Interstitial lung diseases in children

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AIMS

- Interstitial lung disease (ILD) in children represents a heterogeneous group of respiratory disorders that are mostly chronic.
- The mechanisms underlying disease development are dependent on the type of ILD, with the common basis being the interaction between injurious environmental and comorbidity triggers (including oxidants and toxic agents, immune complexes, viruses, gastro esophageal reflux) and genetic predisposition.
- The presenting clinical manifestations are often subtle and non-specific. Therefore, a two-step diagnosis approach is required. The first step is the diagnosis of ILD. The second step is the diagnosis of underlying causes, requiring investigations adapted to the clinical grouping of diseases in immunocompetent children: i) exposure-related ILD; ii) systemic disease-associated ILD; iii) lung-restricted ILD; and iv) ILD specific to infancy.
- Treatment protocols remain difficult to produce due to the diversity of ILD conditions and the lack of randomized clinical trials in groups of well phenotyped paediatric patients. The overall strategies include general measures (oxygen, nutrition and adequate energy intake, immunizations) and pharmacological therapy, mainly anti-inflammatory and immunosuppressive molecules.
- The prognosis is highly variable, dependent on underlying causes, patient age and genetic predisposition. A favorable response to anti-inflammatory therapy can be expected in almost two third of cases, although significant sequelae such as limited exercise tolerance or the need for long-term oxygen therapy are often observed.

SUMMARY

Diagnosis of ILD

The presenting clinical manifestations are often subtle and non-specific. The onset of symptoms is, in most cases, insidious and many children may have had symptoms for months before the diagnosis of ILD is confirmed. Common symptoms at presentation include tachypnea/dyspnea, cough, exercise limitation and frequent respiratory infections. Failure to thrive, tiring during feeding and weight loss are also common symptoms, mainly in young patients. Unexplained fever is also reported in infants. The frequent clinical findings are inspiratory crackles, tachypnea and retraction. In a child with a normal birth history, these are strongly suggestive of ILD. Other findings observed in older patients include finger clubbing and cyanosis during exercise or at rest. Depending on the types on ILD, associated non-respiratory symptoms may be observed, such as cutaneous rashes, joint manifestations, uveitis, and recurrent fever in situations of collagen-vascular disorders.

Chest imaging is an essential contributor for the diagnosis. The most common High Resolution Computed Tomograph feature is widespread ground-glass attenuation, with some observations of
intralobular lines and irregular interlobular septal thickening. Large subpleural air cysts in the upper lobes adjacent to areas of ground-glass opacities are also reported in young patients.

Pulmonary function testing represents a useful investigation for both the diagnosis and the management of ILD in children and adolescent. In preschool children, the techniques currently available are limited. Common pulmonary function abnormalities reflect a restrictive ventilatory defect with reduced lung compliance and decreased lung volumes. Lung diffusing capacity of carbon monoxide is often markedly reduced and may be abnormal before any radiological findings. Hypoxemia as defined by reduced resting arterial oxygen saturation or a reduced resting arterial oxygen tension is often present. Hypercapnia occurs only late in the disease course. During exercise, the above described dysfunctions become even more pronounced, and gas exchange during exercise might be a more consistent and sensitive indicator of early disease.

Bronchoalveolar lavage (BAL) and lung tissue analysis are not commonly proposed in the first step diagnostic approach. Besides infections, BAL can be of diagnostic value in specific situations, which include pulmonary alveolar hemorrhage, Langerhans cell histiocytosis, lipid disorders with lung involvement, or alveolar proteinosis. In other pathological situations, BAL can usefully serve to direct further investigations, by providing specimens for cytological examination, microbial cultures, and molecular analysis.

Histological evaluation of lung tissue usually represents the final step in a series of diagnostic approaches. Different methods of biopsy are reported, based on expertise of the surgical teams and the balance between procedure invasiveness and the potential for obtaining adequate and sufficient tissue for diagnosis. The lung histological patterns observed in various forms of ILD have been reviewed in several reports. The most common abnormalities include thickening of alveolar interstitial walls, accumulation of inflammatory cells, fibrotic components, epithelial cell hyperplasia, and alveolar spaces filled with inflammatory cells, hyaline membranes containing surfactant proteins, or cellular debris.

**Specific diagnosis of ILD and classification**

There have been many different approaches to the classification of pediatric ILD. From a clinical point of view, a step-by-step etiological search is critical, with first a clinical evaluation requiring a careful attention to exposure and environment, systemic manifestations, and family disorders. The main groups are:

- **Exposure-related ILD** refers to diseases caused by a sufficient level of exposure (dose) to components with target organ contact, and subsequent biologic changes and clinical expression. Many agents have been associated with pulmonary complications of various types including ILD. In children, this diagnosis is certainly under-estimated, as pediatricians do not usually have the expertise necessary to take an environmental history. The diagnoses most commonly reported include hypersensitivity pneumonitis, a cell-mediated immune reaction to inhaled antigens in susceptible persons, with mainly bird fancier’s diseases, humidifier lung diseases, and chemical lung diseases.

- **Systemic disease-associated ILD** comprises a complex group of disorders requiring specific investigations oriented by the clinical expression. They include mainly granulomatous diseases, metabolic disorders, connective tissues disorders (CTD), pulmonary vasculitis, and Langerhans’-cell histiocytosis. In situations of granulomatous diseases, the discussed diagnoses are mainly sarcoidosis, infections, and disorders of neutrophil function. ILD in metabolic disorders are reported in lysosomal diseases such as Gaucher's and Niemann-Pick diseases, and Hermansky-Pudlak syndrome. CTD refers to any disease that has the connective tissues of the body as a primary target of pathology and whose development implicates genetic, constitutional and environmental elements. The main disorders to be considered
during childhood are rheumatoid arthritis, systemic sclerosis, and systemic lupus erythematosus.

- **Lung-restricted ILD** includes disorders affecting primarily the components of the distal parenchyma, with main diagnosis being infections, surfactant disorders, pulmonary alveolar proteinosis, diffuse alveolar hemorrhage, eosinophilic lung diseases, as well as diffuse developmental disorders and lymphatic system dysfunction. Surfactant disorders include genetic surfactant protein disorders and pulmonary alveolar proteinosis. Mutations in SFTPC can be identified with the most prevalent mutation being I73T (c.218 T>C). The mode of inheritance is autosomal dominant. The phenotype associated with SFTPC mutations is extremely heterogeneous leading from neonatal fatal respiratory failure to children and adult ILD. The deficiency in SP-B is a rare autosomal recessive condition known to be responsible for mainly lethal neonatal respiratory distress. Recessive mutations in the ABCA3 gene were first attributed to fatal respiratory failure in term neonates but are increasingly being recognized as a cause of ILD in older children and young adults. Mutations in the NKX2.1 gene are associated with “brain-lung-thyroid syndrome” which combines congenital hypothyroidism, neurological symptoms (hypotonia, chorea), and lung diseases.

- **ILD specific to infancy** includes neuroendocrine cell hyperplasia, pulmonary interstitial glycogenosis, and chronic pneumonitis in infancy. Neuroendocrine cell hyperplasia of infancy is a non-lethal disease characterized by tachypnea without respiratory failure. On lung biopsy, the histological abnormality is hyperplasia of neuroendocrine cells within bronchioles documented by bombesin immunohistochemistry. Pulmonary interstitial glycogenosis is also a non-lethal disease, reported in neonates with respiratory distress syndrome developed shortly after birth. The histological hallmark is the accumulation of monoparticulate glycogen in the interstitial cells on lung biopsy.

**Treatment strategies and outcome**

The diversity of ILD conditions and the lack of randomized clinical trials in groups of well phenotyped paediatric patients explain the difficulty to propose treatment strategies. Longitudinal care of these children needs be organized in specialized centres.

General measures are essential with mainly administration of oxygen for chronic hypoxaemia, and maintenance of nutrition with an adequate energy intake. Immunization with influenza vaccine on an annual basis is recommended along with other routine immunizations against major respiratory pathogens. In addition, aggressive treatment of intercurrent infections and strict avoidance of tobacco smoke and other air pollutants are strongly recommended.

Pharmacological therapy includes anti-inflammatory and immunosuppressive molecules. Steroids are the preferred choice, administered orally and/or intravenously. An alternative to steroids is hydroxychloroquine. Other therapeutic options include macrolides. Indeed, these antibiotics have been shown to display a number of anti-inflammatory and immunomodulatory actions. The use of molecules directed against Tumor Necrosis Factor (TNF)-α such as the soluble TNF-α receptor agent etanercept is also under investigation.

Lung transplantation is a viable option in children of all ages, even in young infants, and lung or heart-lung transplantation may be offered as an ultimate therapy for end-stage ILD. The outcome and survival do not seem to be different from those reported in other pulmonary conditions.

The prognosis of children with ILD is extremely variable. It is highly dependent on the causes, the patient care system expertise and environment, and the individual response to treatment. It is also very difficult to predict: some children with relatively severe fibrosis on lung biopsy make good progress, whereas others with mild desquamation have a poor outcome. Overall a favorable response to anti-
inflammatory therapy can be expected in almost two third of cases, although significant sequelae such as limited exercise tolerance or the need for long-term oxygen therapy are often observed. Reported mortality rates are around 15%.

REFERENCES