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Abstract: Hereditary lung diseases can affect the airways, parenchyma and vasculature of the lung. Such diseases comprehend simple monogenic disorders such as Kartagener syndrome and α1-antitrypsin deficiency, in which mutations of critical genes are sufficient to induce well-defined disease phenotypes. A major comprehension of the genetic basis of pulmonary diseases has produced new investigations into their underlying pathophysiology and contributed sometimes to clarify on more frequent sporadic forms. The presence of these structural abnormalities of the respiratory tract can be fatal, so that the identification of causative genes has allowed prenatal diagnosis for many diseases giving a greater hope of survival thanks to a more adequate and prompt management.

1. INTRODUCTION

Hereditary anomalies of the respiratory tract can affect the airways or parenchyma or vasculature of the lung. Broadly, developmental disorders can be divided into anomalies of the larynx, trachea, and bronchi; anomalies of the lung parenchyma; and anomalies of the pulmonary vasculature (Fig. 1).

2. ANOMALIES OF LARYNX, TRACHEA AND BRONCHI

2.1. Laryngeal Atresia

Laryngeal atresia is a rare malformation often incompatible with life that causes fetus’ upper airway obstruction. Distally to the obstruction or to the stenosis the airways dilate, the lungs widen and become echogenic while the diaphragm becomes flat and inverted. A fetal ascites or a hydrops are produced. Partial laryngeal atresia is a membranous formation of the laryngeal lumen at the level of the vocal cords. Its birth prevalence is less than 1 in 10,000. It has an autosomal dominant mode of transmission, in which mutations of critical genes are sufficient to induce well-defined disease phenotypes. A major comprehension of the genetic basis of pulmonary diseases has produced new investigations into their underlying pathophysiology and contributed sometimes to clarify on more frequent sporadic forms. The presence of these structural abnormalities of the respiratory tract can be fatal, so that the identification of causative genes has allowed prenatal diagnosis for many diseases giving a greater hope of survival thanks to a more adequate and prompt management.

2.2. Laryngomalacia

Laryngomalacia is the most frequent congenital laryngeal disorder characterized by a noisy breathing with inspiratory stridor and apnea. It is due, for 60-70% of cases, to congenital weakness of the epiglottis and the arytenoid cartilage severe cases presenting with significant respiratory distress arise usually between 15 days and two months of life, contributing to feeding symptoms. Nasopharyngolaryngoscopy (NPL) is the gold standard for the diagnosis of laryngomalacia [1]. This defect in 90% of affected infants resolves spontaneously within the first year of life and complete recovery occurs at 18 months to 20 months old. About 10% of patients require surgical treatment. Tracheostomy is very rarely needed [2]. The cause is unknown. Most cases occur sporadically in people with no family history of the condition, although laryngomalacia may be inherited in some instances. Only a few cases of familial laryngomalacia have been described in the literature. In some of these cases, autosomal dominant or autosomal recessive inheritance can be associated with various syndromes such asneuraminidase deficiency, XY gonadal dysgenesis, Costello syndrome, DiGeorge syndrome, Cohen syndrome and acrocallosal syndrome [3].
Fig. (1). Genetic anomalies of the respiratory tract.

2.3. Congenital Laryngeal Palsy

Congenital laryngeal palsy may be unilateral or bilateral and represents 15%-20% of all cases of congenital anomalies of the larynx. The cause is often unknown but in some cases, paralysis is caused by reduced or absent function of the vagus nerve or its distal branch, the Recurrent Laryngeal Nerve (RLN) or as a result of central nervous system disorders, such as Arnold-Chiari syndrome, cerebral palsy, hydrocephalus, myelomeningocele or spine bifida. The bilateral abductor vocal cord paralysis (VCP) after laryngomalacia, is the most common cause (10-15%) of stridor. This condition is rare and requires tracheostomy in 35-70% cases. Shatla et al. (2017) reported a family with bilateral VCP affecting four male members in two generations and hence suggesting X-linked recessive inheritance [4]. Some syndromic associations are Robinow syndrome, Goldenhar syndrome, Down syndrome, Williams syndrome, DiGeorge syndrome, Mobius syndrome, Charcot-Marie-Tooth disease (type 1, 1b and 2), JS-X syndrome...
2.4. Tracheal Agenesis

Tracheal Agenesis (TA) is a very rare congenital malformation characterized by complete agenesis and in some cases partial trachea’s deformation with no proximal-distal communication between the larynx and the alveoli of the lung. The prevalence at birth is about 1 in 50,000 with a male predominance of 2:1. This malformation is usually fatal and in 90% of cases there are cardiovascular, gastrointestinal or genitourinary malformations. In animal models, different genetic defects are found, such as inactivation of Gli2, Gli3, Shh, Foxf1, and beatenin. A major role for the BMP (bone morphogenetic protein) type I receptor genes in mouse-models is suggested, however, no causal gene has been identified in human TA patients yet [5].

2.5. Tracheomalacia

Tracheomalacia is a rare congenital clinical condition characterized by flaccidity of the tracheal cartilage with collapse of the airway in exhalation, it is associated with upper respiratory tract infections. This condition occurs in about 1:2100 children [6]. Congenital tracheomalacia may be further subdivided into idiopathic or syndromic conditions. The condition may occur in isolation but may also be associated with other airway abnormalities such as laryngeal clefts, tracheoesophageal fistulas, laryngomalacia and bronchomalacia [7]. The syndromic conditions associated are CHARGE syndrome, DiGeorge syndrome (22q11 deletion), Down syndrome, trisomy 9, absence of the pectoralis muscle (Poland syndrome), congenital absence of the thumbs, pectus excavatum, Ehlers-Danlos syndrome, Hurler and Hunter (Poland syndrome), congenital absence of the thumbs, pectus excavatum, Ehlers-Danlos syndrome, Hurler and Hunter syndromes (mucopolysaccharidoses types I and II). Williams-Campbell syndrome is a rare condition of tracheobronchomalacia characterized by marked reduction or absence of cartilage throughout the tracheobronchial airway. Children with tracheomalacia can develop stridor, prolong inspiratory phase, low lung volumes, dyspnea on exertion, pneumonia or recurrent bacterial bronchitis cyanotic spells, apnea [8, 9]. The definitive diagnosis is based on the collection of a correct anamnesis associated with an appropriate radiological evaluation and fibrobroncoscopy represents the "gold standard". Puvahanditsin et al. reported a term male infant with congenital stridor secondary to tracheomalacia and a mild coarctation of the aorta. Molecular diagnosis was made performing whole genome SNP microarray analysis which showed an ~ 846-kb interstitial duplication of the short arm of chromosome 8 (8p11.21p11.1). The duplicated region includes 4 OMIM genes: FNTA (OMIM 134635), POMK (OMIM 615247), HGSNA (OMIM 610453), and POTEA (OMIM 608915). Array-CGH of the father and the infant’s 3-year-old sister showed the same microduplication [10].

2.6. Tracheal Stenosis

Congenital tracheobronchial stenosis is a rare condition with an estimated incidence of 1 in 64,500 births [11]. It results from a defect or arrest in the development of the foregut at stages 13-15 of embryonic development at around 4 to 6 weeks and this condition may also be associated with tracheoesophageal fistula. The clinical picture of tracheal stenosis includes dyspnea, cyanosis, feeding difficulties wheezing, inspiratory and expiratory stridor.

The pathogenesis of the tracheal stenosis has not been elucidated. It has been shown that the T-type voltage-gated Ca2+ channel Cav3.2 is essential for tracheal chondrogenesis. Mice lacking this channel (Cav3.2−/−) show congenital tracheal stenosis because of incomplete formation of cartilaginous tracheal support [12].

2.7. Tracheoesophageal Fistula

The Tracheoesophageal Fistula (TEF) is caused by a disorder of esophageal-tracheal differentiation. It is rare in an isolated form, more commonly associated with other esophageal malformations and/or Esophageal Atresia (EA). It can be congenital or acquired. The congenital form occurs from a defect of the separation process, between the tracheal diverticulum and the primitive intestine.

Although the exact cellular mechanisms underlying the formation of EA/TEF is undetermined, genetic studies in mouse models have provided some insights into the molecules that regulate the foregut morphogenesis. These studies have shown that the dorsal-ventral patterning of the signaling molecules and transcription factors in the foregut prior to separation is important for the subsequent separation. These factors include Sonic Hedgehog (Shh), Retinoid Acid (RA), Wnt and Bone morphogenetic protein (Bmp) pathway [13].

Other syndromic forms are associated with conditions such as trisomy 13, 18 and 21, de Feingold syndrome, VACTERL association. The VACTERL association is a polyvalent framework in which the acronym VACTERL indicates the presence of: vertebral malformations (V), anal atresia with or without fistula (A), cardiovascular abnormalities (C), esophageal atresia with tracheo-esophageal fistula (TE), renal malformations (R), limb abnormalities (L). Until now, only TNF-receptor associated protein 1 (TRAP1) had been reported as an autosomal recessive disease-gene for the VATER/VACTERL association. Our results suggest HSPA6 as a new candidate gene in VATER/VACTERL-like phenotypes. HSPA6 belongs to the heat shock protein (HSP) 70 family, while TRAP1 belongs to the HSP 90 family. Both of them seem to be important embryonic drivers in the formation of mouse embryonic forelimb tissue [14].

2.8. Abnormalities of Bronchial Branching

Such anomalies can be additive (the most common), or subtractive. The most frequent anomaly is given by the right supernumerary upper lobe bronchus, which can be original from the trachea or the right bronchus while the absence of a bronchus of the upper lobe is the most frequent subtractive anomaly [15]. Instead the most frequent segmental anomaly given by double stem apical lower lobe segmental bronchus, which is more frequent on the right lung [16].
2.9. Bronchial Isomerism Syndromes

A series of syndromes cause symmetric lobar bronchial patterns (bilateral right or left lung). These syndromes have been identified in which anatomic anomalies of the bronchi and are associated with congenital cardiopathies, abnormal visceral situs and/or spleen anomalies (absent, multiple, bifida, accessory spleen). The most common are:

- Ivemark syndrome is a rare disorder characterized by asplenia or hypoplasia of the spleen, cardiac malformations, bilateral eparterial;
- bronchi (bilateral right or 3-lobed lung) and abnormal disposition of the internal organs of abdomen [17];
- M-anisosplenia, characterized by bilateral eparterial bronchi and a normal visceral situs [18];
- Polysplenia, characterized by bilateral hyparterial bronchi (bilateral left or 2-lobed lung), abnormal visceral situs and cardiac malformations [18];
- F-anisosplenia, characterized by bilateral hyparterial bronchi with a visceral situs and cardiac malformations [18];
- Situs inversus, characterized by reversed bronchial pattern (eparterial bronchus on left and hyparterial on right) and reversed visceral situs [18].
- Kabuki Syndrome (KS) is a rare, multiple congenital anomalies/intellectual disability syndrome caused by mutations of MLL2 gene, which codifies for a histone methyltrasferase that regulates the embryogenesis and the tissue development. KS can be associated to left-bronchial isomerism [19].

2.10. Bronchomalacia

Bronchomalacia is characterized by increased compliance of the bronchi with dynamic collapse during exhalation. Typically, bronchomalacia refers to the right and left main bronchi, though any bronchus can be affected [7]. Patients can present with cough and harsh, monophonic wheezing especially during viral illnesses; however, unlike tracheomalacia, wheezing is most often unilateral [20]. Bronchoscopy is the most popular method for an assessment of bronchomalacia and the conventional criterion is more sensitive. Acquired bronchomalacia can be caused by external compression from congenital heart malformations, a bronchial cyst, or other condition and it is not uncommon in premature infants who have received extended mechanical ventilation. Chitayat et al. have identified a syndrome characterized by hyperfalanisms, facial anomalies and primary bronchomalacia associated with missense mutation c.266A>G p. (Tyr89Cys) of the ERF gene (Ets2 Repressor Factor) [22]. Bronchomalacia has also been associated with Larsen syndrome, Fryns syndrome, and pectus excavatum [23].

2.11. Bronchiectasis

Bronchiectasis is conventionally defined as irreversible dilatation of the bronchial tree. Excluding Cystic fibrosis, previous pneumonia and recurrent lower airway infections are the most common causes of pediatric bronchiectasis; others risk factors include primary immune deficiencies, Primary Ciliary Dyskinesia (PCD), foreign body aspiration and structural airways abnormalities such as bronchomalacia and congenital tracheo-bronchomegaly [24]. Kartagener's syndrome is a subset of primary ciliary dyskinesia, a rare autosomal recessive inherited disorder characterized by the clinical trial of chronic sinusitis, bronchiectasis, and situs inversus. Abnormal ciliary structure or function leading to impaired ciliary motility is the main pathophysiologic problem in Kartagener's syndrome [25]. Williams-Campbell Syndrome (WCS) is a rare congenital syndrome characterized by defective or completely absent bronchial wall cartilage in subsegmental bronchi, leading to distal airway collapse, producing a mechanical abnormality that may contribute to the formation of bronchiectasis distal to the collapsed bronchi [26].

2.11.1. Primary Ciliary Dyskinesia

Primary Ciliary Dyskinesia (PCD), also called the immotile-cilia syndrome, is an autosomal-recessive inherited disorder of mucociliary clearance secondary to ciliary dysfunction. The ciliary defect can be structural or functional, causing an incompetent mucociliary clearance and mucus retention. The underlying cause is a defect of cilia in the airways, making them unable to beat (ciliary immotility), unable to beat normally (ciliary dyskinesia), or absent altogether (ciliary aplasia). PCD is characterized by chronic upper and lower respiratory tract infections (otosinopulmonary disease), male infertility, and situs inversus. Respiratory distress in neonates, chronic suppurative lung disease, chronic serous otitis media, and chronic rhinosinusitis are the common respiratory presentations of PCD [27].

Primary Ciliary Dyskinesia (PCD) is inherited as an autosomal recessive disease (Mendelian inheritance in man [MIN] 244400) [28]. More than 30 different PCD causing genetic variants have been described, including mutations in the axonemal outer dynein arms (DANH5, DNH9, DNH12, DNAI1, ARM4, CCDC103), inner dynein arms (DNAL1), assembly proteins (DNAAF3), and radial spokes (RSPH4A, RSPH9) [29].

A diagnosis of PCD is confirmed by either biallelic mutations in a known PCD gene or a classic PCD ultrastructural ciliary defect observed by transmission electron microscopy (TEM) [29]. However, in up to 30% of suspected PCD cases, genetic testing and TEM can be nondiagnostic. Therefore, many ancillary tests may help to clarify the diagnosis, including nasal nitric oxide (nNO), high-speed videomicroscopy analysis (HSVA), and immunofluorescence (IF) [30].

Methods to determine mucociliary transport are limited by availability and difficulties with specificity and, thus, are
infrequently used. Mucociliary transport involves a two-component system, and the abnormality may reside in the mucus rather than in the cilia. For example, patients with cystic fibrosis generate very viscous mucus, which their normal cilia are unable to push forward. Mucus from patients with asthma also is more viscous than in healthy persons.

The European Respiratory Society guidelines for the diagnosis of PCD recommend an assessment for PCD if several of the following clinical features exist: persistent wet cough, situs anomalies, congenital cardiac defects, persistent rhinitis, chronic middle-ear disease with or without hearing loss, history in term infants of neonatal upper and lower respiratory symptoms, or neonatal intensive care admittance [29].

A recent consensus recommendation from the Genetic Disorders of Mucociliary Clearance Consortium in North America proposed PCD diagnostic criteria based on age (Table 1) [31, 32].

The aim of PCD treatment is to maintain or recover lung function by early diagnosis and management of complications. The main objectives are the clearance of mucus, prevention of respiratory infections, and intense treatment of bacterial infections.

Measures used to increase mucus clearance include positive pressure expiratory devices, intrathoracic oscillatory devices, high-frequency chest compression using vest therapy, manual chest physiotherapy, postural drainage, autogenic drainage, active cycle breathing, and exercise [33].

The management is based essentially on a prompt treatment of respiratory tract infections [34]. Bronchiectasis is a prominent feature in PCD, and surgical resection with lobectomy or segmentectomy in patients with bronchiectasis is thought to reduce the risk of infection progressing.

A recent in vitro study demonstrated the efficacy of premature termination codon (PTC) read-through stimulation in PCD-causing mutations with aminoglycosides. PTC readthrough has been shown to repair functional protein expression and decrease symptoms in several genetic disorders caused by loss-of-function mutations [35].

Lung transplantation has been described in a few case reports, and indicated increased 1-year mortality. More recently, an American study demonstrated that the survival outcome of a large group of patients with PCD and Kartagener’s syndrome was similar to that of the general population with lung transplantation for common indications like COPD and CF [36].

### Table 1. Recommended PCD diagnostic criteria by age.

<table>
<thead>
<tr>
<th>Newborns (0-1 month of age)</th>
<th>Situs inversus totalis and unexplained neonatal respiratory distress at term birth plus at least one of the following:</th>
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<td></td>
<td>• Diagnostic ciliary ultrastructure on electron micrography.</td>
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<td></td>
<td>• Biallelic mutations in one PCD-associated gene.</td>
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<tr>
<td></td>
<td>• Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions.</td>
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<th>Children (1 month to 5 years)</th>
<th>Two or more major PCD clinical criteria (see below) plus at least one of the following (nasal nitric oxide not included in this age-group, since it is not yet sufficiently tested):</th>
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<tr>
<td></td>
<td>• Diagnostic ciliary ultrastructure on electron micrography.</td>
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<td></td>
<td>• Biallelic mutations in one PCD-associated gene.</td>
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<td>• Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions.</td>
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<tr>
<th>Children 5-18 years of age and adults</th>
<th>Two or more major PCD clinical criteria (see below) plus at least one of the following:</th>
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<td>• Nasal nitric oxide during plateau &lt;77 nL/min on two occasions, &gt;2 months apart, with cystic fibrosis excluded.</td>
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<tr>
<td></td>
<td>• Diagnostic ciliary ultrastructure on electron micrography.</td>
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<td></td>
<td>• Biallelic mutations in one PCD-associated gene.</td>
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<td></td>
<td>• Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions.</td>
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<tr>
<th>Major clinical criteria for PCD diagnosis</th>
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<tr>
<td>1. Unexplained neonatal respiratory distress (at term birth) with lobar collapse and/or need for respiratory support with CPAP and/or oxygen for &gt;24 hours.</td>
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<tr>
<td>2. Any organ-laterality defect: situs inversus totalis, situs ambiguous, or heterotaxis.</td>
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<tr>
<td>3. Daily, year-round wet cough starting in the first year of life or bronchiectasis on chest CT.</td>
<td></td>
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<tr>
<td>4. Daily, year-round nasal congestion starting in the first year of life or pansinusitis on sinus CT.</td>
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Abbreviations: PCD, primary ciliary dyskinesia; CPAP, continuous positive airway pressure; CT, computed tomography.
3. CONGENITAL LUNG ANOMALIES

Congenital lung anomalies include: lung hypoplasia, lobar agenesis, Congenital Diaphragmatic Hernia (CDH), bronchopulmonary dysplasia (BPD), and surfactant protein abnormalities.

During the last 2 decades, important contributions have been made for a better understanding of the molecular regulation of normal lung development, and by using different methodologies, such as knocking down or up-regulating gene expression, are making relevant discoveries about the molecular mechanisms underlying congenital lung lesions. Therefore, knowledge of the development of normal lung is essential to understand the underlying molecular mechanisms of congenital cystic lung malformations [37].

In contrast to other developmental anomalies, only a few genes have been implicated in the developmental lung diseases [38]. These genes include four T-box genes (TBX2, TBX3, TBX4, and TBX5) and FGF10. While in vivo depletion of Tbx4 in murine lung organ cultures causes reduction of lung branching, coexistent depletion of Tbx4 and Tbx5 inhibits formation of new lung branches. Similar results have been obtained in vivo: Tbx2-deficient mice have hypoplastic lungs, indicating that Tbx2 is one of the key members of the network regulating mouse lung organogenesis [39]. To enlighten the pathogenetics of human lung development, Karolak et al. (2019) studied a collection of samples obtained from deceased individuals interstitial neonatal lung disorders such as acinar dysplasia, congenital alveolar dysplasia, and other lethal lung hypoplasias. They identified rare heterozygous copy-number variant deletions or single-nucleotide variants (SNVs) involving TBX4 or FGF10 in 61% individuals [40]. Nowadays, it is known that biallelic variation at TBX4 or FGF10 can result in a mutational burden and perturbation of the epithelialmesenchymal signaling pathway involved in lung organogenesis, leading to lethal lung disease [40]. Furthermore, Retinoic acid (RA), the active form of vitamin A, is synthesized in the foregut by retinaldehyde dehydrogenase 2 (RALDH2), and mice deficient for this enzyme fail to develop lungs. Furthermore, RA controls the activity of transforming growth factor-beta (TGFβ) in the lung field through its receptors RAR α and RAR β, which control the local mesenchyme expression of FGF10 [41]. Deletion of both RAR α and RAR β leads to pulmonary agenesis, tracheoesophageal fistula, and lobar agenesis [42].

3.1. Pulmonary Hypoplasia

Pulmonary hypoplasia is the incomplete development of lung tissue. A reduced number of lung cells, airways, and alveoli are the hallmark and can be seen unilaterally or in both lungs. Pulmonary hypoplasia can be grouped into primary pulmonary hypoplasia, in which it is the intrinsic lung development that is abnormal, or secondary pulmonary hypoplasia, in which the lung development is compromised secondary to another abnormality. Oligohydramnios is a common cause of secondary pulmonary hypoplasia and can be due to renal malformations, early and prolonged amniotic fluid leak, placental abnormalities, or intrauterine growth restriction. Renal and urinary tract anomalies and other conditions causing oligohydramnios include renal agenesis [43], sirenomelia with renal agenesis [44], renal (hypo)dysplasia [45], urethral atresia and other obstructive uropathies, infantile polycystic disease, and chronic amniotic fluid leak [45]. Lesions that occur in the thorax can cause compression of the lungs and lead to hypoplasia, as is seen with congenital diaphragmatic hernia, cystic lung disease, extreme cardiomegaly [46], thoracic spinal deformity (as in iniencephaly and Kippel-Feil syndrome), thoracic deformity, especially with skeletal dysplasia syndromes (Jeune's thoracic asphyxiating dystrophy, thanatophoric dwarfism, diastrophic dwarfism, spino Ronaldoiphipsyseal dysplasia, Ellis-van Crevel syndrome, achondroplasia, and perhaps others) [47], thoracic deformity due to muscular weakness (e.g., arthrogryposis).

3.2. Lobar Agenesis

Lobar agenesis of lung is rare and usually affects the right upper and middle lobes. Lobar agenesis is classified into three categories:

1. Agenesis shows complete absence of bronchus, lung parenchyma, and associated vessels;
2. Aplasia has a rudimentary bronchus with absent lung parenchyma;
3. Hypoplasia has hypoplastic bronchus and lung parenchyma [48].

The etiopathogenesis is unclear; however, genetic, teratogenic agents (allopurinol), and Vitamin A deficiency during pregnancy have been hypothesized as its causes [49]. The abnormality goes undetected or is incidentally detected in the majority of cases. Symptomatic patients present in early childhood with symptoms of recurrent respiratory tract infection while others remain asymptomatic. Underdevelopment of lung is usually associated with other congenital abnormalities of cardiovascular, musculoskeletal, and genitourinary system, more commonly toward the ipsilateral side.

3.3. Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) has an incidence of approximately 1 in 2500-3000 live births and is characterized by a diaphragmatic defect, pulmonary hypoplasia and HP.CDH may be caused by disturbances in the RA-TGFβ-Fgf10 interactions that are fundamental for airway branching and muscularization of the pulmonary vasculature. There are also mutations in the genes STRA6 (Stimulated by Retinoic Acid 6) and LRP2 (Low density lipoprotein-related protein 2) that play a role in autosomal recessive conditions, like Matthew-Wood syndrome or Donnai-Barrow syndrome, deletions of COUP-TFI on chromosome 15q26.1-26.2, FOG2 (ZFPM2; chromosome 8q23.1) or SOX7 that lead to an autosomal dominant form of CDH with variable penetrance and deletion of the FRAS1-related extracellular matrix 1 (FREM1) gene.
3.4. Bronchopulmonary Dysplasia

BPD is a chronic lung disease characterized by abnormalities of alveolarization and pulmonary microvascular development. It is typical of preterm newborns with birth weight <1000 g and receive prolonged oxygen therapy and mechanical ventilatory support. During fetal lung development, the levels of HIF1a (hypoxia-inducible transcription factor-1) are high and favor the expression of VEGF and other angiogenic factors while in premature children the levels of HIFa are very low. Mechanical ventilation and oxygen therapy in preterm newborns lead to a greater expression of antiangiogenic genes and a reduced expression of proangiogenic genes with consequent lower vascular expansion. In addition to angiogenic factors, the retinoid signaling pathway in the pathogenesis of BPD may play a role. Low levels of vitamin A, found in preterm newborns, would play a role in impairing pulmonary vascular development [50].

4. ANOMALIES OF THE PULMONARY VASCULATURE

Pulmonary vascular malformations include a spectrum of anomalies, ranging from abnormal vascular connections to normal lung tissue, to vascular malformations that connect to abnormal lung tissue.

The pulmonary vascular malformations can regard the pulmonary artery (Pulmonary agenesis-aplasia-hypoplasia complex, proximal interruption of pulmonary artery, pulmonary artery sling), the pulmonary vein (pulmonary vein stenosis, venous varix), both pulmonary artery and vein (pulmonary arterio-venous malformation (AVM), or may be the result of a combination of parenchymal and vascular abnormalities (Pulmonary sequestration intralobar/extra-lobar, Scimitar syndrome/hypogenetic lung syndrome).

Pulmonary vascular diseases of the newborn comprise a wide range of pathological conditions with developmental abnormalities in the pulmonary vasculature. Pulmonary vascular development is fundamental for normal lung development.

4.1. Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PH) is characterized by persistent increased resistance of the vasculature and abnormal vascular response and there are 5 types: idiopathic pulmonary arterial hypertension, pulmonary hypertension due to left heart disease, pulmonary hypertension due to lung diseases and/or hypoxia, chronic thromboembolic pulmonary hypertension, and pulmonary hypertension with unclear multifactorial mechanisms. Idiopathic pulmonary arterial hypertension (iPAH) has an incidence of approximately 0.7 per million. It is often associated in children with genetic syndromes like Down syndrome, DiGeorge syndrome, VACTERL syndrome, CHARGE syndrome, and Noonan syndrome and can also be inherited. Heritable forms of iPAH are caused by mutations and deletions in the bone morphogenetic protein receptor 2 (BMPR2), two receptors of the TGFb/BMP pathway, activin receptor-like kinase 1 (ACVRL1), and endoglin (ENG) and polymorphism detected in the serotonin 5-hydroxy tryptamine transporter (5HTT).

4.2. Alveolar Capillary Dysplasia

Alveolar capillary dysplasia (ACD) is a lethal pulmonary congenital disease characterized by insufficient formation of alveolar capillaries, abnormal gas exchange, severe hypoxemia and pulmonary hypertension. In most patients with ACD mutations of FOXF1 and deletions of the 50 regulatory region of this transcription factor gene have been found while alterations in pattern HIF1/HIF2 could play a role in the premature growth arrest and vascular abnormalities but have not yet been confirmed in human cases [50].

4.3. Pulmonary Artery Stenosis

Congenital peripheral stenosis of the pulmonary artery is a common congenital heart lesion and usually is associated with several genetic syndromes such as Alagille syndrome (deletion in chromosome 20), Williams syndrome (deletion in chromosome 7), cutis laxa, Ehlers-Danlos syndrome, Noonan syndrome (mutation in chromosome 12) and Silver-Russell syndrome. My-Linh D et al. reported an abnormal case of isolated pulmonary stenosis in a non-syndromic subject in which deletion of 16p11.2 on chromosomal microarray is detected. Several other studies are needed to identify any genetic mechanisms underlying other cases of idiopathic pulmonary artery stenosis and to testing ground for new genetic therapeutic entities [51].

4.4. Agenesis of Pulmonary Artery

Agenesis or proximal interruption of the pulmonary artery is a rare anomaly which occurs due to embryological failure of development of the proximal portion of the main pulmonary artery, with the presence of pulmonary artery at the hilum and distally. It is more common on the right side, and leads to lung hypoplasia. Unilateral Pulmonary Artery Agenesis (UPAA) is a rare malformation that can present as an isolated anomaly or may be associated with certain congenital cardiac anomalies, such as tetralogy of Fallot atrial septal defect, coarctation of aorta, right aortic arch, truncus arteriosus and pulmonary atresia. Clinical presentation is non-specific which makes the diagnosis elusive; chronic dyspnea, hemoptysis or recurrent infections are the most common manifestations [52]. Most patients who have no associated cardiac anomalies have only minor or absent symptoms and survive into adulthood. These patients give a history of previous consultation with different specialists that results in a variety of erroneous diagnoses, including tuberculosis, Swyer-James syndrome, and lung tumor [53].

4.5. Pulmonary Artery Sling

Pulmonary artery sling (PAS) is a vascular anomaly in which the left pulmonary artery has an aberrant origin from the proximal right pulmonary artery, and crosses the mediastinum between the trachea and the esophagus, thus forming a ‘sling’ around the distal trachea and causing tracheo-bronchial compression [54]. PAS is an unusual anomaly that has an incidence of 3-6% of all abnormalities.
of the aortic arch system which is found in association with few genetic disorders. It has been repeatedly described in Mowat-Wilson syndrome in association with mutation in exon 7 of the ZFHX1B gene located at 2q22 chromosome. ZFHX1B encodes the protein-1 that interacts with Smad (SMADIP1 or SIP1), widely expressed in embryological development in fact its mutation is associated with congenital malformations, such as Hirschsprung disease, genital anomalies, congenital heart diseases, agenesis of the corpus callosum, typical facies and severe mental retardation [55].

4.6. Pulmonary Vein Stenosis

Primary Pulmonary Venous Stenosis (PVS) is a rare disorder that usually occurs in association with congenital heart disease or anomalous pulmonary venous return [56]. Its incidence ranging from 1.7:100,000 in the general population under 2 to 30:100,000 patients undergoing congenital heart surgery or catheterization. The primary etiology involves a neointimal proliferation of myofibroblasts with progressive stenosis and obliteration of the vessels. Studies on the genetic basis for PVS are limited. Several angiogenesis-related genes have been hypothesized, including Angio-Associated Migratory cell Protein (AAMP), ephrin A4 (EPHRA4) receptor, sphenogeline-1-phosphate phosphatase-2 (SGPP2), C-terminal domain of small phosphatase 1 (CTDSP1), secretogranin II (SCG2), channel voltage-dependent potassium, Isk-related family, member 4 (KCNE4), Serine / Threonine Kinase 16 (STK16), serine / threonine protein kinase 36 (STK36) and serine / threonine protein kinase interacting protein (STK11P). In addition to the classic surgical correction procedure, pharmacological therapies have been attempted with imatinib mesylate with or without bevacizumab. Prosnitz et al. have hypothesized a possible association between the development of pulmonary venous stenosis and the Smith-Lemli-Opitz syndrome (SLOS), an autosomal recessive cholesterol metabolism disease associated with multiple congenital anomalies, including the APV. Numerous other studies are needed to confirm that the metabolic pathway of cholesterol may play a role in promoting intimal proliferation and therefore in the physiopathology of pulmonary venous stenosis. All patients with suggestive syndromic presentation should be screened for Smith-Lemli syndrome-Opitz with serum cholesterol research and if SLOS is confirmed an echocardiogram should be conducted to quickly and early detect a pulmonary venous stenosis [57].

4.7. Pulmonary AVM

A pulmonary AVM is an abnormal communication between pulmonary artery and vein branches, without normal intervening capillaries. It may be congenital or acquired (post-trauma or infections). Pulmonary AVMs show lower lobe predominance in 50-70% cases [56-58]. Lesions smaller than 2 cm are usually asymptomatic. Larger lesions result in right-to-left shunts, and can present with pulmonary hemorrhage or paradoxical embolization.

Hereditary Hemorrhagic Telangiectasia (HHT), or Rendu-Osler-Weber syndrome is an autosomal dominant condition characterized by dilated blood vessels, in which up to 35 % of cases have frequently multiple pulmonary AVMs [59, 60]. The dysplasias can involve all the organs in our body. Almost all patients with HHT suffer from epistaxis; infact mostly, this is the first presenting symptom. The characteristic defects in the vascular wall are seen in HHT results in the development of highly vulnerable lesions with very thin vessel walls [61]. Currently, mutations of 5 different genes have been identified to cause the disease. Mutations in ENG (endoglin) on chromosome 9 encoding a defective endoglin lead to type 1 HHT (61%), and mutations in ACVRL1 (activin A receptor type II-like 1 gene) on chromosome 12 encoding ALK1 lead to type 2 HHT (37%). Both genes are membrane proteins that are essential in modulating the signal pathway of transforming growth factor (TGF)-b. They are expressed on endothelial cells. The homozygous form of HHT leads to death (homozygous lethality) [62]. Once a mutation has been identified in a family of patients with HHT, then specific screening for carriers of this trait can be realized among any children in the family. Screening is performed for the endoglin gene (ENG, HHT1), for activin A receptor type II-like 1 gene (ACVRL1, HHT2) and for mutations of the MADH4 gene on chromosome 18 [63].

4.8. Scimitar (Hypogenetic Lung) Syndrome

Scimitar syndrome also known as hypogenetic lung or venolobar syndrome, is a type of partial anomalous pulmonary venous return affecting the right lung, with associated abnormalities. The anomalous vein most commonly into the inferior vena cava (IVC), and less commonly into the right atrium, superior vena cava, portal vein or hepatic veins. Common associations include hypoplasia of the lung and pulmonary artery, cardiac dextroversion, and abnormal systemic arterial supply to the right lung. In 25% cases other congenital anomalies may be associated; these include atrial and ventricular septal defects, patent ductus arteriosus, tetrology of Fallot, diaphragmatic defects and horseshoe lung. The name ‘scimitar’ (meaning curved Turkish sword) refers to the curved appearance of the anomalous vein as it courses toward the IVC.

CONCLUSION

In conclusion, major advances in our comprehension of the genetic basis of pulmonary diseases have led to new investigations into their underlying pathophysiology and, sometimes, contributed to clarifying on more frequent sporadic forms. The identification of causative genes has allowed prenatal diagnosis for many diseases, thereby increasing the opportunity for survival through adequate and prompt management.

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REFERENCES


