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 Interstitial Lung Disease (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 on-going 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 'childhood interstitial lung disease' (chILD) that are associated with significant morbidity and mortality. Historically, these diseases have been defined based on lung biopsy histopathological findings. However, recent advances have facilitated increased non-invasive diagnosis through genetic testing and use of chest computed tomography (CT) scans.

Definition

'Interstitial lung disease' (ILD) is a term that refers to a heterogeneous collection of disorders characterized by abnormal gas exchange because of altered structure of the interstitial region of the lung. As many entities also affect the distal bronchioles and alveolar spaces, the term 'diffuse lung disease' is probably a more accurate description.[1] ILD occurs in a variety of clinical contexts, including isolated pulmonary disorders, because of environmental exposures, and as part of systemic processes, such as autoimmune diseases. Although some of the conditions that cause ILD in children and adults are similar, however distinct forms only seen in infants.

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 some cases of chILD formar clinical practioner and published than 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 It is important to note that the epidemiology of ILDs in children can vary within south east Asia based on progression of ILDs in children in Bangladesh.

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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[2], and 1.32 cases per million in Germany[3], 4 cases per million in Denmark. There is no data in Bangladesh from net search.

Classification

Children less than 2 years of age often have unique disease processes. Deutsch et al. [4] applied a new classification system to 186 biopsies in children under the age of 2 years from 11 centres as part of the North America Children's Interstitial Lung Disease Research Network.

- **Diffuse developmental disorders**

Disorders in this category occur early in lung development, and diagnosis is via lung biopsy or post-mortem. Alveolar capillary dysplasia associated with misalignment of pulmonary veins (ACDMPV) is a universally fatal disease, with term neonates presenting early in life with rapidly progressive respiratory failure and severe pulmonary hypertension, refractory to intensive therapies[5]. In this disorder, there is inadequate development of the pulmonary capillary bed and malposition of pulmonary veins in the bronchiolovascular bundles adjacent to pulmonary arteries. There are often associated anomalies of the cardiovascular, gastrointestinal, or genitourinary systems. Recently, micro deletions in the FOX gene cluster on 16q24.1 and mutations of FOXF1 have been identified with cases of ACDMPV with different phenotypic associated congenital anomalies.[6]

Pulmonary growth abnormalities

Growth abnormalities are the most common cause of diffuse lung disease in infants. They are usually related to prematurity or pulmonary hypoplasia, but can also be associated with congenital heart disease or chromosomal abnormalities, and, in term infants, with early postnatal lung injury.

Prematurity-associated lung disease is a well-known entity, with the 'new' bronchopulmonary dysplasia consisting of alveolar simplification. Pulmonary hypoplasia, resulting from restricted lung growth in utero, can be acquired because of oligohydramnios, congenital diaphragmatic hernia, hypoxemia, or nutritional deficiencies, among other causes.

In a review of 259 biopsies by Langston and Dishop [7], 11 biopsies fit into the category of congenital heart disease affecting lung growth. Infants with Trisomy 21 (with and without cardiac disease) are known to have simplified alveolar architecture and can be noted to have more severe and earlier pulmonary arterial hypertensive changes. Growth abnormalities in term infants can result from a combination of in-utero and postnatal factors, such as infant of a diabetic mother and infectious insults. Pulmonary vascular disease is a frequent association in this group as well.

- **Surfactant dysfunction disorders**

Mutations in the genes encoding the surfactant proteins B and C (SP-B and SP-C), ATP-binding cassette transporter protein ABCA3, and thyroid transcription factor-1 (TTF-1) have been recognized to cause significant morbidity in infants and children. SP-B deficiency is an autosomal recessive disorder, presents early in life with progressive respiratory distress and failure, and is usually fatal by 3–6 months of age. The typical histopathology is alveolar proteinases with foamy, eosinophilia, lipoproteinaceous material filling alveoli, thickened alveolar septa with alveolar epithelial hyperplasia, and abnormal lamellar bodies on electron microscopy.[8] Other histologic patterns, including infantile DIP, may be seen occasionally. Lung transplant is currently the only therapeutic option for SP-B deficiency.

The presentation of SP-C deficiency is variable, with a large proportion of patients presenting in late infancy/early childhood, although some present in early infancy, and still others are discovered in adulthood. In a recent Dutch study, SP-C mutations accounted for approximately 25% of adult familial pulmonary fibrosis cases.[9] It is an autosomal dominant disorder, but about half of the cases are sporadic with de-novo mutations. Late presentation is associated with symptoms of ILD. The histopathologic picture is of uniform alveolar epithelial hyperplasia with mild alveolar wall thickening with mild lymphocytic inflammation and often masculinization of the alveolar septa, foamy alveolar macrophages, and variable amounts of granular to globular alveolar proteinases with a few cholesterol clefts.[10] Pharmacologic approaches for SP-C deficiency

are based on anecdotal evidence, and include pulse corticosteroids, hydroxychloroquine, and azithromycin. Outcome is variable, as some children with SP-C mutations improve over time,[10] although others progress to end-stage lung disease.[11] Most affected infants present in respiratory failure in the newborn period. Mutations in genes encoding ABCA3 are the most common genetic cause of respiratory failure in full-term infants. Mutations in the TTF-1 (also known as NKX2-1) gene are associated with a syndrome of neurologic (cerebral dysgenesis, chorea, developmental delay), thyroid (hypothyroidism), and pulmonary dysfunction.[12]

- **Pulmonary alveolar proteinases (PAP)**

Pulmonary alveolar proteinases (PAP) is a rare disorder of the lung caused by impaired surfactant homeostasis and characterized by the accumulation of lipoproteinaceous material within the alveolar spaces, resulting in respiratory insufficiency or failure. There are three forms: congenital, primary, and secondary. Primary PAP is an autoimmune disorder and accounts for the majority of cases in adults. Primary PAP is due to high levels of granulocyte/ macrophage-colony stimulating factor (GM-CSF) autoantibodies, resulting in altered surfactant homeostasis and impaired surfactant clearance. GM-CSF is required for pulmonary alveolar macrophage catabolism of surfactant, and also is a critical regulator of innate immunity and lung host defence.[13]

- **Neuroendocrine cell hyperplasia of infancy (NEHI)**

Originally described as persistent tachypnea of infancy, neuroendocrine cell hyperplasia of infancy (NEHI) typically presents in children less than 1 year of age with tachypnea, retractions, hypoxemia, and crackles on examination.[14] The diagnosis is based on the identification of an increased proportion of bombesin-immunopositive neuroendocrine cells in bronchioles, suggested to be at least 10% in any individual airway and to be found in more than 70% of bronchioles in the sample.[7] Lung biopsy otherwise usually has a near-normal appearance. Neuroendocrine cell (NEC) prominence has been shown to be significantly increased in NEHI, as compared with other pulmonary disorders.[15] In their findings, the authors note that the increase in neuroendocrine cells did not correlate with signs of airway injury, suggesting that NEC prominence is not a reparative phenomenon, but is the primary disorder. Characteristic CT findings in NEHI and the presence of normal KL-6, a serum biomarker of type II epithelial cell activation, can help differentiate NEHI from other infant lung disorder entities, such as errors of surfactant metabolism.[16,17] The term 'NEHI syndrome' is used when diagnosis is based on characteristic clinical and CT findings, rather than lung biopsy.

- **Pulmonary interstitial glycogenesis (PIG)**

Although previously described with other names, the entity now known as pulmonary interstitial glycogenesis (PIG) was best detailed in 2002 by Canakis et al.[18] They identified lung biopsies from infants presenting with tachypnea, hypoxemia, and diffuse interstitial infiltrates with a characteristic histology of alveolar septal widening by no inflammatory bland interstitial cells without alveolar epithelial hyperplasia. Periodic acid Schiff-positive material consistent with glycogen was seen irregularly and in minimal amounts in these cells; however, on electron microscopy the interstitial cells contained abundant monoparticulate glycogen. Infants present with respiratory distress in the first weeks of life. Treatment for PIG is largely supportive, and the use of corticosteroid therapy for this condition has been contentious.

Diagnosis

Children with ILD typically manifest nonspecific respiratory signs and symptoms, including tachypnea, hypoxemia, crackles, cough, and poor growth. Because these symptoms overlap those seen in many more common conditions, the first step in diagnostic evaluation is to exclude more common causes of diffuse lung disease (i.e. cystic fibrosis, immunodeficiency, congenital heart disease, pulmonary infection, primary ciliary dyskinesia, and recurrent aspiration). After excluding or treating these more common causes of lung disease, the term 'chILD syndrome' [19] is then used to refer to children who meet three out of four of the following criteria: respiratory symptoms (e.g. cough, rapid and difficult breathing, or exercise intolerance); respiratory signs (e.g. resting tachypnea, adventitious sounds, retractions, digital clubbing, failure to thrive, or respiratory failure); hypoxemia; and diffuse parenchymal abnormalities on chest imaging. The recently published ATS clinical guideline describes the primary diagnostic tools used for the evaluation of chILD: bronchoscopy with bronchoalveolar lavage (BAL), chest CT, genetic testing, and lung biopsy.[20] Not all tests are needed in all cases. Generally, the evaluation proceeds from the least to the most invasive procedures, although the sequence depends on the context, acuity, and severity of the patient's condition.

- **Pulmonary function studies**

Pulmonary function tests (PFTs) done in older children typically demonstrate a restrictive pattern with reduced total lung capacity (TLC), forced vital capacity (FVC), and forced expiratory volume in 1 s (FEV1), with a normal or elevated FEV1/FVC ratio. However, air trapping is suggested by a normal or elevated residual volume, and an elevated residual volume/TLC ratio, resulting in a mixed obstructive/restrictive picture. Infant PFTs can be useful in evaluating paediatric ILD syndromes. The finding that the extent of neuroendocrine cell prominence and severity of small airway obstruction on PFTs are correlated suggests that infant PFTs may aid in the assessment of NEHI. [15]

Pulmonary function testing (PFT) and assessment of oxygenation with sleep and exercise (or feeding in infants) are used to characterize the degree and nature of physiologic impairment. Further, screening for pulmonary hypertension may influence the pace of diagnostic evaluations, alter treatment, and impact prognosis, as pulmonary hypertension associated with ILD predicts higher mortality.[8,21]

Bronchoscopy with bronchoalveolar lavage

This is a common, invasive procedure that is performed to evaluate children with suspected ILD. In addition to enabling evaluation of airway anatomy and physiology, airway and alveolar samples are obtained for cytology and microbiologic diagnosis. Bronchoscopy is relatively well tolerated, widely available, and may help diagnose infection, aspiration, haemorrhage, or pulmonary alveolar proteinases (PAP).

BAL can aid in the diagnosis of specific disease types. In the appropriate clinical setting, the presence of hemosiderin-laden macrophages (diffuse alveolar haemorrhage), lipid-laden macrophages (aspiration syndromes), lymphocytes (hypersensitivity pneumonitis, sarcoidosis), or eosinophil (eosinophilic pneumonia) can help distinguish among disorders, although controversy remains regarding the specificity of some of these alterations. Recent data suggest BAL fluid cytokine levels differ between ChILD syndromes and disease controls [cystic fibrosis (CF), aspiration syndrome, non-CF bronchiectasis], with interleukin (IL)-8 and macrophage inflammatory protein (MIP)-1b found to be significantly lowers.[22] Although lung biopsy remains the gold standard for diagnosis of most of the individual entities that result in ChILD syndrome, this is no longer uniformly the case, as less invasive studies may ascertain diagnosis in some conditions in typical clinical settings.

Imaging studies

Chest CT is very useful for defining the extent and pattern of disease with resolution that is superior to plain chest radiographs. Common findings in chILD may include ground-glass pacification, consolidation, and sepal thickening. Findings may be suggestive of or even specific for some types in cases in which lung biopsy is required, CT imaging will guide the choice of biopsy sites. In infants, anaesthesia or controlled ventilation techniques are often needed to decrease motion artefact and atelectasis that may obscure the detection of lung disease.[23,24] Imaging protocols designed specifically for young children at experienced centres significantly reduce the radiation exposure.[24] The CT sensitivity and specificity for this classic pattern were at least 78 and 100%, respectively. HRCT may also provide prognostic information.

Genetic tests

The availability of clinical genetic testing now allows non-invasive definitive diagnosis in some cases. The currently known genetic causes of chILD include abnormalities in the genes encoding surfactant protein B (SFTPB), surfactant protein C (SFTPC), ATP-binding cassette transporter A-3 (ABCA3), granulocyte- macrophage colony stimulating factor (GM-CSF) receptors a and b (CSFRA and CSFRB), and thyroid transcription factor-1 (NKX2.1/TTF1).[20] The choice of specific genetic tests should be guided by the family history and clinical context. A specific diagnosis provides clinically useful information for the great majority of cases as it informs management, prognosis, and genetic counselling. Currently, only a subset of types of chILD has a defined genetic basis. However, it is likely that additional disease-associated genes will be identified in the future.

Lung biopsy

In the absence of genetic diagnosis, lung biopsy remains the gold standard for diagnosis of many forms of chILD. To optimize the diagnostic yield, standardized protocols have been developed[25], which require timely and effective communication between the clinician, radiologist, and surgeon to select proper biopsy site(s) and process tissue, including fixation in glutaraldehyde for electron microscopy.

Diagnosis of ChILD syndromes A systematic approach, combining history and physical exam, pulmonary function studies, imaging studies, bronchoalveolar lavage (BAL), and lung biopsy, is crucial in establishing the diagnosis.

Discussion

In this systematic review of the literature on chILD we have identified significant gaps in research knowledge in the field. Because chILD is rare there have been few studies of large patient groups and these studies have used different case inclusion/exclusion criteria. The different methods used in the studies included in this review along with the heterogeneity of the chILD group of disorders mean that results are not directly comparable between studies. Notwithstanding these difficulties, this systematic review indicates that:

chILD is associated with high morbidity and mortality but there is wide variability between and within chILD disorders

No specific treatment is effective for all cases of chILD

The impact of chILD on families and the burden on health services has not been evaluated.

There is a need to establish surveillance, registries and randomised controlled trials to provide an evidence base to inform prognosis, resource requirements, and treatments.

The diversity of outcomes associated with chILD reflects the wide range of aetiologies and clinical presentations. chILD is commonly associated with severe respiratory deficit that limits physical activity, may impede physical growth, and necessitates respiratory support, usually oxygen supplementation. It is possible that the morbidity in this review is skewed towards more severe cases because mild cases are less likely to be identified in hospital record reviews. In some studies only children who had a lung biopsy were included, implying a sample skewed towards severe disease. Not all cases of chILD require lung biopsy for diagnosis. For example, NEHI can be diagnosed from chest computed tomography and pulmonary function test findings consistent with air trapping and obstruction, without the need for a lung biopsy.[26,27] Furthermore, genetic diagnosis has helped avoid the need for lung biopsy in children with inherited surfactant disorders. Prospective, cohort studies including well phenotype groups would give a more accurate picture of the morbidity associated with chILD.

At 13%, childhood mortality associated with chILD is high, but varies considerably both between and within chILD disorders. Age of disease onset may contribute to outcome, worse outcomes being associated with earlier onset of disease.[28] Among inherited surfactant disorders the type of mutation will influence outcome. In 2014, a review of 185 cases of chILD or neonatal respiratory failure associated with homozygous or compound heterozygous ABCA3 mutations was published.[29] That study found that by 1 year of age all children (n ¼ 45) with two ABCA3 mutations likely to result in non-functional proteins ("null" mutations) had died or undergone lung transplantation compared with 62% of children with nonnull ABCA3 mutations that did not reliably predict prognosis. chILD inherited surfactant disorders are associated with high morbidity and mortality but for most of these disorders there is considerable heterogeneity in the severity of disease.

Among studies in our review that reported outcomes, the duration of follow-up varied or was not reported, restricting comparisons between studies. Furthermore, no study has reported outcomes beyond 6 years follow-up. In many studies[25,30-32] definitions of outcomes were limited to imprecise descriptions such as "improved" or "stable" making them difficult to interpret.

Since each individual chILD disorder is rare, and therefore rarely encountered by paediatricians, diagnosis may be difficult. Diagnostic delay may have a negative impact on outcome, especially in chILD disorders that progress rapidly, although we did not find evidence for this. Only two studies [34,35] reported the time taken to determine a diagnosis but neither study analysed the association between time to diagnosis and outcome.

The evidence base for chILD treatments is limited because the disorders are so rare and there have been no clinical trials. The general principle of treatment is that minimising inflammation may prevent progression to fibrosis.[36] Corticosteroids and hydroxychloroquine are widely used in the treatment of chILD, not always with success. Both have anti-inflammatory properties but they also may have other effects, for example hydroxychloroquine may inhibit the intracellular processing of the precursor protein of surfactant protein C.[37]As chILD disorders are generally incurable, supportive care (nutritional supplementation, influenza vaccination, oxygen supplementation) is important.[38] chILD disorders have a diverse range of aetiologies and

pulmonary pathologies, thus a common treatment strategy is unlikely to be effective for all chILD disorders. Current treatments are not based on rigorous scientific evidence but on the experience of individual health professionals and the preferences of individual centres. There is an impetus to standardise treatment, follow-up, and collection of biological samples in observational studies with a view to providing evidence to support the first randomised controlled trial of treatment for chILD. It is hoped that the establishment of the United States chILD Research Network (ChILDRN) [39] and a recent $3.0 million European FP7 grant [40] will help to achieve that aim.

The impact of chILD on families and the burden on health services has not been studied. Bronchopulmonary dysplasia, a diffuse lung disease[28] that is usually associated with prematurity [40] and is not a chILD disorder[41] has been studied in this context.[42,43] These studies give an indication of the health services burdens and costs that might be expect for chILD. The median length of the first hospital stay for children with bronchopulmonary dysplasia was 120 days, at a median cost of US $172,717.[42] An analysis of health services use and costs for a single case of chILD due to surfactant protein C deficiency showed 443 days of in-patient care at a cost of AUS $966,531. Families caring for children with bronchopulmonary dysplasia incur loss of wages, loss of jobs, and emotional stress associated with caring for their child.[42,43] From what is known about the chronic morbidity of chILD it is likely that there is a high impacton families. This remains to be demonstrated through rigorous study.

The classification and nomenclature of chILD has rapidly evolved over recent years as underlying genetic causes and new diseases such as NEHI[44] have been identified. The changes in nomenclature and classification causes confusion amongst clinicians who rarely encounter these conditions.[45]

Recent American Thoracic Society clinical practice guidelines for child[41] highlight that the term “interstitial” is confusing in children who present with the clinical features of chILD but with the histopathological process occurring outside the intersititium. The guidelines proposed that the term “diffuse lung disease” encompass specific chILD diagnoses, as a subset of “chILD syndrome”. chILD syndrome includes cases that remain unclassified. Classification is also hampered by the use of similar terms for different entities such as infantile cellular interstitial pneumonitis and chronic pneumonitis of infancy.[28]

These changes in classification schemes are also a potential limitation of this review as some relevant papers may not have been included due to different diagnostic labels being used inconsistently. Furthermore, some of the studies in this review have included diseases that do not fit into the current classification for chILD.

Despite their limitations, the current chILD classification systems serve the important function of distinguishing these disorders from ILD more commonly seen in adulthood. It is likely that the classification of chILD will continue to evolve over the next few years and systematic terminology will be an important step forward. The inadequacy of ICD codes for the classification of rare diseases such as chILD is also an impediment to research. There are initiatives by Orphaned to assign specific codes (Orpha Codes) to individual rare disorders.[46] These would complement ICD codes and, if adopted by clinicians and researchers, would aid in data pooling to improve statistical power and meta-analysis.

Treatment

Management is largely supportive, including 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.[49] Genetic counseling and family support are also important components of care. Treatment is directed to the specific disorder. 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. We recommend the use of intravenous pulse steroids, given as 10– 30 mg/kg with a maximum of 1 g once weekly or on three consecutive days monthly instead of daily steroids, as this appears to be associated with fewer side-effects, though no controlled trials exist. Steroid-sparing agents with anti-inflammatory properties, such as hydroxychloroquine, azathioprine, methotrexate, cyclophosphamide, and intravenous immunoglobulin, have also been used with some success.[47] This is based on anecdotal evidence, as there have been no randomized controlled trials in children with ILD. 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.[48]

Conclusion

In conclusion, the disorders that together constitute the group of diseases known as chILD are extremely heterogeneous and associated with high morbidity and mortality. Prospective, active surveillance of chILD through strategic international collaboration is needed to provide more accurate estimates of frequency. It is important that a single classification system for chILD is adopted globally to support direct comparisons of research evidence. Patient registries and randomised controlled intervention trials through international collaboration are required to provide an evidence based for improving the lives of children with these rare disorders. An increasing proportion of cases are now diagnosed without lung biopsy through the use of chest CT imaging patterns and genetic testing. Obtaining a specific diagnosis often has important implications in patient management and prognosis, as well as for genetic counselling. For health services planning and to support families, the impacts of chILD should be addressed in prospective studies.

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