RESEARCH PAPER

Clinical Profile of Interstitial Lung Disease in Indian Children

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Objective: To describe the clinical spectrum and factors associated with poor short-term outcomes in children with interstitial lung disease (ILD).

Design: Retrospective chart review

Setting: Pediatric Chest Clinic of a tertiary care hospital

Methodology: We retrieved information regarding clinical course and laboratory features of all children diagnosed as ILD between January 1999 and February 2010. Disease severity was assessed using ILD score based on clinical features and SpO_2 at the time of initial evaluation. Outcome was assessed after 3 months of initial diagnosis as improved or death/no improvement in symptoms.

Results: 90 children (median age, 6.8 years; 62% boys) were diagnosed to have ILD during this period. 46 children were classified as having 'definite ILD' while 44 had 'possible ILD'. The commonest clinical features at presentation were cough (82.2%), dyspnea (80%), pallor (50%), and crackles (45.6%). 3 children (3.3%) died while 21 (23%) showed no improvement in clinical status on follow-up at 3 months. A higher ILD score (RR 3.72, 95% CI 1.4, 9.9) and lower alkaline phosphatase levels (median [IQR]: 205 [175.2] vs. 360 [245.7]; *P*=0.006) were found to be significantly associated with worse outcomes.

Conclusion: The common clinical features of ILD in our study included breathlessness, cough and hypoxemia. A working diagnosis of ILD can be made with the help of imaging, bronchoscopy, or lung biopsy. A simple score based on clinical findings and pulse-oximetry might predict those children with poor short-term outcome.

Key words*: ILD; Interstitial lung disease; ILD score; Lung biopsy.*

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The term interstitial lung disease (ILD) encompasses heterogeneous lung conditions with a common denominator of disordered gas exchange and diffuse infiltrates on *X*-ray [1]. The exact incidence of childhood ILD is unknown. A 3-year survey of chronic ILD in immunocompetent children in the United Kingdom and Ireland has reported the prevalence to be 3.6 per million children [2]. Diagnosis of ILD is confirmed with the help of noninvasive and invasive tests. Although lung biopsy is considered to be the gold standard for diagnosis of ILD, its role in every patient of ILD is being questioned by both adult and pediatric pulmonologists alike, and using a systematic approach to diagnosis is being suggested as the way forward in these patients [3-4].

The outcome of children with ILD in terms of death- and disease-free survival is reported to be 15- 60% [5-8] and 50%, respectively [8]. The available data on the clinical profile of children with ILD mostly come from small case series that included less than 30 children [5-11]. Also, many of these reports [6-9] had focused on one or more specific conditions such as fibrosing alveolitis or desquamative interstitial pneumonitis (DIP) rather than looking at the complete spectrum of ILD. Only one study, published in the late 1990 [5], has so far reported the factors influencing outcomes in these children. The objective of this study was therefore to evaluate the clinical profile of children diagnosed to have ILD by noninvasive and/or invasive tests, and to determine the factors associated with poor outcomes in them.

Accompanying Editorial: Pages 57-58

METHODS

We conducted a retrospective chart review of children who were diagnosed to have ILD between January 1999 and March 2010. The diagnosis of ILD was made in the presence of progressive/persistent respiratory distress with duration of illness of at least one month, hypoxemia (documented by oxygen saturation), diffuse bilateral infiltrates on chest *X*-ray and/or characteristic findings in high resolution computed tomography (HRCT) with or without lung biopsy findings suggestive of ILD [5]. Children with underlying congenital heart disease, bronchopulmonary dysplasia (BPD), cystic fibrosis,

malignancy, primary or acquired immunodeficiency, coagulation disorders, vasculitis, pulmonary tuberculosis, celiac disease and vascular malformations were excluded from the study.

We primarily categorized these children into two major groups - 'definite ILD' and 'possible ILD' - based on their clinical features, results of noninvasive tests such as *X*-ray and HRCT, and results of invasive tests like bronchoscopy and biopsy. The definitions used to classify these patients into definite ILD and possible ILD are provided in **Box I**.

Hospital case records of children diagnosed as ILD were retrieved for collection of data regarding the clinical course, laboratory investigations such as HRCT chest (findings such as geographical hyperlucency, septal thickening, ground glass opacity, lung consolidation, and cysts and nodules), bronchospcopy and bronchoalveolar lavage (BAL) analysis etc. Information on the treatment received including steroids, immunosuppressive agents, home oxygen therapy and the follow-up data of these children were also retrieved from the records.

For assessing the disease severity, we assigned an illness score originally proposed by Fan, *et al.* [12] based on information from the patient records at the time of their initial evaluation. We scored the patients from 1 to 5 based on increasing severity of illness; accordingly, patients were given a score of 1 if they were asymptomatic; 2, if symptomatic with normal room air saturations; 3, if symptomatic with abnormal saturation/ cyanosis during exercise; 4, if symptomatic with abnormal room air saturation/cyanosis at rest; and 5, if they were symptomatic with clinical and echocardiographic features of pulmonary hypertension.

BOX I: Definitions used to classify patients into 'definite ILD and 'possible ILD'*

A patient was diagnosed to have definite ILD in the presence of any one of the following criteria:

(*a*) history and physical examination were suggestive of the disorder and the patient improved with the recommended treatment - for example, hypersensitivity pneumonitis that improved with removal of the offending agent in the environment;

(*b*) if history and physical examination findings *along* with the results of noninvasive tests are diagnostic of the condition–for example, pulmonary microlithiasis;

(*c*) if history and physical examination, HRCT findings, and the results of bronchoscopy/ bronchoalveolar lavage are diagnostic- for example, idiopathic pulmonary hemosiderosis;

(*d*) if biopsy was suggestive of the underlying disorder (e.g. LCH, DIP).

A patient was diagnosed to have possible ILD if

- history, physical examination and/or laboratory investigations were suggestive of ILD but not fulfilling the criteria for definite ILD.

** Adapted from Reference 5.*

Outcomes: The short-term outcomes assessed were death and symptomatic improvement at follow up from after 3 months of starting therapy till the time of last follow up record available. By symptomatic improvement we mean improvement in dyspnea, hypoxemia and/or lung function tests. We also evaluated the determinants of poor outcomes (death or no symptomatic improvement) such as age, gender, duration of symptoms prior to presentation, effect of severe malnutrition (defined as grade 3 and 4 protein energy malnutrition (PEM) according to Indian Academy of Pediatrics (IAP) classification for malnutrition [13]), common signs and symptoms at presentation (such as cough, dyspnea, hemoptysis, pallor, clubbing, crackles and murmur), hematological investigations at presentation such as total leucocyte count, liver function tests at presentation such as serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), Alkaline Phosphatase (ALP), presence of abnormal chest *X*-ray and HRCT findings on initial workup, bronchoscopy/ BAL findings and biopsy at presentation(lung/liver, bone marrow, skin) suggestive of specific disease.

Data were collected using a predesigned performa and entered in Microsoft Excel 2003. Statistical analysis was done using Stata 9.1 (StataCorp, College Station, TX). Data are presented as mean (SD) or number (%) as appropriate. We compared the categorical variables between the groups (ILD scores of <3 *vs.* scores of ≥3; improved vs. not improved/died) using Fisher's exact test (if the expected number in any cell of the 2×2 table was <5) or Chi-square test. The continuous variables in these groups were compared using independent Student's t-test (for variables that were normally distributed) or Wilcoxon rank-sum test (for variables that were not normally distributed).

RESULTS

We reviewed the records of 2017 children; 90 were diagnosed to have ILD (46 definite ILD, 44 possible ILD). The median (IQR) age of these children was 6.8 (3,10) years. The youngest child was 7 months and the oldest 17 years of age. Diagnosis was confirmed on histopathology in 14 (15.5%) cases based on clinical features and bronchoalveolar lavage findings alone in 26 (28.9%) patients, and on clinical grounds alone in 6

(6.7%) patients with hypersensitivity pneumonitis.

The age of onset of symptoms in most of the children (*n*=73; 81.1%) was beyond infancy (>1 year). The median duration of symptoms at presentation was 12 months (IQR: 5-36 months). A family history of similar illness and history of exposure to radiation, drugs or chemicals were elicited in eight children each. ***Table* 1** lists the clinical and laboratory features of children with ILD.

Laboratory findings: Of the 45 children with clinical pallor, 23 (56%) had hemoglobin levels of 8 g/dL or less and 8 (19.5%) had hemoglobin of 4 g/dL or less. The other relevant investigations are listed in ***Web Table* 1**. A restrictive pattern of lung disease was found in 30 of the 42 children (71%) whose spirometry results were available. The bronchoscopy findings were available in 53 (58.9%) of the case records. The bronchoalveolar lavage (BAL) was positive for hemosiderin-laden macrophages in 26 (49%) children, who were then diagnosed to have idiopathic pulmonary hemorrhage (IPH). PAS positive macrophages were seen in 4 (7.5%) children – one each had pulmonary alveolar proteinosis and pulmonary alveolar microlithiasis while the other two were diagnosed to have LCH based on tissue biopsy findings. Lung biopsy report was available in 4 (4.4%) cases with findings such as hemosiderin-laden macrophages (*n*=2), histiocytes with S-100 positivity (*n*=1), and diffuse type II pneumocyte hyperplasia (*n*=1). Majority of the reports (*n*=10) of other tissue biopsies confirmed the diagnosis of LCH (S-100 and CD8 positive cells).

Diagnostic subgroups: The most common diagnoses made were IPH, LCH and unclassified ILD (***Table* I**). A diagnosis of IPH was made on the basis of strong clinical suspicion of IPH corroborated with findings of BAL analysis showing hemosiderin laden macrophages. A diagnosis of LCH was made based on clinical features, BAL analysis showing histiocytes/lipid laden macrophages and tissue biopsy findings (lung or otherwise) positive for histiocytes with S-100 positivity. Almost 2/3rd (*n*=56; 62.2%) of the children were investigated for tuberculosis prior to presentation and 15 (16.7%) were already on anti-tuberculous therapy. In all of them, work up for tuberculosis was inconclusive. Work-up for autoimmune disease - ANA (anti-nuclear antibody), perinuclear component of antineutrophil cytoplasmic antibody (p-ANCA) was available in 34 children (37.8%); it was negative in all except for one child with SLE. Hypersensitivity to cow's milk protein (Heiner's syndrome) was suspected in 4 patients with IPH; however, antibodies to cow's milk protein was negative in all of them and none improved clinically on milk-free diet. Hypersensitivity pneumonitis was diagnosed in 6 children with definite history of exposure to bird droppings, feathers, air cooler mist, paint and plastics. Three of them (aged 12-14 years) were working in paint and plastic manufacturing units. They improved with removal of the offending agents from their environment.

A definite diagnosis of Steven Johnson syndrome (SJS) prior to the onset of symptoms of ILD was forthcoming in five patients with the disease. A diagnosis of sarcoidosis was considered in two children with lymphadenopathy and hepatosplenomegaly by HRCT (hilar lymphadenopathy) and elevated angiotensin converting enzyme (ACE) levels. Bronchiolitis obliterans organizing pneumonia (BOOP) was suspected in 3 patients with HRCT showing geographical hyperlucency. One patient with Hodgkin's lymphoma who had received radiotherapy for 6 months presented with features of ILD within 11 months of starting therapy. Two patients had a definite history of measles several months before the onset of symptoms but as none of the investigations were conclusive, they were diagnosed as post measles ILD. Testing for measles or tubercular antibodies was not possible in any of the patients due to logistic reasons. In the remaining patients, there was a

TABLE I DIAGNOSTIC SUBGROUPS IN PATIENTS WITH ILD

	N=90	*Died (n=3)*
Definite ILD	*n*=46 (51.1)	
Langerhans cell histiocytosis	10 (21.7)	0
Desquamative interstitial pneumonitis	1 (2.1)	0
Systemic lupus erythematosus	1 (2.1)	0
Idiopathic pulmonary hemosiderosis	26 (56.5)	0
Hypersensitivity pneumonitis	6 (13)	0
Pulmonary alveolar proteinosis	1 (2.1)	0
Pulmonary microlithiasis	1 (2.1)	0
Possible ILD	*n*=44 (48.8)	
Idiopathic pulmonary hemosiderosis	10 (22.7)	1
Sarcoidosis	2 (4.5)	0
SJ syndrome associated	5 (11.3)	0
BOO pneumonia	3 (6.8)	0
Post infectious (tuberculosis/measles)	8 (18.1)	0
Radiation pneumonitis	1 (2.3)	0
Unclassified ILD	15 (34)	2

Data represented as number (%); ILD, Interstitial lung disease; SJ: Steven Johnson syndrome; BOO: Bronchiolitis Obliterans Organizing.

strong clinical suspicion of ILD which could not be corroborated with either radiological findings or bronchoscopy alone and there were no records of biopsy available in them. They were therefore grouped under unclassified disease.

ILD scores: Majority of the children (53; 58.9%) had an ILD score of ≥3. We chose this cut-off (≥3) based on the area under curve in the receiver operating characteristics (ROC) curves - the area under the ROC curve for this score was 0.72 (95% CI: 0.61-0.84). This cut-off was used to distinguish between severe and mild disease.

Of the baseline variables, only clubbing was found to be significantly associated with higher ILD scores. The severity score was comparable between the two major diagnostic subgroups- definite ILD and possible ILD (***Table* II**).

Treatment: Almost all (87; 96.7%) the children received steroids either in oral (79; 90.8%) or inhaled (8; 9.2%) form. The indication for steroid therapy was symptomatic disease irrespective of the saturations. Oral and inhaled steroids were given depending on the clinical manifestations. The dose for oral steroids was 1-2 mg/kg/day for a minimum period of 6-8 weeks depending on the patients' symptomatology. In addition to steroids, 44 children (54.3%) received hydroxychloroquine and 7 (7.7%) children received azathioprine. Hydroxychloroquine was given as a first line agent in patients of IPH along with steroids or was used as a second line agent

TABLE II ASSOCIATION BETWEEN ILD SCORES AT ADMISSION AND VARIOUS PARAMETERS

Parameters	*ILD score ≥3 (n=53)*	*ILD score 2 or less (n=37)*	*P*
ILD score [*Median (IQR)*]	2 (2, 2)	3 (3, 4)	
Age (mo) [*Median (IQR)*]	96 (58, 120)	72 (30, 196)	0.06#
Duration of symptoms (mo) [*Median (IQR)*]	13 (5, 42)	12 (6, 30)	0.81#
Recurrent respiratory infections	30 (56.6)	19 (51.3)	0.31
Severe malnutrition (PEM grade 3-4)*	9 (17)	2 (5.4)	0.1
Symptoms and signs			
Cough	45 (84.9)	29 (78.4)	0.44
Dyspnea	46 (86.8)	26 (70.3)	0.03
Hemoptysis	21 (39.6)	10 (27.3)	0.22
Pallor	25 (47.2)	16 (43.2)	0.72
Clubbing	32 (60.4)	1 (2.7)	<0.001
Crepitation	26 (49)	15 (40.5)	0.43
Murmur	2 (3.8)	1 (2.7)	1.0
Diagnostic subgroups			0.49
Definite ILD	25 (54.4)	21 (45.7)	
Possible ILD	28 (63.6)	16 (36.4)	
Diagnosis			0.17
IPH	19 (35.85)	16 (43.2)	
LCH	3 (5.7)	7 (18.9)	
Others	19 (35.9)	10 (27)	
Unclassified ILD	11 (20.7)	4 (10.8)	
DIP	1 (1.9))	0	
Outcome			0.008
Died	2 (3.8)	1 (2.7)	
Improved activity by 3 months	27 (50.9)	31 (83.8)	
No improvement by 3 months	18 (34)	3 (8.1)	
Lost to follow up	6 (11)	2 (5.4)	

Data represented as number (%) unless specified otherwise; PEM, Protein energy malnutrition; ILD, interstitial lung disease; LCH, Langerhans cell histiocytosis; DIP, desquamative interstitial pneumonitis; # analysis done using Wilcoxon rank sum test.

like azathioprine in those not responding to steroids alone. Children with LCH were prescribed chemotherapy as per protocol. Majority (58; 64.4%) of the children showed complete remission of symptoms after 3 months of initiation of therapy.

Outcome: Of the 90 children, only 3 died (two of them had unclassified ILD and one had IPH), while the rest were discharged. Eight children (9.1%) were lost to follow-up at the first review period, i.e. at 3 months. The median duration of follow-up in the rest of the survivors was 9 months (IQR 6 to 18.5 months). The duration of follow up was longer in the patients with definite ILD (18.5 months, IQR 6, 22) as compared to those with possible ILD (7.5 months, IQR 5, 15). The frequency and duration of follow-up was decided based on the ongoing symptoms/signs and the response to the treatment.

On univariate analysis, we found two factors to be significantly associated with poor outcome– high ILD scores at initial evaluation and lower alkaline phosphatase levels (***Table* III)**. The group which showed

TABLE III DETERMINANTS OF MORTALITY AND MORBIDITIES IN CHILDREN WITH ILD.

Variable	*Not improved or died (n=24)*	*Improved (n=58)*	*Relative risk/difference in means (95% CI)*	*P*
Age, y	8 (4.3,10)	6 (3,9)	–	0.14
Male gender	39 (67.2)	11 (45.8)	0.54 (0.27- 1.06)	0.08
Duration of illness	15 (12, 36)	12 (5, 36)	-	0.31
Severe malnutrition	3 (12.5)	8 (13.8)	0.92 (0.33- 2.5)	0.87
ILD score [Mean(SD)]	3.5 (1)	2.6 (0.8)	–	0.001*
Signs and symptoms				
Cough	18 (75)	50 (86.2)	0.62 (0.30-1.27)	0.24
Dyspnea	20 (83.3)	48 (82.8)	1.03 (0.42- 2.5)	0.10
Cyanosis	8 (33.3)	11 (19)	1.65 (0.84- 3.2)	0.16
Hemoptysis	10 (41.7)	16 (27.6)	1.53 (0.79-2.99)	0.22
Clubbing	12 (50)	19 (32.8)	1.65 (0.85- 3.2)	0.14
Crackles	11 (45.8)	30 (51.7)	0.85 (0.43- 1.66)	0.70
Diastolic BP, mmHg, [Mean(SD)]	61.7 (20.6)	68.9 (4.9)	-7.2 (-15.2- 0.82)	0.08*
TLC/mm^3 [Median (IQR)]	10150 (7600,14500)	11950 (8600, 14900)	–	0.47#
Liver function tests				
SGOT (U/L)	51 (38, 95)	42 (29,64)		0.40
SGPT (U/L)	37 (19, 78)	25 (20, 38)		0.23
Serum ALP (U/L) [*Median (IQR)*]	205 (175,265)	360 (245,767)		0.006#
Abnormal X-ray chest	24 (100)	57 (98.2)	'Undefined'	0.70
Abnormal HRCT chest	22 (91)	56 (96)	0.56 (0.19-1.6)	0.40
Abnormal bronchoscopy/ BAL findings	14 (58.3)	29 (50)	1.27 (0.64- 2.52)	0.50
Biopsy suggestive (lung/other tissues)	4 (16)	7 (12)	1.3 (0.54, 3.1)	0.58
Diagnosis				
IPH	11 (45.8)	20 (34.5)		
LCH	2 (8.3)	6 (10.3)		
Others	5 (20.8)	23 (39.7)	–	0.4
Unclassified ILD	6 (25)	8 (13.8)		
DIP	0	1 (1.7)		

*Data represented as number (%), unless specified otherwise; ILD, interstitial lung disease; BP, Blood pressure; LCH, Langerhans cell histiocytosis; DIP, desquamative interstitial pneumonitis; IQR, Inter quartile range; SGOT, Serum Glutamic Oxalacetic Transaminase; SGPT, Serum Glutamic Pyruvic Transaminase; ALP, Alkaline Phosphatase; HRCT, High resolution computed tomography; BAL, Bronchoalveolar lavage; * Analysis done using Student's t-test; # analysis performed using Wilcoxon rank-sum test; TLC: Total leucocyte count.*

WHAT IS ALREADY KNOWN?

- ILD is a rare pulmonary disorder of childhood with diverse etiology.
- Lung biopsy is the gold standard for diagnosis of ILD.

WHAT THIS STUDY ADDS?

- In settings where lung biopsy is not feasible in children suspected to have ILD, the diagnosis of ILD may be made based on the HRCT and bronchoscopy findings.
- ILD scores of 3 or more may predict poor outcome in these children.

no/partial improvement required recurrent admissions, blood transfusions, home oxygen therapy, hydroxychloroquine and had longer follow-up.

DISCUSSION

The main aim of presenting our data is to provide clinical details and short term outcome of patients diagnosed as ILD on the basis of history, examination and limited investigations available. At present, in resource limited settings, diagnosis of ILD is rarely made as in most of the circumstances lung biopsy is not available and these children receive inappropriate treatment (antibiotics, antitubercular drugs, etc).

Lung biopsy is considered as gold standard for diagnosis of ILD however, getting a lung biopsy in children is difficult especially when they present in advanced stage of illness and have a very high risk for anesthesia. In addition, biopsy may not always be conclusive [4,5,14]. Of late, the trend is shifting towards a systematic approach to the diagnosis of patients with ILD rather than subjecting every patient to biopsy. Lung biopsy could possibly be reserved for those children in whom the diagnosis is inconclusive even after noninvasive tests and/or there is poor response to therapy. In children suspected to have ILD secondary to systemic disorders such as LCH, sarcoidosis etc., a tissue biopsy of the other affected tissues should suffice.

The clinical profile, radiological features, pulmonary function test results, bronchoscopy findings and tissue biopsy reports were comparable with previous studies from developed as well as developing countries [5,15-17]. The only difference was in the diagnostic yield of HRCT. The diagnostic yield of HRCT was higher in our study (92%) in suspected cases as compared to the study by Copley, *et al.* [18] in which only 66% of HRCT chest was suggestive of diagnosis. Increased awareness of the disease with time and knowledge of specific CT features suggestive of ILD [18] could have played a role in the increased yield. While previous studies have reported the commonest anomaly on HRCT as ground glass appearance [16,18-19] we found septal thickening to be as common. The large number of children with IPH and LCH in our study could have resulted in this finding. Bronchoalveolar lavage proved to be a very useful tool in the diagnosis of patients with alveolar hemorrhage and pulmonary alveolar proteinosis in contrast to a previous study from our country where the BAL showed only neutrophils and did not contribute much to the diagnosis [17].

IPH and unclassified ILD emerged as the most common diagnostic subgroups in our study. This was followed closely by patients with LCH and post infectious ILD. Findings of our study are in agreement with those of Fan et al who reported no specific diagnoses in 19 of their 99 patients despite a complete diagnostic evaluation [5]. Infection associated ILD and pulmonary vascular disorders were the other common diagnostic subgroups reported [5].

Three children died in our study within three months of diagnosis. In view of the retrospective nature of the study and the numbers lost to follow up, we could not precisely estimate the number of children who died after the last documented follow up dates. Fan, *et al.* [5] had reported 15 deaths (15%) out of a cohort comprising 99 patients. Several authors have reported mortality ranging from 15-60% in children with ILD [5,6] and these figures reached 100% in children with specific disorders such as diffuse developmental disorders and abnormal surfactant function [5,8]. We could not establish the histopathologic diagnosis in the three children who died. The only child with DIP survived. The final diagnosis, relatively short follow up duration available from the records and the numbers lost to follow up could have contributed to these differential results in our study.

Similar to findings of Fan, *et al.* we observed that a higher severity of illness score calculated at admission correlated with poor outcomes. As there were only 3 deaths and none of the diagnostic subgroups dominated the worse outcome group, we did not have to control for any diagnostic categories. Delayed diagnosis of the

condition due to the disease mimicking a number of common disorders, particularly tuberculosis in our country is the most probable explanation for these high scores in the study population.

In addition to the ILD score, the median serum alkaline phosphatase levels were found to be higher in the group with better outcome. This could be explained by the high number of patients with LCH with multisystem disease in this group. Paradoxically patients with LCH as such did not have significant bearing on the outcomes. Therefore, it is difficult to explain the association. We could not find any previous studies showing similar association. None of the other factors associated with the disease such as age of onset, gender, duration of illness, clinical signs and symptoms or investigations had any bearing on the outcomes.

The major limitations of our study are its retrospective nature and lack of histopathological confirmation of the disease in most patients. In addition, though the numbers were reasonable considering the rare nature of the disease, it might not have been adequately powered in detecting all the factors influencing the outcomes.

To conclude, in any child with a long drawn history of respiratory symptoms not suggestive of the common infectious or non-infectious conditions in that set up, a possibility of ILD should be strongly considered and confirmed with necessary investigations. With our report we want to raise awareness about ILD among pediatricians so that diagnosis can be made in the initial stages by using HRCT of chest, bronchoalveolar lavage (BAL) and other less invasive procedures and appropriate treatment can be instituted.

Contributors: SKK: conceived and designed the study and revised the manuscript for important intellectual content. He will act as guarantor of the study; JS: conducted the study, analyzed the data and drafted the paper; MP helped in data collection, analysis and in revising the manuscript. MJS and RL: provided inputs regarding the design and revised the manuscript for intellectual content. The final manuscript was approved by all authors.

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