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Interstitial lung disease in children

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Abstract

Purpose of review—There has been tremendous progress in the approach to childhood interstitial lung diseases (ILD), with particular recognition that ILD in infants is often distinct from forms that occur in older children and adults. Diagnosis is challenging due to the rarity of ILD and the fact that presenting symptoms of ILD often overlap those of common respiratory disorders. This review summarizes newly published recommendations for diagnosis and management and highlights recent scientific advances in several specific forms of childhood ILD.

Recent findings—Clinical practice guidelines emphasize the role for chest CT, genetic testing, and lung biopsy in the diagnostic evaluation of children with suspected ILD. Recent studies have better defined the characteristics and molecular understanding of several different forms of ILD, including Neuroendocrine cell Hyperplasia of Infancy (NEHI) and ILD due to mutations in genes affecting surfactant production and metabolism. Despite significant progress, definitive therapies are often lacking.

Summary—Childhood ILD encompasses a collection of rare, diffuse lung diseases. Timely recognition of children with suspected ILD and initiation of appropriate diagnostic evaluations will facilitate medical management. Systematic approaches to clinical care and further study are needed to improve the outcomes of children with these rare disorders.

Keywords

Interstitial lung disease; *ABCA3*; *NKX2.1*; *SFTPC*; NEHI

Introduction

The term childhood interstitial lung disease (chILD) encompasses a broad group of pulmonary disorders that are associated with significant morbidity and sometimes mortality. Historically, these diseases have been defined based on lung biopsy histopathologic

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findings. However, recent advances have facilitated increased noninvasive diagnosis through genetic testing and use of chest computed tomography (CT) scans. In this review, we summarize newly published recommendations for diagnosis and management of chILD and highlight recent progress in specific diseases such as NEHI and ILD due to mutations in genes affecting surfactant production and metabolism.

Definitions

Interstitial lung disease (ILD) is a term that refers to a heterogeneous collection of disorders characterized by abnormal gas exchange due to altered structure of the interstitial region of the lung. As many entities also affect the distal bronchioles and alveolar spaces, the term “diffuse lung disease” is probably a more accurate description. ILD occurs in a variety of clinical contexts, including as isolated pulmonary disorders, due to environmental exposures, as a consequence of chemotherapy or radiation therapy, and as part of systemic processes, such as autoimmune diseases. Although some of the conditions that cause ILD in children and adults are similar, there are many important differences, including distinct forms only seen in infants. Therefore, as detailed in Table 1 and summarized in a prior review on this topic[2], a classification system has been developed specifically for childhood ILD (diffuse lung disease)[1], and an expert panel recently developed an official American Thoracic Society clinical guideline on the classification, evaluation, and management of chILD, focusing on infants < 2 years of age[3**]. Further, specific chILD diagnoses are now included in the International Classification of Diseases 9th edition[4**].

Epidemiology

Overall, ILD is rare in children. Studies have estimated a prevalence of 3.6 cases per million in the United Kingdom and Ireland[5] and 1.32 cases per million in Germany[6]. In France, beginning in 2006, a National Reference Center for Rare Lung Diseases (RespiRare) was created to centralize data collection, and over 200 cases of ILD were identified over 3 years, though a specific diagnosis could not be established for ~25% of cases [7*]. Retrospective studies in North America suggest that increased clinician awareness of childhood ILD and improved use of diagnostic tools has resulted in greater case ascertainment[2,8**], but the prevalence of these disorders may still be under-estimated.

Diagnostic approach

Children with ILD typically manifest non-specific respiratory signs and symptoms, including tachypnea, hypoxemia, crackles, cough, and poor growth. Because these symptoms overlap those seen in many more common conditions, the first step in diagnostic evaluation is to exclude more common causes of diffuse lung disease (i.e. cystic fibrosis, immunodeficiency, congenital heart disease, pulmonary infection, primary ciliary dyskinesia, and recurrent aspiration) (Table 2). After excluding or treating these more common causes of lung disease, the term “chILD syndrome”[9] is then used to refer to children who meet 3 out 4 of the following criteria,: (1) respiratory symptoms (e.g. cough, rapid and or difficult breathing, or exercise intolerance; (2) respiratory signs (e.g. resting tachypnea, adventitious sounds, retractions, digital clubbing, failure to thrive, or respiratory failure; (3) hypoxemia; and (4) diffuse parenchymal abnormalities on chest imaging.

The recently published ATS clinical guideline describes the primary diagnostic tools used for evaluation of childhood ILD, emphasize (1) bronchoscopy with bronchoalveolar lavage (BAL), (2) chest CT, (3) genetic testing, and (4) lung biopsy[3**]. Not all tests are needed in all cases. Generally, the evaluation proceeds from least to most invasive procedures, although the sequence depends on the context, acuity and severity of the patient's condition. Pulmonary function testing (PFT) and assessment of oxygenation with sleep and exercise (or feeding in infants) are used to characterize the degree and nature of physiologic impairment. Further, screening for pulmonary hypertension may influence the pace of diagnostic evaluations, alter treatment, and impact prognosis, as pulmonary hypertension associated with ILD predicts higher mortality[2,10]. The primary diagnostic modalities used in childhood ILD are reviewed below and summarized in Table 3.

Bronchoscopy with bronchoalveolar lavage (BAL)

This is a common, invasive procedure that is performed to evaluate children with suspected ILD. In addition to enabling evaluation of airway anatomy and physiology, airway and alveolar samples are obtained for cytology and microbiologic diagnosis. Bronchoscopy is relatively safe, widely available, and may help diagnose infection, aspiration, hemorrhage, or pulmonary alveolar proteinosis (PAP).

Imaging studies

Chest CT is very useful for defining the extent and pattern of disease with resolution that is superior to plain chest radiographs. Common findings in chILD may include ground glass opacification, consolidation, and septal thickening. Findings may be suggestive or even specific for some types of ILD, including surfactant dysfunction disorders, bronchiolitis obliterans and Neuorendocrine cell Hyperplasia of Infancy (NEHI)[3**,11–14] and therefore may reduce need for lung biopsy. In cases where lung biopsy is required, CT imaging will guide the choice of biopsy sites. In infants, anesthesia or controlled ventilation techniques are often needed to decrease motion artifact and atelectasis that may obscure detection of lung pathology[15,16]. Imaging protocols designed specifically for young children at experienced centers significantly reduce radiation exposure[17].

Genetic tests

The availability of clinical genetic testing now allows for non-invasive definitive diagnosis in some cases. The currently known genetic causes of chILD include abnormalities in the genes encoding surfactant protein B (*SFTPB*), surfactant protein C *(SFTPC)*, ATP-binding cassette transporter A-3 *(ABCA3)*, GM-CSF receptors α and β (*CSFRA and CSFRB*), and thyroid transcription factor-1 *(NKX2.1/TTF1)*[3**]. The choice of specific genetic tests should be guided by the family history and clinical context. A specific diagnosis provides clinically useful information for the great majority of cases as it informs management, prognosis and genetic counseling. Currently, only a subset of types of childhood ILD has a defined genetic basis. However, it is likely that additional disease-associated genes will be identified in the future.

Lung Biopsy

In the absence of genetic diagnosis, lung biopsy remains the gold standard for diagnosis of many forms of chILD. To optimize diagnostic yield, standardized protocols have been developed[18], that require timely and effective communication between the clinician, radiologist, and surgeon to select proper biopsy site(s) and process tissue, including fixation in glutaraldehyde for electron microscopy.

Approach to classification of childhood ILD

Definitive diagnosis can be achieved in most cases using the approaches described above. The published classification system (Table 1) provides a useful framework for organizing the large spectrum of ILD diagnoses and has been validated in several studies. However, despite invasive evaluations, a portion of ILD cases (11% in one study)[1] remain unclassifiable, attributable in part to insufficient tissue sampling. Further, the current classification has some conceptual and practical limitations, and recent studies have suggested modifications to better incorporate cases diagnosed using genetic and/or radiographic criteria [8**] and the breadth of diseases seen in older children[19*].

As reviewed below, there several forms of ILD where considerable progress in clinical description and understanding of disease pathogenesis has recently unfolded.

ILD due to defects in *NKX2.1*/*TTF-1*

TTF-1 (encoded by the gene *NKX2.1*) is a transcription factor and early marker of epithelial differentiation in the lung. TTF-1 is critical for lung development and surfactant homeostasis, regulating expression of molecules such as surfactant proteins B and C, and the ATP-binding cassette transporter 3 (ABCA3). Mutations or deletions of one *NKX2.1* allele can result in neurologic abnormalities including chorea, hypothyroidism, and neonatal respiratory distress syndrome (RDS) that have been clinically characterized as the brain-thyroid-lung syndrome (MIM 610978)[20,21]. A recent study found highly variable clinical, radiographic, and histologic phenotypes in children with *NKX2.1* mutations or deletions. Some children presented with respiratory failure in the newborn period while others manifested chronic ILD later in life[22**]. Genetic testing for mutations and deletions in *NKX2.1* is recommended in infants with chILD syndrome and evidence of thyroid dysfunction or neurologic deficits, though lung disease can also occur in the absence of brain or thyroid abnormalities. Although no specific molecular-based therapy is currently available, identification of this mutation in a child with ILD can obviate the need for additional invasive testing and prompt aggressive infection prevention measures, as recurrent pulmonary infections have been reported in children with *NKX2.1* haploinsufficiency[20,21,22**].

ILD due to *ABCA3* mutations

Recessive mutations in the gene encoding ABCA-3 have been associated with neonatal respiratory failure in full-term infants (attributed to defects in surfactant metabolism) [23–25] as well as ILD in older children and adults[12,26–28]. In addition, there are several prior reports of patients with a clinical presentation consistent with ABCA3 deficiency, with

identification of only a single mutation in *ABCA3*. Another case report demonstrated ABCA3 deficiency by histologic and ultrastructural analysis, yet no mutations were detected by exon-based sequencing[29]. A recent publication establishes one potential explanation for such cases, as a novel intronic variant was identified in a full-term infant with neonatal respiratory failure and radiographic evidence of ILD, but for whom initial conventional sequencing only identified a single *ABCA3* mutation[30*]. In addition, 2 cases have now been published demonstrating ILD due to gene deletions (one in *ABCA3* and one in *SFTPC*) [31*]. These cases highlight the importance of understanding the limitations of specific genetic testing protocols, as traditional single-gene exon-based sequencing will not detect deleterious mutations in non-coding regions, deletions, or duplications within the candidate gene. Thus, the clinician must re-assess the clinical suspicion for ILD and pursue additional evaluation if the radiographic or histologic features support a specific diagnosis.

While homozygous or compound heterozygous mutations in *ABCA3* are a cause of lethal neonatal failure in term infants, Wambach et al. found that a having a single *ABCA3* mutation significantly increases risk for RDS in term or late pre-term infants[32**], without ILD. This study estimated a carrier allele frequency of ~1 in 3100 individuals of European-descent and ~1 in 18,000 individuals of African-descent, making these frequencies similar to cystic fibrosis. This study demonstrates how insights from studying rare conditions can contribute to understanding pathogenesis of more common conditions.

ILD due to surfactant protein C (*SFTPC)* gene mutations

While *SFTPB* mutations are almost exclusively associated with lethal neonatal lung disease, *SFTPC* mutations can be associated with ILD presenting in older children and adults[33–36]. The clinical presentation and natural history of lung disease in children with *SFTPC* mutations is highly variable, though systematic long-term data are lacking. A recent publication by Avital *et al* describes the outcomes of 5 children with *SFTPC* mutations who are now young adults. The authors suggest these children may have benefited from early hydroxychloroquine treatment[37*], though clinical trials are needed to formally test treatment regimens, particularly in light of the known variability in natural history.

The pathogenesis of *SFTPC* mutations is thought to be due to cytotoxic accumulation of misfolded surfactant protein-C (SP-C) proprotein and endoplasmic reticulum (ER) stress in at least some cases[38–42]. A recent *in vitro* study showed that the small molecule 4-pheynlbutryic acid (PBA) restores proper trafficking of one form of mutant SP-C[43*]. While further pre-clinical and clinical trials are needed, this study emphasizes the potential importance of understanding genotype-specific disease pathogenesis in developing patient-specific targeted therapies.

Neuroendocrine cell hyperplasia of infancy (NEHI)

Infants with NEHI typically present during early infancy with indolent onset of persistent tachypnea, retractions, and hypoxemia[44]. Lung biopsies have shown a characteristic excess of neuroendocrine cells in the setting of otherwise strikingly normal histology[45,46]. Although lung biopsy has been the traditional gold-standard for diagnosis, NEHI is associated with a highly specific chest CT pattern such that many patients are now

diagnosed without lung biopsy (Figure 1). In one study, the sensitivity of chest CT in diagnosing NEHI was 78% compared to lung biopsy, and the specificity was 100%[14].

Other non-invasive means of evaluating children with NEHI include infant pulmonary function testing (iPFT). A retrospective single center study demonstrated significant obstruction and air-trapping in NEHI patients[47*]. There is some evidence that physiologic obstruction may correlate with extent of neuroendocrine cell prevalence[46] and with future abnormalities in physiologic parameters[47*]. Additional prospective and longitudinal studies will be needed to better define the diagnostic accuracy and prognostic value of iPFTs in NEHI. iPFT requires sedation, experienced personnel, and specialized equipment that is not available at all pediatric pulmonary centers.

Despite needing supplemental oxygen for many years and exhibiting significant respiratory distress during infancy and early childhood, current experience indicates that NEHI patients gradually improve over time, though long-term data are lacking. Recent longitudinal studies from Finland and Brazil examined small cohorts (n=9 and 12, respectively) of infants followed for 3–10 years after initial diagnosis[48*,49]. The majority of infants in both studies received corticosteroids, but did not show clinical response and continued to exhibit physiologic evidence of airflow obstruction during the follow-up period. This is consistent with prior reports and the overall lack of inflammation observed in NEHI lung biopsies, and emphasizes how establishing a diagnosis of NEHI can mitigate use of unnecessary therapies [44,45].

Reported familial cases suggest that there may be a genetic basis for NEHI. Using a candidate gene approach, Young et al. report a novel heterozygous mutation in *NKX2.1* in a subject with classic NEHI presentation and biopsy, and this mutation segregated with lung disease in 5 other members of the family. However, mutations in *NKX2.1* were not found in 8 other unrelated individuals with sporadic and familial NEHI, suggesting that *NKX2.1* mutations are not the predominant cause of NEHI[50*]. Future studies using whole genome or exome sequencing may reveal additional genetic causes and may provide insight into the underlying pathogenesis of this disease.

Management and treatment

The pathogenesis of many forms of ILD remains poorly understood and treatment approaches remain largely empirical. Indeed, there have been no controlled trials of any therapeutic intervention in chILD. Management is largely supportive, including supplemental oxygen and ventilatory support, nutritional support, proper immunizations, and avoidance of harmful environmental exposures. While rheumatologic disorders generally respond well to immunosuppressive medications, there is no clear evidence of efficacy of systemic corticosteroids or hydroxychloroquine in most other forms of childhood ILD. Treatment decisions are thus highly individual, carefully considering potential treatment associated side effects. Lung transplantation is an option for children with end-stage lung disease[51*]. Genetic counseling and family support are also important components of care.

Conclusion

Childhood ILD is a group of heterogeneous disorders which are associated with significant morbidity and sometimes mortality. Recently published guidelines describing systematic diagnostic approaches and establishment of standardized nomenclature are improving clinical care and promoting advances in mechanistic understanding of disease pathogenesis. An increasing proportion of cases are now diagnosed without lung biopsy through use of chest CT imaging patterns and genetic testing. Obtaining a specific diagnosis often has important implications in patient management and prognosis, as well as for genetic counseling. Ongoing research to reveal genetic and molecular defects will ultimately lead to specific therapies in this diverse group of rare respiratory diseases. Moreover, these rare disorders continue to provide insight into pathogenesis of more common forms of lung disease.

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Abbreviations

ABCA3	ATP-binding cassette member A-3
BAL	bronchoalveolar lavage
chILD	childhood interstitial lung disease
CSFRA and CSFRB	genes encoding the GM-CSF receptors α and β, respectively
CT	computed tomography
ILD	interstitial lung disease
iPFT	infant pulmonary function testing
NEHI	neuroendocrine cell hyperplasia of infancy
NKX2.1/TTF1	gene encoding the thyroid transcription factor-1
PAP	pulmonary alveolar proteinosis
PFT	pulmonary function testing
RDS	respiratory distress syndrome
SFTPB	gene encoding surfactant protein B
SFTPC	gene encoding surfactant protein C

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KEY POINTS

1. Childhood ILD manifests non-specific respiratory signs and symptoms including tachypnea, hypoxemia, crackles, cough, and poor growth, and systematic evaluation for more common diseases presenting similarly should be undertaken prior to consideration of ILD.
2. ILD in children younger than 2 years of age is typically distinct from ILD presenting in older children and adults.
3. Specific forms of ILD (i.e. NEHI, and disorders of surfactant metabolism) may be diagnosed without lung biopsy.
4. Clinical guidelines for evaluating and classifying ILD in children < 2 years of age have been developed. Application of this classification system has been validated in recent studies.

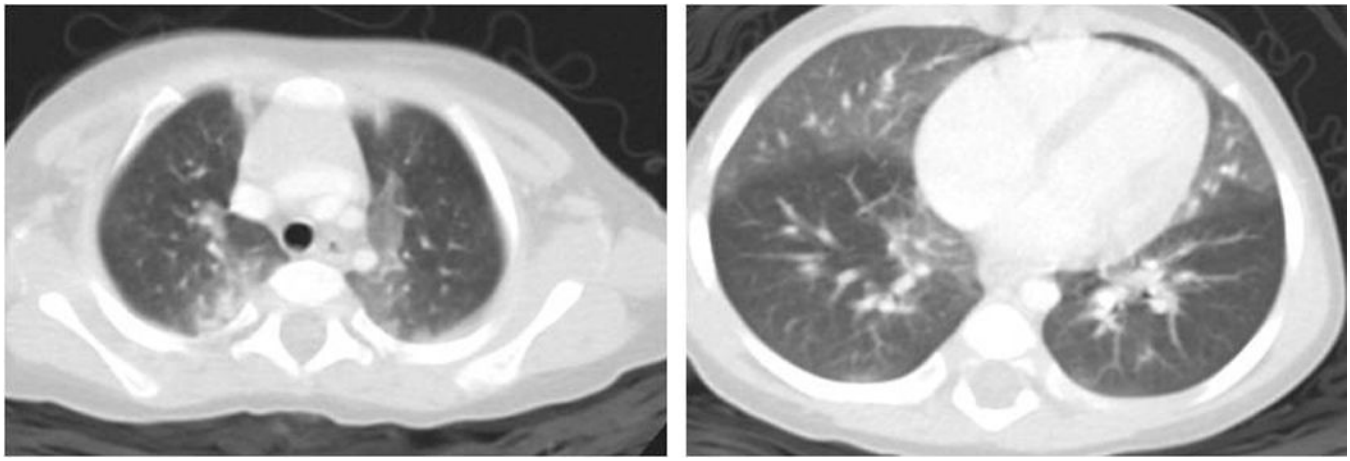

Figure 1.

High resolution computed tomography (CT) image showing geographic ground-glass attenuation in bilateral perihilar regions, right middle lobe, and lingula in a pattern considered characteristic for neuroendocrine cell hyperplasia of infancy (NEHI). Note that the absence of bronchiectasis, architectural distortion or other significant findings is required for radiographic diagnosis of NEHI. Air-trapping is commonly demonstrated through comparison of inspiratory and expiratory images (not shown).

Table 1

Classification of childhood ILD

Disorders more prevalent in infancy	
Category	**Specific Diagnoses***
Diffuse developmental disorders	Acinar dysplasia Congenital alveolar dysplasia Alveolar-capillary dysplasia with pulmonary vein misalignment
Lung growth abnormalities	Pulmonary hypoplasia Chronic neonatal lung disease (BPD) Associated chromosomal disorders (Trisomy 21, others) Associated with congenital heart disease
Specific conditions of uncertain etiology	Neuroendocrine cell hyperplasia of infancy (NEHI) Pulmonary interstitial glycogenosis (PIG)
Surfactant dysfunction	Mutations in *SFTPB, SFTPC, ABCA3, NKX2.1/TTF1* Histology consistent with surfactant dysfunction disorder but without recognized genetic etiology
Disorders not specific to infancy	
Disorders of normal host (immune-competent)	Infectious/post-infectious Aspiration Related to environmental agents (hypersensitivity pneumonitis, toxic inhalation) Eosinophilic pneumonia
Disorders related to systemic disease processes	Immune-related disorders (SLE, polymyositis/dermatomyositis, systemic sclerosis) Storage diseases Sarcoidosis Langerhans cell histiocytosis Malignant infiltrates
Disorders of immune-compromised host	Opportunistic infections Transplantation/rejection syndromes
Disease masquerading as ILDs	Arterial hypertensive vasculopathy Veno-occlusive disease Lymphatic disorders
Unclassified	Conditions that do not clearly fit into specific category (i.e. end-stage disease, inadequate or non-diagnostic biopsy specimen)

Abbreviations: BPD=bronchopulmonary dysplasia; ILD=interstitial lung disease; SLE=systemic lupus erythematosis;

* Includes examples of specific diagnoses classified within each category.

Adapted from [1] Deutsch et al, AJRCCM 2007.

Table 2

Initial Diagnostic Approach for ILD: Exclude more common conditions

Possible diagnoses to exclude before evaluating for childhood ILD*	**Diagnostic Approaches**
Infection	Appropriate cultures Consider bronchoscopy and bronchoalveolar lavage
Cystic fibrosis	Sweat chloride
Immunodeficiency (primary vs. secondary)**	Complete blood count and differential, HIV, immunoglobulins, vaccine response, others as indicated
Recurrent aspiration	Barium swallow study
Congenital heart disease/pulmonary hypertension	Echocardiogram, cardiac catheterization (select cases)

* Note that identification of these diagnoses does not completely preclude diagnosis of ILD. If respiratory symptoms persist despite treatment of the identified abnormalities or severity is out proportion to the identified causes, additional ILD evaluations may be further considered.

** Certain forms of ILD also occur in children with immunodeficiency and immune dysfunction.

Table 3

Summary of key methods for evaluation of children with suspected ILD

Test	Pros	Cons	Comments
Flexible bronchoscopy with bronchoalveolar lavage	Evaluate anatomy of airways and sample alveolar cellular composition Obtain specimen for microbiological evaluation Cytologic studies may support specific diagnoses (i.e. pulmonary hemorrhage, PAP)	Though minimally invasive, general anesthesia required in children Potential risks: hypoxemia, bronchospasm Rarely provides definitive diagnosis of ILD	Infection, aspiration, or airway anatomical abnormalities may be co-morbid conditions
Chest CT	Characterizes nature, extent, and distribution of diseased lung Provides findings that are specific for some types of ILD and thus may provide definitive diagnosis in some cases May guide lung selection of lung biopsy sites if needed	May require sedation or anesthesia for raised volumes and to reduce motion artifact in young children (CV-HRCT) Involves radiation exposure	Technique critical, with coordination between radiologist and anesthesiologist for infants/ young children Protocols developed for infants and children limit radiation exposure
Genetic testing	Can provide definitive diagnosis for known single-gene disorders Non-invasive May lead to avoidance of unnecessary diagnostic procedures Potentially provides prognostic information	Relative cost Known limitations of current sequencing technologies	Genetic basis not known for many forms of childhood ILD
Lung biopsy	Gold-standard for diagnosis of many forms of ILD*	Invasive Small number of cases remain unclassifiable even after lung biopsy	VATS is preferred due to lower rates of morbidity compared to open lung biopsy Tissue processing critical

*Genetic testing is considered a gold-standard for certain forms of childhood ILD and generally obviates the need for lung biopsy if positive

Definition of abbreviations: CV-HRCT = controlled ventilation high resolution chest CT, ILD=interstitial lung disease, PAP = pulmonary alveolar proteinosis