Paediatric Respiratory Reviews 13 (2012) 2–9

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

Mini-Symposium: Pulmonary Complications of Paediatric Systemic Disorders

Pulmonary Complications of Genetic Disorders

Beth A. Pletcher [1,*], Nelson L. Turcios [2]

[1] UMDNJ- New Jersey Medical School, Newark, NJ, USA
[2] Robert Wood Johnson University Hospital, New Brunswick, NJ, USA

EDUCATIONAL AIMS THE READER WILL BE ABLE TO:

a. Recognize constellations of findings suggestive of a syndromic diagnosis when caring for a patient with an apparently isolated pulmonary defect.
b. Develop appropriate management strategies for patients with pulmonary-related syndromes.
c. Provide accurate recurrence risks and family planning guidance for couples with an affected child or for affected individuals.

ARTICLE INFO

Keywords:
anomaly
isolated
recessive
dominant
x-linked

SUMMARY

Many different pulmonary manifestations are seen in conjunction with genetic disorders. Pulmonary findings have been noted with some cytogenetic conditions, many single gene or mendelian disorders, as well as with a number of inborn errors of metabolism. In addition, congenital lung anomalies are relatively common, occurring as isolated anomalies and as part of multiple anomaly syndromes. Recognition of pulmonary problems in patients with genetic disorders may lead to prompt treatment and intervention, which ultimately might translate into improved outcome. This review is focused on the clinical aspects rather than the basic science; comprehensive reviews on specific disease entities are readily available.

OVERVIEW OF PRENATAL LUNG DEVELOPMENT

Lung morphogenesis can be subdivided into distinct periods on the basis of the morphologic characteristics of the tissue.

Embryonic Period

Prenatal lung development begins during the embryonic stage of foetal development, as early as four weeks gestation, with lung buds emerging from the ventral side of the foregut. The trachea is separated from the primitive oesophagus beginning at week five. Secondary bronchi then form, three on the right and two on the left, which will ultimately form the five lobes of the lungs. Developmental anomalies occurring during this period may include tracheal, laryngeal, and oesophageal atresia, tracheal stenosis, pulmonary agenesis, tracheo-oesophageal fistulas (TOFs), and bronchial malformations.

Pseudoglandular Period

From six to sixteen weeks of gestation, branching of the airways continues, and formation of the terminal bronchioles and primitive acinar structures is completed by the end of this period. Surfactant proteins are first detected during this stage. Bronchial arteries arise from the aorta and form along the epithelial tubules. Various congenital defects may arise during this stage of lung development, including tracheomalacia, bronchomalacia, pulmonary sequestration, cystic adenomatoid malformation (CAM), ectopic lobes, bronchogenic cyst, and congenital pulmonary lymphangiectasia. The pleuroperitoneal canal also closes early in the pseudoglandular period. Failure to close the pleural cavity is often associated with congenital diaphragmatic hernia (CDH), leading to pulmonary hypoplasia (PH).

Canalicular Period

From 16 to 26 weeks of gestation, the mesenchyme thins and the acinar structures in the distal tubules and the capillary bed are formed. By the end of this period, the terminal bronchioles have divided to form two or more respiratory bronchioles, each of which have divided into multiple acinar tubules, forming the primitive alveolar ducts and pulmonary acini. Abnormalities of lung development occurring during this period include PH (caused by CDH or compression by thoracic or abdominal masses and prolonged rupture of membranes causing oligohydramnios) and renal agenesis, in which amniotic fluid production is impaired.

* Corresponding author. Tel.: +1 973 972 3300.
E-mail address: pletchba@umdnj.edu (B.A. Pletcher).

1526-0542/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.prrv.2011.01.006

Saccular and Alveolar Periods

Saccular and alveolar periods occur between 26 and 36 weeks and from 36 weeks through adolescence respectively. Thinning of the respiratory epithelium and pulmonary mesenchyme, further growth of the lung acini, and development of the distal capillary network characterize these stages. In the periphery of the acinus, maturation of type II epithelial cells occurs in association with increasing numbers of lamellar bodies and increased synthesis of surfactant phospholipids. After birth, alveoli expand somewhat and lung growth remains active throughout the first 10 years of life. There is a six-fold increase in the number of alveoli during postnatal life.[1]

Before birth, foetal respiratory movements allow lung fluid to efflux into the amniotic fluid. These respiratory efforts promote further lung development and strengthen the muscles of respiration. As discussed in the next section, prenatal circumstances that prevent adequate respiratory movements before birth (i.e., oligohydramnios, thoracic cage abnormalities, or neuromuscular disease) may lead to life-threatening PH.

TRACHEAL ATRESIA, LUNG AGENESIS, AND PULMONARY HYPOPLASIA

Tracheal atresia accompanied by bilateral agenesis of the lungs is most likely to arise as an isolated (non-hereditary) defect, possibly secondary to a vascular event occurring early in the embryonic period. Nonetheless, variable degrees of pulmonary agenesis have been reported in a number of sibships, with and without consanguinity.[2] Developmental anomalies of the lungs have also been described in association with other birth defects: as part of at least two possible mendelian disorders[3,4] and occasionally in a microdeletion syndrome.

Primary PH is sometimes reported as an isolated finding and has been described in a number of sibships, suggesting autosomal recessive inheritance in some cases.[5] This serves as a reference point for some families who have given birth to one child with primary pulmonary hypoplasia because risks for recurrence may be 25% in subsequent pregnancies.

More often, PH identified at birth in association with severe respiratory distress is found to be secondary to another underlying defect or disorder**,** which can be divided into three broad categories: (1) renal problems leading to oligohydramnios, (2) skeletal dysplasia resulting in thoracic cage limitation and pulmonary insufficiency, and (3) neuromuscular disorders leading to PH due to poor respiratory efforts *in utero*.

Any renal abnormality, developmental or obstructive, leading to decreased urine output *in utero* with concomitant oligohydramnios has the potential to cause PH. The degree of oligohydramnios and length of time the foetus is limited in movement will likely determine the severity of PH and long-term survival potential. Most instances of non-renal oligohydramnios are not genetically determined, but instead are secondary to prolonged membrane rupture. Late loss of amniotic fluid with a relatively short duration of foetal constriction is less likely to cause significant respiratory compromise. In contrast, prolonged, severe oligohydramnios secondary to renal agenesis or syringomyelia results in the Potter sequence with severe PH and neonatal death.

Between these two extremes are variable findings and prognoses associated with decreased amniotic fluid volume. A common isolated birth defect in male foetuses, posterior urethral valves, may result in oligohydramnios, bladder distension, hydronephrosis, and ultimately renal damage. In severe cases, the bladder distension leads to anterior abdominal wall musculature hypoplasia and renal failure (prune–belly syndrome). These boys may also have respiratory compromise that tends to correlate with the duration and severity of the oligohydramnios.

Suboptimal urine output associated with a number of genetic conditions may be seen with varying degrees of PH at birth. Bilateral or unilateral renal agenesis may occur as an isolated defect during early foetal development.

In some instances, skeletal dysplasias with associated thoracic anomalies can result in secondary PH. In addition to severe and universally fatal skeletal dysplasias such as achondrogenesis, osteogenesis imperfecta type II, a few short-rib polydactyly syndromes, and thanatophoric dysplasia, there are many less severe skeletal dysplasias that may result in pulmonary compromise and respiratory difficulties at or shortly after birth, but with the possibility of long-term survival.

Severe neuromuscular disorders associated with lack of foetal movement (foetal akinesia) may cause a host of problems in addition to PH. Prenatal history is often significant for polyhydramnios (felt to be secondary to decreased foetal swallowing), joint contractures, and clubfeet. Whether the foetal akinesia is secondary to an inherent muscle or peripheral nerve problem or a central nervous system problem, the clinical presentations are similar. Severe, congenital forms of inborn errors of metabolism, myopathies, or neuropathies may be clinically indistinguishable unless specific diagnostic tests are done. Table 1 summarizes genetic conditions with neuromuscular underpinnings that may result in secondary PH.[6,7]

CONGENITAL DIAPHRAGMATIC HERNIA

CDH is an anomaly seen in approximately one in 2000 liveborns and frequently associated with secondary PH. This birth defect occurs both as an isolated event as well as with more than 15 genetic syndromes. CDH is also seen with numerous cytogenetic deletion and duplication syndromes as one of many congenital anomalies[8,9]; 15% of infants with CDH have a structural or numeric cytogenetic abnormality.[8–10] Prenatal or postnatal detection of a CDH would require a thorough examination for dysmorphic features or additional birth defects that may be diagnostic of a specific syndrome.

The overall outcome of CDH is worsened when associated with certain syndromes, such as Fryns syndrome. A recurrence risk for sibs of a child with an isolated CDH, based on empirical data, is approximately 2%.[11]

Isolated CDH is generally believed to be a sporadic occurrence, although autosomal dominant and autosomal recessive pedigrees have been described. Several loci and putative predisposition genes have been found in cases of CDH, with cytogenetic deletions, duplications, and translocations often uncovering a CDH locus.

SEGMENTATION DEFECTS AND HETEROTAXY

During the embryonic stage, the right and left bronchial buds begin to grow, subsequently dividing into secondary bronchi. Normally, the right lung bud divides into three segments, and the left lung bud into two segments. Rarely, segmentation or lobulation defects occur, and may or may not be associated with other visceral heterotaxies. Nearly 80% of children with right isomerism (bilateral right lung) have asplenia, leading to a risk for overwhelming pneumococcal sepsis. A similar proportion with left isomerism (bilateral left lung) has multiple small spleens (polysplenia). A few genetic syndromes have been associated with these types of defects (Table 2).[12,13]

CONGENITAL CYSTIC MALFORMATIONS

Cystic Adenomatoid Malformations (CAMs)

CAM of the lungs is a developmental abnormality that results from overgrowth of the terminal respiratory bronchioles modified by