M. Reisi[1], G. Azizi[2,3], F. Kiaee[3], F. Masiha[4], R. Shirzadi[4], T. Momen[5], H. Rafiemanesh[6], N. Tavakolinia[3], M. Modaresi[4], A. Aghamohammadi[3]

Evaluation of pulmonary complications in patients with primary immunodeficiency disorders

[1]Pediatric Pulmonology Department, Child Growth and Development Research Center, Research Institute of Primordial Prevention of non-communable Disease, Isfahan University of medical sciences, Isfahan, Iran
[2]Department of Laboratory Medicine, Imam Hassan Mojtaba Hospital, Alborz University of Medical Sciences, Karaj, Iran
[3]Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[4]Pediatric Pulmonary Department, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[5]Pediatric Immunology, Allergy and Asthma Department, Child Growth and Development Research Center, Research Institute of Primordial Prevention of Non-Communable Disease, Isfahan University of Medical Sciences, Isfahan, Iran
[6]Department of Epidemiology, School of Public Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Key words

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Corresponding Author
Asghar Aghamohammadi
Children's Medical Center Hospital
62 Qarib St., Keshavarz Blvd., Tehran 14194, Iran
Phone: + 98 21 6642 8998
Fax: + 98 21 6692 3054
Email: aghamohammadi@tums.ac.ir

Summary

Background. *Primary immunodeficiencies (PIDs) are inherited disorders in which one or several components of immune system are defected. Moreover, affected patients are at high risk for developing recurrent infections, particularly pulmonary infections. The spectrum of pulmonary manifestations in PIDs is broad, and includes acute and chronic infection, structural abnormalities (eg, bronchiectasis), malignancy and dysregulated inflammation resulting in tissue damage. In this study, our aims are to evaluate pulmonary complications in PID patients.* ***Patients and Methods.*** *We studied 204 cases with confirmed PID. To evaluate pulmonary complications in these patients, we used pulmonary function test (PFT), high resolution computed tomography (HRCT) scan and bronchoalveolar lavage (BAL).* ***Results.*** *Our results showed that pneumonia was the most frequent clinical manifestations in all PID patients. There were significantly greater numbers of episodes of pneumonia in HIgM, XLA and CVID patients with delayed diagnoses < 6 years. Moreover, of 57.4% CVID patients, 55% XLA patients and 33.3% HIgM patients had abnormal PFT results, and bronchiectasis was showed in 9 (42.9%) of XLA, 6 (11.8%) of HIES, 3 (21.4%) of HIgM and 38 (62.3%) of CVID patients.* ***Conclusion.*** *Pulmonary complications should be considered in cases with PIDs especially in CVID cases.*

Introduction

Primary immunodeficiency diseases (PID) are a group of more than 200 rare, chronic disorders, in which a part or functions of the immune system is missing or improperly working (1,2). However, defects in the immune system cause a spectrum of complications, including increased susceptibility to infection, autoimmunity and malignancy (3-5). Recurrent respiratory tract infections (RTIs) are the most common clinical manifestation of them, especially in CVID (6), XLA (7), HIgM (8,9) and selective IgA deficiency (10). The most common RTIs include upper airway infections (e.g. otitis media and sinusitis) and lower airway infections (e.g. bronchial abnormalities, especially bronchiectasis, interstitial lung diseases, obstructive lesions and chronic obstructive pulmonary disease). Lower respiratory tract complications are generally considered to be more significant

and more particular for PIDs and their prognosis (11). Clinical warning symptoms of PID would facilitate early diagnosis and appropriate treatment, and can prevent later severe outcomes such as mastoiditis and bronchiectasis.

Retrospective studies in patients with PIDs have shown the existence of bronchiectasis, peribronchial thickening, air trapping, lung volume reduction, atelectasis, follicular bronchiolitis and parenchyma nodule, which lead to more clinical studies of pulmonary complications in PIDs (12,13). Bronchiectasis and bronchial wall thickening were the most frequent pulmonary complications in CVID patients (13). It is demonstrated that early diagnosis along with adequate immunoglobulin replacement therapy in patients with primary antibody deficiencies, could reduce the number of pulmonary infections (14). Therefore, the increasing of knowledge in this field is critical for the achievement of optimal patient management and for the increase of life expectancy of PIDs. Even though several studies have reported pulmonary complications in patients with different PID disorders, there are only a few reports comparing the pulmonary complications between these diseases. The aims of this study were to investigate the prevalence of pulmonary complications in patients with PID, and to evaluate the probable associations between pulmonary complications and other clinical and immunological features in these patients, in order to raise the known science in this field.

Material and Methods

Patients

This cross sectional study was performed in Immunodeficiency Clinic at the Children's Medical Center affiliated to Tehran University of Medical Sciences during 2013-2014. A total of 204 patients with PID (94 with CVID, 41 with XLA, 51 with HIES, 15 with HIgM, 3 with SCID), who were diagnosed and treated at this center, agreed to participate in this study. It should be noted that written informed consent was obtained from all patients.

Demographic and clinical information

An appropriate questionnaire was developed to be completed by patients, interviewing for demographic information including age, sex, type of PID, age at onset of symptoms, age at diagnosis and history of respiratory and pulmonary infections as well as lung complications. Diagnostic delay was defined as the time between the onset of symptoms and the time of diagnosis. Moreover, for each patient, the total number of pneumonia episodes before and after diagnosis was recorded. The diagnosis of pneumonia was based on international criteria by using clinical, radiological and laboratory evidence of lower respiratory tract infections.

Pulmonary function tests

Pulmonary function test (PFT) was evaluated according to the American Thoracic Society recommendations, using a computerized pneumotachograph (Jaeger, Wurzburg, Germany) in PID patients who were six years and older and cooperative, with patients tested in the seated position (within a volume displacement body plethysmograph). FEV1, FVC, FEV1/FVC and maximal mid-expiratory flow (MMEF 25-75%) were recorded for each tested patients.

Chest radiographs and HRCT scanning

Standard postero-anterior and lateral chest X-ray, as well as high-resolution computed tomography (HRCT) scans, were obtained for each patient. Radiographs were evaluated to detect interstitial involvement of upper, middle and lower areas of both lungs. To confirm the presence of chronic lung disease, the HRCT was performed in patients who had persistent symptoms for more than four weeks. HRCT was evaluated using the modified Bhalla scoring method to check the presence and severity of different parameters, including: 1, the presence and extent of bronchiectasis; 2, the average severity of bronchial dilatation; 3, bronchial wall thickness; 4, the extent of decreased attenuation of the lung parenchyma; 5, the presence or absence of mucus within the large airways; 6, the extent of bronchial wall collapse; and 7, the extent of tracheal collapse. The mentioned parameters were scored separately for each lung lobes and the lingual. The total lung score was derived by summing the lobar grades. Bronchiectasis was determined as bronchial dilatation, often with thickening of the walls.

Bronchoscopy and bronchoalveolar lavage

Bronchoscopy and BAL was performed by a pediatric pulmonologist as previously described (15), in the PID patients who showed in their chest X-ray persistent respiratory symptoms, including refractory pneumonia, persistent infiltration and resistant atelectasis. The recovered lavage fluid was evaluated cytologically (global and specific cytology) by using light microscopy at × 1000 for differential cell count of lymphocytes, macrophages, neutrophils and eosinophils. Finally, pulmonary needle biopsy was obtained from patients with persistent respiratory symptoms who did not response to treatments; also, other mentioned work up could not help determine the etiology of pulmonary complications.

Statistical Analysis

Clinical information, including PFT, HRCT and BAL results, was compared among the patient groups. Fisher's exact test and

chi-square tests were used for 2 × 2 comparison of categorical variables, whereas t-tests and one-way Annova were used to compare numerical variables. Statistical analysis was performed using the SPSS software package, version 21 (SPSS Inc., Chicago, IL, USA). A P-value < 0.05 was considered significant.

Results

Characteristics baseline of the patients

There were 204 PID patients (137 male, and 67 female), aged 3-66 years, who had been diagnosed with PIDs, including 94 (46.1%) with CVID, 41 (20.1%) with XLA, 51 (25.0%) with HIES, 15 (7.3%) with HIgM, 3 (1.5%) with SCID (**table 1**). Immunological data, including serum immunoglobulin levels and lymphocyte subset percent at the time of diagnosis, are shown in **table 2**.

Pulmonary infections before and after diagnosis

Pulmonary infections, particularly pneumonia, were the most frequent clinical manifestation in all PID patients. Before diagnosis and immunoglobulin replacement therapy, 73 CVID patients (78%), 34 HIES patients (67%), 25 XLA patients (60%), and 15 HIgM patients (100%) experienced at least one episode of pneumonia (P = 0.014). The characteristics of the patients with a history of pneumonia are shown in **table 3**. In order to adjust the probable effect of delayed diagnosis of pneumonia incidence rate, patients were stratified into those with delays of < 6 years and those with delays > 6 years. Comparison of the pneumonia incidence rates within the stratified groups, showed that there were significantly greater numbers of episodes of pneumonia in HIgM, XLA and CVID patients with delayed diagnosis < 6 years (P = 0.024).

Table 1 - *Characteristics of the patients with PID (n = 204).*

	Number of patients	Gender (male / female)	Age at the study time (y/o)		Age at onset of symptoms (y/o)		Age at the time of diagnosis (y/o)		Delayed diagnosis time (y)	
			Min - Max	Median (IQR)	Min - Max	Median (IQR)	Min - Max	Median (IQR)	Min - Max	Median (IQR)
CVID	94	54/40	10-66	25 (11.75)	0-46	2 (6)	4-54	9 (11.75)	0-39	4 (6.88)
XLA	41	41/0	6-43	22 (11.10)	0-6	1 (1.20)	0-24	4 (4.60)	0-23	2 (2.95)
HIES	51	25/26	4-45	15 (15)	0-28	0 (1)	0-41	9 (10)	0-38	8 (10)
HIgM	15	14/1	8-39	15 (14)	0-7	1 (1)	1-25	4 (6)	0-18	3 (5)
SCID	3	3/0	3-5	3 (.)	0-1	0 (.)	0-1	0 (.)		

Table 2 - *Immunologic features of PID patients at diagnosis stage.*

	CVID (Mean ± SD)	HIES (Mean ± SD)	HIgM (Mean ± SD)	XLA (Mean ± SD)	SCID (Mean ± SD)
WBC (/µL)	8774.1 ± 3602.9	13699.7 ± 8998.0	8683.3 ± 5857.4	5601.8 ± 3632.5	6680 ± 3056.5
Lymphocyte (%)	34.1 ± 16.2	39.6 ± 21.1	54.5 ± 23.4	47.6 ± 21.8	6.7 ± 4.2
CD3 (% of lymphocytes)	71.5 ± 16.4	74.3 ± 18	69.2 ± 12.3	86.9 ± 9	16.7 ± 24.8
CD4 (% of lymphocytes)	32.2 ± 14.4	50 ± 12.5	33.7 ± 12.4	41.3 ± 14.9	1.7 ± 1.2
CD8 (% of lymphocytes)	39.6 ± 13.8	26 ± 8.3	30 ± 12.6	43 ± 19.8	6 ± 10.4
CD19 (% of lymphocytes)	7.6 ± 5.3	14.5 ± 2.1	15.6 ± 7.4	1.2 ± 1.6	0.7 ± 0.6
IgG (mg/L)	149.4 ± 134.1	1359.8 ± 789.8	137 ± 158.0	43.2 ± 67.4	116.7 ± 116.5
IgA (mg/L)	17.7 ± 31.4	116.2 ± 86.2	26.5 ± 38.5	7 ± 9.1	1.7 ± 1.5
IgM (mg/L)	27.7 ± 33.1	135.8 ± 119.2	419.3 ± 346.3	13.2 ± 19.7	4.7 ± 3.8

Table 3 *- Comparison of pneumonia episodes in different PID patients.*

		CVID	XLA	HIES	HIgM	SCID	Value[1b] (P-Value)
		Number of patients with pneumonia (%)					
Before diagnosis	Delay diagnosis < 6 y	43/58 (74.1)	21/37 (56.0)	12/23 (52.2)	12/12 (100)	3/3 (100)	13.129 (0.007)
	Delay diagnosis > 6 y	30/36 (83.3)	4/4 (100)	22/28 (78.6)	3 (100)	0 (0.0)	0.955 (0.876)
	Total patients (N[a] = 150/204)	73/94 (77.7)	25/41 (61.0)	34/51 (66.7)	15/15 (100)	3/3 (100)	12.198 (0.011)
After diagnosis (N[a] = 131/204)		55/94 (58.5)	18/41 (43.9)	46/51 (90.2)	9/15 (60.0)	3/3 (100)	27.206 (0.001)

[1]Test between positive and negative pneumonia episodes in different PID patients. a, positive pneumonia episodes/tested for pneumonia; b, Fisher's Exact Test.

The majority of patients with PID were receiving intravenous immunoglobulin (IVIG) at a dose of 400-600 mg/kg/month and also prophylactic antibiotics according to the type of PIDs. The frequency of pneumonia after treatment decreased significantly in CVID (P = 0.001) and HIgM (P = 0.01) patients. In addition, the frequency of pneumonia was decreased in XLA cases; however, it wasn't significant (P = 0.1).

Pulmonary function tests

Excluding children under the age of 6 years, who cannot cooperate appropriately for spirometry, PFT was performed for 54 patients with CVID, 20 patients with XLA and 9 patients with HIgM. 57.4% CVID patients, 55% XLA patients, and 33.3% HIgM patients, had abnormal PFT results (**table 4**). There were no significant differences between the frequency of pneumonia occurrence in patients with different patterns of spirometry (P = 0.5). Moreover, there were no significant differences in patterns of PFT between CVID, HIgM and XLA patients (P = 0.398). Pattern of obstruction in patients with bronchiectasis was prominently more than those without bronchiectasis (P = 0.005).

HRCT scanning

We evaluate lung complications in 149 PID patients by HRCT which bronchiectasis was confirmed in 56 (37.6%) patients. The age of patients with bronchiectasis (median age 13 years, range 41 years) differed from those of non-bronchiectasis patients (median age 6.7 years, range 52.90 years). Bronchiectasis was showed in 9 (42.9%) of XLA, 6 (11.8%) of HIES, 3 (21.4%) of HIgM and 38 (62.3%) of CVID patients. Our results showed a correlation between delay in diagnosis and the frequency of bronchiectasis in PID patients, so delay in diagnosis in bronchiectatic patients was higher than non-bronchiectatic patients. This difference was significant in HIgM (P = 0.007) and HIES (P = 0.008) patients; however, it wasn't significant in CVID (P = 0.07) and XLA (P = 011) patients. Moreover, the prevalence of bronchiectasis in CVID patients was more than HIgM, HIES and XLA patients. Although the difference was statistically significant for XLA and HIES (P = 0.029, P = 0.001, respectively), but was not significant for HIgM (P = 0.137). For evaluation of severity of bronchiectasis, HRCT data were independently evaluated by an expert radiologist using a modified Bhalla scoring system. In this evaluation, the presence,

Table 4 *- PFT pattern in patients with PADs.*

PADs	Abnormal PFT			Normal PFT	P value
	Obstructive	Restrictive	Mixed		
CVID (n = 54)	8 (14.8%)	13 (24.0%)	10 (18.6%)	23 (42.6%)	0.24
HIGM (n = 9)	0	0	3 (33.3%)	6 (66.6%)	0.18
XLA (n = 20)	1 (5.0%)	6 (30.0%)	4 (20.0)	9 (45.0%)	0.98

Table 5 *- Cellular and Microbiological Analysis of BAL Fluid.*

P.N	Disease	Cell counts (103)/ml	Neu (%)	Lym (%)	Molecular evaluation				PCP Staining	Culture
					CMV	HSV	EBV	TB		
1	CVID	600	85	10	Neg	Neg	Neg	Neg	Neg	*Haemophilus influenzae*
2	CVID	400	70	20	Neg	Neg	Neg	Neg	Neg	*Streptococcus pneumoniae*
3	HIgM	250	16	11	Neg	Neg	Neg	Neg	Neg	
4	HIgM	320	30	55	Pos	Neg	Neg	Neg	Neg	
5	HIgM	230	62	30	Neg	Neg	Neg	Neg	Pos	
6	SCID	180	85	7	Pos	Neg	Neg	Neg	Neg	*Klebsiella pneumoniae*
7	SCID	175	80	7	Neg	Neg	Neg	Neg	Neg	*Staphylococcus aureus*
8	SCID	250	80	5	Neg	Neg	Neg	Neg	Pos	
9	SCID	150	90	3	Neg	Neg	Neg	Neg	Pos	

P.N, Patient number; Neu, Neutrophils; Lym, Lymphocyte; PCP, Pneumocystis pneumonia; CN, Congenital neutropenia; CMV, Cytomegalovirus; HSV, herpes simplex virus; EBV, Epstein-Barr virus; TB, Tuberculosis.

extent and severity of bronchiectasis, peribronchial thickening, mucus plugging and atelectasis or consolidation were analysed. The result showed that the mean score was higher in CVID (3.78 ± 3.72) compared with XLA (2.43 ± 4.65) patients, however it wasn't significant (P = 0.64).

Cellular and Microbiological Analysis of BAL Fluid

The cytological and microbiological analysis of BAL fluid is shown in **table 5**. Moreover, lung biopsy was performed in 7 patients with refractory respiratory symptoms. In 5 CVID patients, one case had granuloma, 3 cases had lymphoid interstitial pneumonitis and 1 case had maltoma. Interstitial lung disease was also seen in lung biopsy of two patients with SCID and HIGM syndrome.

Discussion

Respiratory complications present a significant cause of morbidity and mortality among patients suffering from different forms of PIDs. They can affect primarily either upper airways such as sinusitis and otitis media or lower respiratory tract such as pneumonia, bronchitis, bronchiectasis, and interstitial lung diseases (ILDs) (2). Patients with cellular immunodeficiency with symptoms begin at an early age, and are diagnosed before one year of age. Patients with PADs have more frequent and early respiratory symptoms. The most common respiratory diseases are otitis media, with sinusitis and pneumonia more common in PADs and phagocytic defects. In addition, PFT showed greater impairment in patients with phagocyte defects, but no statistical significance (16).

Recurrent pulmonary infections are the major cause of morbidity and mortality among patients suffering from different forms of PIDs both in children and adults (2). There are a few studies which have evaluated respiratory complications, bronchiectasis, BAL and lung biopsy in different types of PIDs, simultaneously. Recent studies have reported that about 75-84% of CVID patients and 62-82.5% of XLA patients had at least one pneumonia episode before diagnosis and treatment (17-20). In this study, our results showed that 78% of CVID, 67% of HIES, 60% of XLA and all of HIgM patients had a history of pneumonia episodes before the treatment. However, in our previous study 77.6% of CVID and 82% of XLA patients had at least one pneumonia episode before the treatment (1). Moreover, in other studies Grimbacher et al. and Winkelstein et al. reported that 77% of patients with HIES (21) and 81% of patients with HIgM (22) had at least one pneumonia episode before treatment, respectively. It is proposed that the delayed diagnosis and treatment leads to chronic lung diseases in PID patients. However, in this study we found that less delayed diagnosis is associated with increased number of pneumonias. We think this appears to be disease-specific, with SCID and XLA percentages different from CVID and HIES syndrome.

In PADs, the pneumonias are typically caused by *encapsulated bacteria*. In X-linked HIGM, pathogens are similar to the patients with combined immunodeficiencies. The underlying infectious cause of the pneumonias includes encapsulated bacteria, cytomegalovirus, histoplasmosis, and *P. jirovecii*. Fungal pneumonias caused by *Candida, Cryptococcus*, and *Histoplasma* can be also found (23,24). In SCID, respiratory tract is the most common site of infections and the most frequently involved microorgan-

isms are *P. jirovecii*, cytomegalovirus, adenovirus, parainfluenza virus type 3, and respiratory syncytial virus (25). In our study isolated pathogens in PAD patients were *H. Influenza* and *S. Pneumoniae*, while in SCID were *K. Pneumoniae* and *S. Aureus.*

Our results showed that the rate of pneumonia after receiving IVIG reduced to 58.5% in CVID, 43.9% in XLA and 60% in HIgM. This study confirms the efficacy of IVIG to reducing the rate of pneumonia in humoral immunodeficiencies as it demonstrated previously. In a study, Dukes et al. reported that after immunoglobulin therapy in CVID patients, the frequency of pneumonia episodes were reduced from 69% to 22% after immunoglobulin therapy (26). In another study, Aghamohammadi et al. showed that 82% of patients with XLA presented episodes of pneumonia before diagnosis, whereas 38.4% of patients experienced pneumonia after immunoglobulin replacement therapy (14).

Nevertheless, PID patients are prone to progressive lung disease despite optimal immunoglobulin therapy and prophylactic antibiotics (27). In our study, 57.4% of CVID patients, 55% of XLA patients and 33.3% of HIgM patients had abnormal PFT results. These results were consistent with results of Gharagozlou et al. reported decrease of FEVI and FVC to 65% and 55% in primary hypogammaglobulinaemic patients, respectively. They also showed that pathological bronchial findings were observed in 13 (59%) of 22 patients: three patients showed only peribronchial thickening, and the remaining ten patients suffered from both bronchiectasis and peribronchial wall thickening (28).

It should be noted that up to 73% of CVID patients develop chronic structural pulmonary complications, of which bronchiectasis and bronchial wall thickening are most frequently detected (29). In addition, more studies noted the incidence of 7-68% of bronchiectasis and bronchial thickening in CVIDs (30,31). Our results confirmed the higher rate of bronchiectasis in CVID patients in comparison to other types of Primary Antibody Deficiency (PAD) as shown in the mentioned studies (14,30). This may cause more delay in diagnosis, which can result in more episodes of infections including pneumonia. It is demonstrated that the delay of diagnosis in patients with bronchiectasis was significantly higher than in those without bronchiectasis (28).

Therefore, pulmonologist should consider PID diseases in every patient with refractory respiratory problems, because early diagnosis can reduce complications of long lasting infections in these patients.

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