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EDITORIAL ARTICLE

PEDIATRIC INTERSTITIAL LUNG DISEASES

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DEFINITION

Chronic interstitial lung disease (ILD) in children is defined as the presence of respiratory symptoms, diffuse infiltrates on chest radiographs, abnormal pulmonary function tests with evidence of restrictive ventilatory defect and/or impaired gas exchange, and persistence of these findings for >3 months with considerable mortality and morbidity.(1)

Interstitial lung diseases (ILDs) in childhood are a diverse group of conditions that primarily involve the alveoli and perialveolar tissues. Children's interstitial lung disease (chILD) has become the preferred term.

The relative frequencies of these disorders are quite different in children compared with adults and, more importantly, there are unique forms seen mainly in infants and very young children that have not been reported in adults such as neuroendocrine cell hyperplasia in infancy (NEHI) and pulmonary interstitial glycogenesis (PIG).(2) Idiopathic pulmonary fibrosis (IPF, also known as cryptogenic fibrosing alveolitis [CFA]), the most prominent adult ILD, mostly occurs after the fifth decade of life and is almost never seen in children.(3)Unlike in adults, most ILDs in children are found to have an underlying cause.

PATHOPHYSIOLOGY

Childhood ILD is not a disease but a group of disorders. However, most ILDs share a common pathophysiologic feature, namely, structural remodeling of the distal airspaces, leading to impaired gas exchange. In general, this remodeling has been believed to be the sequela of persistent inflammation; however, more recently, the paradigm has shifted away from inflammation to one of tissue injury with aberrant wound healing resulting in collagenous fibrosis.(4) Wound healing and fibrosis are complex pathophysiologic processes that involve numerous cell types and cellular processes, such as adhesion; migration; proliferation; apoptosis; and a vast array of soluble mediators, extracellular matrix (ECM) molecules, and signaling intermediates. In children these processes occur in an organ that is still developing, further complicating the pathophysiology.(5)

Resolution of fibrotic remodeling involves a complex series of orderly steps, including matrix breakdown and restructuring, reepithelialization, and apoptosis of fibroblasts and inflammatory cells. Proliferation of type II pneumocytes is seen in most types of ILD. The proliferation and migration of type II pneumocytes over the provisional wound matrix are believed to be crucial events in the resolution of fibrosis. Fibrotic remodeling is responsible for most of the

morbidity and mortality associated with ILD. Remodeling of distal airspaces results in hypoxemia. Persistent hypoxemia results in pulmonary hypertension and vascular remodeling, leading to cor pulmonale. The increased work of breathing associated with reduced compliance results in increased energy expenditure, which, combined with the effects of inflammatory mediators, can result in cachexia. Portions of the lung may be replaced by fibrotic septae between dilated airspaces, the so-called honeycomb changes of end-stage interstitial disease.[4]

CLASSIFICATION

ILD in children can be classified into idiopathic disorders, those of known or suspected causes, those associated with systemic diseases, and forms of ILD most prevalent in infancy.

1. ***Idiopathic:***
   - Idiopathic pulmonary hemosiderosis.
   - Desquamative interstitial pneumonia (DIP).
   - Lymphocytic interstitial pneumonitis (LIP).
   - Lymphangiomatosis. Nonadenoviral bronchiolitis obliterans (4%).
   - Pulmonary alveolar proteinosis (PAP).
   - Eosinophilic syndromes.
   - Nonspecific interstitial pneumonia
2. ***Disorders with known causes:***
   - Infection: Viral infection, bacterial infection (eg, pertussis, Legionella, Mycoplasma, Chlamydia, or Mycobacterium species), and parasitic infection (eg, visceral larva migrans).
   - Environmental conditions: Exposure to organic dusts (hypersensitivity pneumonitis), and exposure to inorganic particulates (eg, silica, asbestos, talc, zinc).
   - Drugs: Use of antineoplastic agents, penicillamine, nitrofurantoin, gold).
   - Previous lung injury: Chronic aspiration pneumonitis
   - Lymphoproliferative disorders.
   - Neoplasia (eg, lymphoma, leukemia).
   - Lysosomal storage disorders: Gaucher disease, Niemann-Pick disease.
   - Degenerative disorders: pulmonary microlithiasis
3. ***ILD associated with systemic diseases:***
   - Connective tissue diseases: Juvenile rheumatoid arthritis, dermatomyositis/polymyositis, systemic sclerosis, systemic lupus erythematosus [SLE], ankylosing spondylitis, and Sjögren syndrome
   - Pulmonary vasculitis (polyarteritis nodosa, Wegener granulomatosis, Churg-Strauss syndrome).
4. ***Forms of ILD most prevalent in infancy:***

Progress has been made in addressing this problem with the recent descriptions of several specific diffuse lung disorders that appear to be unique to infants and young children. These include infantile cellular interstitial pneumonitis.[6] Chronic pneumonitis of infancy.[7] And persistent tachypnea of infancy associated with neuroendocrine cell hyperplasia (NEHI). In 2005, Deterding et al[8] reported a case series of 15 patients with a clinical picture of persistent tachypnea, crackles, and hypoxemia. About 85% of the patients were born at full term, and none of those born prematurely had a history of chronic lung disease. In those infants, chest radiographs revealed hyperinflation; hyperinflation and a ground-glass appearance were revealed on HRCT. Lung biopsy did not demonstrate a characteristic histologic pattern, and interstitial involvement was minimal. They observed mild, nonspecific changes, including airway smooth muscle hyperplasia, increased alveolar macrophages, and increased airway clear cells. Immunostaining of the cells demonstrated strong staining for bombesin and serotonin, which identified these cells as pulmonary neuroendocrine cells (PNECs).In addition, the genetic basis of some

forms of ILD, including surfactant protein B and C deficiencies[9,10] has been identified mainly from the study of infants and children.

Canakis and colleagues describe a form of neonatal ILD that they term pulmonary interstitial glycogenosis (PIG).[11] The case histories presented and the pathology illustrated suggest that this is the same entity as infantile cellular interstitial pneumonitis, originally described by Schroeder and colleagues[6] The light microscopic findings and immunostaining characteristics are identical with those seen in infantile cellular interstitial pneumonitis with the characteristic widening of the interstitium by primitive mesenchymal cells containing a paucity of organelles and a generally empty cytoplasm. The demonstration of glycogen-laden, immature interstitial cells, in the absence of significant inflammation or abnormalities of epithelial or endothelial cells, is diagnostic.[12]

Fortunately, pulmonary interstitial glycogenosis carries a favorable prognosis. Thus, it is critical to distinguish it from other pediatric conditions that are associated with higher morbidity and mortality. Infantile cellular interstitial pneumonitis has sometimes been confused with a more severe and potentially lethal form of ILD, known as chronic pneumonitis of infancy.[12] Patients with pulmonary interstitial glycogenosis/infantile cellular interstitial pneumonitis can avoid the need for prolonged and potentially toxic treatment reserved for other children with more severe types of ILD.

Chronic pneumonitis of infancy resembles some of the variant defects of surfactant proteins with prominent alveolar epithelial hyperplasia and interstitial widening with generally only a minor inflammatory component, but with increased numbers of macrophages.[13]

The chILD (Children's Interstitial Lung Disease) network has published what is without doubt the most significant article in the field,[14] in which a comprehensive classification, based on independent pathologic review of nearly 200 open-lung biopsies in children younger than 2 years, categorized 88% of 187 biopsies. The categories that are proposed are as follows: diffuse developmental disorders (the alveolar-capillary dysplasia–acinar dysplasia spectrum), lung growth abnormalities (pulmonary hypoplasia from a variety of causes), pulmonary interstitial glycogenosis, NEHI, surfactant protein (SP) dysfunction (SpB, SpC, and ABCA3 deficiency), disorders of the normal host (mainly infectious or postinfectious, aspiration, or allergic alveolitis), disorders resulting from systemic disease processes (very few cases, mainly pulmonary hemorrhagic syndromes), disorders of the immunocompromised host (infectious and postinfectious predominant, and iatrogenic complications), and disorders masquerading as chILD (mainly pulmonary vascular and lymphatic disorders). Chronic neonatal lung diseases (prematurity-related BPD and acquired chronic lung diseases in term infants).

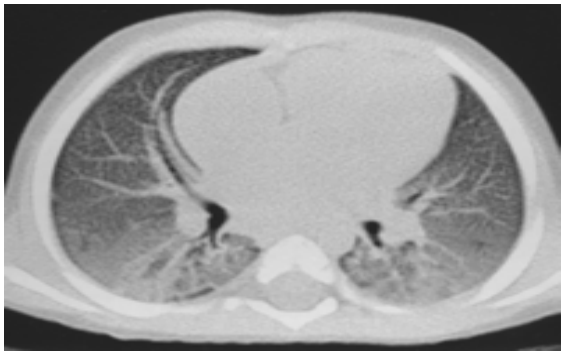
DIAGNOSIS

The international consensus statement defining pathologic, radiologic, and clinical manifestations of idiopathic interstitial pneumonias in adults is largely not applicable to children. CT scanning, specifically HRCT, provides a noninvasive means for determining the extent and distribution of changes associated with pulmonary fibrosis. CT is especially useful in demarcating the most appropriate areas for tissue biopsy. Fan and Langston[15] stated that "our early experience in pediatric interstitial lung disease is similar to the adult experience in that high-resolution CT is generally more useful than a plain chest radiograph in defining severity and extent of disease. "Clearly, conclusions drawn from experience with CT in adult patients cannot always be applied to pediatric practice. For example, the prognosis of desquamative interstitial pneumonitis, is reported to be worse in children than in adults.[16]

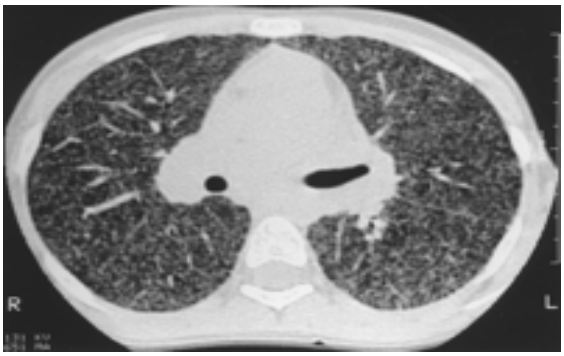
The high resolution CT appearance of chILD include ground-glass attenuation, a tree-in-bud appearance, lobular airtrapping, reticular attenuations, and centrilobular nodules.[17]

In a study of HRCT in 20 children with ILD,

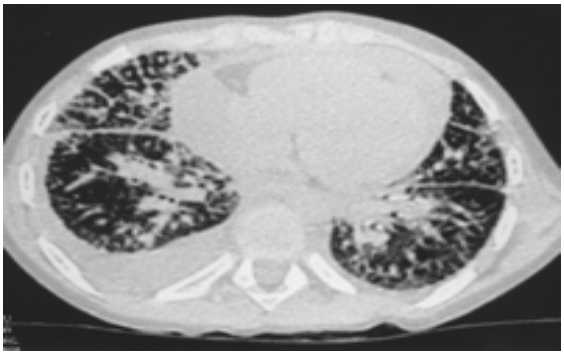
specific patterns were correlated with certain types of pathology, with little overlap.[18] Regions with hyperlucency, with or without bronchiectasis, were well correlated with airspace-localizing diseases, such as bronchiolitis obliterans or bronchocentric granulomatosis. Septal thickening was correlated with lymphangiomatosis. Ground-glass changes were seen in infiltrative ILD, such as DIP, hypersensitivity pneumonitis. A characteristic CT pattern appears to be associated with NEHI.[19] In another study, investigators evaluated
the ability of expert readers to correctly diagnose pediatric diffuse lung disease with HRCT.[20] The correct first-choice diagnosis of ILD was made in 61%, and the conditions correctly diagnosed with greatest frequency were desquamative interstitial pneumonia, pulmonary lymphangiomatosis and alveolar proteinosis, as shown in figures.



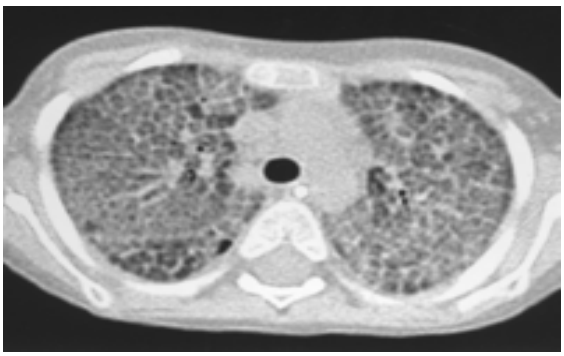
2-year-old boy with biopsy-proven desquamative interstitial pneumonitis and Gaucher's disease. Thin-section CT scan shows widespread ground-glass opacification and denser parenchymal opacification in dependent lung.



13-year-old girl with biopsy-proven lymphocytic interstitial pneumonia. Patient was immunocompromised because of postviral neutropenia. Thin-section CT scan shows profuse nodules (2-3 mm in diameter) with random distribution.



8-year-old boy with biopsy-proven pulmonary lymphangiomatosis. Thin-section CT scan shows bilateral pleural effusions, thickened interlobular septa, and thickened bronchovascular bundles.



3-year-old girl with pulmonary alveolar proteinosis. Thin-section CT scan shows typical features of thickened interlobular septa on background of ground-glass opacification.

Other non invasive diagnostic techniques include pulmonary function testing, echochardiography, and pulse oximetry.

Analysis of tissue obtained during lung biopsy is the best way to make a definitive diagnosis if it cannot be established by noninvasive means. Much of the classification of ILD, especially in disorders of unknown cause, is based on histopathology. A pediatric lung biopsy protocol has been developed and supported by the ChILD Pathology Cooperative Group.[21] However, a diagnosis is not reached in a notable percentage of patients, even after biopsy is performed.

STAGING

Fan devised a simple scoring system for ChILD. A score of 5 indicates the worst outcome, with a 38% survival rate at 60 months. A score of 2, 3, or 4 indicates a survival rate of 76%. The Fan scoring system is as follows (1998):[22]

1. Asymptomatic.
2. Symptomatic with normal oxyhemoglobin saturation.
3. Symptomatic with nocturnal or exercise-induced desaturation.
4. Desaturation at rest.
5. Pulmonary hypertension.

TREATMENT

Activity may be limited by the patient's degree of dyspnea. Oxygen saturation during exercise should be measured. A prescribed, monitored, exercise program may be beneficial to prevent deconditioning in older children. Conditions that may exacerbate pulmonary symptoms (high levels of ozone or other environmental pollutants) should be avoided. Patients with hypersensitivity pneumonitis should be removed from exposure to the precipitating substances (eg, birds, organic dusts). Air travel or travel to high altitudes must be carefully planned in patients with arterial desaturation.

Corticosteroids have been the mainstay of therapy in most children and adults with interstitial lung disease (ILD), despite little conclusive evidence of their efficacy. The theoretical basis for the use of corticosteroids is the assumption that the lung remodeling is in large part the result of persistent inflammation. Steroids may be administered daily or by pulse. Steroid responsiveness is often considered an important prognostic indicator.

Data in adults indicate that the specific histopathologic pattern seen on biopsy specimens correlates with the degree of response to steroids. This has not been verified in children. Time to response is variable, but steroids should be continued for at least 8-12 weeks at full dose (2 mg/kg/d) before therapy is deemed to have failed. Improvement may be seen in symptoms, physical signs, or chest radiographic appearance alone. Then gradual tapering and adjust dose to clinical response and PFT results; symptom relapse warrants return to maximum dosing.

PROGNOSIS

- Fan et al reviewed the outcomes of 99 children with ILD over 15 years (23): Survival rates at 24, 48, and 60 months after the appearance of initial symptoms were 83%, 72%, and 64%, respectively. Patients with histopathologic DIP have a prognosis worse than this.
- Familial IPF manifesting in the neonatal period is associated with a high mortality rate.

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