

Interstitial Lung Disease in Childhood: Clinical and Genetic Aspects

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ABSTRACT: Interstitial lung disease (ILD) in childhood is a heterogeneous group of rare pulmonary conditions presenting chronic respiratory disorders. Many clinical features of ILD still remain unclear, making the treatment strategies mainly investigative. Guidelines may provide physicians with an overview on the diagnosis and therapeutic directions. However, the criteria used in different clinical studies for the classification and diagnosis of ILDs are not always the same, making the development of guidelines difficult. Advances in genetic testing have thrown light on some etiologies of ILD, which were formerly classified as ILDs of unknown origins. The need of genetic testing for unexplained ILD is growing, and new classification criteria based on the etiology should be adopted to better understand the disease. The purpose of this review is to give an overview of the clinical and genetic aspects of ILD in children.

KEYWORDS: interstitial lung disease, diffuse lung disease, surfactant protein, genetic testing, classification

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Introduction

Interstitial lung disease (ILD) in childhood is a heterogeneous group of rare pulmonary conditions associated with high morbidity and mortality, which presents chronic respiratory disorders accompanied with immunological problems as well as growth and developmental abnormalities.¹ These disorders have various lung pathologies, including inflammatory and fibrotic changes. As the disease involves areas in the lung other than the interstitium, the term “diffuse lung disease” (DLD) is often used in the literature describing the same group of disorders.^{2,3} Recently, the term “childhood interstitial lung disease (chILD) syndrome” has been adopted in a practical guideline written by the American Thoracic Society to provide specific criteria to help the diagnosis of unexplained respiratory distress in infants.⁴ The chILD syndrome requires the presence of three of the following criteria in the absence of known primary disorders: (1) respiratory symptoms (cough, difficult breathing, or exercise intolerance), (2) respiratory signs (tachypnea, retractions, crackles, digital clubbing, failure to thrive, or respiratory failure), (3) hypoxemia, and (4) diffuse chest infiltrates on chest X-ray (CXR) or computed tomography (CT) scan.^{2,5} There is an increasing number of reports concerning chILD, especially because of advances in genetic testing methods, but many points still remain unclear. Here, we review the following

clinical features of chILD: epidemiology, classification, genetic aspects, diagnosis and treatment.

Epidemiology

The frequency of chILD was reported in three studies,¹ in which the incidence of ILD was estimated, respectively, at 1.3 cases/1,000,000 children <17 years of age/year⁶; 108–162 cases/1,000,000 children <15 years of age/year⁷; and 3.6 cases/1,000,000 children <17 years of age/year.⁸ The large variation observed between the three studies can be explained by the difference in the population included in each study and the difference in criteria used for ILD diagnosis. At present, it is difficult to fix a precise number for the frequency of chILD, and multicenter studies using the same diagnostic criteria with a central database are expected to be able to conduct more accurate epidemiological study in the future.⁴

Classification of ILD

The classification of ILD in children was formerly based on adult pathological ILD classification. However, children's cases do not always fall into this classification method since many cases in children have etiologies and pathologies specific to childhood. Additionally, lung biopsy specimens are not always available in young children, so a histological



classification may not be adequate for this age group. Recently, classifications based on the etiology of ILDs have been presented,⁹ and these seem more rational for chILD. Since new etiologies for chILD were found relatively recently, such as the *COPA* gene involvement,¹⁰ the classification of chILD is still changing continuously. Here, we summarize the classification of chILD, adapted from several past works,^{4,11,12} based on etiology and clinical characteristics (Table 1). We divided ILDs into three subtypes according to the origin of the primary condition involving pulmonary conditions: ILD specific to infancy (including inborn anomalies and genetic aberration); ILD related to a primary systemic disease; and exposure-related ILDs.

ILD specific to infancy. ILD observed mainly in infancy is often related to congenital malformations, genetic mutations, or chronic damage of the lung because of premature birth or other congenital anomalies.

- Acinar dysplasia is a rare developmental disorder characterized by diffuse malformation of the alveolar structure.¹³ It is a rare cause of neonatal death shortly after delivery at term. The histology shows poorly subdivided parenchyma and a virtual absence of saccular or alveolar spaces necessary for gas exchange.¹⁴ The etiology of acinar dysplasia is still unknown, but an altered genetic mechanism in epithelial differentiation and branching morphogenesis is suspected.^{15,16}
 - Alveolar-capillary dysplasia with pulmonary vein misalignment (ACD/MPV) is a rare fatal developmental lung abnormality associated with severe hypertension and progressive respiratory failure in term newborn.¹⁷ Histologically, there is inadequate development of the capillary bed and a malposition of pulmonary veins in the bronchovascular bundles adjacent to the pulmonary arteries. The veins and venules are typically dilated and congested. Although the largest pulmonary veins may be normally located in the interlobular septa, the smaller dilated veins and venules are abnormally positioned, accompanying the artery branches. There is also a striking reduction in the capillary bed, with most capillaries in the center of the widened alveolar walls, lacking the usual proximity to the alveolar epithelium.⁹ ACD/MPV may be familial and associated with congenital cardiovascular, gastrointestinal, or genitourinary anomalies. *FOXF1* gene mutations and deletion have been reported to be a cause of ACD/MPV.^{18–20} Fetal and postnatal growth abnormalities of the lung may impair alveolization and then cause ILD.
 - Impaired alveolar growth during gestation or early after birth is a common cause of chILD in premature infants.⁵ Congenital alveolar dysplasia is a rare abnormality of lung development in which the lungs present incomplete alveolization despite term gestation. It is considered to be a severe form of lung hypoplasia in which the growth is stopped at the saccular stage of development.²¹
- Restriction of the fetal thoracic space, abnormalities in the amniotic fluid volume, or cardiac anomalies can lead to deficient lung growth, known as pulmonary hypoplasia.²² Postnatal growth abnormality of the lung is seen in chronic lung disease of prematurity or bronchopulmonary dysplasia.
- Additionally, lung growth could be impaired in cases of chromosomal aberration (ie, trisomy 21²³) or congenital heart diseases leading to a secondary ILD state.^{11,24}
 - Genetic surfactant dysfunctions, including *SPFTB*, *SPFTC*, or *ABCA3* gene mutation, are a group of rare lung diseases occurring predominantly in infants and children, caused by mutations in genes affecting surfactant production and processing.^{25–27} This group of diseases is heterogeneous, and the severity of symptoms and age of onset are associated with the gene affected. More precise features of genetic surfactant dysfunction will be explained further in this paper.
 - Conditions specific to infancy such as pulmonary interstitial glycosgenesis (PIG) or neuroendocrine cell hyperplasia of infancy (NEHI) are also causes of chILD and still poorly understood.⁹ PIG is associated with early onset respiratory distress characterized by interstitial expansion because of increased mesenchymal cellularity.²⁸ These interstitial cells have bland, uniform ovoid nuclei with pale chromatin and increased cytoplasmic glycogen demonstrable by periodic acid–Schiff (PAS) stain. PIG may show diffuse but also patchy distribution. The prognosis of PIG is usually good, and the symptoms can improve over the time or by addition of steroid therapy.⁹ NEHI was described in 2005 as the pathologic correlate of the clinical syndrome of persistent tachypnea of infancy. The typical clinical signs of patients presenting NEHI are tachypnea, hypoxemia, and retractions and crackles on examination. Radiological studies show hyperexpansion of the lungs and patchy ground-glass opacities, most prominent in the central right middle lobe and lingula. The etiology of NEHI is still unclear but genetic factors, secondary response to lung injury, viral infection, and chronic hypoxia may be possible causes of the disease. Immunohistochemistry using bombesin is needed to highlight the increased number of neuroendocrine cells.²⁹ Guidelines for histologic diagnosis include (a) neuroendocrine cells in at least 75% of total airway profiles, (b) neuroendocrine cells representing at least 10% of epithelial cells in individual airway profiles, (c) large and/or numerous neuroepithelial bodies, and (d) absence of other significant airway or interstitial disease.⁹ The clinical course of NEHI is usually good, and the disease may improve with time, but in some cases the symptoms may persist in toddlers and older children.⁹
- ILD related to a primary systemic disease.** ChILD may also be associated with systemic diseases.³⁰

**Table 1.** Classification of pediatric interstitial lung disease by etiology.

1) Interstitial lung disease observed mainly in infancy
– Developmental disorders and growth abnormalities
+ Acinar dysplasia
+ Alveolar-capillary dysplasia with pulmonary vein misalignment
+ Primary alveolar growth abnormalities: congenital alveolar dysplasia / pulmonary hypoplasia / bronchopulmonary dysplasia
+ Structural alveolar anomalies due to congenital heart disease or chromosomal abnormalities
– Genetic surfactant dysfunctions
+ <i>SPFTB</i> gene mutations
+ <i>SPFTC</i> gene mutations
+ <i>ABCA3</i> gene mutations
+ <i>NKX2.1</i> gene mutations
– Conditions specific to infancy
+ Pulmonary interstitial glycolipidosis
+ Neuroendocrine cell hyperplasia of infancy
2) Interstitial lung disease related to a primary systemic disease
– Autoimmune diseases
+ Rheumatoid arthritis
+ Systemic sclerosis
+ Systemic lupus erythematosus
+ Sjögren syndrome
+ Dermatomyositis and polymyositis
+ Ankylosing spondylitis
+ Mixed connective tissue disease
– Pulmonary vasculitis
+ Wegener's granulomatosis
+ Churg-Strauss syndrome
+ Microscopic polyangitis
+ Goodpasture syndrome
+ Henoch-Schönlein purpura
+ Cryoglobulinemic vasculitis
– Granulomatous diseases
+ Sarcoidosis
+ Post-infectious chronic granulomatous diseases
+ Histiocytosis X
+ Pulmonary vasculitis (see above)
– Langerhans cell histiocytosis
– Metabolic disorders
+ Lysosomal diseases (Gaucher's disease, Niemann-Pick disease, Hermansky-Pudlak syndrome)
+ Familial hypercalcemia with hypocalciuria
– Others
+ Eosinophilic lung diseases
+ Malignancy

(Continued)

Table 1. (Continued)

+ Inflammatory bowel diseases and celiac disease
+ Primary biliary cirrhosis and chronic hepatitis
+ Neurocutaneous disorders (tuberous sclerosis, neurofibromatosis)
+ Amyloidosis
+ Transplantation related interstitial lung disease and graft-versus-host disease
3) Exposure-related Interstitial lung disease
– Hypersensitivity pneumonitis
– Interstitial lung disease caused by environmental factors (pollution, tobacco, toxic inhalation)
– Post-infectious non-granulomatous interstitial lung disease
– Aspiration
– Interstitial lung disease following medical treatments (radiation, drugs)

- Autoimmune diseases are one of the major causes of chILD.³⁰ The main disorders to be considered in childhood are rheumatoid arthritis, systemic lupus erythematosus (SLE) and systemic sclerosis. Sjögren syndrome, dermatomyositis and polymyositis, ankylosing spondylitis and mixed connective tissue disease are other causes of ILD though with a lesser frequency. The primary diagnosis should be made by clinical history, physical examination and serological analysis of auto-antibodies. The main auto-antibodies are rheumatoid factor (RF) and anticyclic citrullinated peptide for rheumatoid arthritis; antinuclear antibodies, anti-native DNA and anti-nucleosome antibodies for SLE; and anti-centromere, anti-topoisomerase I and II antibodies for systemic sclerosis. Each disease has specific laboratory features, which are summarized by Clement et al.¹² In some cases, ILD can appear prior to systemic symptoms, and the onset of the autoimmune disease may develop only few months after the ILD episode. Common histologic patterns in the rheumatologic disorders include fibrotic bronchiolitis and other forms of lymphoid hyperplasia.
- Systemic vasculitis can present ILD when they affect pulmonary small vessels (Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangitis, Goodpasture syndrome, Henoch-Schönlein purpura, cryoglobulinemic vasculitis). Here also, specific serological features may be present (ie, p-ANCA), and the primary diagnosis should be investigated carefully.¹²
- Granulomatous diseases, including sarcoidosis, histiocytosis X, post-infectious chronic granulomatous diseases and pulmonary vasculitis, are characterized by the presence of granulomas defined as a "focal, compact collection of inflammatory cells in which mononuclear cells predominate." The inflammatory mechanism could be



the cause of lung injury leading to ILD. The diagnosis of the primary granulomatous disease may be useful to treat correctly the respiratory symptoms.

- Langerhans cell histiocytosis is characterized by an abnormal proliferation of Langerhans' cells.³¹ Children with pulmonary Langerhans cell histiocytosis present in a variety of ways. They can be asymptomatic or present common symptoms such as nonproductive cough and dyspnea. CT of the chest is a useful and sensitive tool for the diagnosis. The combination of diffuse, irregularly shaped cystic spaces with small peribronchiolar nodular opacities, predominantly in the middle and upper lobe, is highly suggestive of pulmonary Langerhans cell histiocytosis.³² The presence of increased numbers of Langerhans' cells in bronchoalveolar lavage (BAL) fluid (identified by staining with antibodies against CD1a) is also strongly suggestive of pulmonary Langerhans cell histiocytosis.³³
- Some metabolic disorders such as lysosomal diseases may show ILD in some cases. Gaucher's syndrome is an autosomal recessive disease in which the enzyme lysosomal glucocerebrosidase is deficient. The deposit of glucocerebroside in the lung is the cause of ILD.³⁴ Niemann–Pick disease is caused by a primary deficiency of sphingomyelinase. Sphingomyelin accumulates in organs such as the brain, spleen, liver and also the lungs. Histology shows lipid-laden macrophages in the marrow and “sea-blue histiocytes” on pathology. The infantile form of the disease is often fatal, and ILD has been reported essentially in older cases.³⁵ Hermansky–Pudlak syndrome is a heterogeneous group of autosomal recessive disorders associated with the accumulation of a ceroid-like substance in lysosomes of various tissues. The disease is characterized by albinism, bleeding tendency and systemic complication associated with lysosomal dysfunction.³⁶ The progressive development of ILD and fibrosis may be the result of a chronic inflammatory process.³⁷ Familial hypercalcemia with hypocalciuria is caused by autosomal dominant loss-of-function mutations in the gene encoding the calcium-sensing receptor. Respiratory symptoms are usually mild and associated with the reduction in the lung diffusion capacity. Lung histology indicates the presence of foreign body giant cells and mononuclear cells infiltrating the alveolar interstitium, without circumscribed granulomas.³⁸
- Eosinophilic lung disease (ELD) is a heterogeneous group of disorders characterized by pulmonary infiltrate on radiography and peripheral eosinophilia. Increased amount of eosinophils in the BAL fluid or lung tissue may give confirmation of the diagnosis. The known causes of ELD in children are allergic bronchopulmonary aspergillosis, parasitic infections, drug reactions and eosinophilic vasculitis.¹² ELDs of unknown origin include Loeffler syndrome, acute eosinophilic pneumonia,³⁹

chronic eosinophilic pneumonia,⁴⁰ and idiopathic hyper-eosinophilic syndrome.⁵

- Several other systemic conditions may lead to chILD development with variable frequency. Malignant tumors, such as lymphomas, can present pulmonary infiltrate.^{41,42} Other reported diseases that may present ILD's features are inflammatory bowel diseases and celiac disease,⁴³ primary biliary cirrhosis and chronic hepatitis,^{44,45} neurocutaneous disorders (tuberous sclerosis, neurofibromatosis) and amyloidosis.⁴⁶ Bone marrow transplantation may trigger a strong systemic immunologic reaction affecting multiple organs including the lungs. Graft-versus-host disease may present severe pulmonary involvement, which may be lethal.^{47,48} Additionally, the preparation for transplantation usually requires chemotherapy and radiation, which may also be an increasing risk for exposure-related ILD discussed below.

Exposure-related ILDs. Exposure-related ILDs comprise a group of pulmonary manifestations that follow a harmful exposure to irritable antigens. The origin of the exposure may be natural (ie, infections) as well as human (ie, drugs, chemicals).

- Hypersensitivity pneumonitis (HP) is a cell-mediated immune reaction to inhaled antigens in susceptible persons.⁴⁹ In children, HP is caused by repeated exposure to various organic or inorganic dusts of animal or vegetal origin, to occupational antigens and, more rarely, to chemical agents in the home environment as well as related to certain hobbies.^{5,12,49} The most frequent types of HP include bird fancier's diseases, humidifier lung diseases and chemical lung diseases. Bird fancier's diseases are induced by the exposure to birds' antigens identified as glycoproteins in avian droppings and on feathers. Importantly, respiratory symptoms in exposed patients who have even one pet bird at home should raise the suspicion of HP.⁵⁰ Pneumonias related to humidifiers (air conditioner lung, misting fountain lung, basement lung diseases) are mostly caused by exposure to bacterial antigens, thermophilic actinomycetes, fungi, amoebas, or nematodes present in the mists.⁵¹ Chemical lung diseases can be induced by various inorganic antigens such as those from vaporized paints and plastics.^{12,52} As children can develop interstitial inflammatory reactions in the lung without noticeable symptoms for months, children's HP is often diagnosed at the chronic stage of the disease, resulting of a long-term exposure to low levels of inhaled antigens.⁵³ Clinical features include nonproductive cough, dyspnea, malaise, asthenia and, occasionally, cyanosis.⁴⁹ CT may vary from ground-glass attenuation, mainly in the mid-upper zones, to nodular opacities and signs of air-trapping.^{32,54,55} Laboratory diagnostic tests are mainly based on the search for IgG antibodies



against the offending antigens, although these tests are not specific since these antibodies are present in up to 50% of nonsymptomatic exposed individuals.⁴⁹ BAL cell profile usually indicates an increased total cell count, in particular an elevation of lymphocyte count, which often exceeds 50%.^{49,53} The CD4/CD8 ratio is often reduced in older cases, although this may not be the case in most children.⁵⁶ Histopathologic evaluation of lung tissue is in general not required for the diagnosis of HP. At present, there is no specific diagnostic test for HP. The most significant diagnostic tool is a detailed environmental exposure history. Other diagnostic features include positive precipitating antibodies to the offending antigen, recurrent episodes of symptoms, occurrence of diffuse parenchymal lung disease by CT, BAL abnormalities with lymphocytic alveolitis and increased CD8+ T cells.^{5,12}

- Environmental exposure can also be a cause of ILD. ILD may develop after exposure to tobacco smoke, air pollution,⁵⁷ or chemical toxic inhalation⁵¹ in a context of damage and repair cycle of the lung tissue.
- Infectious diseases, mainly viral, are also an important feature of secondary chILD. Recent knowledge strongly suggests that latent viral infections may be involved in the pathogenesis of ILD through targeting of the alveolar epithelium.¹² The main viruses implicated include adenovirus, members of human herpes virus family (Epstein-Barr virus and cytomegalovirus) and respiratory syncytial virus.⁵⁸ A number of other viruses can also be involved, such as influenza,⁵⁹ hepatitis C,⁶⁰ or even human immunodeficiency virus (HIV) in immunocompetent children.⁶¹
- Accidental aspiration could lead to ILD through chemical and infectious mechanisms. Children who are particularly exposed to aspiration are those with neurological disorders with impaired swallowing and children under tube feeding. Gastroesophageal reflux assessment should be performed in high-risk children in order to avoid cumulative damage caused by aspirations.
- Finally, ILD may be observed following medical treatments. Drugs used in inflammatory diseases or pediatric malignant tumors can cause ILD.⁶² They include anti-inflammatory agents (eg, aspirin, etanercept), immunosuppressive and chemotherapeutic agents (eg, azathioprine, methotrexate,^{63,64} cyclophosphamide), antibiotics, cardiovascular agents and, for teenagers, illicit drugs.^{65,66} There are no distinct clinical, radiographic, or pathologic specific patterns, and the diagnosis is usually made when a patient is exposed to medication known to result in lung disease, with a timing of exposure appropriate for disease development and elimination of other causes of ILD. Treatment relies on avoidance of further exposure and corticosteroids in markedly impaired patients. Exposure to therapeutic radiation in the management of pediatric cancer may also result in ILD. Patients presenting within

six months of therapy generally have radiographic abnormalities with ground-glass patterns in both radiation-exposed and unexposed tissues.⁶⁷

Genetic Disorders

Genes associated with primary ILD development can be categorized by the specific mechanism in which they induce ILD into genes related to surfactant metabolism, forkhead box transcription factor 1 gene and genes encoding the receptor for granulocyte-macrophage colony stimulating factor (GM-CSF). Other known genetic mutations could lead to a primary systemic disease that can be incidentally associated with ILD (ie, metabolic disorders). Some other new genes mutations (*COPA*, MIM 601924¹⁰ or *TMEM173*, MIM 612374⁶⁸) have been identified to be associated with systemic autoinflammatory diseases involving the lung. Mutations in the *COPA* gene, encoding the protein coatomer subunit α , lead to defective intracellular transport and subsequent endoplasmic reticulum stress. The clinical manifestations are systemic autoimmunity involving joints (inflammatory arthritis) and lungs (ILD).¹⁰ Here, we will focus only on the first cited group of genetic disorders that are directly involved in ILD development (Table 2).

Genetic surfactant disorders. Pulmonary surfactant is a mixture of lipids and specific proteins that reduce alveolar surface tension. A deficiency of surfactant because of prematurity is the primary cause of neonatal respiratory distress syndrome.⁶⁹ In addition, some of the ILDs found in full-term infants and young children have a genetic basis related to the dysregulation of surfactant metabolism.²⁶ Two major classes of surfactant-related disorders have been recognized: disorders disrupting the functions of proteins critical for surfactant homeostasis and disorders generating alveolar cell injury mediated by protein misfolding or toxic gain of function.⁷⁰ Mutations in the genes encoding surfactant protein B (SP-B) and surfactant protein C (SP-C) (*SFTPB*, MIM 178640; and *SFTPC*, MIM 178620)⁷¹⁻⁷³ and also mutations in the ATP-binding cassette subfamily A member 3 gene (*ABCA3*, MIM 601615)^{26,74-76} are frequently reported causes of severe neonatal or chronic ILD. Another rare cause of surfactant protein production disorder is thyroid transcription factor gene (*TTF1/NKX2.1*, MIM 600635) aberration.⁷⁷

SP-B deficiency is a rare lung disease occurring in newborns presenting severe progressive respiratory distress, with a poor prognosis. Affected patients die at the age of three to six months. The typical histologic pattern is a granular PAS-positive eosinophilic proteinaceous alveolar material and prominent uniform alveolar epithelial hyperplasia, but relatively little evidence of lobular remodeling or inflammation. Electron microscopy typically shows deficient mature lamellar bodies and increased multivesicular bodies and multilamellated structures.⁷⁸ Lung transplant is currently the only therapeutic option for SP-B deficiency and only rare reports

**Table 2.** Summary of genes involved in the etiology of childhood interstitial lung disease.

GENE	ENCODED PROTEIN	LOCATION	EXON COUNT	MODE OF INHERITANCE	PERIOD OF SYMPTOMS' ONSET	SEVERITY	OTHER SPECIFIC CHARACTERISTICS
<i>ABCA3</i>	ATP-binding cassette, sub-family A (ABC1), member 3	16p13.3	33	AR	Neonatal period to adulthood	Various	- Abnormal surfactant protein - Abnormalities of lamellar bodies
<i>SFTPC</i>	Surfactant protein C (SP-C)	8p21	6	AD	Neonatal period to adulthood	Various	- Abnormal surfactant - I73T (c.218 T > C) is the most prevalent mutation
<i>SFTPB</i>	Surfactant protein B (SP-B)	2p12-p11.2	14	AR	Neonatal early onset	Severe	- SP-B deficiency
<i>NKX2-1</i>	NK2 homeobox 1 (TTF-1: thyroid transcription factor 1)	14q13	3	AD	Neonatal period to childhood	Various	- Abnormal surfactant protein production - brain-lung-thyroid syndrome
<i>FOXF1</i>	Forkhead box F1	16q24	2	AD	Neonatal period	Severe	- Pulmonary hypertension
<i>CSF2RA</i> <i>CSF2RB</i>	Colony stimulating factor 2 receptor, alpha and beta, low-affinity (granulocyte-macrophage)	Xp22.32 and Yp11.3 22q13.1	19 14	X-linked AR	Infants and young children	Progressive	- Familial alveolar proteinosis

Abbreviations: AR, autosomal recessive; AD, autosomal dominant.

of survivals have been described in cases presenting partial genetic deficiencies.^{79,80}

The phenotype associated with SP-C deficiency is heterogeneous, varying from fatal respiratory failure of newborns to chronic respiratory insufficiency in adults,⁸¹ with some children improving over time. The typical histopathology shows a marked diffuse alveolar epithelial hyperplasia, mild alveolar wall thickening with lymphocytic inflammation, foamy alveolar macrophages, simplification of the lobular parenchyma and variable amounts of intraalveolar proteinosis material with cholesterol clefts,⁸² but no consistent abnormalities of lamellar bodies have been associated with SP-C deficiency. *SFTPC* mutations are autosomal dominant mutations, explaining the fact that many sporadic cases with *de novo* mutations may occur.^{72,83} Mechanisms of lung damage caused by *SFTPC* mutations include a “toxic gain of function,” in which the accumulation of the misfolded protein within type II pneumocytes leads to injury or apoptosis with subsequent fibrosis.⁸⁴

The protein encoded by *ABCA3* is a member of the ATP-binding cassette protein family, which is highly expressed in alveolar epithelial cells at the limiting membranes of lamellar bodies, where it plays a role in lipid homeostasis. Recessive mutations in the *ABCA3* gene were first attributed to fatal respiratory failure in term neonates⁷⁵ but are increasingly being recognized as a cause of ILD in older children and young adults.^{85,86} Over 100 *ABCA3* mutations have been identified in neonates with respiratory failure and in older children with ILD.^{87–90} *ABCA3* deficiency may present various histological features: primary atypical pneumonia or desquamative interstitial pneumonia pattern is seen in neonates and young infants and nonspecific interstitial pneumonia pattern with focal proteinosis and cholesterol clefts (endogenous lipid pneumonia)

in older children.⁹¹ *ABCA3* deficiency is associated with absent lamellar bodies or distinctive round electron-dense bodies within small abortive lamellar bodies.^{78,92} Interestingly, one report of an adult ILD patient presenting heterozygous mutations in both the *SFTPC* and *ABCA3* loci raises the possibility of the coexistence and interactive effect of more than one surfactant mutation in some adult-onset ILD.^{93,94}

Loss-of-function mutation or deletion of one *NKX2.1* allele is associated with the “brain–lung–thyroid syndrome,” which combines congenital hypothyroidism, neurological symptoms (hypotonia, chorea)⁹⁵ and ILD with impaired surfactant protein production of variable intensity.^{96–99} The precise mechanisms for lung disease caused by *NKX2.1* mutations have not been elucidated but presumably relate to the importance of this transcription factor in the expression of surfactant-related genes, including *SFTPB*, *SFTPC* and *ABCA3*. Most reported *NKX2.1* genetic variants have resulted from apparent *de novo* mutations causing sporadic disease, although disease transmitted in an autosomal dominant pattern has been reported (benign familial chorea).⁹⁸

Gene encoding the receptor for GM-CSF and pulmonary alveolar proteinosis (PAP). Loss-of-function mutations or deletions of both alleles in the genes (*CSF2RA*, MIM 306250, and *CSF2RB*, MIM 138981) encoding the subunits of the receptor for GM-CSF have been identified in infants and young children with DLD associated with alveolar proteinosis.^{100,101} A block in GM-CSF signaling impairs normal catabolism of surfactants by alveolar macrophages, leading to the accumulation of the proteinaceous material in the airspaces and the gradual onset of respiratory symptoms.¹⁰² This cellular mechanism is similar to that seen in patients with alveolar proteinosis secondary to the development of autoantibodies to GM-CSF.¹⁰³



Additionally, another form of primary PAP independent of GM-CSF was identified in a geographically restricted region (ie, Reunion Island). Biallelic missense mutations in the gene coding methionyl-tRNA synthetase (MARS) (*MARS*, MIM 156560) were identified. MARS is an enzyme whose function is to catalyze the ligation of methionine to tRNA and is critical for protein biosynthesis. A reduced enzyme activity, with *MARS* mutations, is the cause of PAP.¹⁰⁴

Gene encoding forkhead box transcription factor 1 (FOXF1). Loss-of-function mutations or deletions of one allele of the gene encoding the forkhead box transcription factor 1 (*FOXF1*, MIM 601089) have been identified as a cause of ACD/MPV, which is usually fatal in the neonatal period. The clinical phenotype is severe hypoxemic respiratory failure and pulmonary hypertension in full-term infants.^{20,104} These children also have cardiac, gastrointestinal, or genitourinary tract malformations.^{20,105}

Other genes reported to be involved in adult onset ILDs. They include surfactant protein A2 (*SFTPA2*, MIM 178642), telomerase components genes¹⁰⁶ (*TERT*, MIM 187270; *TERC*, MIM 602322 and *RTEL1*,¹⁰⁷ MIM 608833), and hereditary pulmonary alveolar microlithiasis (*SCL34A2*, MIM 265100).⁷⁰

Future direction. In adult-onset ILDs, the genetic analysis of several kindreds made possible the identification of some genetic etiology.¹⁰⁷ Adult-onset diseases often present mild symptoms and progress slowly. In neonates and young children, the clinical course may not always allow live genetic testing on time; however, efforts should be made to gather samples maybe at autopsy, especially if a family history of sudden respiratory distress of siblings is present.⁸⁷ In such cases, ethical considerations should be taken into account for sample collection. More knowledge about genetic features causing ILDs is further required; but in order to complete it, the sharing of information will be important. The development of a centralized database and multicenter analysis with common diagnostic and histologic criteria is needed.⁴

Diagnosis of ILD

As the prognosis, clinical course, therapeutic strategies and outcomes are variable among the different causes of ILD, the diagnostic evaluation should aim to identify the specific etiology and characteristics of the disease.¹⁰⁸

Clinical signs. The most common symptoms observed in ILD patients are cough, dyspnea, tachypnea and exercise intolerance. A nonproductive, dry cough is observed in about 75% of patients, and 80% of children present tachypnea. More general symptoms including weight loss, unexplained fever, or failure to thrive can be observed in some cases, especially in young patients.

At clinical examination, patients with ILD show chest wall retraction, inspiratory crackles and tachypnea. In severe cases with chronic respiratory distress, patients may present finger clubbing or cyanosis during exercise but also at rest.

A precise past history, family history, clinical signs history and environmental exposure history should be checked at the medical interview.^{3,5} The family history, especially the presence of siblings with the same clinical presentation, is very important in cases with familial ILD. The assessment of non-respiratory symptoms such as poor weight gain, recurrent episodes of infections, joint pain, skin rash, or episodes of fever of unknown origin could be helpful in ILD cases associated with systemic disease (ie, autoimmune disease). Additionally, the verification of environmental exposure to chemicals, drugs, or dust could be important in some cases of HP.

Radiological studies. Plain CXRs are commonly the first imaging studies performed in patients presenting ILD symptoms. They are frequently diffusely abnormal, but the information they provide is often limited and has low diagnostic specificity.^{3,4,12,26}

High-resolution computed tomography (HRCT) is actually the preferred diagnostic imaging tool for ILD in children.²⁶ This technique can give not only information about the extent and structural pattern of the disease but also about the involvement of the interstitium, airway and air space.^{3,4,12} The most commonly observed feature of ILD is widespread ground-glass attenuation. Less common signs are honeycombing, irregular interlobular septal thickening, intralobular lines and cyst formation.¹² Controlled ventilation HRCT under general anesthesia may enable more precise assessment by reducing artifacts made by tachypnea in children with ILD.^{3,4,109} Easily performed, HRCT is also a useful tool for the monitoring of the disease progression during the follow-up.¹²

Magnetic resonance imaging (MRI). MRI for the assessment of chILD presents the advantage of avoiding the use of ionizing radiation for children who will need a continuous regular follow-up. MRI was shown to accurately assess ILDs in adults.⁷⁴ In children, MRI for the assessment of cystic fibrosis^{71,110} or pulmonary hemorrhage⁷² has been reported. However, the use of MRI in chILD faces two major problems, which are related to the size of the target organ and the age of the patients.⁷⁵ In children, it may be difficult to get a clear image of the parenchyma because of the poor water density in the lung. Second, rapid breathing, high heart rate and inability to cooperate would cause motion artifacts. To perform an accurate analysis, sedation would be required, but in case of severe respiratory distress, it will not always be possible or recommended. Interestingly, technical progress in lung functional MRI methods by the use of hyperpolarized gas (ie, ¹²⁹Xe or ³He), molecular oxygen, or fluorinated gas resulting in a shortening of the data acquisition time, provides new opportunities.⁷³ It would be a great advantage if the follow-up of lung damage could be made by this noninvasive, nonradiative imaging method.

Echocardiography. Structural cardiovascular disease and pulmonary vascular disease are conditions that may present similar clinical signs with ILD.⁸ Echocardiography is recommended to rule out those confusing conditions.⁴



Additionally, ILD could result in pulmonary hypertension, which can worsen the clinical course of the disease.¹¹¹ Early detection of pulmonary hypertension by echography and early intervention could lead to a better prognosis.^{26,112} Although echocardiography is not able to provide a great amount of information about the respiratory system itself, the testing is noninvasive and could be easily performed, even on infants, and we strongly recommend it to assess the general cardiovascular state in chILD patients.

Pulmonary function testing and exhaled nitric oxide. Pulmonary function testing does not provide specific diagnostic information but can be a useful tool for the monitoring of the progression and management of ILD.^{3,12} However, only children over a certain age (mostly of school age) can be correctly assessed.

The exhaled nitric oxide (eNO) level could be a potential respiratory biomarker to assess the progression and activity of ILD.¹¹³ But again, the testing needs cooperation from the patient and is difficult to perform on young children. Additionally, the specificity of eNO measurement is low, so that the interpretation of the results may, sometimes, be confusing.

Bronchoscopy with BAL. Bronchoscopy with BAL is an invasive technique used to assess the airways and alveoli. The specificity of the diagnosis is low, but it allows the differentiation of some specific disorders: infection,¹¹⁴ aspiration,^{115,116} HP,⁵⁶ alveolar hemorrhage,^{117–120} alveolar proteinosis,¹²¹ Langerhans cell histiocytosis,^{122,123} sarcoidosis,¹²⁴ congenital lipid-storage diseases (Gaucher's disease, Niemann–Pick disease),¹²⁵ or eosinophilic pneumonia.^{3,12,126}

Laboratory testing. Laboratory testing should be performed for the diagnosis of systemic diseases such as autoimmune disease, but also to assess the severity and progression of the lung damage. Various cytokines, chemokines, surfactant protein D, Krebs von den Lunge-6 antigen (KL-6), defensins and matrix metalloproteinases (MMP) 1 and 7 are the studied biomarkers in blood and the BAL fluid. The diagnosis of autoimmune diseases and systemic vasculitis needs assessment of serum autoantibodies (RF, anti-DNA antibodies, etc).¹²

Lung biopsy. Since the knowledge about the variety of pediatric ILD etiologies is increasing, lung biopsy and histological investigation have become increasingly important as the final step in the series of diagnostic approaches.⁴ Different surgical techniques can be used for the biopsy. Open lung biopsy (OLB) was formerly the more frequently chosen approach. Video-assisted thoracoscopy (VATS) can visualize a greater percentage of the lung, allowing sampling from different lobes with the same incision sites. As VATS can be performed safely even in young children, it has gradually supplanted conventional OLB as the first choice for lung biopsy.^{4,127,128}

A previous HRCT assessment is essential before the biopsy, in order to decide about the sites of specimen sampling. A multidisciplinary approach including radiology,

surgery, pathology and physician's assessment will be needed to reach the final diagnosis.^{26,108}

Genetic testing. Genetic testing can provide the final answer in the diagnosis of ILD. Several single-gene disorders have been identified, but the clinical manifestations of those diseases overlap considerably, so that a single-gene investigation is not always sufficient to reach the diagnosis.⁴ Very specific clinical features can help considerably the choice of the gene to investigate. For example, hypothyroidism and neurological findings may be, with a very high probability, related to a loss-of-function mutation in the *NKX2.1* gene. The recurrence of the disease in the family, the age of onset of the disease, the severity of the disease and nonrespiratory symptoms should be carefully taken into account to perform efficient genetic testing.

Treatment of Pediatric ILD

Management of general physical conditions and supportive care. ILD in the neonatal period is often severe and could require intensive supportive care. The general physical state of the affected children is critical for ILD treatment. Children who develop ILD can face very exhaustive conditions because of severe respiratory distress, so that good nutritional management and adequate energy intake are essential.^{5,12} For neonates, enteral feeding should be started as soon as possible when the respiratory symptoms allow it. Poor energy intake could deteriorate the healing capacity of children.

As children with ILD are very vulnerable to respiratory tract infections, preventive measures are essential. Immunodeficient children require preventive antibacterial therapies to combat severe bacterial infections, and for children with normal immunological functions, early scheduling of vaccination against respiratory pathogens should be considered.^{3,118}

In cases with severe respiratory failure presenting hypoxemia, mechanical ventilation and continuous oxygen therapy should be provided as needed.⁵

Pharmacological therapy. Immunosuppressive and anti-inflammatory drugs remain the main therapies used for ILD; however, no randomized control trials have been conducted to confirm the efficacy of these therapeutic strategies because of the rarity of the disease.¹²⁹ Corticosteroids are the mainstream of ILD treatment, with prednisolone given orally or intravenously at a dose varying between 1 and 2 mg/kg daily.^{8,26} Intravenous pulses of methylprednisolone should be preferred for severe progressive cases at a dose of 10–30 mg/kg given for three consecutive days^{3,12,26,87,130,131} once a month for a period of at least three months. When the disease has been brought under control, corticosteroid use could be reduced to oral prednisolone every two days.¹² However, the side effects of corticosteroids require other therapeutic options to be considered.

As a complement or substitute to corticosteroid therapy, the antimalarial drug hydroxychloroquine is accepted as a useful, effective, and relatively safe treatment. The recommended



dose is 6–10 mg/kg/day.^{26,131–133} Retinal toxicity of the drug is a rare complication in children, which needs to be followed regularly in an ophthalmologic checkup. In many cases, the decision of the therapeutic choice between corticosteroids or hydroxychloroquine use does not depend on the histology or the clinical course and is mainly a choice depending on the institution that is in charge of the patient.¹³⁴ In some severe cases, steroids and hydroxychloroquine may be associated.

Other immune-modulatory drugs such as methotrexate,⁸ azathioprine,⁸ cyclophosphamide, tacrolimus, cyclosporine and mycophenolate mofetil have been reported in case reports, but no evidence has been found to strongly recommend one drug rather than another.^{3,129,131}

Macrolides,¹³⁵ including azithromycin^{26,136} and clarithromycin, have immunomodulatory and anti-inflammatory effects and represent a potential therapeutic option for ILDs.^{137–139}

Lung transplantation. Progression of ILD can lead to severe irreversible fibrosis of the lung. In such cases, lung transplantation (LTx) can be used as a final option in children of all ages, even in young infants.^{3,78} Although LTx in adults is commonly performed in many centers, pediatric LTx is possible only in a restricted number of specialized centers. Some of the factors specific to pediatric LTx include the size of both donor's lung and recipient's thoracic cavity, the immature immune system in young children, the nutritional status of the recipient, gastroesophageal reflux and also the need of intensive familial support for post-transplant care.¹⁴⁰ The survival rate after LTx is quite similar to the adult rate, and the major causes of early death after LTx are graft rejection and graft dysfunction.^{140,141} The use of adult allografts for pediatric LTx does not affect the outcomes,¹⁴² and living related adult donor lobe transplant⁷⁶ could provide an option in end-stage chILD cases presenting severe respiratory distress.

Conclusion

ChILDs comprise a heterogeneous group of diseases in which many points still have to be elucidated. Advances in genetic testing provide us a better understanding of genetic mechanisms of chILD; but new genes and genetic mutations involved in ILD formation are still being regularly discovered. The need for further studies to clarify the frequency, classification methods and therapeutic strategies to treat chILD is obvious but difficult, because of the rarity and the rapid clinical course of the diseases. To optimize studies concerning chILD, multicenter studies with a central database system may be efficient and helpful for future works. Such consortia of centers implicated in chILD care are emerging. The French RespiRare[®] network has been sharing data on chILD at a national level since 2008,¹⁴³ and the chILD-EU collaboration in Europe was established to share standardized directives to keep common diagnosis criteria and to harmonize treatment protocols for this rare disease entity.²⁶ In the United States, the American Thoracic Society has provided a clinical practice guideline for chILD.⁴

Some fields related to chILD care have still to be explored. For the diagnosis, HRCT is still the most preferred imaging method. The cumulative use of radiation could become a problem for long-term follow-up in very young infants. MRI can provide an interesting option, but the scanning itself is still time consuming and requires sedation in children. New methods to assess children with ILD safely are needed. Genetic testing is now available through many centers but is still limited to well-known genes. Since new genes are discovered periodically, frequent renewal of the database is needed. A worldwide database system would be welcome to update information about genes, symptoms and clinical findings of genetic ILDs, and would be of great help in clinical practice all over the world. From the perspective of the therapeutic strategies of chILD, LTx seem to be the most radical way to treat progressive cases of chILD. Unfortunately, the number of centers performing pediatric LTx is still small compared to those in adults and the prognosis has to be improved. Research on safer LTx methods with better prognosis is required and better access to LTx for children needs to be established. Since lobular transplantation can be enough for very young children, assessment of the restrictions concerning the size of donor should be reconsidered.

ChILD is a rare disease entity for which improvements are still needed, especially in the clinical fields. A worldwide collaboration should be of great interest to make efficient advances in the knowledge of chILD.

Author Contributions

Conceived the concepts: HK. Analyzed the data: HK. Wrote the first draft of the manuscript: HK. Contributed to the writing of the manuscript: HK. Agree with manuscript results and conclusions: HK, SK. Jointly developed the structure and arguments for the paper: HK, SK. Made critical revisions and approved final version: HK, SK. Both authors reviewed and approved of the final manuscript.

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