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Original Research Article

Clinical profile of interstitial lung disease in children from Western India

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ABSTRACT

Background: The epidemiology of interstitial lung disease in children (chILD) remains largely unknown, particularly in developing countries. This study aims to estimate the spectrum of ILD in children in India
Methods: We retrospectively analysed data from consecutive subjects aged 0 to 18 years with interstitial lung diseases (ILD) recorded in the hospital registry at the Paediatric Respiratory Unit of Bai Jerbai Wadia Institute of Child Health from January 2018 to December 2023. We determined the proportion of each ILD subtype among children.
Results: Out of 30 enrolled children, 60% were male. Symptoms began within the first year in 17 (56%) children, predominantly with a dry cough (77%) and dyspnea. Respiratory compromise signs were common, including tachypnea, tachycardia and hypoxemia, with 17% exhibiting clubbing. Chest X-rays showed reticular/reticulonodular patterns (63%) and HRCT revealed ground glass opacities (63%). Lung function tests indicated a restrictive pattern in 33%. Bronchoscopy aided in diagnosing pulmonary alveolar proteinosis, hypersensitive pneumonitis and diffuse alveolar hemorrhage. Genetic analysis (43% cases) identified surfactant protein disorder as the most common (13%). ILD subtypes included pulmonary hemosiderosis (23%), surfactant protein disorder, pulmonary alveolar proteinosis and Langerhans cell histiocytosis (each 13%).
Conclusions: In Western India, Paediatric interstitial lung diseases exhibit a different pattern compared to adults. Pulmonary hemosiderosis spectrum, pulmonary alveolar proteinosis and surfactant protein disorder emerge as the predominant burdens among children.

Keywords: chILD, Infantile ILD, Niemann pick disease, Pulmonary alveolar microlithiasis, Pulmonary alveolar proteinosis, Pulmonary hemosiderosis, Surfactant disorder

INTRODUCTION

Interstitial lung disease in children (chILD) represents a rare and heterogeneous group of chronic respiratory conditions associated with significant morbidity and mortality.[1]

Despite its complexity, there's a lack of data on chILD in India, leading to under-diagnosis and under-reporting, partly due to limited awareness among paediatricians, inadequate diagnostic resources and challenges in genetic work-up affordability. This study aims to analyse the spectrum of chILD in a tertiary referral centre in Western India to elucidate its clinical profile and aetiologies.

METHODS

This retrospective review encompassed children diagnosed with interstitial lung disease from January 2018 to December 2023. Medical records of patients aged 0 to 18 years meeting the chILD criteria, including those with BAL/lung biopsy/genetically proven interstitial lung disease, were analysed over a six-year period.[1] A total of 30 patients meeting these criteria were included in the

study group. The diagnosis of chILD syndrome can be suspected when at least 3 out of the following 4 criteria are met. Respiratory symptoms such as cough, exercise intolerance or rapid breathing. Respiratory signs including resting tachypnea, retractions, pathological sounds on auscultation even without infection, digital clubbing, failure to thrive and respiratory failure. Hypoxemia. Chest imaging revealing diffuse abnormalities.[2]

Additionally, less rare aetiologies of diffuse chronic lung diseases, such as immunodeficiencies, infections, recurrent aspirations, cystic fibrosis, primary ciliary dyskinesia, vascular malformations and congenital cardiac diseases, were excluded from the study. Ethical approval was taken from Institutional Review Board of Wadia Hospitals. Since this is a retrospective study, informed consent from the patients was not taken. Children were categorized into two main groups: "Definite chILD-classifiable" and "Definite chILD-not classifiable," using a diagnostic algorithm.[3] This classification relied on clinical features, imaging (including chest X-ray and high-resolution chest tomography), genetic analysis and invasive tests such as bronchoscopy and lung biopsy.

Statistical analysis

Data were analysed using SPSS version 21 and presented descriptively with a level of significance set at 5%. Descriptive statistics of explanatory and outcome variables were calculated by mean, standard deviation for quantitative variables, frequency and proportions for qualitative variables.

RESULTS

In the study group, males predominated with a M: F ratio of 1.5:1. Consanguinity was reported in 8 children (27%), while three patients had a significant family history of chronic lung diseases affecting a family member. Total 17 children (56%) had symptom onset by infancy, out of which four children (13%) presented in the neonatal period with unexplained respiratory distress despite being born full term.

The most common presenting complaints were persistent dry cough and dyspnoea in 77% (n=23) and 43% (n=13) children, respectively. Additional clinical features included failure to thrive, haemoptysis, recurrent fever, skin lesions, joint pain and neurological issues such as hypotonia and developmental delay. Clinical signs of tachypnea and chest wall retractions were observed in all patients, with fine crackles on auscultation noted in 20% (n=6) of children. In the study, clubbing was observed in 17% (n=5) of children, while cyanosis was noted in 3% (n=1). Almost all children presented with hypoxemia (93%, n=28) (Table 1). The predominant chest X-ray pattern observed was reticular and reticulonodular, present in 63% (n=19) of children (Figure 1a, 2a). Other X-ray imaging findings included a miliary pattern, diffuse infiltrates and micro nodular opacity or a sandstorm appearance (Figure 1d). Ground glass opacities (GGOs) were the most common elementary lesion found on HRCT chest, seen in 63% (n=19) of children. Additionally, findings such as septal thickening, cystic lesions and septal calcification were noted (Figure 1b, 2b and 3b). Some children exhibited GGOs alongside septal thickening, mosaic attenuation and centrilobular nodules. Septal thickening was associated with patchy consolidation and fibrotic changes in a few cases (Table 2). Pulmonary function tests, conducted soon after diagnosis by spirometry, were performed in children based on their age and condition. Among the seventeen patients who underwent spirometry, ten children exhibited a restrictive pattern, while the rest had normal spirometry. Additionally, pulmonary artery hypertension was observed in eight children (26%) on echocardiography.

Flexible bronchoscopy and Broncho alveolar lavage (BAL) were performed based on medical necessity and feasibility. Twenty-six children underwent the procedure, with BAL samples from 7 children (23%) appearing macroscopically bloody and showing more than 30% hemosiderin-laden macrophages on Perl's stain, suggestive of diffuse alveolar haemorrhage (DAH). Immunological workup in two children with DAH revealed c-ANCA positivity, indicating vasculitic aetiology of pulmonary hemosiderosis. Four children had milky BAL samples with foamy macrophages and PAS positivity, suggestive of pulmonary alveolar proteinosis. In three children, BAL CD8>CD4 with lymphocytes more than 30% suggested hypersensitive pneumonitis (Table 2 and 3).

Although the role of lung biopsy is diminishing with advancements in genetics, it was still performed in cases where definitive diagnosis remained elusive despite imaging, BAL and genetic testing or for children with rapidly progressive disease awaiting genetic work-up. Open lung biopsy was conducted in 14 patients (47%). Histological features of chronic pneumonitis of infancy with possible surfactant disorders were observed in three children (10%) (Figure 1c). Non-specific interstitial pneumonia (NSIP) and desquamative interstitial pneumonia (DIP) were among the other non-specific histopathological findings noted. Definitive diagnosis was achieved through lung biopsy in 7 children (23%).

Intralamellar concentric alveolar calcifications suggestive of pulmonary alveolar microlithiasis (Figure 1f) were found in two children (7%). Hemosiderin-laden macrophages indicative of pulmonary hemosiderosis was seen in two children (Figure 3c). Among the 7 children with DAH, 5 were diagnosed with idiopathic pulmonary hemosiderosis based on BAL and biopsy findings. Ovoid PAS-positive cells confirming pulmonary interstitial glycogenesis were seen in one child. Four children were diagnosed with langerhans cell histiocytosis based on

tissue histopathology specimens showing foamy macrophages, confirmed by immunohistochemistry displaying CD1a antigen and protein S100 (Figure 2c). Lung tissue samples were obtained in 2 children, while skin and bone samples were taken in the remaining two due to extra pulmonary involvement.

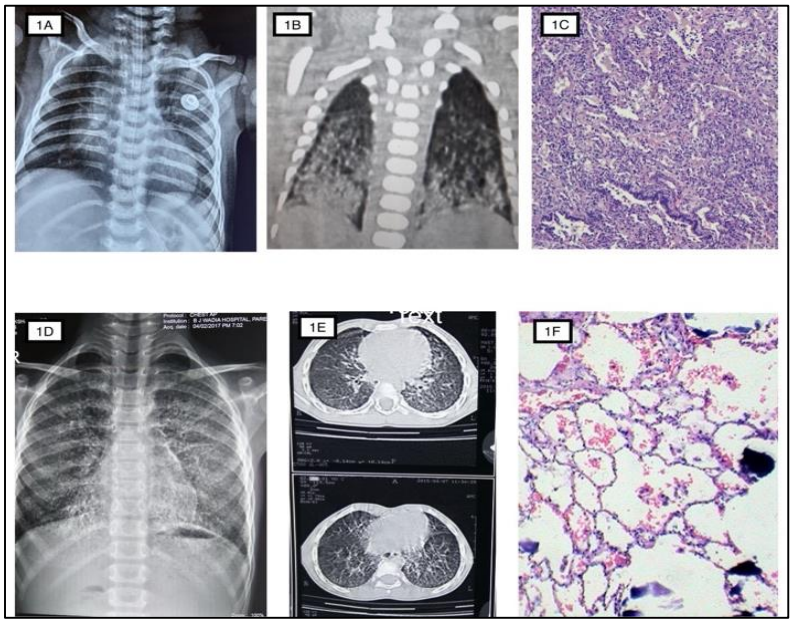

Figure 1: Upper panel: Diagnostic features of Surfactant Dysfunction Disorder (A) CXR showing fine reticular pattern with patchy consolidation (B) high resolution CT showing diffuse ground-glass opacities with patchy consolidation (C) Photomicrograph shows diffuse interstitial thickening, moderate fibrosis, inflammatory infiltrate, foamy macrophages and proteinaceous material, indicative of chronic pneumonitis of infancy (H&E x10). Lower panel: Imaging and Histopathological Features of Pulmonary Alveolar Microlithiasis: (D) Chest X-ray showing reticulonodular opacity resembling a "Sandstorm" appearance. (E) High resolution computed tomography showing diffuse septal calcification. (F) Photomicrograph shows multiple intralamelar concentric calcifications indicative of alveolar microlithiasis (H&E x40).

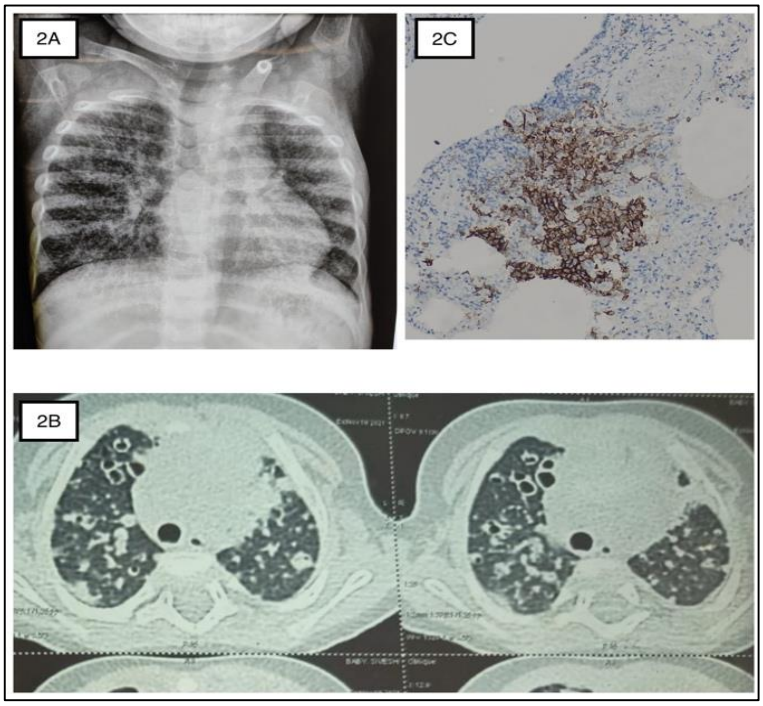

Figure 2: Diagnostic features of Langerhans cell histiocytosis (A) CXR showing fine reticular pattern (B) HRCT showing cystic lesions noted in bilateral lung fields (C) Photomicrograph showing lung tissue with foamy macrophages and IHC showing CD1a Ag and Protein S100.

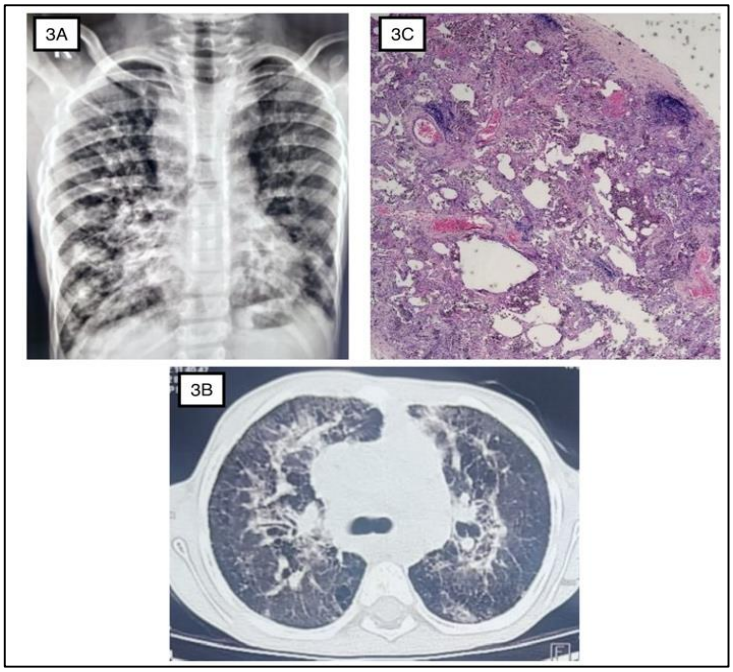

Figure 3: Imaging and Histopathological Features of Pulmonary Hemosiderosis. (A) Chest X-ray showing reticulonodular opacities. (B) HRCT showing heterogeneous patchy consolidation with septal thickening s/o possible pulmonary haemorrhage. (C) Photomicrograph showing abundant Hemosiderin Laden Macrophages within alveoli (H&E x10).

Sixteen children underwent genetic analysis through whole exome sequencing, resulting in a diagnosis confirmation in 13 children (43%). Autosomal recessive inheritance was the predominant mode noted in 6 children (20%), followed by autosomal dominant pattern in 3 children (10%). Other patterns including X-linked, de novo and combined autosomal dominant or recessive were also observed in some cases. Among the genetically diagnosed cases, mutations in genes encoding surfactant metabolism proteins were the most common, found in 4 children (13%). Genes involved in surfactant dysfunction disorders included SFTPC and ABCA3. One neonatal-onset chILD case was diagnosed with MUC5B gene mutation indicative of pulmonary interstitial glycogenesis. CSF2RA, CSF2RB and MARS1 gene mutations were associated with the diagnosis of pulmonary alveolar proteinosis. Pulmonary alveolar microlithiasis was diagnosed through SLC34A2 gene mutation in 2 children. A de novo mutation in the TMEM173 gene was instrumental in diagnosing STING (Stimulation Interferon Gamma) associated vasculopathy with onset in infancy in one child (Table 3). Two children born to consanguineous parents presented in infancy with persistent dry cough, respiratory distress (tachypnea, retractions), hypotonia, developmental delay, neuroregression and hepatosplenomegaly on clinical examination. Chest imaging revealed diffuse lung involvement suggestive of possible interstitial lung disease (ILD). Genetic workup confirmed a diagnosis of Niemann-Pick disease with NPC1 gene mutation and autosomal recessive inheritance. Out of 30 children with interstitial lung diseases (chILD), only 6 (20%) were diagnosed in infancy. Pulmonary hemosiderosis was the most common diagnosis, followed by surfactant dysfunction, pulmonary alveolar proteinosis and Langerhans cell histiocytosis. Two cases were labelled 'Definite chILD- Not classifiable' due to negative BAL and genetic workup but with lung biopsy showing NSIP. Key diagnoses were made through genetics and lung biopsy in cases of pulmonary alveolar microlithiasis, surfactant dysfunction disorder and pulmonary interstitial glycogenesis (Table 3). Among the cohort, 2 children (6%) died-one with surfactant dysfunction and another diagnosed with SAVI. Three children (10%) were lost to follow-up at the 3-month mark.

Table 1: Clinical manifestation chILD patients at initial presentation to reporting centre.

	Number of patients (n=30)	(%)
Sex (Male/female)	18/12	60 /40
Onset of symptoms before 1 year	17	57
Distribution of subjects based on age of onset of symptoms (<1month/ 1 month – 1 year / > 1 year)	4/13/13	13/43/43
Parental consanguinity	8	27
Family History (Affected siblings/ other family members affected)	1/2 (all three expired)	1/7
Age at diagnosis (<1 year / > 1 year)	6/24	20/80

Continued.

	Number of patients (n=30)	(%)
Symptoms		
Persistant dry cough	23	77
Dyspnea on exertion or at rest	13	43
Failure to thrive	5	17
Unexplained respiratory distress in term neonate	4	13
Hemoptysis	6	20
Presence of pulmonary hypertension	2	7
Recurrent fever	4	13
Skin lesions	2	7
Joint pain	1	3
Hypotonia / developmental delay	2	7
Signs		
Tachypnea	30	100
Retractions	30	100
Crackles	6	20
Clubbing	5	17
Cyanosis	1	3
Chest wall deformity	1	3
Hepatomegaly	2	7
Hepatosplenomegaly	2	7
Bone lytic lesions	2	7
Recurrent blood transfusion	2	7
Hypoxemia	28	93

Table 2: Investigations conducted at the time of diagnosis.

	Number of patients (n=30)	(%)
Chest X-ray		
Diffuse reticular and reticulonodular opacities	19	63
Miliary infiltrates	7	23
Micronodular opacities or sandstorm appearance	2	7
Hazy infiltrates	2	7
HRCT chest		
Ground glass opacities (Isolated/associated with mosaic attenuation, septal thickening or centrilobular nodules)	10/9	33/ 30
Septal thickening	5	17
Septal calcifications	2	7
Cystic lesions	4	13
Distribution of lesions in HRCT chest		
Diffuse	26	87
Patchy	4	13
Pulmonary function test (n=17)		
Restrictive pattern	10	33
Normal	7	23
Broncho alveolar lavage	26	87
BAL testing suggestive of definite diagnosis (n=26)	14	47
Bloody on macrophagic appearance with hemosiderin laden macrophages>30% (s/o Pulmonary hemosiderosis)	7	23
Milky on macrophagic appearance and PAS positivity (s/o Pulmonary alveolar proteinosis)	4	13
CD8>CD4 (s/o Hypersensitivity pneumonitis)	3	10
Whole exome sequencing	16	53
Whole exome sequencing suggestive of definite diagnosis (n=16)	13	43
SFTPC3	2	7
SFTPC3 and ABCA3 (combined)	2	7
MUC5B	1	3
CSF2RA	1	3
CSF2RB	1	3
MARS1	1	3
TMEM173	1	3

Continued.

	Number of patients (n=30)	(%)
SLC34A2	2	7
NPC1	2	7
Mode of Inheritance (n=13)		
Autosomal dominant	3	10
Autosomal recessive	6	20
Compound heterozygous (AD & AR)	2	7
X-linked	1	3
De Novo	1	3
Surgical open lung biopsy	14	47
Lung Biopsy suggestive of definite diagnosis	7	23

Table 3: Summary of final ILD diagnosis.

Final diagnosis	BAL/other biochemical investigations	Genetic mutations	Biopsy (pulmonary/ extrapulmonary)	No. of patients
Idiopathic pulmonary hemosiderosis	BAL hemosiderin laden macrophages+	Not done	Pulmonary hemosiderosis	5
Surfactant dysfunction disorder	Not helpful	SFTPC3, ABCA3	Chronic pneumonitis of infancy	4
Langerhans cell histocytosis	Not done	Not done	Skin and lung biopsy tissue showing foamy macrophages with IHC staining showing CD1a Ag and Protein S100	4
Pulmonary alveolar proteinosis **MARS mutation-pulmonary alveolar proteinosis (interstitial lung and liver disease)**	PAS +, elevated LFT (In MARS mutation child)	CSF2RA, CSF2RB, MARS	Not done	4
Hypersensitive pneumonitis	BAL lymphocytes >40%, BAL CD4:CD8 ratio decreased	Not done	Not done	3
Pulmonary alveolar microlithiasis	Not helpful	SLC34A2	Intra-alveolar lamellar calcification	2
DAH/pulmonary hemosiderosis secondary to vasculitic etiology	BAL Hemosiderin laden macrophages+, MPO ANCA positive	Not done	Not done	2
Niemann pick disease	BAL foamy cell macrophages +	NPC1	Not done	2
Definite child-not classifiable	Not helpful	No mutation identified	Desquamative interstitial pneumonia	2
Pulmonary interstitial glycogenesis	BAL PAS+	MUC5B (+)	Chronic pneumonitis of Infancy with ovoid PAS positive cells	1
STING associated vasculopathy with onset in infancy (SAVI)	Not helpful	TMEM173	Non-specific Interstitial Pneumonia	1

DISCUSSION

Interstitial lung disease (ILD) in children, with a prevalence of less than one per 2000, falls under the category of rare or orphan diseases. These conditions necessitate lifelong healthcare support.[2] The spectrum of ILD in children is broad, with some disorders more prevalent in infants and others specific to older children.[4] This study underscores that childhood ILD encompasses a heterogeneous group of rare disorders. Children with ILD often present with subtle and nonspecific clinical signs. The most common symptoms observed in our study were dry cough and dyspnoea, consistent with findings by Jhuma et al, However, our study revealed a predominant onset of symptoms in infancy, contrasting with Jhuma et al,'s observation of symptom onset beyond infancy in over 80% of cases.[5] On the other hand, Fan et al, reported predominantly respiratory complaints in infants.[6] Neonatal-onset chILD often manifests as unexplained respiratory failure in term neonates, aligning with findings by Saddi et al, Additionally, male preponderance, noted in our study, has also been observed in other case series.[7,8] High-resolution computed tomography (HRCT) scans offer superior characterization of disease involvement, morphological changes and extent of disease compared to chest x-rays. While CT imaging aids in diagnosing general interstitial lung disease (ILD), it may not always pinpoint a specific cause. However, certain distinctive patterns, such as the "crazy paving pattern," can strongly suggest specific aetiologies like pulmonary alveolar proteinosis.[9] Additionally, ground-glass opacities (GGOs) in the middle lobe and lingula may indicate neuro-endocrine hyperplasia of infancy.[10]

In our study, HRCT revealed various elementary lesions suggestive of ILD, including GGOs, irregular septal thickening, honeycombing and occasionally large sub pleural air cysts.[11,12] Among these, GGOs were the most common elementary lesion observed on HRCT imaging. In summary, HRCT scans excel in detailing disease characteristics and extent, although they may not always offer a definitive etiological diagnosis. Recognizing specific patterns such as the "crazy paving pattern" or location-specific findings like GGOs in particular lobes can aid in narrowing down potential causes.

Flexible bronchoscopy with Broncho alveolar lavage (BAL), incorporating macroscopic assessment and specific staining, is instrumental in guiding the diagnosis of interstitial lung disease (ILD). Conventional stains like eosin/haematoxylin, PAS, iron and Sudan aid in morphological analysis. BAL provides crucial clues for diagnosing conditions like alveolar haemorrhage, pulmonary alveolar proteinosis and hypersensitive pneumonitis, as demonstrated in our study.[13,14] Its utility extends to excluding infections, including opportunistic ones like pneumocystis pneumonia, which can mimic ILD.[15] While analysis of BAL solutes such as SP-B (SFTPB) and SP-C (SFTPC) can offer insights, their usefulness is limited and genetic analysis is often recommended for further evaluation.[16] Despite potential limitations in yield, BAL should be included in the diagnostic workup of ILD.[3]

Our study observed a higher genetic diagnostic rate of 43% in children with paediatric interstitial lung disease (chILD), with surfactant protein disorders being the predominant genetic diagnosis, consistent with other studies.[17-19] Commonly implicated mutations include ABCA3, SFTPB, SFTPC and NKX2-1 genes.[20,21] Mutations in CSF2RA, CSF2RB and MARS genes are linked to pulmonary alveolar proteinosis, with MARS mutations associated with liver involvement.[22,23] In our study, we did not observe cutaneous involvement in the boy with TMEM173 gene mutations, which typically leads to STING-associated vasculitis in infancy (SAVI). SAVI, characterized by skin manifestations like cutaneous vasculitis, tissue loss and rash, along with interstitial lung disease (ILD), recurrent fever and systemic inflammation, underscores its association with auto inflammatory and autoimmune conditions.[24] Secondary causes of chILD include metabolic diseases such as alveolar microlithiasis (SLC34A2) and Niemann-Pick disease (NPC1 and NPC2), with our study showing two cases of NPC1 gene mutations in children with Niemann-Pick.[9] Genetic identification aids in non-invasive diagnosis, but limitations exist due to expenses and incomplete mutation detection.

The advancement in genetic diagnosis has diminished the necessity for lung biopsy in chILD, once considered the gold standard but now reserved as a last resort.[25] Surgical lung biopsies are preferred over trans bronchial biopsies due to higher diagnostic yield, with samples ideally obtained from two different lung lobes, excluding the right middle lobe or lingula.[26] Although lung biopsy established specific diagnoses in 23% of children, emphasizing its ongoing significance, its role has decreased compared to previous standards. Biopsy from alternate accessible organs may be considered in cases of chILD with extra pulmonary involvement, such as Langerhans cell histiocytosis (LCH) involving skin, liver or bone marrow.[9]

Pulmonary hemosiderosis emerged as the most prevalent ILD diagnosis in children, consistent with findings from prior research by Sankar et al, Unfortunately, two children in our study passed away within three months of diagnosis.[5] However, due to the retrospective nature of our study, we couldn't precisely determine the number of children who died beyond the last documented follow-up, representing a significant limitation.

CONCLUSION

chILD encompasses a diverse range of rare chronic respiratory ailments. A systematic diagnostic process can simplify the identification of chILD. Beginning with a thorough history, assessment of signs and symptoms,

imaging studies, Broncho alveolar lavage (BAL) and advancing to genetic analysis and lung biopsy if necessary constitutes a stepwise approach. Although these conditions are rare, it's imperative for paediatric pulmonologists to be well-versed with these conditions to enable prompt detection, improved management and personalized treatment strategies.

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