DOI: 10.4274/tpa.297

Childhood idiopathic interstitial pneumonia: diagnosis, treatment and follow-up

Güzin Cinel[1], Bora Gülhan[2], Nural Kiper[1], Ebru Yalçın[1], Deniz Doğru[1], Uğur Özçelik[1], Dicle Orhan[3]

[1]Hacettepe University, Pediatric Chest Diseases, Ankara, Turkey

[2]Hacettepe University, Pediatric Nephrology and Romatology, Ankara, Turkey

[3]Hacettepe University, Pediatric Pathology, Ankara, Turkey

Summary

Aim: There is not an exact consensus about the terminology, classification, therapy and follow up of childhood interstitial lung diseases(ILD) because of its rarity and wide clinical spectrum. The aims of this study are to describe the clinical features and follow-up of our patients with idiopathic interstitial pneumonia on an appropriate terminology and introduce this group of illnesses which have difficulties in terms of diagnosis and therapy.

Material and Method: We investigated the files of patients who were diagnosed with interstitial lung disease by lung biopsy between 1985 and 2009 retrospectively and the group which was classified as "idiopathic interstitial pneumonia" according to the European Respiratory Society Task Force was included.

Results: Ten patients (6 females, 4 males) with a median age of 10.8 years were diagnosed with idiopathic interstitial pneumonia by lung biopsy. The most common complaints included cough, sputum expectoration, failure to thrive, cyanosis, dyspnea and reduction in exercise capacity. Five patients received systemic steroid, 2 patients received systemic steroid and hydroxychloroquine, 2 patients received systemic steroid and cyclophosphamide and 1 patient received systemic steroid and azathioprine therapies. Eight patients could be followed up regularly; 3 patients improved, 2 patients are being followed up regularly. 2 patients developed exacerbation and end-stage pulmonary disease developed in one patient with idopathic lung fibrosis whose diagnosis was delayed.

Conclusions: Any child with a normal birth history presenting with signs and symptoms suggestive of ILD lasting for 3 months should be evaluated for this disease. Early diagnosis and treatment of childhood ILD has an important effect on prognosis. Lung biopsy is necessary for histopathologic diagnosis, but it is rarely performed. The number of patients will increase with awareness of this disease. Multicenter studies are needed to constitute an appropriate diagnosis, therapy and follow-up consensus. *(Turk Arch Ped 2013; 48: 281-287)*

Key words: Interstitial lung disease, idiopathic interstitial pneumonia, systemic steroid therapy

Introduction

Childhood interstitial lung disease (ILD) is a heterogeneous group of diseases with common histologic findings which generally have a regular course and a high morbidity and mortality rate (1,2). In this group of diseases which are familial and observed rarely, gas Exchange is disrupted as a result of interstitial and alveolar inflammation and fibrosis and findings of restrictive lung disease develop (3). Interstitial lung diseases are observed very rarely in children; the estimated prevalence is 3.6/one million. The development and course of the disease show differences in children compared to adults (2). Its pathophysiology is also more complex compared to adults, since lung damage occurs during the process of growth and differentiation. Interstitial lung diseases in the childhood including "pulmonary interstitial glycogenosis", "neuroendocrine cell hyperplasia of infancy" and "genetic disorders of surfactant metabolism" are diagnosed more frequently in the first year of life (4). In older children, the pathogenesis of ILD is similar to adults and irregularities due to incrased focal fibroblast are observed in the alveolar septum histopathologically. The number of this patchy fibrotic lesions is related with dysfunction in pulmonary functions and poor prognosis (5).

Address for Correspondence/Yazışma Adresi: Dr. Güzin Cinel, Hacettepe University, Pediatric Chest Diseases, Ankara, Turkey
E-mail: guzincinel@yahoo.com **Received/Geliş Tarihi:** 01.09.2012 **Accepted/Kabul Tarihi:** 24.03.2013

Since childhood ILDs are rare and have a wide spectrum, there is still no consensus on terms, classification, treatment and follow-up. Chronic ILD work group in children with immune failure of the "European Respiratory Society" (ERS) constituted the largest pediatric patient series in the literature (n=185) and reported reccomendations related with the diagnosis, treatment and follow-up of these patients making a classification (Table 1) (6).

The objective of this study was to introduce this disease group for which difficulties in diagnosis and treatment are experienced by discussing the clinical and follow-up findings of our patients who were diagnosed with idiopathic interstitial pneumonia with lung biopsy in our hospital under appropriate terms.

Material and Method

The files of the children who were diagnosed with ILD by lung biopsy between January 1985 and August 2009 in our hospital were examined retrospectively and the group classified unter the title of "idiopathic interstitial pneumonia" according to the classification of ERS working group were included in the study. The findings of the patients were evaluated using SPSS for Windows program and descriptive statistical analyses were presented.

Results

The clinical, radiological and histological findings and follow-up findings of our 10 patients who were diagnosed with ILD classified under the title of "idiopathic interstitial pneumoniae" were presented. The demographic properties and clinical signs and symtopms of our patients are summarized in Table 2.

6 of our patients were female and four were male. The median age at the time of diagnosis was 10.8 (2.5-190 months) years. 50% had a history of third-degree consanguineous marriage; only two of our patients who had lymphocytic interstitial pneumonai (LIP) were siblings. Our patients were diagnosed a mean period of 31.5 months (4-168 months) after their symptoms began. The most common symptoms during this period included cough (80%), sputum (60%), growth retardation (%60), cyanosis (60%), reduced exercise capacity (60%) and dyspnea (50%).

Table 1. Histopathological classification of ILD in children

DLPD related with known causes (for example: drug, aspiration, connective tissue diseases, infections, environement)	Idiopathic interstitial penumoniae	Other interstitial penumonia forms	Congenital disorders
Hypersensitivity pneumonia	NSIP cellular/fibrotic	LAM	DIP (DMB)
Interstitial pneumonia types (NSIP, DIP, LIP, UIP, DAD, CP)	DIP	LCG	LIP (İYS)
	LIP	Alveolar proteinosis	Lipoid pneumonia (CMD)
	DAD (AIP)	Sarcoidosis	?NSIP/UIP (Familial CFA)
	OP (COP)	Eosinophilic pneumonia	Disease specific (?HPS)
	UIP (?Familial CFA/IPF)	Idiopatic/infantile pulmonary hemosiderosis	Alveolar proteinosis (Surfactant B deficiancy)
	CPI	Persistent tachypnea of infancy	Other surfactant deficiencies (for example: Surfactant C)
		Pulmonary interstitial glycogenosis	

DLPD: diffuse lung parenchymal disease in children; NSIP: nonspecific interstitial pneumonia; DIP: desquamative interstitial pneumonia; LIP: lymphocytic interstitial pneumonia; UIP: usual interstitial peumonia; DAD: diffuse alveolar damage; CP: chronic pneumonia; AIP: alveolar interstitial penumonia; OP: organized pneumonia; COP: cryptogenic organized pneumonia, CFA: cryptogenic fibrozing alveolitis; IPF: idiopatic pulmonary fibrosis; LAM: lymphangioleiomyomatosis; LCG: Langerhans cell granulomatosis; DMB: congenital metabolism disorders; IDS :immune deficiency syndromes; HPS: Hermansky-Pudlak syndrome.

The mean body mas index (BMI) of the patients at the time of first presentation to our hopital was found to be 15.9. tachypnea was found in 70%, clubbing was found in 70%, rales were found in 60%, cyanosis was found in 20% and decreased lung sounds were found in 20%. Oxygen saturation measured by pulse oxymeter at room temperature was found to be below 92% in 80% of the patients; the mean oxygen saturation was found to be 82%.

On the first evaluation, venous blood gases were measured in 6 patients. Three of these were found to be acidotic (pH<7.35). Pulmonary function test could be performed in five patients. A restrictive pattern was observed in four of them and forced vital capacity (FVC) in the other patients was found to be 82%. The mean FVC value was found to be 51.2% (19-82). Pletismography was performed in only two patients; their vital capacity was found to be %84-77 and total lung capacity was found to be 85-77%.

Lung graphy was taken in all patients at presentation and extensive involvement was observed in four patients, interstitial involvement findings were observed in three patients, nodular involvement was observed in two patients and reticulonodular appearance was observed in one patient. Lung graphy of a patient with LIP is shown in Picture 1. Lung tomography was performed in nine patients; ground-glass appearance was found in four patients, fibrotic retractions and interlobular thickenings were found in three patients, intensity changes and patchy involvement areas were found in three patients and traction retraction (bronchiectasis) was observed in one patient (Table3). One of the high-resolution computarized tomography (HRCT) sections of a patient with nonspecific interstitial pneumonia (NSIP) is shown in Picture 2.

Underlying immune deficiencies and connective tissue diseases were excluded by detailed investigations. Hypogammaglobulinemis was found in only one patient who was diagnosed with “desquamative interstitial pneumonia”.

With all these findings ILD was considered in our patients, lung biopsy was performed and the diagnosis of ILD was confirmed histopathologically. Thus, three patients were diagnosed with NSIP, two patients were diagnosed with LIP, two patients were diagnosed with “idiopathic pulmonary fibrosis”(IPF), one patient was diagnosed with “usual interstitial pneumonia” (UIP), one patient was diagnosed with “desquamative interstitial pneumonia (DIP) and one patient was diagnosed with “chronic infantile pneumonia” (CIP) (Table 3).

In treatment, systemc steroid was started in five patients, systemic steroid plus hydroxychloroquine treatment was started in two patients, systemic steroid plus cyclophospamide treatment was started in two patients and systemic steroid plus azathioprine treatment was started in one patient considering present clinical findings and fibrosis degree in histopathological examination (Table 3). Systemic steroid treatment was started as oral prednisolone (1-2 mg/kg/day) and was gradually tapered according to the clincal status. At the time of discontinuation of steroid, inhaled steroid treatment was added in 7 patients.

High dose intensive steroid treatment (10-30 mg/kg/day methyl prednisolone, for three days) was given to two patients in the period when the signs showed exacerbation. Oxygen saturation was monitored in all patients and oxygen was given when needed. One patient never came for a follow-up visit after treatment was started. Nine patients who came for regular follow-up visits received steroid treatment for a mean period of 16.8 months (1.5-35). Treatment of six patients is stil being continued.

The mean follow-up time of nine patients who came for short-term follow-up vizits was 42.2 (1.5-105) months. During this period, improvement was observed in three patients, recurrence was observed in two patients and worsening was observed in two patients. The clinical states of two patients are being followed up continuously. If three or more of the criteria in Table 4 were met, it was considered as recovery.

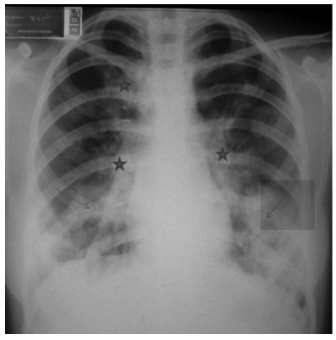
One of the patients who had recurrence had LIP and the other one had NSIP. These patients were diagnosed 4 and 2 months, respectively after their symptoms started. One of the patients whose clinical states worsened during the follow-up had IPF and the other one had DIP. They were diagnosed 14 years and 1 year, respectively after their symptoms started. The fact that they had a delayed diagnosis suggested that their fibrosis was severe and thus they did not respond to treatment.

Three of seven patients who could be followed up for a long

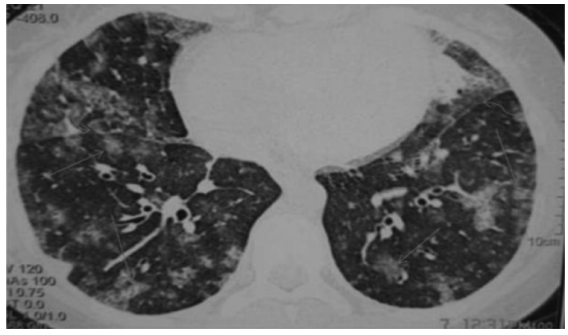
Table 2. Demographic properties and clinical symptoms and signs of the patients

n=10	Number (n)	Percent (%)
Female/male	6/4	60/40
Consanguinity between the mother and father	5	50
Sibling with a history of similar complaints	2	20
Symptoms		
Cough	8	80
Sputum	6	60
Growth failure	6	60
Cyanosis	6	60
Decrease in exercise capacity	6	60
Dyspnea	5	50
Signs		
Tachypnea	7	70
Clubbing	7	70
Rales	6	60
Cyanosis	2	20
Decrease in respiratory sounds	2	20

Table 3. Radiological findings, histopathological diagnoses and therapies administered in the patients		
	Number (n)	Percent (%)
High resolution computarized tomography (HRCT) findings	9	
Ground-glass appearance	4	44.4
Reticulonodular infiltration	3	33.3
Fibrotic retractions and interlobular thickennings	3	33.3
Density changes and patchy infiltration areas	3	33.3
Traction bronchiectasis	2	22.2
Histopatologic diagnoses	10	
Non-specific interstitial pneumonia (NSIP)	3	30
Lymphocytic interstitial pneumonia (LIP)	2	20
Idiopathic pulmonary fibrosis (IPF)	2	20
Usual intestitial pneumonia (UIP)	1	10
Desquamative interstitial pneumonia (DIP)	1	10
Chronic infantile pneumonia (CPI)	1	10
Therapies administered	10	
Systemic steroid	5	50
Systemic steroid + hydroxychloroquine	2	20
Systemic steroid + cyclophosphamide	2	20
Systemic steroid + azathiopyrine	1	10



Picture 1. Diffuse involvement in bilateral basal areas (blue arrows) and congestion in the right parathracheal area and bilateral hili on lung graphy of a patients with lymphocytic interstitial pneumonia (blue stars).



Picture 2. Bilateral patchy consolidation areas and ground-glass appearances (blue arrows) and interlobular spetal thickennings (twisted arrows) on HRCT section of a patients with non-specific interstitial pneumonia.

term are stil being followed up without any symptoms, three patients still need oxygen and one patient is still symptomatic although oxygen is not needed. In a patient with IPF who was followed up in our hospital for 18 months, end-stage lung disease developed and lung transplantation was recomended for this patient. This patient had symptoms since the time of birth, but could only be diagnosed at the age of 14 years with biopsy. He later developed pulmonary hypertension and needs oxygen continuosly.

Discussion

This study discussed pediatric cases of ILD according to the "extensive parenchymal lung diseases in children" classification of ERS. Accordingly, 10 patients who were being followed up in our hospital under the title of "idiopatic interstitial pneumonias" were disccussed. Since the prevelance of interstitial lung diseases is very low and these results are the results of patients followed up in a single center, the number of patients is not sufficient to make some generalisations. It is thought that the number of patients diagnosed will increase as this group of diseases are recognized better and the disease is suspected.

Each child with a normal birth history and signs and symptoms suggestive of ILD for longer than 3 months should be investigated in terms of ILD. A systematic approach is needed to make a diagnosis of ILD in children. The first step starts with clinical history taking and physical examination;

Table 4. Recovery criteria in patients with interstitial lung disease
A) General recovery:
Weight gain
Decrease in symptoms
Decrease in school absenteesim
Decrease in the frequency of hospitalization
B) Improvement in oxygen saturation
C) Improvement in respiratory function tests (> %5)
D) Radiological improvement

afterwards, appropriate laboratory analyses are performed to exclude systemic diseases with lung involvement (7).

The clinical findings of patients with interstitial lung disease are frequently subtile and nonspecific. The begining of these signs are insidious in most cases and these signs are present for years before a diagnosis of ILD is made in many pediatric cases. In our patients, the findings had been present for a mean time of 31.5 (4-168) months before the diagnosis was made.

Epidemiological studies have determined the estimated prevelance of familial ILD to be 1.3-5.9/one million (5). It is thought that the familial form of interstitial lung disease is transmitted by autosomal dominant inheritance with low "penetration". Recently, some mutations in surfactant protein-B (SFTP-B), -C (SFTP-C) and "adenosine triphosphate-binding cassette family of proteins (ABCA3)" genes were shown to be related with pediatric ILD cases (8-11). In a multi-center study performed by Deutsch et al. (12), 187 patients below the age of 2 years with diffuse lung disease were examined and SFTP-C mutations were foun in seven of these and ABCA3 mutations were found in six. Five patients with SFTP-C mutation had CIP, one patient had pulmonary alveolar proteinosis (PAP) and one patient had fibrotic NSIP. The histopathological diagnoses of the patients with ABCA3 mutation were as follows: PAP in four patients and DIP in two patients (12). In 50% of our patients, there was a history of consanguinity and two patients with LIP were siblings. However, the genetic analysis of these mutations can not be performed in our country. Therefore, mutation analysis in only these two siblings was performed in a center abroad and SFTP-C and ABCA3 mutations were found.

The clinical findings in patients with interstitial lung disease range from asymptomatic state with radiological findings suggestive of the disease to more prominent respiratory findings including cough, dyspnea, tachypnea and exercise intolerance (6). Cough is present in 75% of the patients and is usually not productive. Tachypnea is observed in 80% of the patients and is usually the first and most common respiratory finding (6). Fan et al. (13) evaluated the clinical findings and physical examination findings of 99 pediatric patients with ILD who were followed up in Colorado University Hospital between 1980 and 1994 systematically and showed that the symptoms observed commonly at presentation included cough, dyspnea, tachypnea, retractions, exercise restriction and frequent respiratory infections. In our study, the most common symptoms included cough, reduced exercise capacity, cyanosis, dyspnea, sputum production and growth failure.

The most common clinical signs include inspiratory rales, tachypnea and retractions. Presence of these findings in a child with a normal history of birth should suggest ILD. Findings which are observed rarely and in more advanced stages of the disease include clubbing and cyanosis during exercise or at rest (6). In our patients, tachypnea (70%), rales (60%), clubbing (70%) and cyanosis (20%) were found during the first examination.

Laboratory tests are rarely diagnostic in interstitial lung diseases. They are helpful in excluding other systemic diseases including collagenous vascular diseases and immune deficiencies related with lung involvement. In addition, laboratory tests are also used to exclude respiratory diseases including cystic fibrosis, tuberculosis or chronic lipid aspiration and gastroesophageal reflu which are observed frequently in the childhood. Detailed laboratory tests were also performed in our patients in terms of these diseases and hypogammaglobulinemia was found in only one patient with DIP.

Hypoxemia in room air is found in the majority of patients with ILD. Hypercarbia develops in the advanced stages of the disease (14). Oxygen saturation which was measured with pulse oxymeter in room air was found to be below 92% 8mean: 82%) in 80% of our patients.

Although pulmonary functions tests do not provide a specific information, they are important in the diagnosis and follow-up of ILDs. Decreased lung compliance and restrictive respiratory disorder characterized with decreased lung volume are generally observed in ILDs (14,15,16,17,18). In our study, pulmonary function test could be performed in five patients and restrictive findings were found in four of them. The mean FVC value was found to be 51.2% (19-82). Plethysmography could be performed in only two patients; the vital capacity was found to be 84-77% and total lung capacity was found to be 85-77%.

Lung graphy is usually taken during the first assessment in children who are suspected to have ILD, but this generally provides limited information. It is known that lung graphy was found to be normal in some patients who were confirmed to have ILD by biopsy (6). The most reliable imaging method in a patient with ILD is high-resolution computarize tomography (HRCT). In the pediatric literature, there are publications showing that the reliability of HRCT has increased in the diagnosis of ILD (19,20,21). HRCT is also directive in selection of the area of biospy in pediatric ILDs in addition to its importance in diagnosis. Additionally, it is also important in the follow-up of the activity and/or severity of the disease (6). In the early stage, HRCT findings include patchy ground-glass opacities and peribronchial or centrilobular small nodules. In the advanced stages, fibrotic

lesions may be observed. Seely et al. (19) reported that ground-glass areas were mostly observed in the subpleural areas and intralobular lines, irregular interlobular septal thickennings and honey comb appearance were observed less frequently. Large subpleural air cysts adjacent to the ground-glass areas in the upper lobes are specific for pediatric ILD. These cysts are interpreted as paraseptal or irregular emphysema (6). In our study, ground-glass appearance was observed in four of 9 patients in whom HRCT was performed, reticulonodular appearance was found in three, fibrotic retractions and interlobular thickennings were found in three, intensity changes and patchy involvement areas were found in three and traction bronchiectasis was found in two.

Histological evaluation of lung tissue is the last step of many diagnostic tests. The importance of histopathological evaluation is gradually increasing with definition of different types of interstitial lung diseases and recognition of the clinical significance of these. ILD is less well understood and classified in children compared to adults. Fan et al. (5) divided ILDs into three groups by making a diagnostic classification: 1) ILD with known etiology; 2) ILD with unknown etiology and 3) ILD specific for infancy. Generally, most biopsies are obtained from the second and third groups and are classified as interstitial pneumonia types histopathologically. Different methods can be used to obtain lung tissue in adults and children. The most commonly preferred methods include open lung biopsy and video-assisted thoracoscopic biopsy. Other include transbronchial lung biopsy and percutaneous needle biopsy, but the roles of these methods in the diagnosis and classification of pediatric ILDs have not been clearly defined yet (22,23,24). Generally, sufficient tissue can be obtained with open lung biopsy. Specific histopathological diagnosis can be obtained in the majority of pediatric patients (93%) by open lung biopsy. Complications directly related with biopsy procedure are observed rarely (11%) (25). In all of our patients, sufficient sample could be obtained for histopathological diagnosis by open lung biopsy. Long-term thoracic tube drainage was needed because of pneumothorax after biopsy in one patient with lung fibrosis. With histopathological examination NSIP was diagnosed in three of our patients, LIP was diagnosed in two, IPF was diagnosed in two, UIP was diagnosed in one, DIP was diagnosed in one and CIP was diagnosed in one.

Since ILD is observed rarely in children, it is difficult to perform controlled studies related with specific therapies. The methods used in treatment are determined by experience obtained from studies performed in a few centers with a low number of patients. The course of the disease is vary variable; some patients can be cured spontaneously without treatment (PIG, NECHI), some may worsen despite all therapies and show a fatal course. Most patients need oxygen treatment and specific therapies. Oral prednosolone (1-2 mg/kg/day) or intravenous intensive high dose metylprednisolone alone or in combination with hydroxychloroquine are the most commonly used medical therapies (7,26). Patients with a milder course and diffuse fibrotic changes on biopsy can be treated with hydroxychloroquine alone (6-10 mg/kg/day in 2 doses) (27,28). The decision of the agent to be used in treatment is made according to the lung biopsy findings. If diffuse desquamation and inflammation is present, steroids should be selected. If changes predictive of increased fibrosis are present, hydroxychloroquine alone can be preferred. In patients with severe findings, both agents are used in combination (6). Other treatment options include immunosupressive agents including azathiopyrine, cyclophosphamide, cyclosporine or methotrexate. Lung transplantation or heart-lung transplantation is a treatment option even below the age of 10 years (6). In our patient group, systemic steroid was started in five patients, systemic steroid plus hydroxychloroquine treatment was started in two patients, systemic steroid plus endoxane treatment was started in two patients and systemic steroid plus azathiopyrine treatment was started in one patient according to lung biopsy findings. Systemic steroid treatment was initiated as oral prednisolone (1-2 mg/kg/day) and tapered gradually according to the clinical status. Inhaled steroid treatment was added to seven patients at the time of discontinuation of oral prednisolone. Intensive high dose steroid treatment (10-30 mg/kg/day metylprednisolone for three days) was given to two patients in the period when the symptoms showed exacerbation. Oxygen was given when needed by monitoring oxygen saturation in all patients. Last-stage lung disease developed in a patient with IPF who was followed up in our hospital for 18 months and lung transplantation was recommended for this patient.

Recovery in patients with interstitial lung disease is decided with decrease in cough and dyspnea, increase in oxygen saturation and improvement in pulmonary functions. Improvement in lung graphy and HRCT findings lasts for a long period of 2-4 years. No correlation could be shown between histopatholgoical findings and the prognosis of the disease in studies conducted with children (14,29). While some children with relatively more severe fibrosis on biopsy show a better improvement, patients with more severe desquamation may show a worse prognosis. This is probably related with the fact that the disease has different severity in different parts of the lung (6). The number of our patients is too small to establish a relation between lung biopsy findings and the prognosis. However, it was observed that the clinical states of two patients who had a more delayed diagnosis compared to others worsened gradually and that they did not respond to treatment. It is expected that 40-65% of the patients with idiopathic interstitial pneumonia give a good response to corticosteroid treatment (29). 55.5% of our patients gave a good respone to corticosteroid treatment. In the short-term follow-up, recovery was observed in three of nine patients; the clinical states of two patients are being followed up continuously.

Conclusively, each child with a normal birth history and signs and symptoms suggestive of ILD including cough, dyspnea, tachypnea, cyanosis, growth failure for longer than 3 months should be investigated in terms of this disease. Early diagnosis and treatment of ILD affects the prognosis in children. While lung biopsy which is necessary for histopathological diagnosis is still a rarely used method, analyses for SFTP-B and SFTP-C mutations and ABCA3 mutation which are necessary for genetic diagnosis in a group of patients are not performed in our country. Although the number of patients seem to be low, it

is thought that the number of patients diagnosed will increase as the suspicion level is kept high. Multi-center studies are needed including genetic studies to establish appropriate diagnostic, therapeutical and follow-up methods in this wide-spectrum disease group which seems to be rare.

Conflict of interest: None declared.

References

1. Fan LL, Kozinetz CA. Factors influencing survival in yychildren with chronic interstitial lung disease. Am J Respir Crit Care Med 1997; 156: 939-942.
2. Dinwiddie R, Sharief N, Crawford O. Idiopathic interstitial pneumonitis in children: a national survey in the United Kingdom and Ireland. ediatr Pulmonol 2002; 34: 23-29.
3. Das S, Langston C, Fan LL. Interstitial lung disease in children. Curr Opin Pediatr 2011; 23: 325-331.
4. Clement A, Nathan N, Epaud R, Fauroux B, Corvol H. Interstitial lung diseases in children. Orphan J Rare Dis 2010; 5: 22.
5. Fan LL, Deterding RR, Langston C. Pediatric interstitial lung disease revisited. Pediatr Pulmonol 2004; 38: 369-378.
6. Clement A, ERS Task Force. T Task force on chronic interstitial lung disease in immunocompetent children. Eur Respir J 2004; 24(4): 686-697.
7. Fan LL, Langston C. Pediatric interstitial lung disease: children are not small adults. Am J Respir Crit Care Med 2002; 165: 1466-1467.
8. Bullard JE, Wert SE, Whitsett JA, Dean M, Nogee LM. ABCA3 mutations associated with pediatric interstitial lung disease. Am J Respir Crit Care Med 2005; 172: 1026-1031.
9. Nogee LM. Genetic mechanisms of surfactant deficiency. Biol neonate 2004; 85: 314-318.
10. Nogee LM, Dunbar AE 3rd, Wert S, Askin F, Hamvas A, Whitsett JA. Mutations in the surfactant protein C gene associated with interstitial lung disease. Chest 2002; 121(Suppl 3): 20-21.
11. Deterding R, Fan LL. S Surfactant dysfunction mutations in children's interstitial lung disease and beyond. Am J Respir Crit Care Med 2005; 172: 940-941.
12. Deutsch GH, Young LR, Deterding RR, Fan LL, Dell SD, Bean JA, Brody AS, Nogee LM, Trapnell BC, Langston C; Pathology Cooperative Group, Albright EA, Askin FB, Baker P, Chou PM, Cool CM, Coventry SC, Cutz E, Davis MM, Dishop MK, Galambos C, Patterson K, Travis WD, Wert SE, White FV; ChILD Research Co-operative. Diffuse lung disease in young children: application of a novel classification scheme. Am J Respir Crit Care Med 2007; 176: 1120-1128.
13. Fan LL, Kozinetz CA, Deterding RR, Brugman SM. Evaluation of a diagnostic approach to pediatric interstitial lung disease. Pediatrics 1998; 101: 82-85.
14. Sharief N, Crawford OF, Dinwiddie R. Fibrosing alveolitis and desquamative interstitial pneumonitis. Pediatr Pulmonol 1994; 17: 359-365.
15. Kerem E, Bentur L, England S, Reisman J, O'Brodovich H, Bryan AC, Levison H. Sequential pulmonary function measurements during treatment of infantile chronic interstitial pneumonitis. J Pediatr 1990; 116: 61-67.
16. Gaultier C, Chaussain M, Boulé M, Buvry A, Allaire Y, Perret L, Girard F. Lung function in interstitial lung diseases in children. Bull Eur Physiopathol Respir 1980; 16: 57-66.
17. Z Zapletal A, Houstk J, Samánek M, Copová M, Paul T. Lung function in children and adolescents with idiopathic interstitial pulmonary fibrosis. Pediatr Pulmonol 1985; 1: 154-166.
18. Steinkamp G, Müller KM, Schirg E, von der Hardt H. Fibrosing alveolitis in childhood. A long-term follow-up. Acta Paediatr Scand 1990; 79: 823-831.
19. Seely JM, Effmann EL, Müller NL. High-resolution CT of pediatric lung disease: imaging findings. AJR Am J Roentgenol 1997; 168: 1269-1275.
20. Lynch DA, Hay T, Newell JD Jr, Divgi VD, Fan LL. Pediatric diffuse lung disease: diagnosis and classification using high-resolution CT. AJR Am J Roentgenol 1999; 173: 713-718.
21. Copley SJ, Padley SP. High-resolution CT of paediatric lung disease. Eur Radiol 2001; 11: 2564-2575.
22. Smyth RL, Carty H, Thomas H, van Velzen D, Heaf D. Diagnosis of interstitial lung disease by a percutaneous lung biopsy sample. Arch Dis Child 1994; 70: 143-144.
23. Spencer DA, Alton HM, Raafat F, Weller PH. Combined percutaneous lung biopsy and high-resolution computed tomography in the diagnosis and management of lung disease in children. Pediatr Pulmonol 1996; 22: 111-116.
24. Whitehead B, Scott JP, Helms P, Malone M, Macrae D, Higenbottam TW, Smyth RL, Wallwork J, Elliott M, de Leval M. Technique and use of transbronchial biopsy in children and adolescents. Pediatr Pulmonol 1992; 12: 240-246.
25. Coren ME, Nicholson AG, Goldstraw P, Rosenthal M, Bush A. Open lung biopsy for diffuse interstitial lung disease in children. Eur Resp J 1999; 14: 817-821.
26. Fan LL, Langston C. Chronic interstitial lung disease in children. Pediatr Pulmonol 1993; 16: 184-196.
27. Balasubramanyan N, Murphy A, O'Sullivan J, O'Connell EJ. Familial interstitial lung disease in children: response to chloroquine treatment in one sibling with desquamative interstitial pneumonitis. Pediatr Pulmonol 1997; 23: 55-61.
28. Blyth C, Lane C. Hydroxychloroquine retinopathy: is screening necessary? BMJ 1998; 316: 716-717.
29. No authors listed. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000; 161: 646-664.