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Pediatric Interstitial Lung Disease

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This study was done to ascertain the symptomatology, clinical features and investigations pertaining to interstitial lung diseases (ILD) in children. The medical records of 16 children admitted over a 4-year period from June 2000 to May 2004 with progressive cough, dyspnea, and chest X-ray/High Resolution Computerized Tomography (HRCT) abnormalities suggesting ILD were retrospectively evaluated. Clinical findings, investigations, chest skiagrams, HRCT, bronchoalveolar lavage (BAL) and lung biopsy reports were analyzed. An acute presentation of symptoms was seen in 4 cases (25%). Velcro crackles were the commonest clinical finding, present in 15 cases (93.8%). Serial X-rays revealed findings suggestive of ILD in 12 cases (75%) and HRCT was diagnostic in 13 cases (86.6%). Spirometry done in 5 cases showed a restrictive ventilatory defect, BAL analysis done in 8 cases demonstrated increased neutrophils and lung biopsy done in 5 cases was consistent with idiopathic pulmonary fibrosis. Mean survival duration of 2 years and 7 months after initial diagnosis was observed.

Key words: *Bronchoalveolar lavage, Interstitial lung disease, Lung biopsy*

INTERSTITIAL lung disease (ILD) is a generic term used to denote a heterogenous group of disorders involving the pulmonary interstitium, presenting with common clinical features(1). In addition to the interstitium, alveolar and distal air spaces are also invariably involved in ILD. Though ILD occurs usually in adults, pediatric populations do succumb to this condition.

Most children with ILD share a common presentation, with signs and symptoms of restrictive lung disease. Both noninvasive and invasive tests aid in the diagnosis of ILD but lung biopsy remains the gold standard(2). Since the differential diagnosis of ILD includes more than 100 conditions in adults

and children(1,3), it presents enormous diagnostic challenges. Therefore, studies on the predisposing environmental factors, diagnostic approach and response to treatment regimens of pediatric ILD are the need of the hour. We conducted a retrospective analysis to study the symptomatology, clinical features and investigations of ILD in children.

Subjects and Methods

Children admitted in the Pediatric Pulmonology Department of the Institute of Child Health and Hospital for Children, Chennai, during the 4-year period between June 2000 and May 2004 with progressive cough, dyspnea, and chest *X*-ray/High Resolution Computerized Tomography (HRCT) abnormalities suggestive of ILD were included in the study. Chest *X*-ray findings of bilateral reticular shadows at the base of the lungs and/or peripheral interstitial changes as suggested by diffuse infiltrates and ground glass appearance; and HRCT findings of ground glass attenuation and interstitial thickening, with/without nodules, honeycombing, parenchymal distortion and traction bronchiectasis, were the findings interpreted as consistent with ILD(4). The data was retrieved from the Medical Records Department of the hospital. Children who were diagnosed as bronchopulmonary dysplasia, congenital heart disease, primary malignancy, primary immunodeficiency, and primary autoimmune disorders were excluded from the analysis.

An analysis of presenting symptoms, past history and clinical findings was done. In addition to the basic investigations, the results of spirometry, serial chest skiagrams, HRCT, bronchoalveolar lavage (BAL) and lung biopsy were evaluated.

Results

Sixteen cases were included in the analysis. Seven cases (43.8%) had onset of symptoms in infancy (*Table I*). The mean duration of symptoms at presentation was 12.81 months (range 2 to 24 months), with 4 cases (25%) having an acute presentation of <3 months(5). The mean time interval between initial presentation to the institution and the diagnosis of suspected/confirmed ILD was 3.93 months (range 1 month to 12 months).

Velcro crackles were the commonest physical finding, present in 15 cases (93.8%). Ten cases (62.5%) were undernourished and pulmonary hypertension confirmed by echocardiogram was present in 5 cases (31.5%). Skin lesions in the form of erythematous maculopapular rashes were noticed in 4 cases (25%) and these persisted during follow up examinations

Routine blood investigations were not contributory in any of the cases. A workup for tuberculosis (Mantoux, resting gastric juice analysis for acid fast bacilli and screening of parents for tuberculosis) was negative in all cases.

The chest *X*-rays were initially abnormal in all cases but commonly reported as bronchopneumonia. Though initial *X*-rays were not contributory in any case, serial *X*-rays revealed findings suggestive of ILD in 12 cases (75%).

HRCT of the chest was done subsequently in all but one case. The HRCT findings were consistent with ILD in 13 cases (86.6%). Four cases, where chest *X*-rays did not aid in the diagnosis, had HRCT findings suggesting ILD. HRCT revealed bilateral findings and lower lung zone involvement in all cases. Ground glass opacification was the commonest radiological abnormality, seen in all the cases, followed by interstitial thickening in 7 cases (53.84%) and interlobular septal thickening, traction bronchiectasis and honeycomb pattern in 3 cases (23.07%).

TABLE I–*Clinical Features of Interstitial Lung Disease*

Factors	Number (percentage)
Male to Female ratio	1.2 : 1
Age of onset of symptoms:	≤12 mo - 7 (43.8) ; >12 mo - 9 (56.2)
Duration of symptoms at initial presentation *	Acute (≤ 3 mo) - 4 (25) ; Chronic (> 3 mo) -12 (75)
Velcro crackles	15 (93.8)
Hepatosplenomegaly	11 (68.8)
Prior treatment with ATT	11 (68.8)
Fever	10 (62.5)
Protein energy malnutrition	10 (62.5)
Clubbing	8 (50)
Lymphadenopathy	7 (43.8)
Cyanosis	6 (37.5)
Pulmonary hypertension	5 (31.5)
Skin lesions	4 (25)
Recurrent respiratory infection	2 (12.5)
Exposure to dusts +	2 (12.5)

* The term "chronic" is used to indicate disease lasting > 3 months(5).
\+ exposure to asbestos and talcum powder.

Hypoxemia was documented by blood gas analysis in all the patients. Spirometry, done in 5 children (31.2%), showed a restrictive pattern from the time of initial presentation, with a progressive reduction of forced vital capacity. BAL analysis done in 8 cases (50%) revealed the presence of increased inflammatory cells in all cases, mainly neutrophils, with varying proportion of other inflammatory cells.

Five cases in our study were subjected to open lung biopsy. The histopathology report revealed variable degrees of interstitial fibrosis, collagen deposition, thickened alveolar septa, focal nests of proliferating fibroblasts and interstitial inflammatory infiltrate. In one case Pneumocystis carinii was found.

The analysis of readmission records revealed that 12 children had died, all of respiratory failure, with mean survival duration of 2 years and 7 months after initial diagnosis. All the 4 children who had an acute presentation died within 3 months of diagnosis.

Discussion

Chronic ILD in children is defined as the presence of respiratory symptoms and/or diffuse infiltrates on chest radiographs, abnormal pulmonary function tests with evidence of restrictive ventilatory defect and/or impaired gas exchange, and persistence of any of these findings for >3 months(5). Due to the lack of organized reporting systems, determining the incidence or prevalence of ILD in children is difficult. Indian studies on ILD have largely been limited to adults(6,7) and studies in Indian children have been few(8).

Onset of symptoms in infancy in 7 cases (43.8%) might suggest a possible genetic role. This young age of presentation has been described in previous series(1,5,9). The chronic presentation of symptoms in 12 cases (75%) was consistent with most other western studies. The reason could be the fact that an acute presentation of ILD is likely to be confused with a constellation of atypical pneumonias and missed.

Bibasilar, dry, superficial, end inspiratory crackles, usually described as "velcro crackles" were present in most cases, compared to only 44% of the cases reported in the ERS task force study(5). With advanced disease, clubbing of the fingers, cyanosis and lymphadenopathy became evident. The usual end stage complications were growth failure and pulmonary hypertension, noted in other studies also(5,10).

The diagnostic value of serial chest *X*-rays in our study, was comparable with the results of the National Jewish Center study(1). ILD is usually suspected because of abnormal radiological lung findings in spite of adequate antibiotic therapy including antituberculous drugs (ATT). The endemic nature of tuberculosis, its varied presentation, contact with an adult tuberculosis patient and persistent clinical and radiological features in spite of antibiotics, are the common reasons necessitating ATT in such children.

HRCT is useful, especially with a normal or nonspecific chest *X*-ray, when there is a strong clinical suspicion of ILD and this has been shown by positive HRCT findings in the four children in whom serial *X*-rays did not reveal ILD. In our study, HRCT was suggestive of ILD in 86.6% of the cases compared to 66% in a study by Copley, *et al.*(11). Ground glass opacification was the commonest abnormality seen, an observation consistent with most other studies(5,12,13). Honeycombing on a background of widespread ground glass attenuation was present in three cases. Copley, *et al.* had also reported three cases of nonspecific interstitial pneumonia, a subset of idiopathic pulmonary fibrosis, with similar HRCT features(12).

BAL is the collection of airway lining fluid through fibreoptic bronchoscopy and has been regarded as the "Liquid biopsy" of the lung. Predominance of neutrophils, as seen in the BAL analysis of our patients, is a finding associated with idiopathic pulmonary fibrosis (14,15). In none of the cases the specific etiology of ILD was arrived at.

Lung biopsy is considered the cornerstone of diagnosis of ILD. Convincing the patient for lung biopsy proved to be a major hurdle, as did the critical nature of illness, which made biopsy impossible in few other cases. The five cases where open lung biopsy was done showed histopathological features of idiopathic pulmonary fibrosis. A specific diagnosis in accordance with the standard classification of ILD was not forthcoming in any case.

All cases were started on steroids and tapering was done as per response. The four cases, with an acute presentation, deteriorated fatally within 3 months of presentation, suggesting acute interstitial pneumonitis (Hamman Rich syndrome).

In conclusion, a systematic approach with clinical examination, serial *X*-rays, HRCT and BAL, is helpful in the diagnosis of pediatric ILD since lung biopsy is often not possible. The retrospective nature of our study is a limitation as is the small study population. Since no single pediatric center can see large numbers of pediatric ILD patients, multicenter collaboration will be required to extend these observations.

Key Messages

- Diagnosis of ILD requires a high index of suspicion, as the clinical presentation is subtle, variable, nonspecific and is likely to be confused with other pneumonias.
- Progressive nature of the illness, clinical findings, serial chest skiagrams, HRCT and BAL will be helpful in the diagnosis of ILD, in the absence of lung biopsy.

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