CONGENITAL LUNG MALFORMATIONS
A REVIEW

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Abstract
Congenital lung malformations are a group of rare, nonhereditary conditions that can be the source for important morbidity and mortality in infants and children. The histopathologic characteristics, clinical presentation, diagnostic tools and management options of the most important congenital lung malformations are briefly reviewed. The lesions analyzed are cystic adenomatoid malformation, pulmonary sequestration, bronchogenic cyst and congenital lobar emphysema. The antenatal diagnosis, by ultrasound scan, permits early recognition and thus adequate management. After birth thoracic computed tomography is the most useful diagnostic tool. Management of the lesions is dictated by the characteristics of the lesion and the clinical status of the patient. Resection of nearly all, even asymptomatic, congenital lung lesions is advocated.

Key words: lung malformations; cystic adenomatoid malformation; bronchopulmonary sequestration; bronchogenic cyst; congenital lobar emphysema; child

Introduction
Congenital lung malformations occur rarely but could represent an important cause of respiratory distress in the new-born. The most important congenital bronchopulmonary malformations include congenital cystic adenomatoid malformation (CCAM), pulmonary sequestration (PS), bronchogenic cysts (BC) and congenital lobar emphysema (CLE). Other malformations are agenesis of the lung or agenesis of a lobe of the lung.

Embryology
The respiratory system development begins with the evagination of cells from the foregut endoderm into the splanchnic mesenchyme at 3 weeks of gestation (1). The respiratory mucosa derives from the endoderm of the ventral foregut, while the supporting tissue and the vasculature have a mesodermal origin (2). Following the anatomic changes that occur in its architecture lung morphogenesis can be divided into five stages: embryonic, pseudoglandular, canalicular, saccular, and alveolar (1) (fig. 1):

1 Embryonic period (3-7 weeks). At 26 embryonic days in the ventral wall of the foregut a laryngotraheal groove appear (2). Grooves lips fuse at the caudal end and form the tracheal diverticulum. From this diverticulum the two main bronchi buds bulge out. The main bronchi divide into two lobar bronchi on the left and three on the right side, defining the lobar anatomy of the human lung. All lobar airways can be detected by the sixth gestational week. Development of the pulmonary vasculature uses the primordial airways as a template (3). The human lungs are supplied by two vascular systems, which develop sequentially. First, the pulmonary circulatory system is established after five gestation weeks, and then the bronchial arteries arise from the aorta after a delay of approximately 3 weeks (3).

2 Pseudoglandular period (7–17 weeks). The conducting airways continue to branch and bud. The airway conducts expand in the periphery producing a glandular appearance (1). During this period mucous glands, bronchial cartilage, and epithelial airway cells develop (3). By the 16th gestation week the tree of conducting airways has fully developed.

Fig.1 Embriology - From: Jeffrey A. Whitsett, Susan E. Wert and Bruce C. Trapnell. Genetic disorders influencing lung formation and function at birth. Human Molecular Genetics, 2004, Vol. 13, Review Issue 2 R207-R215.
3 Canalicular period (16–26 weeks). Tubules expand to form saccules widening the airway lumina. The mesenchyme thins and the airspaces come into increasingly close apposition to capillary network to form the gas exchange region (1). During this period the type I cells differentiate and surfactant components start to be produced by the cuboidal type II cells (1). After 23-24 gestation weeks despite the pulmonary immaturity preterm babies could survive with intensive care support (1-3).

4 Saccular period (22–36 weeks). During this stage the lung tissue maturate in preparation for birth. The acinar tubules continue to proliferate and expand. The surface area of the gas exchange region increases and additional alveoli septae form. At 30 week of gestation surfactant is detectable in the amniotic fluid (3).

5 Alveolar period (36 weeks to maturity). The alveolar septation is completed in this period. Alveolar structures can be recognize histological after 32 weeks and are uniformly present at 36 gestation weeks (3). Most of the alveoli are formed after birth in the first two years of life (3). Each of this stages associate specific disorders in correspondence with the developmental processes (Table 1).

<table>
<thead>
<tr>
<th>Embryonic</th>
<th>Pseudoglandular</th>
<th>Canalicular</th>
<th>Saccular</th>
<th>Alveolar</th>
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<tr>
<td>Bronchogenic cysts</td>
<td>Pulmonary hypoplasia</td>
<td>Pulmonary hypoplasia</td>
<td>Pulmonary hyperplasia</td>
<td>Lobar emphysema</td>
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<td>Pulmonary/lobar atresia</td>
<td>Cystic adenomatoid malformation</td>
<td>Alveolar capillary dysplasia</td>
<td>Respiratory distress syndrome</td>
<td>Pulmonary hypertension</td>
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<td>Extralobar sequestration</td>
<td>Intralobar sequestration</td>
<td>Bronchopulmonary dysplasia</td>
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<td>Pleural effusions</td>
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<td>Tracheal/bronchial atresia/stenosis</td>
<td>Pulmonary lymphangiectasis</td>
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<td></td>
<td>Alveolar simplification</td>
</tr>
<tr>
<td>Laryngeal/ esophageal atresia/ stenosis</td>
<td>Diaphragmatic hernia</td>
<td></td>
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</table>

Table 1. Lung formation stages and specific lesions,

Congenital cystic adenomatoid malformation (CCAM)

Is a rare pulmonary malformation with an estimated incidence between 1/25000 and 1/35000 (4). It is produced by the abnormal and extensive overgrowth of the bronchiolar structures. The cause for appearance is unknown but the error occurs sometimes between the fifth to the sixth week of gestation in the pseudoglandular stage of lung development (2). Stocker described in 1977 three distinct histological subtypes which later were expanded to five in 2002 (5). Each type was related with specific symptoms and radiographic findings (Table 2).

Type 1 is present in 50-70 % of cases and has the best prognosis (2). Type 2 has a poor prognosis and associates frequently other structural and chromosomal abnormalities (2). A more useful classification seems to be the one introduced by Adzick et al (4-5) using prenatal ultrasound examination. This classification simply differentiates antenatally lung lesions into macrocystic and microcystic.

| 0 | Involvement of all lung lobes, incompatible with life |
| 1 | Single or multiple cysts, more 2 cm, lined by pseudostratified columnar epithelium |
| 2 | Single or multiple cysts (under 2 cm). Cuboidal or columnar epithelial lining |
| 3 | Predominantly solid lesions, with small (under 0.5 cm) cysts, lined by cuboidal epithelium |
| 4 | Large air-filled cysts, lined by flattened epithelial cells |

Table 2. Stocker’s classification (5).

Clinical presentation is variable. About 10% become symptomatic during fetal life (4). The large mass inside the lung can restrict lung growth, can produce mediastinal shift, cardiovascular compromise and cava obstruction leading to non-immune hydrops fetalis (HF). 60% of patients become symptomatic within one month of life, another 10% between one and six months and 15 % by adolescence (6). The key symptom in neonatal period is the respiratory distress. Outside of the neonatal period recurrent pulmonary infections in the affected lung with poor response to medical treatment is the commune presentation mode (6-7).

Postnatal the diagnostic is made on X-ray showing multiple air filled spaces (macrocystic) or a solid area (microcystic) (6). It is essential to take the X-ray with an in situ nasogastric tube in order to avoid mistaken with a
Computed tomography (CT) is the most useful technique for diagnostic and pre-therapeutic evaluation (5-7). It shows large air-filled, fluid-filled cysts or containing air-fluid levels (type 1); solid mass with multiple small cysts (type 3) (7) (fig. 2).

Other diagnostic means include magnetic resonance (MRI) and bronchoscopy. One of the most recent developments in the area is virtual bronchoscopy (VB). VB is a non-invasive three-dimensional (3D) technique that uses multidetector CT generated image. It can evaluate the airways down to the sixth- to seventh-order bronchial subdivisions (8).

Antenatal diagnostic is made by ultrasound scan (US) at 20th gestation week (2-4-5-6). After the condition is detected the fetus is evaluated and monitored using ultrasound or MRI. MRI is more accurately providing besides structural, functional information also (3). The natural history of antenatal diagnosed CCAM is difficult to determine accurately. Although largely silent during fetal life and rare spontaneous regression of CCAM has been reported there are certain cases when fetal intervention is required: high CCAM volume ratio, presence of HF, mediastinal shift, cardiovascular compression, lung hypoplasia (4). The optimal type of fetal intervention is still a subject debate. Treatment options include: fetal surgical resection, cyst-amniotic shunting, thoracentesis, and steroid therapy (4). In some cases of CCAM associated with HF antenatal steroid therapy was sufficient. Cyst-amniotic shunting may be the treatment of choice for macrocystic CCAM with HF while microcystic CCAM require surgical resection. Termination of pregnancy should be considered by the family when the fetus has insufficient pulmonary tissue to support life after birth (4).

Even if complications do not occur during intrauterine life there are still certain risks that require a delivery at a unit with appropriate neonatal and surgical expertise. After birth management is dictated by the clinical status of the new-born (5). If the early respiratory distress is present immediate management is required: appropriate management of the respiratory distress followed by surgical resection of the lesion (2).

Surgical resection of CCAM lesions is necessary even for asymptomatic patients in order to prevent infection and avoid malignant transformation of the lesion (5).

Excision of the CCAM is accomplished by lobectomy or segmentectomy and in certain cases even pneumonectomy (7). The usual intervention is lobectomy via thoracotomy or thoracoscopic approach. Lobectomy is preferred because of potential early air-leak after segmentectomy and long-term complications after pneumonectomy (9). Thoracoscopy provides several potential advantages over thoracotomy: lower pain, better postoperative pulmonary mechanics (10). Moreover up to 30% of neonates develop scoliosis after thoracotomy (10). Anesthetic management includes tracheal intubation and ventilation, central venous line, isoflurane/oxygen analgesia, muscle relaxation. For a better surgical access, protection of the normal lung and reduced blood loss one-lung ventilation (OLV) should be used (17).

Open thoracoscopic lobectomy follows the same principles. After the exposure of lung hilus the visceral pleura is opened carefully. The hilar vessels and lobar bronchus are exposed. The main segmental artery branches are identified, ligated with 3-0 silk and divided. The second stage consists in the identification, ligation and division of the segmental vein branches. The last to be approached is the lobar bronchus which is divided after a vascular clamp is placed proximal from the resection. The bronchus is sutured with continuous 3-0 silk and the closure is tested for air leak. After a lobectomy it is important to divide the inferior pulmonary ligament in order to enable the remaining lung to develop freely in the thoracic cavity. Postoperative a drain tube is left inside the pleural cavity for 48 h (2).

Early complications include sepsis, air leaks with pneumothorax, bronchopleural fistula, wound infections. Later complications and sequelae are incomplete excision, asthma, pneumonia (2-5).

Prognosis depends of several factors such as: cyst volume, histological type (type I has the best prognosis), the presence of complications during fetal life, the presence and severity of early respiratory distress (2-4-5). Neonates tolerate well lobectomy and the remaining lung usually evolves and expands into the remaining cavity replacing the lost pulmonary tissue (2).
**Pulmonary sequestration (PS)**

Pulmonary sequestration is a rare congenital lung malformation characterized by a mass of nonfunctioning lung tissue with no connection with the normal tracheobronchial tree (2-11-12). The lesion has distinguished blood supply originating from the systemic artery system. The term “sequestration,” was first used in the medical literature by Pryce in 1946 (5-11-13). It represents 0.15- 6% of all pulmonary malformations (11). The origin of the lesion is uncertain but the most widely accepted hypothesis is that it results from an accessory lung bud developing inferior to the normal lung bud (11). There are 2 distinctive forms of pulmonary sequestration: intralobar and extralobar.

Intralobar sequestration is contained within the normal visceral pleura and it is usually located into the posterior basal segments of the lower left lobe (2-13). The arterial supply is from the descending thoracic aorta through inferior pulmonary ligament in 90% of cases (2-13). Other arterial sources could be the intercostal artery, subclavian arteries, internal thoracic arteries and sometimes coronary arterial circulation which predispose to myocardial ischemia (13). Venous drainage is via the pulmonary veins in 98% and sometimes into the azygos or hemiazygos veins (2-13).

Extralobar sequestration is three times less frequent than the intralobar type (2-12) and usually is associated with other congenital anomalies (congenital diaphragmatic hernia, pectus excavatum, vertebral anomalies, and pericardial defects) (2). It is a mass of abnormal lung tissue invested in its own pleural covering. It is located usually in the left costophrenic groove nearby left suprarenal gland (2). About one-sixth are located below the diaphragm (13). The arterial supply is in most of the cases directly from the thoracic or abdominal aorta (2-13). Venous drainage is almost always in the azygos or hemiazygos veins (13). Rarely venous drainage is in the pulmonary veins or portal vein (2).

Clinical features of the 2 types of PS are different (Table 3).

<table>
<thead>
<tr>
<th>Feature</th>
<th>Intralobar sequestration</th>
<th>Extralobar sequestration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>Child to adult</td>
<td>Neonate</td>
</tr>
<tr>
<td>Sex distribution</td>
<td>Equal</td>
<td>80% male</td>
</tr>
<tr>
<td>Location</td>
<td>Posterior basal left segment</td>
<td>Independent of lung</td>
</tr>
<tr>
<td>Associated anomalies</td>
<td>Uncommon</td>
<td>common</td>
</tr>
<tr>
<td>Venous drainage</td>
<td>Pulmonary</td>
<td>Systemic</td>
</tr>
<tr>
<td>Bronchial communications</td>
<td>Present</td>
<td>none</td>
</tr>
</tbody>
</table>

Table 3. Clinical features.

Intralobar sequestration is rarely symptomatic and when present symptoms are nonspecific (chest pain, pleuritic pain, shortness of breath, and wheezing, recurrent infection) (2-11). The recurrent localization of the pathology in the lower lobe suggests the diagnostic.

Extralobar sequestration is confined to neonates because of the high frequency of concomitant congenital anomalies but usually it is asymptomatic and discovered incidentally on a routine X-ray (11). Extralobar sequestration may cause severe respiratory distress in newborn (2). Older infants and children may present with congestive heart failure, mitral regurgitation. In some particular uncommon cases the sequestration can produce even frank hemoptysis (13).

Diagnostic is made on plain X-ray: ill-defined consolidation inside the lung or a soft tissue mass with well- or ill-defined borders (11). A cystic area or air-fluid level can also be seen. There are certain difficulties in diagnosing from chest plain X-ray extralobar sequestration. The image could be obscured by cardiac or vertebral shadow. Angiography is a really useful mean for diagnostic and pretherapeutic evaluation (2). A higher value has CT with contrast medium when the abnormal blood supply can be identified (11). CT can also give useful information about regional anatomy, the relations between the sequestration and the surrounding structures, about other concomitant anomalies. Bronchoscopy and bronchography are not useful (2).

The key of pulmonary sequestration diagnostic is to identify the aberrant systemic blood supply.

Differential diagnostic refer to other congenital lung malformations (CCAM type 1 and 3, bronchogenic cyst, diaphragmatic hernia), lung infections (pneumonia, tuberculosis), malignant or nonmalignant mediastinal masses (13).

Antenatal diagnostic can be established by ultrasound scan (US) from the 20-th gestation week (12) and MRI seems to be the best evaluation and monitoring technique in the second and third trimester (3-14).

The management of a pulmonary sequestration diagnosed during fetal life involve in the first stage conservative treatment and ultrasound or MRI follow-up. Partial or complete regression during sequential scanning throughout pregnancy is possible (13). Fetal intervention and excision of the lesion during fetal life is required only if complications like surface exudation and a pleural effusion, signs of fetal distress, cardiac or cava compression appears (5-13).

After birth therapy will have to be individualized depending on symptoms, the nature of the sequestration, and the presence of any associated malformation. Small intralobar asymptomatic lesions benefit in many cases of conservative treatment with careful long-term CT scan...
surveillance (13). Other experts advocate that even asymptomatic lesions should be surgical removed (11). Reasons for surgical excision of an asymptomatic lesion include the risk of recurrent infections, an increase in the arterio-venous shunt, pressure effect on adjacent normal lung, airway compression (11-12). When symptoms are present the consensus is that surgical treatment is required. Surgery usually involves lobectomy via thoracotomy or thoracoscopy (2-11). Special care must be taken when dissect vessels are handled because of their increased fragility. Care must be taken also during dissection not to produce injury to the phrenic nerve. If the risk of surgery is too high alternative treatment options like catheter-based embolization or ligation of the feeding artery are considered (2).

Extralobar sequestration is treated by sequestrectomy without sacrificing normal lung tissue (2). In both cases intra- and extralobar sequestration the key for a successful surgical treatment is the correct and complete visualization of all supply vessels. For this reason a careful preoperative CT scan evaluation is imperative (11-13).

The most apprehensive intraoperative accident is to injure the arterial supply with massive bleeding. Other accidents and complications are the usual one for thoracic surgery.

Prognosis after surgical treatment is good. Exception is made by extralobar sequestration associated with other congenital malformations.

**Bronchogenic cysts (BC)**

It is a rare congenital lung malformation resulting from an abnormal growth of the aerial conduct. The lesion occurs sometime between the third and the sixth gestation week. It is usually unilocular, has no communication with the bronchial tree and filled with clear mucous secretion (2-15). It is almost always closely attached to major airways or the esophagus by dense fibrous tissue. Inside it is lined with ciliated columnar epithelium and the wall contains fibrous and elastic tissue, smooth muscle, and cartilage (2-15). In 65% it is located in the mediastinum (2). Intrapulmonary cysts are in most of the cases located in the lower lobes. Less frequent locations are pericardium, pleural cavity, cervical, paravertebral and occasional in extra-thoracic positions (2).

The clinical course of the cyst is strongly influenced by the presence or absence of communication with the parent bronchia. Non-communicating cysts cause symptoms by local compression but in most of the cases are asymptomatic (15). On the other hand a cyst-bronchial communication can cause two complications: tension cyst and infection. A tension cyst produces by rapid expansion acute cardio-respiratory embarrassment that necessitates urgent therapeutic intervention (2). Cyst infection is more frequent for the intrapulmonary cysts and have typical clinical presentation (fever, cough, spatum even hemoptysis) (2). Infections are recurrent and have poor response to treatment.

Diagnostic is made on plain chest X-ray or with more accuracy using thoracic computed tomography (15).

Beyond CT there are no diagnostic means that can bring additional significant information. Intrapulmonary bronchogenic cyst appears as a solitary, sharply defined round mass with water density. An air-fluid image indicates a communication between the cyst and the bronchial tree (14).

Treatment options include evacuations trough percutaneous or transbronchial needle aspirations and complete or partial resection by thoracoscopic or open surgery.

Needle aspiration is required in case of a tension cyst that expand rapid and can lead to death by acute cardio-respiratory embarrassment (14). Otherwise the cyst should be surgical removed. For intrapulmonary cysts the excision options are segmentectomy, lobectomy or simple cyst removal. Extrapulmonary cysts are removed with best results using thoracoscopic surgery (14). The precise vascular supply to these lesions is difficult to determine. Both extra- and intrapulmonary bronchogenic cysts are supplied by numerous small branches. Therefore special attention should be paid during the dissection of the cyst. Other peculiar situation is when cyst is adherent to a vital structure (trachea, main vessels, heart) (14). In this situation the resection is partial and the cyst epithelium must be destroyed using electrocautery to prevent recurrence or malignant degeneration (2-14).

Postoperative evolution is usually favorable with low mortality and morbidity.

**Congenital lobar emphysema (CLE)**

Congenital lobar emphysema is a rare condition characterized by the overinflation and distension of one or more pulmonary lobes (6). The basic defect is the inability of the affected lobe to deflate normally (2). The overexpander portion compresses the rest of the lung affecting the normal respiration. By mediastinal shift can also compress the contralateral lung. The cause of the disease is represented by an intrinsic or extrinsic bronchial narrowing (16). Intrinsic narrowing can be produced by the weakness or absence of bronchial cartilage so that there is air entry but collapse of the narrow bronchial lumen during expiration (6). A large pulmonary artery, a prehilar bronchogenic cyst, an enlarged mediastinal node, an aneurismal ductus arteriosus could compress the bronchial tree and affect the cartilage rings. The affected cartilage rings become malformed, soft, and collapsible in response to the long-term in utero extrinsic effect. In about 50% of cases the etiology remains uncertain. The upper left lobe is the most frequent affected (42%) followed by right middle (35%) and right upper lobe (21%) (6). Multiple lobar involvements are possible but usually there is only one lobe affected. In about 10% of patients associated congenital anomalies are present, primarily congenital heart disease (16). Male to female ratio is about 3 to 1 (6).

Symptoms are the result of the compression of the normal lung tissue and vary according to the size of the affected lobe and the degrees of compression. Respiratory distress in varying severity is present at 50% of the cases at birth (2). The remaining 50% develop symptoms in the first 4 months (2). The typical postnatal presentation is that of a
new-born showing signs of progressive respiratory distress (progressive dyspnoea, cyanosis and tachypnoea) (6). Physical examination shows asymmetry of chest, abdominal retractions on inspiration, hyper resonance and diminished air or absent breath sounds in the affected area (2-6-16).

The diagnostic is made on X-ray of the chest showing a hyperlucent overexpanded area with attenuated but defined vascularity and compression of the remaining lung on that side (2-16). It can show also widening of the ribs spaces, depression of the diaphragm, mediastinal shift and compression of the contralateral lung (16). A lateral X-ray will show anterior herniation of the expended lobe and the posterior displacement of the heart (2). Computed tomography scanning can provide more accurate information of the overdistended lobe and its vascularity, as well as information about the remaining lung (16). It shows a hyperlucent, overexpanded lobe with compression of the remaining lung and mediastinal shift. Bronchoscopy may be done in order to exclude a foreign body inside the bronchi but only in the nearby of a surgery facility because of the high risk of sudden respiratory deterioration (6). Other diagnostic tools are: pulmonary scintigraphy, MRI and ultrasound. Ultrasound is particular useful for antenatal diagnostic of the disease. It shows a large, fluid-filled lobe that compresses the rest of the lung (16). Antenatal diagnostic is not made as frequently as in other intrapleural fetal masses.

Treatment options are in concordance with the clinical presentation of the disease. If early severe and progressive respiratory distress is present prompt surgical intervention and resection of the affected lobe is required (2-6). The surgical procedure in most of the cases is lobectomy and sometimes segmentectomy by open or thoracoscopic approach (6). It is important that prior to pulmonary resection to perform a careful mediastinal exploration in order to exclude an eventually extrinsic cause of bronchial compression (2). Patients who present milder symptoms could benefit from conservatively management (5).

Conclusions

Congenital lung malformations are a group of rare, nonhereditary conditions that can be the source for important morbidity and mortality in infants and children. They are an important source for early respiratory distress. Outside neonatal period they can produce recurrent and hardly curable pulmonary infections. Antenatal diagnostic is possible using ultrasound scan (US) from 20-th gestation week. After birth thoracic computed tomography (CT), with or without contrast, is the most useful diagnostic tool. It can provide high resolution images of the lesion and surrounding tissue and it is also an important pre-therapeutic and follow-up evaluation tool. New diagnostic techniques include fetal MRI, virtual bronchoscopy (VB). Ideal management include antenatal ultrasound diagnostic, follow-up during pregnancy using MRI, controlled delivery in a unit with appropriate neonatal and surgical expertise. If complications occur during fetal life prompt intervention is required and, in some cases, even pregnancy termination should be considered. After birth management is dictated by the type of the lesion and the clinical status of the patient. Except for CCAM (long-term high malignant potential), expectancy and careful CT follow-up is an option for small, peripheral asymptomatic lesions. Due to the inherent risk of infection or malignant transformation resection of nearly all, even asymptomatic, congenital lung lesions are advocated and lobectomy by thoracoscopic approach is the procedure of choice. Postoperative the remaining lung usually expands into the remaining cavity replacing the lost pulmonary tissue and yields excellent long-term results. With appropriate management, overall prognosis of congenital lung malformations is favorable with low long-term complications and sequelae ratio.

References


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