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Childhood Interstitial Lung Disease: Foundational Insights for Clinicians

Abu Zahra M* and Al-Dhmour H

Department of Pediatrics, The Children's Hospital at Montefiore, USA

***Corresponding author:** Mahmoud Abu Zahra, Division of Pediatric Respiratory and Sleep Medicine, Department of Paediatrics, The Children's Hospital at Montefiore, Albert Einstein College of Medicine, 3415 Bainbridge Avenue, Bronx, NY, USA, Tel: +17189203000; Email: mabuzahra@montefiore.org

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Abstract

Childhood Interstitial Lung Disease (chILD) consists of a diverse group of disorders that involve the pulmonary parenchyma and interfere with gas exchange. Patients with chILD may present with respiratory failure, or with more indolent or chronic symptoms including tachypnea, cough, hypoxemia, prolonged respiratory infection, exercise intolerance, or failure to thrive. The differential diagnosis for such a presentation is broad, and it is recommended to exclude more common causes first including infections, immunodeficiency, structural airway abnormalities, congenital heart disease, and cystic fibrosis. Once more common explanations are excluded, a child with unexplained pulmonary symptoms and diffuse pulmonary infiltrates should be given a provisional diagnosis of chILD, and further investigations to determine a specific cause are warranted. In any case, establishing a definitive diagnosis is essential, as it may inform prognosis, genetic counselling for families, and could alter treatment decisions. To date, treatment options for many forms of diffuse lung disease (DLD) are limited and often include drugs of unproven efficacy with substantial side effects. In addition, key differences are present when comparing chILD with adult forms of DLD. Certain diseases are unique to paediatrics and others could present in different proportions with dissimilar prognosis. Thus, chILD presents a diagnostic and therapeutic challenge, even to the most experienced pediatric pulmonologist. In this review we will focus on the presentation, diagnostic approach, treatments, and prognosis of chILD.

Keywords: chILD; Interstitial Lung Disease (ILD); Chest CT; Bronchoscopy; Lung Biopsy; Diffuse Lung Disease

Abbreviations

DLD: Diffuse Lung Disease; ILD: Interstitial Lung Disease; ATS: American Thoracic Society; AI: Artificial Intelligence; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; UTE: Ultrashort Echo Time; BAL: Bronchoalveolar Lavage; VATS: Video-Assisted Thoracoscopy; FDA: Food and Drug Administration

Introduction

In 2013 the American Thoracic Society (ATS) published a practice guideline for childhood interstitial lung disease which defined chILD syndrome by the presence of three out of the following criteria: respiratory symptoms (cough, rapid breathing), signs (tachypnea, retractions, adventitious sounds), hypoxemia, and diffuse lung imaging abnormalities

[1]. However, the traditional description of these disorders as interstitial lung disease (ILD) seems to be less accurate as the interstitium is not involved in certain diseases, such as neuroendocrine cell hyperplasia of infancy (NEHI), and the use of diffuse lung disease (DLD) has been suggested [2]. Throughout the literature, chILD, ILD, and DLD have been used interchangeably to describe disorders with diffuse lung involvement which often includes alterations of alveolar and airway architecture, in addition to interstitial compartment changes [2,3]. These conditions were classified within the pediatric age group to disorders more prevalent in infancy and disorders not specific to infancy [1-3].

chILD is rare and epidemiologic studies report dissimilar prevalence estimates due to the use of different definitions and ascertainment methods. A study from Germany reported 1.32 cases per million in children ≤16 years but it excluded those with underlying systemic disease [4]. More recent studies reported a prevalence between 0.15 to 4.6 per 100,000 children [5]. We believe that chILD prevalence is underestimated, and the numbers reported will most probably increase with the use of broader definitions and the advances in imaging modalities and genetic testing. This article will provide useful insights for physicians to help address these diseases and provide treatment for patients.

Discussion

Clinical Presentation

Patients with chILD present with a variety of symptoms including history of cough (usually chronic), rapid breathing (persistent or intermittent), retractions, exercise intolerance, or failure to thrive [1,2]. They could have an indolent course which may delay the diagnosis [1,3]. Physicians should pay attention to neonates who present with unexplained respiratory failure, term infants with chronic lung disease out of proportion to the degree of their comorbidities, and children with severe disease or prolonged hospital course with an acute viral respiratory infection, as they could have an underlying DLD [1-3].

History should focus on symptoms that may suggest an underlying cause, including feeding and swallowing difficulties (aspiration), fever (infection), recurrent infections (immunodeficiency), hemoptysis (pulmonary hemorrhage), and steatorrhea (cystic fibrosis) [1,6]. Also look for history of connective tissue disease or autoimmune disease, suggestive symptoms could include rashes, arthritis, skin thickening, and nail dystrophy [5]. Family history is important, as it may reveal an inherited form of DLD and guide the diagnostic approach [1].

Physical examination could reveal tachypnea and retractions. Failure to thrive is sometimes present with chronic or advanced disease [1,5,6]. Crackles (more common) and wheezing (less common) often heard with auscultation [6]. Cardiac examination is usually normal except in patients with comorbid heart condition or in patients with advanced DLD leading to pulmonary hypertension or cor pulmonale [5,6]. Hypoxemia and cyanosis indicate severe disease, and clubbing is typically a late manifestation and more common in older kids [5,6]. Extrapulmonary physical findings may narrow the differential diagnosis and reveal the underlying diagnosis. Physicians should perform a thorough evaluation and examine the skin, nails, joints, eyes, and abdomen, and look for rashes, hyperpigmentation, nail dystrophy, contractures, lymphadenopathy, and hepatosplenomegaly [5,6]. General non-respiratory examination can also show signs of anemia and malnutrition [1,5,6].

Diagnostic Approach

DLD present a diagnostic challenge for physicians due to overlapping symptoms and imaging findings. It is recommended to follow a stepwise approach which starts with a detailed history and physical examination, followed by non-invasive tests, then eventually, invasive investigations which could include a lung biopsy [1,3]. Physicians should try to exclude more common causes first, like infections, immunodeficiencies, aspiration, structural airway abnormalities, congenital heart disease, bronchopulmonary dysplasia, and cystic fibrosis [1,3]. Keeping in mind that patients with DLD can have these as comorbidities, in such cases, investigating for DLD is justified if respiratory symptoms persist despite treating the comorbid condition and when symptoms are out of proportion or progressing [1-3].

Common blood tests like complete blood counts and general chemistries are not specific, but could provide evidence of inflammation, infection, systemic or multi-organ disease, malnutrition, and anemia [1,2]. More specific laboratory tests include investigating for infections with nasal viral swabs, bacterial cultures from sputum or throat, and testing for fungal infections, evaluating for immunodeficiency with lymphocyte subset analysis and quantitative immunoglobulins measurements, serologic studies for autoimmune disorders, swallowing evaluation to diagnose aspiration, and echocardiography to look for structural or functional heart disease [1-3].

Chest x-rays can show abnormalities such as interstitial infiltrates, alveolar, or mixed patterns, but usually not diagnostic [1,7]. Chest x-rays in NEHI may look normal or show hyperinflation or peribronchial cuffing which can be seen in reactive airway disease [7,8]. The recent use of artificial intelligence (AI) has led to increased diagnostic sensitivity of these films [7]. Chest computed tomography (CT) is the gold standard for confirming and describing DLD,

and can better correlate with the severity [1,2,7]. Chest CT can be highly specific for certain diseases, in NEHI it will show ground-glass opacities in the perihilar regions, right middle lobe, and lingula without other abnormalities [1,8]. In bronchiolitis obliterans it will show mosaic attenuation with irregular areas of ground-glass and hyperlucency [2,7]. Non-specific CT scans findings can also inform next steps and narrow differential diagnosis, for example, a scan showing diffuse ground glass opacities in a term newborn with respiratory failure could highly suggest surfactant deficiency disorders [1,7,9].

Newer CT techniques which utilize dynamic imaging with several series of cuts during the respiratory cycle may be beneficial in certain types of DLD and it would decrease the need for anesthesia [2,7]. Photon- counting CT has enhanced resolution and better detection for subtle findings not appreciated with traditional CT scans [7]. AI and quantitative CT (qCT) have been utilized to interpret findings and to differentiate between DLD types [7]. Magnetic resonance imaging (MRI) has been used to examine DLD by means of structural imaging using ultrashort echo time (UTE) MRI, and functional assessment using hyperpolarized gas (129Xe) MRI [7]. UTE MRI can identify parenchymal as well as airway abnormalities, and 129Xe MRI is useful for evaluating ventilation and gas exchange [7]. CT scans (the gold standard) remain superior to MRI with higher sensitivity, but MRI showed some beneficial features including increased specificity in differentiating inflammatory from fibrotic disease, in addition to being more pediatric patient friendly due to the absence of radiation [7]. The expanding scope of these modalities and FDA approval for hyperpolarized gas MRI use in DLD are exciting news which may lead to improved patient care.

Genetic testing is often warranted, especially in infants and in cases with family history of chILD [1-3,9]. These tests could be diagnostic, helping avoid more invasive procedures such as lung biopsy. Mutations in SFTPB, SFTPC, ABCA3, and NXK2-1 genes affect the quantity and or quality of surfactant production [2,9]. Mutations in CSF2RA, CSF2RB, SLC7A7, and MARS1 genes impact surfactant catabolism via macrophage dysfunction [2,9]. Mutations in the FOXF1 gene were found to be associated with alveolar capillary dysplasia (ACD) [2,9]. There is a growing list of genetic mutations that have been found associated with DLD, which may assist the development of targeted therapy in the future [9].

Flexible bronchoscopy has been traditionally used to evaluate for infection, airway anatomy, and to obtain bronchoalveolar lavage (BAL) samples [1-3]. BAL cultures, cytology, and fluid analysis could diagnose infectious etiologies, hemorrhage, and provide evidence for certain diseases like pulmonary alveolar proteinosis and sarcoidosis [1-3,10].

Lung biopsy remains the mean of definitive diagnosis in many forms of DLD [11]. Although the need for biopsy has decreased significantly due to recent advancements in genetic testing and imaging modalities [7,9,11]. To maximize diagnostic yield, standardized published protocols for tissue processing should be applied, including fixation for electron microscopy [1,11]. Biopsies should be interpreted by a pathologist experienced with pediatric DLD [11]. Video-assisted thoracoscopy (VATS) is the procedure of choice for pediatric lung biopsy [11]. Transbronchial biopsy is not usually performed due to the small size of the specimens which rarely provide sufficient architectural detail to allow for definitive histologic diagnosis [1,11]. However, recent applications of cryoprobes (cryo-biopsies), a bronchoscopic procedure that freezes and extracts lung tissue, preserving its structure for histopathology, are showing promising results which may decrease the need for VATS in the future [11,12].

Although this stepwise approach is generally recommended, in clinical practice multiple factors play a role in determining the urgency and choice of diagnostic tests. Decisions should be made while taking into account disease severity, progression, and the patient's overall clinical status. Pediatric pulmonology consultation is advised and multidisciplinary team evaluation may be warranted in atypical cases.

Treatment

Treatment of chILD focuses on providing supportive care for all cases and disease specific therapy if available [3,13]. Supportive therapy includes optimizing nutrition, vaccinations, oxygen and respiratory support, and limiting exposure to smoke or other irritants [13]. Specific treatments include antimicrobials for infections, whole lung lavage in pulmonary alveolar proteinosis, and avoidance of the offending antigen in hypersensitivity pneumonitis [3,13,14].

Glucocorticoids empirical treatment is commonly used in forms of DLD with inflammation or inappropriate cellular proliferation [13,14]. These conditions include hypersensitivity pneumonitis, lymphocytic interstitial pneumonia, DLD secondary to connective tissue disease, and eosinophilic pneumonia [13,14]. Different doses and durations have been discussed in pediatrics, the use of methylprednisolone 10 to 30mg/kg per day, for three consecutive days administered monthly is often preferred with fewer reported side effects. Another alternative is the use of oral prednisolone 1-2 mg/kg per day. Treatment trials of 3-6 months have been suggested while monitoring clinical response and side effects [13,14].

Hydroxychloroquine was found to be helpful in cases with SFTPC and ABCA3 mutations, and lymphocytic interstitial

pneumonia [14,15]. Azithromycin has been tried given its anti-inflammatory and immunomodulatory effects, and commonly used in combination with steroids [10,14]. Other drugs which have been used include cyclophosphamide, azathioprine, methotrexate, and rituximab, that were typically reserved for patients with connective tissue disease [10,14,16]. Nintedanib and pirfenidone (antifibrotic agents) demonstrated effectiveness in attenuating decline in vital capacity in adults [17]. In paediatrics, phase 2 multicentre study of nintedanib demonstrated safety and suggested efficacy in maintaining vital capacity, and open label extension study is ongoing [17]. Biological therapies which target the mutant variant or affected molecule are being evaluated in animal models [18,19]. An antagonist of Calcitonin gene related peptide (CGRP) which is increased in NEHI, was found to alleviate the symptoms in affected mice [18,19]. Other studies focused on FOXF1 mutation variants responsible for ACD and identified many targeted molecules for possible future biological treatments [18,19].

Lung transplantation might be needed in cases with severe and progressive disease and it is sometimes the only effective treatment, like in cases with surfactant protein B deficiency and ACD [9,18]. In such diseases, timely referral is essential and may improve outcomes [20].

Prognosis

The prognosis in chILD is based on the underlying etiology [1,9,20,21]. Patients with NEHI and many with pulmonary interstitial glycogenosis improve over time [8,20-22]. However, those with ACD and SFTPB mutations have a very poor prognosis and will not survive without lung transplant [9,20]. Survival rate after transplantation is reported to be similar to that of pediatric lung transplant for other causes, close to fifty percent at five years [20]. Recurrence of the primary DLD post-transplant has not been reported in paediatrics [20].

Conclusion

chILD syndrome presents significant complexities due to its diverse etiologies and overlapping clinical features. A structured diagnostic approach, beginning with a thorough history and physical examination followed by non-invasive testing, coupled with advanced imaging and genetic testing, can facilitate early and accurate diagnosis while minimizing unnecessary interventions. While specific treatment options remain limited, empirical therapies and timely lung transplantation have shown favorable outcomes.

Future research should focus on developing targeted therapeutic strategies to enhance the prognosis for children affected by these rare conditions.

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