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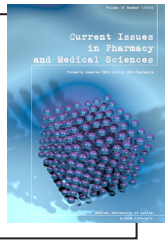

Is childhood interstitial lung disease (chILD) still a mystery in infants?

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ABSTRACT

Childhood interstitial lung disease (chILD) comprises a heterogeneous group of several hundred disorders that affect not only the pulmonary interstitium, as suggested by the name, but also other components of the respiratory system. The prevalence of chILD remains unclear and depends largely on the data source. Many patients die before a definitive diagnosis is established, which further complicates the estimation of disease incidence in infants.

In recent years, increased recognition of chILD has drawn growing attention within the medical community. As a result, these disorders have been classified into two major groups: those presenting in children younger than 2 years of age and those affecting older children. Nevertheless, the diagnostic process remains highly challenging. These diseases are rare, and their onset during the neonatal period is often associated with high mortality before a comprehensive diagnostic evaluation can be completed.

Currently, several therapeutic options for chILD are available; however, none ensures consistent treatment success. Ongoing research is exploring novel therapeutic strategies, including stem cell transplantation, which may offer new hope for improving outcomes and survival in patients with chILD in the future.

INTRODUCTION

Childhood interstitial lung disease (chILD) encompasses a heterogeneous group of more than 200 rare conditions that impair normal gas exchange in the lungs [1,2]. These abnormalities affect not only the pulmonary interstitium surrounding the alveoli but also the distal airways, including the terminal bronchioles, as well as the alveolar spaces themselves [2,3]. A key factor in the etiology of chILD is abnormal activation of the alveolar epithelium and mesenchymal cells, leading to disrupted lung development and function [3].

Epidemiological data on chILD are limited and inconsistent. According to the available literature, the estimated incidence ranges from 1 to 46 cases per million children [4]. Other reports suggest a higher incidence, from 1 to 162 cases per million children under 17 years of age [5]. Approximately 50% of cases are diagnosed during the first year of life; however, the disease may also be identified later, including during adolescence [6].

In recent years, advances in diagnostic approaches and disease classification have led to the division of chILD into two major groups based on age at presentation [1]. This classification reflects differences in underlying pathological mechanisms and disease entities observed in children younger than 2 years of age compared with those aged 2–18 years [7]. Many chILD conditions may be triggered by infections and affect lung tissue through diverse pathogenic pathways [1,2]. As the disease progresses, thickening of the interstitial space around the alveoli commonly occurs, resulting in impaired lung expansion during inspiration and reduced recoil during expiration [2]. Consequently, gas exchange is compromised, leading to hypoxemia and compensatory tachypnea aimed at maintaining adequate oxygen levels. This increased respiratory effort is energetically demanding and often results in fatigue [2].

The clinical course of chILD varies widely. Some conditions show gradual improvement over time, whereas others follow one of two severe trajectories: progressive respiratory failure beginning in the perinatal period or a slowly advancing yet relentless respiratory insufficiency, manifesting as dyspnea on exertion or at rest [8].

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CLASSIFICATION OF CHILD IN INFANTS

The causes of childhood interstitial lung disease (chILD) in infants include a broad spectrum of developmental abnormalities involving the cilia, respiratory epithelium, alveolar sacs, and pulmonary capillaries (capillary dysplasia), as well as disorders of alveolar growth, genetic surfactant dysfunction syndromes, and specific entities of unclear etiology, such as neuroendocrine cell hyperplasia of infancy (NEHI), pulmonary interstitial glycogenosis (PIG), and others [1,3]. According to the available literature, the most common causes of chILD in infants are NEHI and mutations in the *ABCA3* gene, which plays a crucial role in surfactant metabolism [4,9].

Diffuse developmental disorders constitute a group of conditions characterized by abnormal lung development with early clinical manifestation. They are associated with mutations in genes such as *FOXF1*, *FLNA*, *TBX4*, *FGFR2*, and others [7]. Affected patients typically develop severe hypoxemic respiratory failure that is unresponsive to conventional treatment. Clinical deterioration begins in the neonatal period and often necessitates prolonged mechanical ventilation; lung transplantation remains the only life-saving therapeutic option. Owing to the rarity of these disorders, detailed imaging descriptions are limited; however, areas of hypoinflation and pulmonary opacities may be observed [10]. In many cases, a definitive diagnosis can only be established postmortem [8].

Disorders of alveolar growth represent another important subgroup leading to chILD. Radiographic findings may include cystic lesions, ground-glass opacities, and linear abnormalities on chest imaging. The clinical presentation is variable, and these disorders are frequently associated with chromosomal abnormalities [10]. Mortality in affected infants is estimated at approximately 34% [6].

Another etiological group comprises genetic disorders of surfactant metabolism. Several gene mutations have been identified as causative factors in chILD, including *SFTPB*, *SFTPC*, *ABCA3*, *NKX2-1*, *CSF2RA*, and *CSF2RB* [7]. These genes encode proteins essential for surfactant synthesis, function, and degradation. Defects in these pathways result in severe respiratory distress [6]. Neonates typically present with profound hypoxemia from the perinatal period. High-resolution computed tomography (HRCT) commonly reveals interlobular septal thickening and diffuse pulmonary opacities [10].

The most likely underlying mechanism of pulmonary interstitial glycogenosis (PIG) and neuroendocrine cell hyperplasia of infancy (NEHI) is pulmonary immaturity [3]. NEHI, also referred to as persistent tachypnea of infancy, is a disorder of unknown etiology. Although familial cases have been described, no specific disease-associated genetic mutations have been identified to date. During intrauterine life, pulmonary neuroendocrine cells present in the airways stimulate epithelial proliferation and surfactant secretion by alveolar type II cells; their number normally decreases rapidly after birth [3]. Persistent elevation of neuroendocrine cell numbers in respiratory bronchioles may lead to airway obstruction. Experimental studies suggest that excessive production of vasoactive and bronchoconstrictive mediators, such as serotonin, calcitonin, and bombesin, may contribute to disease manifestations [3].

Clinical symptoms of NEHI typically begin around the third month of life, although diagnosis is often delayed until approximately 6 months of age [3]. The disease is characterized by hypoxemia, chronic tachypnea, intercostal retractions, and abnormal auscultatory findings, with symptom exacerbation during respiratory infections [3]. Patients demonstrate reduced tidal volumes compensated by an increased respiratory rate. Imaging findings usually involve at least four lung lobes, with air trapping and ground-glass opacities predominantly affecting the lingula and the right middle lobe [6]. On HRCT, ground-glass opacities serve as a biomarker of disease severity [3]. Definitive diagnosis is established by identifying increased numbers of bombesin-immunopositive neuroendocrine cells within the bronchioles [11]. Most patients experience gradual clinical improvement over time, although cases of severe asthma have been reported. In such patients, treatment with systemic glucocorticosteroids has not demonstrated clinical benefit [3,6].

Pulmonary interstitial glycogenosis (PIG) is a rare interstitial lung disorder that manifests in early infancy [6]. It results from abnormal accumulation of glycogen within mesenchymal cells of the pulmonary interstitium and is considered a consequence of delayed lung maturation [3]. Glycogen-rich mesenchymal cells are normally present during fetal lung development, but their numbers decline after birth [3]. PIG typically presents within the first months of life with hypoxemia requiring mechanical ventilation, and symptoms are generally not exacerbated by infection [3]. Imaging findings are nonspecific and less characteristic than those observed in NEHI, and may include ground-glass opacities, cystic changes in the posterior lung fields, consolidations, interlobular septal thickening, subpleural reticular patterns, and areas of hyperinflation [3,6]. Because clinical and radiological features are insufficient for diagnosis, lung biopsy demonstrating glycogen accumulation and mesenchymal cell proliferation is essential [3]. Management includes oxygen supplementation and systemic corticosteroid therapy, which is believed to enhance lung maturation and surfactant production, similar to effects observed during the perinatal period [3]. By 2–3 years of age, approximately half of affected children become asymptomatic, while the remainder continue to experience symptoms such as tachypnea and reduced exercise tolerance [3].

ALARMING SYMPTOMS

Infants presenting with symptoms such as dyspnea, tachypnea, exercise intolerance, cyanosis or a grayish discoloration of the lips, a prolonged afebrile cough without signs of infection—particularly when accompanied by tachypnea—auscultatory abnormalities, hypoxemia, or persistent abnormalities on chest imaging lasting longer than one month should be closely monitored. Additional concerning features in the patient's medical history include a lack of response to standard therapy, recurrent respiratory illnesses (such as atypical pneumonia or *Pneumocystis jirovecii* pneumonia), symptoms suggestive of aspiration, or recurrent fungal infections. During physical examination, particular

attention should be paid to digital clubbing and failure to thrive, including poor weight gain or weight loss [1].

Other symptoms that may be observed include signs of pulmonary hypertension, recurrent fevers, hemoptysis, and unexplained respiratory distress, especially when occurring early in life. These manifestations may be accompanied by extrapulmonary features such as hypothyroidism, skin lesions, joint pain, hypotonia, chorea, and sensory deficits [4].

THE DIAGNOSTIC PROCESS

Because childhood interstitial lung diseases are rare, establishing a diagnosis is challenging [2]. In infants and young children, symptoms of chILD often overlap with those of more common conditions presenting at a similar age [6]. These include bronchopulmonary dysplasia, primary ciliary dyskinesia, recurrent aspiration, gastroesophageal reflux disease, cystic fibrosis, congenital or acquired immunodeficiencies, congenital heart disease, storage disorders, connective tissue diseases, and pulmonary infections [6,8]. Before a diagnosis of chILD is made, these more prevalent causes of interstitial lung disease must be carefully excluded [8].

When chILD is suspected, the patient's case should be discussed with a specialist experienced in the diagnosis and management of interstitial lung diseases in children [2]. The diagnosis should be considered when at least three of the following criteria are met: respiratory symptoms (cough, dyspnea, exercise intolerance), clinical respiratory signs (tachypnea, auscultatory abnormalities, digital clubbing, or respiratory failure), hypoxemia, and abnormal findings on chest imaging [7]. Initial diagnostic steps include a detailed medical history, thorough physical examination, routine laboratory tests, and chest radiography [4,6]. Fine inspiratory crackles at end inspiration are a characteristic auscultatory finding [6]. High-resolution computed tomography (HRCT) should also be performed as part of the diagnostic evaluation [4].

Typical imaging features at early stages of the disease depend on both the specific type of chILD and the patient's age. In infants, imaging predominantly reveals reduced lung transparency due to ground-glass opacities and an increased or distorted pulmonary pattern [4,6]. In older children, cystic, nodular, or fibrotic changes are more commonly observed [4]. Notably, similar radiological findings may be seen in premature neonates with respiratory distress syndrome [6]. When noninvasive diagnostic methods fail to establish a diagnosis and symptoms persist for more than three months or show progression, invasive diagnostic procedures should be considered. These include bronchoscopy with bronchoalveolar lavage (BAL) and lung biopsy, which allow cytological and microbiological analyses and help exclude other conditions with overlapping clinical features [4,5].

The American Thoracic Society recommends a stepwise diagnostic approach, beginning with the least invasive methods [7]. Until recently, lung biopsy was considered the diagnostic gold standard for chILD. Currently, molecular diagnostic techniques have largely replaced biopsy, which is now reserved for cases in which other diagnostic modalities are inconclusive [4]. Nevertheless, according to the literature, more than 60% of patients ultimately diagnosed with chILD undergo lung biopsy [7,12]. When indicated, video-assisted thoracoscopic surgery is preferred over open thoracotomy [7]. It is also emphasized that in cases of rapidly progressive disease, lung biopsy may provide a definitive diagnosis more quickly than genetic testing [8].

Echocardiography should be performed in all patients, as it enables the detection of pulmonary hypertension and coexisting cardiac anomalies, which may complicate the course of chILD [2,4]. Genetic testing, particularly next-generation sequencing (NGS) and whole-exome sequencing (WES), identifies a genetic etiology in approximately 20% of patients. Sanger sequencing may be used to confirm specific pathogenic variants [8]. Mutations in genes associated with surfactant metabolism account for a substantial proportion of genetically confirmed cases [4]. Early implementation of genetic testing may obviate the need for lung biopsy in selected patients [8].

In older, cooperative children, pulmonary function testing should be performed. ChILD is typically associated with a restrictive ventilatory pattern, reduced lung volumes, decreased lung compliance, and a reduced diffusing capacity for carbon monoxide (DLCO) [5]. Overall, the diagnosis of chILD remains complex and requires consideration of a broad differential diagnosis, as well as a multidisciplinary and stepwise diagnostic approach [2,4].

THERAPEUTIC APPROACHES

Currently, only limited guidelines are available for the management and treatment of childhood interstitial lung disease (chILD). The clinical course varies considerably: many children experience gradual improvement, some adapt to living with chronic disease, and others eventually outgrow their condition [2]. Treatment is primarily supportive and symptomatic, often combined with respiratory physiotherapy [13]. Therapeutic interventions include oxygen supplementation, anti-inflammatory agents, antibiotics, and, in severe cases, lung transplantation [1,2].

At present, systemic corticosteroids represent the most commonly used pharmacological treatment because of their immunosuppressive and anti-inflammatory effects. Corticosteroids inhibit leukocyte migration to inflamed tissues, suppress humoral immune responses, and interfere with fibroblast and endothelial cell function [14]. Reduction of pulmonary inflammation is considered a desirable therapeutic outcome [5]. Treatment with oral or pulse corticosteroids typically lasts 6–8 weeks. In cases of treatment failure, significant adverse effects, or the need for prolonged therapy, alternative agents such as hydroxychloroquine or azithromycin may be considered. Azithromycin is usually administered at a dose of 10 mg/kg three times per week [5].

It should be emphasized that no definitive curative therapies for chILD currently exist, and relatively few studies have evaluated the efficacy and safety of available treatment options [15]. Recently, experimental studies investigating the use of stem cells in chILD have shown promising results [13]. Stem cells are capable of differentiating into mesoderm-derived tissues and may therefore contribute to the regeneration of damaged lung parenchyma [13]. In addition,

anti-inflammatory effects have been reported, as evidenced by reductions in C-reactive protein levels following stem cell transplantation [13]. However, the cited studies were conducted in adults aged 40–80 years with chronic obstructive pulmonary disease (COPD) and a history of long-term smoking [16]. Consequently, the applicability of stem cell therapy to pediatric chILD remains uncertain and requires further investigation [13].

SUPPORTIVE CARE IN CHILD

Management of chILD requires a multidisciplinary approach. Children with chILD often have significantly increased energy expenditure due to elevated respiratory rates and therefore require higher caloric intake than their healthy peers. Adequate nutrition is essential for normal growth and has a positive impact on prognosis. Poor weight gain or weight loss should prompt intensification of supportive care measures [2].

Other key aspects of management include prompt treatment of respiratory infections, adherence to routine vaccination schedules, and respiratory syncytial virus (RSV) prophylaxis in the youngest and most vulnerable patients [5]. Although children with chILD who do not have underlying immunodeficiencies are not more susceptible to infections than healthy children, infections tend to follow a more severe clinical course in this population [2]. Complete isolation from social environments is neither feasible nor beneficial, as it significantly reduces quality of life [2]. Most children with chILD are able to attend nursery or school, provided that caregivers and teachers are adequately informed about the disease and receive clear instructions for emergency situations [2].

Physical activity should be encouraged, as it has a beneficial effect on lung function and overall well-being [2]. In addition, many countries provide social or financial support to families caring for children with chronic conditions such as chILD, which may help reduce the burden associated with long-term disease management [2].

CONCLUSIONS

The prognosis of childhood interstitial lung disease varies widely, ranging from complete recovery in conditions such as neuroendocrine cell hyperplasia of infancy (NEHI) or pulmonary interstitial glycogenosis (PIG) to an almost uniformly fatal outcome in severe developmental lung disorders [13]. Overall mortality among patients with chILD is estimated at approximately 15% [13]. Pulmonary hypertension has been identified as the most important predictor of mortality, while poor growth, inadequate weight gain, and the presence of pulmonary fibrosis are associated with an unfavorable prognosis [6].

Despite these challenges, growing awareness of chILD and rapid advances in diagnostic techniques and emerging therapeutic strategies offer hope for improved outcomes and survival in affected children in the future.

CONFLICT OF INTEREST

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