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Review Article

An Update Review on Childhood Interstitial Lung Diseases (chILD)

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Abstract

In recent times, we have encountered several cases of childhood Interstitial Lung Disease (chILD) in our clinical practice in Bangladesh. In developed world, there has been tremendous progress in the approach to chILD, with particular recognition that chILD in infants is often distinct from the forms that occur in older children and adults. Confirmation of diagnosis is challenging because of the rarity of ILD and the fact that the presenting symptoms of ILD often overlap those of common respiratory disorders. There are few case reports and almost no study on chILD in Bangladesh from net search. A growing part of the etiologic spectrum of chILD is being attributed to molecular defects. The pathogenesis of the various chILD is complex and the diseases share common features of inflammatory and fibrotic changes of the lung parenchyma that impair gas exchanges. We are trying to diagnose chILD by excluding methods of suspected children in our aspects. However, in developed nations, clinical practice guidelines emphasize the role for high resolution computed tomography (HRCT) of chest, genetic testing, and lung biopsy in the diagnostic evaluation. Despite improvements in patient management, the therapeutic strategies are still relying mostly on corticosteroids although specific therapies are emerging. Larger longitudinal cohorts of patients are being gathered through ongoing international collaborations to improve disease knowledge and targeted therapies. Thus, it is expected that children with ILD will be able to reach the adulthood transition in a better condition.

Keywords: *Review, childhood, interstitial lung diseases*

INTRODUCTION

The term chILD that are associated with significant morbidity and mortality. Rare lung diseases in children comprise a variety of pulmonary disorders that include cystic fibrosis, primary ciliary dyskinesia, congenital malformations of the lung, pulmonary hypertension, abnormal ventilatory drive and chILDs. The latter is, by itself, a heterogeneous group of very rare lung diseases with an overall estimated prevalence of 1.6–46 per million depending on the few available reports.[1] Thus, they appear to be around 10 times rarer than in adults, covering different aetiologies with some of them being extremely severe.[4] Most general practitioners and paediatricians will face none or one of these patients in their whole career and even paediatric pulmonologists may manage only a few cases of chILD. Unspecific and often inconspicuous, clinical signs could also delay the diagnosis and worsen the prognosis for child.[2]. When an ILD in a child is suspected, further investigations should be performed by experienced radiologists, geneticists and pathologists. Despite an exhaustive workup, a proportion of 6–12% of chILD remains unexplained or undefined.[5]

Chronic ILD in children – "the presence of respiratory symptoms and/or diffuse infiltrates on chest radiograph, abnormal pulmonary function test with evidence of restrictive ventilatory defect and/or impaired gas exchange, and persistence of any of these findings for >3 months."

Clement, 2004.[8] Diffuse lung disease – "a heterogeneous group of uncommon disorders characterized by impaired gas exchange and diffuse infiltrates by imaging.[7]

chILD – "a heterogeneous group of respiratory disorders that are mostly chronic and associated with high morbidity and mortality. These disorders are characterized by inflammatory and fibrotic changes that affect alveolar walls. Typical features include diffuse infiltrates on chest radiograph, abnormal pulmonary function tests with evidence of a restrictive ventilatory defect (in older children) and/or impaired gas exchange.[2]

chILD syndrome – diffuse lung disease in children < 2 years of age with common causes of diffuse lung diseases excluded as the primary diagnose as the presence of at least three of a) respiratory symptoms b) respiratory signs c)hypoxia d) diffuse abnormalities on CXR or CT scan.[13]

EPIDEMIOLOGY

The prevalence of ILDs in children in Bangladesh is not well-established. ILDs are generally considered rare, and specific epidemiological data are limited. We have found

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some cases of chILD form our clinical practice and published them as case report in Bangladesh. Environmental factors, including air pollution (indoor and outdoor), exposure to biomass fuels, and other pollutants, may contribute to the development or progression of ILDs in children in Bangladesh. Epidemiology of ILDs in children can vary within S outh East Asia based on regional and socioeconomic factors, access to healthcare, and environmental exposures. Due to the rarity of pediatric ILDs, larger-scale studies, collaboration among healthcare professionals, and establishment of dedicated registries can help improve our understanding of the epidemiology and management of ILDs in children in these countries.

Overall, ILD is rare in children. Studies have estimated a prevalence of 3.6 cases per million in the United Kingdom and Ireland,[10] and 1.32 cases per million in Germany,[11] 4 cases per million in Denmark. There is no data in Bangladesh from net search.

CLASSIFICATION

Many different approaches have been used for the classification of chILD. According to Kabra it is classified into 2 groups, below 2 years age of children and above. Below 2 years these are a) Diffuse Developmental disorders b) Alveolar growth abnormalities c) Neuroendocrine Hyperplasia of Infancy (NEHA) d) Pulmonary Interstitial Glycogenesis (PIG) e) Surfactant Protein Deficiency Disorders f) Disorders related to systemic illnesses g) Disorders of normal immune responces h) Disorders of immuno compromised host i) Disorders masquerading as interstitial disease j) Aspiration syndromes.

chILD above 2 years are a) Hypersensitivity pneumonitis b) Usual Interstitial Pneumonitis (UIP) c) Recurrent pulmonary hemorrhage d) Lymphocytic Interstitial Pneumonitis (LIP)

The 2004 report of the ERS Task force on chronic ILD in immuno-compitant children presented the 1st classification system for children that was closely linked to the classification system in adult.[15] In 2007, pathologists, together with clinicians, proposed a classification system based on the history of lung tissue for children <2 years of age.[5] This system was later extended to all paediatric age groups.

DIAGNOSIS

Diagnostic approach depends upon many factors. Over the past decade, USA and European Union work groups have proposed some diagnostic approaches.[13,14] The first was in 2013 based on a careful family screening for ILD, followed by the elimination of other diagnoses before proceeding to more specific chILD investigations such as CT scan, genetic tests and lung biopsy.[13]At that time, the number of involved genes was limited to surfactant-related genes (SFTPB, SFTPC, ABCA3 and NKX2-1), pulmonary alveolar proteinosis genes (CSF2RA and CSF2RB) and FOXF1 for diffuse abnormalities of lung development. Two years later, on behalf of the chILD-EU working group proposed another flowchart for the diagnosis of chILD, primarily based on CT scan and placing blood tests, especially genetic testing, before more invasive tests such as bronchoalveolar lavage and lung biopsy.[14] The genetic evolution reflected the expansion and the wider availability of new molecular techniques allowing the study of a panel of genes (next-generation sequencing (NGS) and whole-exome sequencing (WES)) instead of one by one (Sanger sequencing). This led to the discovery of new genetic entities in chILD, such as MARS mutations, other cytosolic aminoacyl-tRNA synthetase (ARS) mutations or OAS1 in pulmonary alveolar proteinosis.[19,20] COPA and STING1 mutations for ILD related to autoinflammatory disorders, and many other even rarer diseases related to mutations in FLNA, TBX4, NHLRC2 or ZNFX1. [17,21,22]

HISTORY

Meticulous history taking and clinical examination is important to diagnose a case of chILD. This remains the first and major step of chILD workup as valuable information can be retrieved from the patient and their family history. Establishing a genealogical tree, also called a pedigree chart, is mandatory in all chILD. It is estimated that up to 20–30% of chILDs are due to monogenic diseases, some of them being associated with extrapulmonary involvement. Thus, collecting information on relatives and siblings can be highly useful: oxygen therapy, lung transplantation, neonatal respiratory distress or unexplained death, neurological issues such as hypotonia, developmental delay, chorea (NKX2-1), cerebral aneurysms (FARSA and FARSB), sensorial defects (ARS), peripheral hypothyroidism (NKX2-1), autoimmune diseases or general symptoms such as fever, skin lesions, joint pains (autoinflammatory disorders, connective tissue diseases), age and cause of death of older generation family members may be of interest. The age at onset of the ILD is crucial information. Now well documented that almost all chILD can occur at any age, some diagnoses are much more frequent in newborns, infants or older children.[23,24]

INVESTIGATIONS

Radiology and imaging (CXR, HRCT)

In the initial stages, CXR may be normal. Subtel radiological findings may be missed. In advanced stages, may find ground glass haziness and prominent interstitial shadows. HRCT play as a vital role for chILD diagnosis. If the diagnosis of chILD is suspected, a high-resolution CT (HRCT) scan is the first-line investigation to be performed.[25,26] The HRCT scan will allow to confirm ILD and to identify the ILD pattern.[27,28] The use of intravenous contrast is indicated if lymphadenopathies, gross structural abnormalities, or associated cardiac or vessel abnormalities need to be differentiated. The lung parenchyma analysis will search for elementary lesions of ILD such as ground-glass anomalies, consolidations, thickening of the bronchovascular interstitium, thickening of the interlobular septa, visualisation of intralobular lines, cystic lesions and micronodules or nodules. Their association, distribution, extent as well as the presence of signs of fibrosis will be sought.[29, 30] The CT pattern observed varies depending on the age of the child. Infants most often present with diffuse ground-glass anomalies associated or not with other abnormalities/ findings. Older children may have more cystic, nodular or even fibrosing abnormalities.

Lung Function Test and Gas exchange

Oxygen saturation at rest, during sleep and with exercise, the absence or presence of clinical signs, and pulmonary hypertension are used in the Fan severity score for chILD {rated 1 (low severity) to 5 (high severity)}.[31] Blood gas may be of interest to determine impairment of gas exchange. The 6-min walk test is particularly interesting in chILD because of its high sensitivity and ease of use from the age of 4– 5 years.[32] The first pulmonary function tests (PFTs) should be performed as soon as possible after chILD diagnosis, if the child's condition allows it and depending on their age.[33,35]

ILD is often characterised by a restrictive ventilatory disorder, with a decrease in total lung capacity and vital capacity. Measurement of diffusing capacity of the lung for carbon monoxide (DLCO) should be systematically performed according to the age of the child. Additionally, measurement of pulmonary compliance is done exceptionally to complete the evaluation.[34] In infants, PFTs can only be performed during sleep and therefore require the use of chloral pre-medication, the use of which is unauthorised in some countries and subject to signed informed consent in others. Between the ages of 3 and 6 years, PFTs require active cooperation. After the age of 6–8 years, exploration approaches that of adults. Functional residual capacity is the most common measurement.

Fiber Optic Bronchoscopy (FOB) and Broncho Alveolar Lavage (BAL)

Flexible bronchoscopy with bronchoalveolar lavage (BAL) should be performed and it allows cytological and microbiological analysis (bacteria, viral and fungi). Collected alveolar fluid will provided information regarding: 1) the volume and appearance of the fluid, 2) cell count and staining for cellular morphology, 3) Perls to detect the presence of iron-containing cell samples, 4) Periodic acid–Schiff (PAS) to detect polysaccharides such as glycogen, glycoproteins, glycolipids and mucins, and 5) targeted staining (Ziehl and Grocott) to detect mycobacteria and fungi, respectively. A global increase of the BAL cell count in the presence of a proven case of chILD and after exclusion of an infection may reflect alveolitis.[36, 39] The cytological examination makes it possible to search for pathogenic agents, viral inclusions, unusual macrophages, foreign bodies and abnormal cell populations.[40] These results, together with those of the HRCT scan, allow a definite chILD diagnosis.[64]

Cardiac ultrasound

Cardiac ultrasound must be carried out early and systematically as part of the severity assessment. It has three main purposes in the evaluation of chILD: 1) the search for pulmonary hypertension, which is an important prognostic factor and part of the Fan severity score items,[13] but can also guide toward specific aetiologies such as diffuse developmental disorders of the lung and surfactant disorders in newborns,[41] 2) the search for a left-sided heart pathology, and 3) the search for cardiac involvement in the context of a general illness).

Genetic study

A genetic cause is currently identified in ~20% of patients with chILD . Genetic analysis is recommended for all paediatric patients with chronic ILD, whether sporadic or familial with no identified cause.[42,44] The analysis must be carried out by specialised genetics centres, and the detection of a genetic.[71,73] The majority of patients in whom a genetic abnormality related to chILD is identified have a mutation in the genes encoding proteins of surfactant metabolism.[46] Mutations in the SFTPB and SFTPC genes, encoding surfactant protein (SP)-B and

SP-C, the surfactant transporter ABCA3 (ATP binding cassette subfamily A member 3), and the transcription factor NKX2-1 (or TTF1 (thyroid transcription factor 1) are most often implicated.[46,47] SFTPA1 and SFTPA2 (SP-A1 and SP-A2) and FLNA (filamin A) mutations have also very rarely been involved in chILD (but more often in adult ILD).[49,50] If alveolar proteinosis is suspected, the genes MARS (methionyl-tRNA synthetase), particularly when elevated liver values are noted, and CSF2RA and CSF2RB (subunits α and β of the receptor) are studied.[51,52] Other ARS (FARSA, FARSB, YARS, IARS and LARS) mutations have also been associated with rare cases of syndromic child.[53,54] Genetic abnormalities responsible for autoinflammatory diseases with autoimmunity have also been described in early chILD such as SAVI syndrome (STING-associated vasculitis of infancy) related to mutations in TMEM173 and COPA syndrome due to mutations in COPA) [55,56].

Lung biopsy

The indications for lung biopsy are currently declining with the progress of genetic diagnostics. Previously considered as the gold standard for chILD diagnosis, it is now discussed as a last line of investigation.[13,14] Microscopic examination is carried out on standard stains (haematoxylin/eosin), special stains (Perls, PAS, Grocott, reticulin and Masson's Trichrome) and immunostaining (TTF-1, bombesin, surfactant proteins and vascular markers). In the case of chILD with extrapulmonary involvement, the diagnosis may be obtained by biopsy of an organ that is easier to access than the lung. This is the case, for example, for sarcoidosis (salivary glands, adenopathy, liver, etc.) or dermatomyositis (skin, muscle, etc.) .[57]

Treatment

In general, supportive care, including oxygen and ventilator therapy when needed, nutritional intervention, prevention of infection, and conditioning and rehab are of utmost importance. Corticosteroids remain the first-line therapy for a number of these disorders, including the surfactant dysfunction disorders, idiopathic interstitial pneumonias, hypersensitivity pneumonia, eosinophilia pneumonia, alveolar haemorrhage, and connective tissue diseases. Use of intravenous pulse steroids. Steroid-sparing agents with anti-inflammatory properties, such as hydroxychloroquine, azathioprine, methotrexate, cyclophosphamide, and intravenous immunoglobulin, have also been used with some success.[27] Lung transplantation is an option for children with end stage diffuse lung disease, with long-term outcomes that appear to be comparable to those with CF and pulmonary hypertension.[28]

Supplemental oxygen and ventilator support, nutritional support, proper immunizations, and avoidance of harmful environmental exposures. Lung transplantation is an option for children with end-stage lung disease.[28] Genetic counselling and family support are also important components of care.

CONCLUSIONS

The disorders that together constitute the group of diseases known as chILD are extremely heterogeneous and associated with high morbidity and mortality. The chILD diagnostic process can be simple and relatively short if a systematic two-step approach is followed. The role of the general paediatrician is crucial in untangling the personal and family medical history and the clinical signs, and in referring the patient to specialised centres when chILD is suspected. Even if easily accessible, the HRCT scan should be performed in a specialised centre to optimise its profitability. Lung biopsy is being dethroned by the fantastic progress in molecular diagnostics. However, a low number of expert geneticists may induce a prolonged delay in getting the results. Thus, for each patient, a multidisciplinary case-by-case discussion based on coherent algorithms could minimise chILD diagnostic delay and reduce the proportion of undefined chILD, allowing a maximum of these young patients to receive personalised treatments and to benefit from an improved prognosis.

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