effusions (Gumpeni et al, 2008). Surfactant may be administered as deemed necessary (Dempsey et al, 2005).

Post-discharge from hospital, patients with CPL may require home oxygen, and vigilant monitoring and treatment of respiratory infections is vital for maintenance of pulmonary health (Esther and Barker, 2004; Bellini et al, 2006).

Pharmaceutical interventions

Steroids may be used in the case of premature delivery, to promote lung maturity, with corticosteroids used in cases where a primary inflammatory condition is present (Dempsey et al, 2005; Akcakus et al, 2007). Inotropic support may be required (Dempsey et al, 2005; Bellini et al, 2006).

Octreotide, a long-acting somatostatin analogue, which suppresses chyle formation, has been used to treat chylothorax, in both pulmonary lymphangiectasia and intestinal lymphangiectasia, as well as non-lymphangiectasia-related chylothorax (MacLean et al, 2002; Sivasli et al, 2004; Foo et al, 2011). However, questions have been raised about its long-lasting efficacy, and it has been suggested as a treatment for refractory chylothorax rather than as a first-line treatment (Tibballs et al, 2004; Gumpeni et al, 2008).

Surgical/invasive interventions

In the case of rapid formation of pleural effusions, placement of a chest tube for drainage may be indicated until the effusion can resolve, either spontaneously, or as the result of adjunctive treatment (Esther and Barker, 2004; Sadiq, 2013). Thoracocentesis is used for diagnostic purposes, but is also an appropriate first step in the therapeutic treatment of pleural effusions, and to relieve respiratory pressure (Bellini et al, 2006; Gumpeni et al, 2008; Soto-Martinez and Massie, 2009).

For cases where large volumes of fluid continue to be drained, either via chest tube drainage or thoracocentesis, pleuroperitoneal shunting is a possible management option. However, other options for intractable pleural effusions may be considered first (Dempsey et al, 2005; Gumpeni et al, 2008). One paper reports the use of subcutaneous lymph drainage in the successful relief of respiratory distress in a 10-month-old girl diagnosed with systemic lymphangiomatosis complicated with pulmonary lymphangiectasia.
but this therapy does not appear to have been utilised specifically in cases of CPL (Hamamoto et al, 2003). For pleural effusions detected antenatally, thoracoscopic shunting is a management option shown to improve outcomes in the neonatal period (Picone et al, 2004).

Thoracic duct ligation is an accepted therapy for chylothorax. Ligation of the site of leakage only, which is usually found through thoracoscopy or thoracotomy, is preferred, with mass ligation of the thoracic duct and surrounding tissue only suggested when the site cannot be specifically identified (Gumpeni et al, 2008; McGrath et al, 2009; Soto-Martinez and Masse 2009). Some time for more conservative treatment options to take effect can be allowed; a limit of 2 weeks up to 3 or 4 weeks has been described, but cases of chylothorax with greater than one litre of drainage per day or those with an easily identifiable leakage site may prompt earlier surgical intervention (Gumpeni et al, 2008; Soto-Martinez and Masse, 2009). Mele and Sridhar (2012) recommended that this intervention should be considered as a management option in CPL-related chylothorax. This view is also taken by Bellini et al (2006).

Pleurectomy — removal of the parietal pleura from the rib cage and mediastinum — was first described as a treatment for chylothorax by Barrett et al (1987). Teitelbaum et al (1996) published three case studies describing a modified technique for use of pleurectomy in treating chylothorax in infancy. It has been used in the management of chylothorax in both lymphangiomatosis and intestinal lymphangiectasia (Barrett et al, 1987; Burgess et al, 2006). Pleurectomy has also been utilised in pulmonary lymphangiectasia, and could be considered for treatment of intractable chylothorax, but may not be the first surgical option of choice due to the high morbidity associated with blood loss (Bellini et al, 2006; Laje et al, 2008; Mettauer et al, 2009).

Pleurodesis is the adherence of the parietal and visceral pleura via mechanical or chemical means (Rodriguez-Panadero and Montes-Worboys, 2012). Completely successful pleurodesis results in the absence of any further pleural effusions, but partial success may result in some reduction in the accumulation of fluid. Talc has been shown to be the most effective sclerosing agent (Huggins et al, 2011), but other agents — by no means an exhaustive list — include iodopovidone, silver nitrate and doxycycline (Rodriguez-Panadero and Montes-Worboys 2012). Pleurodesis can also be carried out using fibrin glue (Lee et al, 2002).

In a case described by Akcakus et al (2007), successful pleurodesis was carried out on a newborn with CPL using autologous blood therapy. Pleurodesis, either as a stand-alone surgical intervention or in combination with other invasive interventions, such as thoracic duct ligation, has been suggested as part of the management options for CPL (Bellini et al, 2006; Mele and Sridhar, 2012), and can be effective in preventing the reoccurrence of chylothorax.

Fluid and nutritional support
Any fluid or protein loss needs to be replaced, and the correct fluid and electrolyte balance maintained (Dempsey et al, 2005; Bellini et al, 2006; Laje et al, 2008). Standard nutritional support in the case of chylothorax consists of a medium-chain triglyceride formula, given via the nasogastric route or parenterally. Parenteral administration is usually recommended on persistence of chylothorax (Bellini et al, 2006; Tibballs et al, 2004). The medium-chain triglycerides bypass the intestinal and thoracic lymphatics and are absorbed directly in the portal system, maintaining nutrition while minimising thoracic duct flow (Gumpeni et al, 2008). Vitamin and protein supplementation may also be appropriate, to replace those fat-soluble vitamins and proteins lost through chylothorax (Scott et al, 2003; Bellini et al, 2006).

Genetic counselling
Although genetic defects are suspected as the underlying cause of CPL, with some of the subject of current research, the rarity of the condition, the variety of genetic syndromes with which CPL has been associated and the sporadic nature of CPL render genetic counselling a difficult and perhaps inapplicable task (Bellini et al, 2006). However, in families with affected siblings and identifiable causative genetic
defects, this may become more relevant, and perhaps needs to be considered on a case-by-case basis.

**Prognosis**

Previously, CPL has been described as being almost uniformly fatal (Faul et al., 2000). However, as various retrospective reviews and case studies have shown, progression in antenatal and neonatal care and the willingness of practitioners to engage in aggressive interventions have changed this situation. Infants who died within the neonatal period generally tended to suffer from multiple congenital conditions with a contributory effect towards mortality (Barker et al., 2004; Esther and Barker, 2004). Case study reports by Bellini et al. (2003), Scott et al. (2003), Dempsey et al. (2005), Laje et al. (2008), and Mele and Sridhar (2012) all found that infants diagnosed with CPL in the neonatal period are able to survive with appropriate interventions. Case series and retrospective studies reported by Chung et al. (1999), Barker et al. (2004) and Mettauer et al. (2009) show the same.

The rarity of CPL makes it difficult to ascertain specific figures for mortality and survival, but although blind optimism regarding survival cannot be justified in the face of manifestations of CPL, such as hydrops fetalis, chylothorax and severe neonatal respiratory distress, the outcome of CPL need no longer be viewed as pessimistically as it once was, particularly in the absence of co-morbidities, such as congenital heart disease. This can be attributed in the most part to improvements in the interventions available to treat especially the respiratory consequences of CPL since the condition was first recognised and codified (Bellini et al., 2006; Sadiq, 2013).

**Conclusions**

CPL is a rare but serious condition marked by dilatation of the pulmonary lymphatic vessels. It can manifest in utero as hydrops fetalis and/or polyhydramnios; immediately or shortly after birth as cyanosis, tachypnoea and respiratory distress; or weeks to months into the neonatal period. Early diagnosis of CPL, either antenatally or neonatally, allows for management that is primarily aimed at supporting respiratory function and treating associated symptoms. Early and aggressive interventions increase the likelihood of survival, and should be considered in consultation with the parents of the affected infant.

Although an association between CPL and various chromosomal abnormalities, such as Noonan syndrome, has been documented, and specific genes have been implicated in the development of CPL, the molecular basis for CPL remains poorly understood. A failure of the pulmonary lymphatic vessels to regress at approximately 20 weeks gestation is considered to be the underlying factor, but the cause of this failure is unknown. Further research into the molecular development of the pulmonary lymphatic system and exploration of potential gene mutations involved in CPL may aid in providing a definitive cause and also targets for future treatments. On a more immediately applicable basis, continued and systematic evaluation of the use of interventions in treating CPL, currently informed in the majority by isolated case reports, will contribute to clinical knowledge and encourage the use of potentially life-saving treatments for the infant with CPL.

**References**


