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Respiratory system evaluation of adult primary immunodeficiency patients: a tertiary care center experience

Original Study

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Abstract

Introduction. Primary immunodeficiencies (PIDs) are rare diseases in which chronic pulmonary diseases are common. Chronic pulmonary complications affect the long-term survival of these patients. The aim of this study was to evaluate the accompanying lung diseases and respiratory functions in adult PID patients in the Turkish population.
Materials and Methods. Patients' files who applied to the immunology clinic between 2015 and 2020 were evaluated retrospectively. The respiratory system was evaluated by physical examination, and if necessary, computed tomography, chest radiography, and pulmonary function test (PFT) were performed. The diagnosis of PIDs was based on the European Society of Immunodeficiency's (ESID) criteria.
Results. A total of 186 patients were included in the study. The median age of the patients was 38 years. The distribution of the diseases included in the study in order of frequency is: Common Variable Immunodeficiency (CVID) (47.8%), Severe Combined Immunodeficiency (SCID) (22.6%), Selective IgA deficiency (SIgAD) (10.8%), X-Linked Agammaglobulinemia (XLA) (10.2%), Chronic Granulomatous Disease (CGD) (8.6%). The most common findings on chest radiology were bronchiectasis (37.1%), parenchymal nodule (32.8%), ground glass opacity (31.2%), lymphadenopathy (24.7%), fibrotic changes (24.8%), reticular opacities (23.7%) and bronchial wall thickening (23.1%). PFT's results were lower in patients with CGD. Bronchiectasis (37.1%), asthma (22%), and tuberculosis (9.7%) were the most common lung complications.
Conclusion. We think that the frequency of other lung complications, especially asthma and bronchiectasis, is higher in adult patients with PIDs, and patient management is poor as there are no guidelines for the follow-up, diagnosis, and treatment of pulmonary complications.

Keywords

radiology • severe combined immunodeficiency • pulmonary disease • immunology • common variable immunodeficiencies

1. Introduction

PIDs are a rare group of inborn errors of the immune system predisposing to infections, inflammation, autoimmunity, allergies, lymphoproliferation, and malignancy. To date, more than 500 different genetic defects have been determined, affecting the immune system components [1].

According to the ESID data, 8% of patients with PIDs are aged >65 years [2]. Of the PID groups, humoral immunodeficiency is the most common in the adult population[3]. Although PIDs are more common in children than adults, 69.4% of newly diagnosed patients are aged >15 years and more than 50% > 25 years [3].

Chronic pulmonary diseases are common in PIDs, and chronic pulmonary complications affect the survival of patients with PID. The decrease in the incidence of pulmonary complications parallels survival. According to the frequency of pulmonary complications, infections, interstitial lung diseases, and malignancies can be listed.

The aim of this study was to evaluate the accompanying lung diseases and respiratory functions in patients with PID in the Turkish population.

2. Materials and methods

An evaluation was made of 186 PID patients followed up in the immunology outpatient clinic between 2015 and 2020 retrospectively. The pulmonary findings of the patients were evaluated with computed tomography (CT), X-ray and pulmonary function test (PFT). The chest X-ray and CT reports were reported by the same radiology specialists in the hospital. The spirometric measurements were evaluated according to references based on age, height, gender, and race. The diagnoses of CVID, CGD, SCID, SIgAD, and XLA were based on the criteria of the ESID.

2.1. Statistical analysis

The data were analyzed using SPSS 20 software (IBM). The conformity of numerical data to normal distribution was analyzed using the Kolmogorov-Smirnov test. If the p-value was >0.05 in the Kolmogorov-Smirnov test, the numerical data were considered to be normally distributed. Numerical data were reported as mean ± standard deviation or median (minimum-maximum). Categorical data were stated as number (n) and percentage (%). Pearson Chi-square test and Fisher's Exact test were used for relationships

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between categorical variables. Fisher's Exact test was used instead of the Pearson Chi-square test to compare patient groups with small numbers of subjects. One-way ANOVA analysis was used to compare groups with two or more numerical data (FEV1, FVC, FEV1/FVC, and smoking) that were found to be normally distributed in the Kolmogorov-Smirnov test ($p>0.05$). The Levene test was used to evaluate the homogeneity of variances, and the Tukey test was used for pairwise post-hoc tests. For FEV1, FVC, and FEV1/FVC values detected as $p>0.05$ in the Levene test, the variances were considered to be homogeneously distributed, and the post hoc Tukey test was performed. A value of $p<0.05$ was accepted as significant.

3. Results

A total of 186 patients were included; the median age of the patients was 38 (19-70) years. The distribution of the diseases included in the study in order of frequency is: CVID (n=89, 47.8%), SCID (n=42, 22.6%), SIgAD (n=20, 10.8%), XLA (n=19, 10.2%), CGD (n=16, 8.6%). The most common comorbid condition is autoimmune diseases (n=39, 21%). Intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg) treatment was being administered to 121 (65.1%) patients. The demographic and clinical characteristics of the patients are shown in Table 1.

The accompanying lung diseases and PFT of the patients were evaluated. The most common accompanying lung diseases were bronchiectasis (n=69; 37.1%), asthma (n=41; 22%), and tuberculosis history (n=18; 9.7%). The FEV1 (Forced expiratory volume in 1 second) (%) and FVC (Forced vital capacity) (%) were lower in patients with CGD (p=0.002 and p=0.002) (Statistically significant p values in pairwise comparisons, for FEV1(%): p=0.04 for CGD-CVID, p=0.004 for CGD-SIgAD, p=0.013 for CGD-XLA; for FVC(%): p=0.001 for CGD-CVID, p=0.005 for CGD-SIgAD, p=0.009 for CGD-XLA). A significantly higher rate of CGD patients had a history of tuberculosis (p=0.000). Granulomatous-lymphocytic interstitial lung disease (GLILD) was present in significantly more patients with CVID (p=0.005). The accompanying lung diseases and pulmonary function test results of the patients are shown in Table 2 and Table 3.

In the whole patient group, the most common findings in chest radiology were bronchiectasis (n=69; 37.1%), parenchymal nodule (n=61; 32.8%), ground glass opacity (n=58; 31.2%), lymphadenopathy (n=46; 24.7%), fibrotic changes (n=45; 24.8%), reticular opacities (n=44; 23.7%) and thickening of the bronchial wall (n=43; 23.1%). Bronchiectasis was the most common radiological finding in CVID, SigAD, and XLA. Consolidation, ground glass opacity, and parenchymal nodules were the most common radiological findings in CGD. The parenchymal nodule was the most common radiological finding in SCID. Consolidation (p=0.001), lymphadenopathy (p=0.017), pleural thickening (p=0.018), parenchymal nodule (p=0.033), emphysema (p=0.000), cavitation or air cyst (p=0.001), reticular opacities (p=0.033), mosaic perfusion or air trapping (p=0.002), and fibrotic changes (p=0.012) in CGD patients were detected higher than other diseases. Tracheal deviation was higher in XLA (p=0.003), and pulmonary artery enlargement was higher in SCID (p=0.032). The radiological findings of the patients are shown in Table 4.

4. Discussion

The results of the study, in which the respiratory system of adult PID patients was evaluated, showed that respiratory functions in CGD patients were significantly lower than in other adult PID patients. In the current study, radiologically, bronchiectasis was detected in 69 of 186 adult PID patients (37.1%), and bronchiectasis was the most common accompanying lung disease. In studies conducted on PID patients, it was observed that the most frequently detected radiological finding on CT, especially in CVID patients, was bronchiectasis. The rate of bronchiectasis in PID patients varies between 33-42.1% [4].

CGD is a PID caused by defects in the nicotinamide adenine dinucleotide phosphate oxidase complex, which is responsible for the respiratory burst in phagocytic leukocytes [5]. Life-threatening fungal and bacterial infections are frequently observed in CGD, and the involvement of the lungs is common. The results of this study, in which the respiratory system of adult PID patients was evaluated, showed that FEV1 and FVC in CGD patients were significantly lower than in other adult PID patients. The reason for this may be that the frequency of lung infections is higher than other diseases. History of tuberculosis was also significantly higher than other PID patients. Thoracic imaging findings on CGD are nonspecific and may include bronchiectasis, emphysema, consolidation, nodules, tree-in-bud or ground-glass opacities, abscess formation, mediastinal lymphadenopathy, and pleural thickening [6]. In this study, the common radiological findings of the patients with CGD were bronchiectasis, consolidation, ground glass opacities, mediastinal lymphadenopathies, parenchymal nodules, reticular opacities, and fibrotic changes.

CVID is a rare group of diseases characterized by low serum Ig levels and recurrent pulmonary infections [7]. Lower zone predominant bronchiectasis is frequently observed in lung radiology in CVID [8]. In studies, pulmonary complications were determined to have taken place in 65-73% of the patients, most commonly bronchiectasis and bronchial wall thickening reported [9]. In the current study, the most common radiological findings in patients with CVID were bronchiectasis (n=30; 33.7%) and parenchymal nodule (n=26; 29.2%). The findings also showed GLILD in 7.9% of the patients with CVID. In the literature, the incidence of GLILD in patients with CVID varies between 5-15%.

XLA, also known as Bruton's agammaglobulinemia, is a disease characterized by a decrease in Ig levels resulting from a defect in B lymphocyte development [10]. In XLA, recurrent lung infections begin early in life and can lead to bronchiectasis. In

Table 1. Demographic and clinical characteristics of the patients

	CVID(N=89)	CGD(N=16)	SCID(N=42)	SIgAD(N=20)	XLA(N=19)	Total(N=186)
Age (years)	53 (28-70)	24.81±11.11	49 (28-70)	26.45± 8.76	25.53 ± 6.69	38 (19-70)
Age at diagnosis (years)	44 (14-62)	11.12 ± 13.63	14.26 ± 15.09	22.40 ±8.36	5.42 ± 3.39	30 (1-70)
Gender(male) N(%)	45 (50.6)	10 (62.5)	29 (69)	11 (55)	19 (100)	114 (61.3)
Smoking (yes) N(%)	9 (10.1)	1 (6.3)	4 (9.5)	6 (30)	4 (21.1)	24 (12.9)
Smoking (pack/year)	17.89 ± 11.62	35	15.25 ± 20.12	6.33 ± 3.77	3.50 ± 1.29	12.88 ± 12.71
Comorbid diseases						
Chronic kidney disease N(%)	-	-	3 (7.1)	-	-	3 (1.6)
Autoimmune disease N(%)	24 (27)	1 (6.3)	8 (19)	3 (15)	3 (15.8)	39 (21)
Hematological diseases N(%)	6 (6.7)	-	7 (16.7)	-	-	13 (7)
Neurological diseases N(%)	2 (2.2)	-	3 (7.1)	-	1 (5.3)	6 (3.2)
Gastrointestinal system diseases N(%)	7 (7.9)	-	7 (16.7)	1 (5)	2 (10.5)	17 (9.1)
Thyroid diseases N(%)	1 (1.1)	-	4 (9.5)	-	-	5 (2.7)
Malignancy N(%)	7 (7.9)	1 (6.3)	8 (19)	-	-	16 (8.6)
Allergy (drug, food, bee, pollen etc.) N(%)	8 (9)	5 (31.3)	-	-	3 (15.8)	16 (8.6)
Treatment of immunodeficiency						
IVIg or SCIg N(%)	76 (85.4)	1 (6.3)	25 (59.5)	-	19 (100)	121 (65.1)
Prophylactic antibiotic N(%)	23 (25.8)	16 (100)	16 (38.1)	4 (20)	4 (21.1)	63 (33.9)
Prophylactic antifungal N (%)	1 (1.1)	16 (100)	4 (9.5)	-	-	21 (11.3)
Prophylactic antiviral N(%)	-	-	4 (9.5)	-	-	4 (2.2)
Systemic steroid N(%)	5 (5.6)	-	4 (9.5)	-	1 (5.3)	10 (5.4)
Immuno-suppressive therapy N(%)	8 (9)	4 (25)	9 (21.4)	-	1 (5.3)	22 (11.8)
GM-CSF N(%)	-	-	5 (11.9)	-	-	5 (2.7)
SCT N(%)	1 (1.1)	2 (12.5)	10 (23.8)	-	-	13 (7)

(CVID: Common variable immunodeficiency, CGD: Chronic granulomatous disease, SCID: Severe combined immunodeficiency, SIgAD: Selective IgA deficiency, XLA: X-linked agammaglobulinemia, IVIg or SCIg: intravenous immunoglobulin or subcutaneous immunoglobulin, GM-CSF: Granulocyte-macrophage colony-stimulating factor, SCT: Stem Cell Transplant)

Table 2. Lung function test results of the patients

	CVID (N=89)	CGD (N=16)	SCID (N=42)	SIgAD (N=20)	XLA (N=19)	Total (N=186)	P
FEV1(%)	78.45 ± 23.15	48.12 ± 21.18	68.37 ± 17.45	86.33 ± 14.32	81.50 ± 25.89	74.76 ± 23.23	0.002*
FVC(%)	84.20 ± 18.94	56.88 ± 17.91	76.32 ± 15.69	87.89 ± 13.04	85.70 ± 20.71	80.64 ± 19.40	0.002*
FEV1/FVC (%)	78.55 ± 15.26	71.88 ± 16.47	72.32 ± 11.41	81.89 ± 8.11	77.80 ± 13.66	76.89 ± 13.99	0.305
Smoking (pack/year)	17.89 ± 11.62	35	15.25 ± 20.12	6.33 ± 3.77	3.50 ± 1.29	12.88 ± 12.71	0.062

FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capacity.
**p<0.05*

Table 3. Accompanying lung diseases of the patients

Comorbid lung disease	CVID (N=89)	CGD (N=16)	SCID (N=42)	SIgAD (N=20)	XLA (N=19)	Total (N=186)	P
Asthma N(%)	24 (27)	1 (6.3)	7 (16.7)	5 (25)	4 (21.1)	41 (22)	0.355
COPD N(%)	1 (1.1)	2 (12.5)	3 (7.1)	-	-	6 (3.2)	0.06
Bronchiectasis N(%)	30 (33.7)	8 (50)	16 (38.1)	5 (25)	10 (52.6)	69 (37.1)	0.307
Tuberculosis history N (%)	5 (5.6)	7 (43.8)	6 (14.3)	-	-	18 (9.7)	0.000*
Respiratory failure#N(%)	1 (1.1)	-	1 (2.4)	-	-	2 (1.1)	0.866
PTE N(%)	-	1 (6.3)	-	-	-	1 (0.5)	1.000
Lung cancer N(%)	1 (1.1)	1 (6.3)	-	-	-	2 (1.1)	0.297
GLILD N(%)	7 (7.9)	-	-	-	-	7 (3.8)	0.005*
BOOP N(%)	4 (4.5)	-	1 (2.4)	-	-	5 (2.7)	0.619

CVID: Common variable immunodeficiency, SCID: Severe combined immunodeficiency, CGD: Chronic granulomatous disease, XLA: X-linked agammaglobulinemia, SIgAD: Selective IgA deficiency, COPD: Chronic obstructive pulmonary disease, PTE: Pulmonary thromboembolism, GLILD: Granulomatous-Lymphocytic interstitial lung disease, BOOP: Bronchiolitis obliterans organizing pneumonia
*# Respiratory failure requiring oxygen therapy, PaO2<60 mmHg, * p<0.005*

Table 4. Radiological findings of the patients

Thoracic radiological findings N(%)	CVID (N=89)	CGD (N=16)	SCID (N=42)	SIgAD (N=20)	XLA (N=19)	Total (N=186)	P
Atelectasis	16 (18)	6 (37.5)	11 (26.2)	1 (5)	5 (26.3)	39 (21)	0.125
Bronchiectasis	30 (33.7)	8 (50)	16 (38.1)	5 (25)	10 (52.6)	69 (37.1)	0.307
Consolidation	12 (13.5)	9 (56.3)	11 (26.2)	1 (5)	5 (26.3)	38 (20.4)	0.001*
Ground glass opacity	25 (28.1)	9 (56.3)	15 (35.7)	3 (15)	6 (31.6)	58 (31.2)	0.094
Lymphadenopathy (> 1 centimeter)	19 (21.3)	8 (50)	14 (33.3)	1 (5)	4 (21.1)	46 (24.7)	0.017*
Tracheal deviation	3 (3.4)	3 (18.8)	7 (16.7)	-	5 (26.3)	18 (9.7)	0.003*
Pleural thickening	10 (11.2)	6 (37.5)	8 (19)	-	4 (21.1)	28 (15.1)	0.018*
Pleural effusion	9 (10.1)	4 (25)	5 (11.9)	-	2 (10.5)	20 (10.8)	0.207
Thickening of the bronchial wall	21 (23.6)	4 (25)	10 (23.8)	2 (10)	6 (31.6)	43 (23.1)	0.559
Enlargement of the bronchial wall	15 (16.9)	3 (18.8)	9 (21.4)	2 (10)	4 (21.1)	33 (17.7)	0.842
Parenchymal nodule (< 3cm)	26 (29.2)	9 (56.3)	17 (40.5)	2 (10)	7 (36.8)	61 (32.8)	0.033*
Parenchymal mass (> 3 cm)	2 (2.2)	1 (6.3)	3 (7.1)	-	-	6 (3.2)	0.392
Emphysema	1 (1.1)	4 (25)	7 (16.7)	-	-	12 (6.5)	0.000*
Thymic enlargement	1 (1.1)	-	-	-	-	1 (0.5)	0.478
Cavitation or air cyst	7 (7.9)	5 (31.3)	13 (31)	-	4 (21.1)	29 (15.6)	0.001*
Reticular opacities	19 (21.3)	8 (50)	11 (26.1)	1 (5)	5 (26.3)	44 (23.7)	0.033*
Centrolobular opacity	19 (21.3)	6 (37.5)	10 (23.8)	-	3 (15.8)	38 (20.4)	0.072
Fibrotic changes	21 (23.6)	8 (50)	10 (23.8)	-	6 (31.6)	45 (24.8)	0.012*
Pulmonary artery enlargement	3 (3.4)	2 (12.5)	7 (16.7)	-	3 (15.8)	15 (8.1)	0.032*
Mosaic perfusion or air trapping	10 (11.2)	7 (43.8)	10 (23.8)	-	5 (26.3)	32 (17.2)	0.002*

CVID: Common variable immunodeficiency, SCID: Severe combined immunodeficiency, CGD: Chronic granulomatous disease, XLA: X-linked agammaglobulinemia, SIgAD: Selective IgA deficiency
**p<005*

a study investigating lung complications of patients with XLA, bronchiectasis on thin-section CT was detected to be 44.8% [10]. In this study, similar to the literature, the most common radiological finding in XLA patients was bronchiectasis (n=10; 52.6%).

SIgAD is the most common PID characterized by a reduced level of IgA, with normal other Ig levels [11]. Most people with IgA deficiency may be asymptomatic. Pulmonary infections may be common in symptomatic patients. As SIgAD may be associated with bronchiectasis, patients with SIgAD should be followed up for pulmonary involvement. In the current study, the most common lung diseases in patients with SIgAD were seen to be asthma and bronchiectasis. In a study, bronchiectasis was determined to have affected six (2%) of 330 pediatric SIgAD patients, although in the current study, five of 20 patients (25%) had bronchiectasis. This may be due to the fact that the patients in this study were adults, and the number of patients was lower [12].

SCIDs CD4+ and CD8+ are severe inherited diseases characterized by dysfunction of T lymphocytes, and recurrent severe lung infections are frequently observed. On CT of SCID patients, bronchiectasis, mucus plugs, consolidation, and ground glass opacities due to recurrent pneumonia, air trapping, interstitial thickenings, and mediastinal lendaphenopathies can be observed [13]. In the current study, parenchymal nodules, mediastinal lymphadenopathy, bronchiectasis, and ground glass opacity were common radiological findings in SCID patients.

5. Limitations of the study

There were some limitations in the current study, primarily the retrospective design and that the number of patients in the PID groups was not similar. The number of subjects was small in some pairwise comparisons, which is another limitation of the study. Despite these limitations, this can be considered a unique study evaluating lung findings together with radiology and PFT in adult PID patients.

6. Conclusions

In conclusion, pulmonary findings are common in adult PID patients, and functional loss may be observed in the lungs. Bronchiectasis and asthma are common in adult PID patients and pulmonary findings may vary according to the diseases.

Authors' contribution

Saltuk Buğra Kaya: Writing– review & editing, Writing-original draft, Methodology, Formal analysis, Data curation. Mehmet Erdem Çakmak: Writing– review & editing, Writing– original draft, Methodology, Formal analysis, Data curation, Conceptualization. Özge Can Bostan: Writing– review & editing, Data curation. Ebru Damadoğlu: Writing– review & editing, Writing–original draft, Methodology, Conceptualization. Gül Karakaya: Writing– review & editing, Data curation. Ali Fuat Kalyoncu: Writing– review & editing, Data curation. Saliha Esenboğa: Writing– review & editing, Data curation. Deniz Çağdaş Ayvaz: Writing– review & editing, Data curation. İlhan Tezcan: Writing– review & editing, Data curation.

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Conflict of interest

The authors have no conflicts of interest to declare.

Ethics approval

This study was approved by the Hacettepe University Ethics Committee of (Approval no: GO 15/45-12).

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