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Alpha-1 Antitrypsin Levels and Polymorphisms in Interstitial Lung Diseases

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Background/aim: Alpha-1 antitrypsin deficiency may be a potential predisposing factor for interstitial lung fibrosis. We investigated alpha-1 antitrypsin levels and its polymorphisms in patients with interstitial lung disease.

Materials and methods: A total of 103 interstitial lung disease patients were compared.

Results: The mean alpha-1 antitrypsin level in idiopathic interstitial pneumonia patients was 1.67 ± 0.33 g/L, and it was 1.54 ± 0.37 g/L in patients with nonidiopathic interstitial pneumonia (P = 0.13). Low alpha-1 antitrypsin levels were more frequently observed in nonidiopathic interstitial pneumonia patients compared with idiopathic interstitial pneumonia, but the difference was not statistically significant (8.9% vs. 0%, respectively, P = 0.4). In 100 patients, the normal PiMM genotype was detected, while abnormal ones (PiMZ, n = 2, 1.9%; PiMS, n = 1, 0.97%) were determined in three cases. When the frequency of alpha-1 antitrypsin polymorphism in interstitial lung disease patients was compared with the data of the healthy population, no significant difference was detected for the PiMZ and PiMS variants (P = 0.15 and P = 0.44, respectively).

Conclusion: Lower levels of serum alpha-1 antitrypsin were more frequent in nonidiopathic interstitial pneumonia patients than idiopathic interstitial pneumonia without an increase in genetic polymorphism. The difference was not statistically significant.

Key words: Alpha-1 antitrypsin deficiency, idiopathic interstitial pneumonias, interstitial lung disease

1. Introduction

Alpha-1 antitrypsin (α1-AT) deficiency is a hereditary disorder characterized by a severe decrease in plasma levels of α1-AT. The condition is associated with a substantially increased risk for the development of pulmonary emphysema by the third or fourth decade of life and is associated with risk of hepatic disease, cutaneous panniculitis, arterial aneurysm, bronchiectasis, and renal disease development. A tentative association with granulomatosis with polyangiitis is also suggested. A number of other conditions, including rheumatoid arthritis and some forms of cancer, have been reported to occur with increased frequency in patients with α1-AT deficiency (1).

Neutrophil elastase (NE) is the main protease in relation to the development of pulmonary emphysema. In the extracellular space, NE has additional functions such as the regulation of inflammation and it is implicated in inflammatory and fibrotic conditions, including fibrotic lung disease (2,3). The major inhibitor of NE in the lungs is α1-AT, which limits the local degradation of the extracellular matrix by migrating cells (4). α1-AT is a serine protease inhibitor. The gene coding for α1-AT is located on 14q32.13. Over 75 allelic variations have been reported and classified using the protease inhibitor (PI) nomenclature, which assesses antitrypsin mobility using isoelectric focusing analysis. Mutations are inherited by a simple Mendelian trait; the normal genotype is designated as PiMM, a heterozygote for the Z gene as PiMZ, and a homozygote for the Z gene as PiZZ. The variants are those associated with deficiency, namely the S and Z genes and the uncommon "null" (nonproduction gene) (1). PiM expresses the normal level of α1-AT in serum (150–350 mg/dL), whereas PiS and PiZ express lower levels of α1-AT (100–200 mg/dL and 15–50 mg/dL, respectively). It should be kept in mind that serum levels of α1-AT in PiM and PiS subjects may overlap (5).

The S and Z genes are the most important genes, commonly found in Europeans. About 6% of people of North European descent carry the S gene and 3%–4% carry the Z variant (6,7). In the Turkish population, the frequencies of the α1-AT alleles, PiMS, PiMZ, and

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PiMF, are 70, 72, and 48 per 10,000, respectively (8). Therefore, α1-AT deficiency is a rare hereditary disorder in asymptomatic healthy people in our country.

α1-AT deficiency is usually detected initially by measuring the plasma level, followed by specific phenotyping or genotyping.

Elevations in serum elastase have previously been reported in patients with systemic sclerosis (SSc) associated with lung disease (9). It was determined that α1-AT deficiency contributes to the inflammation and fibrosis in SSc. There are limited data about other interstitial lung disease (ILD) groups such as scleroderma and rheumatoid arthritis, however, and no study covering all types of ILDs has been reported yet. Considering the lung parenchyma destruction in ILDs, a protease/antiprotease imbalance may be a contributing factor. On the basis of recent studies, α1-AT deficiency could also be a predisposing factor for interstitial fibrosis. Therefore, we conducted a study to determine α1-AT levels and polymorphisms in ILDs and to evaluate its effect on the clinical and radiological characteristics of such patients with or without α1-AT deficiency and polymorphism.

2. Materials and methods

A prospective study was conducted with 103 ILD patients older than 18 years of age who had been followed between April 2011 and June 2012 at our university hospital. Subjects with COPD or acute/chronic hepatic disease were excluded.

Demographic features, smoking history, environmental and occupational exposure, comorbidities, pulmonary and extrapulmonary symptoms, physical examination and laboratory findings (whole blood count, routine biochemical analysis, C-reactive protein, erythrocyte sedimentation rate), thorax high-resolution computed tomography (HRCT), spirometry, diffusion capacity of carbon monoxide (DLco), arterial blood gas analysis (ABG), and 6-min walk test distance (6MWD) results were recorded. Venous blood samples were obtained during outpatient clinic admissions. α1-AT levels were measured in venous blood samples of patients. Genomic DNA was isolated from peripheral blood samples using a spin column method and stored at –20 °C until further processing. Genotyping for the α1-AT polymorphisms was performed by reverse dot blot method. The quantitative determination of α1-AT in human serum was performed by means of immunonephelometry on the BN* II and BN ProSpec System. The reference range for α1-AT in human serum is 0.9–2.0 g/L.

Patients with α1-AT deficiency and/or polymorphism were evaluated in each disease group and investigated for a probable relationship with other factors such as HRCT or echocardiographic findings.

The local institutional ethics committee approved (2012, BAP-project no: 11B3330007) the study and all patients gave informed consent.

2.1. Statistical analyses

All statistical analyses were performed using SPSS 11.0. Demographic data were evaluated by t-test and chi-square test. Chi-square and Fischer exact tests were used for parametric variables. The Mann–Whitney test was used for nonparametric variables. $P < 0.05$ was considered as significant.

3. Results

Sixty-nine female and 34 male patients (total: 103 patients) with ILDs were enrolled in the study. Mean age was 55.81 ± 13.91 years. Thirty-four subjects had a smoking history (6 active smokers, 28 ex-smokers, mean: 28.79 ± 26.18 pack-years). Twenty-five patients had idiopathic interstitial pneumonia (IIP), and 78 with ILDs due to other causes (connective tissue diseases, sarcoidosis, etc.) were grouped as non-IIP subjects (10). The diagnoses of study subjects can be seen in Table 1. Pulmonary symptoms were present in 81 (78.6%) of the patients. The most common symptoms were dyspnea (n = 56, 54%) and cough (n = 42, 41%) (Table 1). The most common physical examination finding was crackles (n = 59, 57%). Thorax HRCT findings are documented in Table 2. Patients had mild hypoxemia (mean partial O_2 = 70.79 ± 15.89 mmHg), reduced DL_{CO} (mean DL_{CO} (%) = 71.02 ± 28.03), and reduced 6MWD results (mean 6MWD = 425.69 ± 141.16 m).

α1-AT levels of all subjects ranged between 0.72 and 2.98 g/L. IIP subjects and non-IIP subjects did not differ in respect to mean serum α1-AT levels (1.67 ± 0.33 g/L vs. 1.54 ± 0.37 g/L, respectively, P = 0.13). Seven subjects (6.8%) had serum α1-AT levels lower than the normal reference range (0.9-2.0 g/L). The subjects with low serum α1-AT levels were in the non-IIP group (8.9%) and none of the IIP patients had α1-AT deficiency (0%) (P = 0.4). The diagnoses of the patients with α1-AT deficiency were systemic sclerosis (n = 3, 2.9%), rheumatoid arthritis (n = 1, 0.9%), sarcoidosis (n = 2, 1.9%), and granulomatosis with polyangiitis (n = 1, 0.9%) (Table 3).

Genetic analysis of 100 subjects showed the normal PiMM variant. Three subjects (2.9%) had the α1-AT heterozygote polymorphism. Two of them (1.9%) with the MZ variant polymorphism had low α1-AT levels while one with the MS variant had a normal α1-AT level (0.97%) (Case 1 in Tables 4 and 5). A positive correlation was observed between α1-AT deficiency and polymorphism (P = 0.01). The clinical diagnoses of the patients with α1-AT polymorphism were systemic sclerosis in two cases (1.9%, PiMZ and PiMS) and sarcoidosis in one (0.9%, PiMZ). The IIP subjects and non-IIP subjects did not differ significantly in respect to the prevalence of α1-AT polymorphisms (P = 0.6) (Tables 3–5).

Table 1. The characteristics of the study group.

	n (%)	Mean
Female/male	69/34 (66.9/3.0)	
Mean age, years		55.81 ± 13.91
Smoking history	34 (33)	28.79 ± 26.18 (pack-years)
History of environmental and occupational exposure (biomass, asbestos, inorganic dust, metal)	20 (19.4)	
Comorbidities	59 (57.2)	
Diagnosis		
IIP*	25 (24.3)	
IPF	14 (13.6)	
NSIP	6 (5.8)	
COP	3 (2.9)	
LIP	1 (1.0)	
RB-ILD	1 (1.0)	
Non-IIP	78 (75.7)	
Connective tissue diseases	54 (52.4)	
♦ Systemic sclerosis	31 (30.1)	
♦ Rheumatoid arthritis	16 (15.5)	
♦ Sjögren's syndrome	3 (2.9)	
♦ Mixed connective tissue disease	2 (1.9)	
♦ Polymyositis/dermatomyositis	1 (1.0)	
Sarcoidosis	15 (14.6)	
Histiocytosis X	3 (2.9)	
Vasculitis	2 (1.9)	
Hypersensitivity pneumonitis	2 (1.9)	
Granulomatosis with polyangiitis	2 (1.9)	
Pulmonary symptoms		
Dyspnea	56 (54.4)	
Cough	42 (40.8)	
Sputum	18 (17.5)	
Chest pain	12 (11.7)	
Mortality	2 (1.9)	

*Idiopathic interstitial pneumonia (IIP) groups: IPF: idiopathic pulmonary fibrosis; NSIP: nonspecific interstitial pneumonia; COP: cryptogenic organizing pneumonia; LIP: lymphoid interstitial pneumonia; RB-ILD: respiratory bronchiolitis-associated interstitial lung disease (n = 25, 24%).

Table 2. Thorax high-resolution computed tomography (HRCT) findings of the patients with interstitial lung disease.

	n (%)
Thorax HRCT findings	
Ground glass opacity	58 (56.3)
Fibrotic changes	44 (42.7)
Pulmonary nodules	43 (41.7)
Interseptal thickening	41 (39.8)
Mediastinal lymphadenopathy	40 (38.8)
Honeycomb pattern	37 (35.9)
Traction bronchiectasis	37 (35.9)
Reticular changes	31 (30.1)
Hilar lymphadenopathy	21 (20.4)
Linear atelectasis	16 (15.5)
Peribronchial thickening	16 (15.5)
Bullae-cyst	14 (13.6)
Pleural fluid-thickening	14(13.6)
Subpleural nodules	12 (11.7)
Hyperinflation	12 (11.7)
Mosaic perfusion	11 (10.7)
Intrapulmonary lymph node	8 (7.8)
Consolidation	7 (6.8)
Centrilobular nodules	4 (3.9)
Tree-in-bud	2 (1.9)

In this study, the homozygote polymorphism for α1-AT was not detected in any subject. When compared with the data of the healthy population (n = 8), the frequency of α1-AT polymorphism in study subjects did not differ significantly for the PiMZ and PiMS variants (P = 0.15 for PiMZ and P = 0.44 for PiMS) (Table 6).

Smoking history, hypoxemia, reduced diffusion capacity, and the presence of pulmonary hypertension on echocardiography (systolic pulmonary arterial pressure ≥ 40 mmHg) did not correlate with α1-AT deficiency and/or polymorphism in this study (P > 0.05). Patients were followed for 2 years. Mortality was not observed in any study subjects.

4. Discussion

Clinical manifestations of α1-AT deficiency represent two different pathophysiologic processes: protease/antiprotease imbalances as typified by emphysematous lung disease, and the conformational disease typical in the liver.

The potential cellular source of α1-AT production in the lungs includes epithelial cells, macrophages, and possibly neutrophils. In vitro data indicate not only that lung-derived epithelial cells are capable of α1-AT production but also that this local production is increased in response to specific inflammatory mediators (11–13). Studies on the peripheral blood mononuclear cells of healthy volunteers show two- to threefold increased secretion of α1-AT in response to treatment with LPS, IL-1b, and TNF-α (14). These data suggest the important defensive role of locally produced α1-AT in acute lung inflammation. The lung damage and emphysema resulting from α1-AT deficiency has traditionally been attributed to unchecked protease activity (15,16). Free neutrophil elastase not only causes direct tissue destruction but also induces the expression of proinflammatory cytokines and neutrophil chemoattractants. However, α1-AT itself has a potential role in the lung inflammation experienced in α1-AT-deficient individuals. Formation of complexed and polymerized α1-AT in the lungs not only exacerbates existing protease/antiprotease imbalances but also potently induces IL-8 expression and attracts neutrophils as a direct conformational effect of the α1-AT protein (1).

Thus, we suggest that α1-AT deficiency can be a predisposing factor for interstitial fibrosis and inflammation in ILDs. This study is the first report addressing α1-AT deficiency in various ILDs.

Increased heterozygote phenotype deficiency in patients with rheumatoid arthritis, juvenile polyarthritis, vasculitis, cutaneous panniculitis, arterial aneurysm, bronchiectasis, and renal disease has been reported (17). A tentative association with granulomatosis with polyangiitis has also been suggested (1). In the present study, among

Table 3. The frequency of α1-antitrypsin deficiency and polymorphism in patients with idiopathic interstitial pneumonia and nonidiopathic interstitial pneumonia.

Disease groups	Patients with α1-AT deficiency*	Patients with α1-AT polymorphism**	
		MZ	MS
IIP (n = 25)	0	0	0
Non-IIP (n = 78)	7	2	1

*P = 0.4, **P = 0.6.
α1-AT: α1-antitrypsin
IIP: Idiopathic interstitial pneumonia.

Table 4. The patients' characteristics with α1-antitrypsin deficiency and polymorphism, part 1.

Patients	Age/sex	Diagnosis	Smoking history	HRCT findings
Case 1	20/F	Systemic sclerosis	-	Reticular changes, pulmonary nodules
Case 2	48/F	Systemic sclerosis	-	Pulmonary nodules, interseptal thickening
Case 3	43/M	Granulomatosis with polyangiitis	Ex-smoker (20 pack-years)	Ground glass opacity, fibrotic changes, traction bronchiectasis
Case 4	28/F	Systemic sclerosis	-	Ground glass opacity, traction bronchiectasis, pulmonary nodules
Case 5	73/F	Systemic sclerosis	-	Ground glass opacity, traction bronchiectasis, pulmonary nodules, fibrotic/reticular changes, peribronchial thickening, honeycomb pattern
Case 6	58/F	Rheumatoid Arthritis	-	Ground glass opacity, traction bronchiectasis, honeycomb pattern, interseptal thickening, pulmonary nodules
Case 7	57/F	Sarcoidosis	-	Ground glass opacity, mediastinal/hilar lymphadenopathy, linear atelectasis
Case 8	74/F	Sarcoidosis	-	Mediastinal/hilar lymphadenopathy, pulmonary nodules, interseptal thickening

HRCT: High-resolution computed tomography.
F: Female.
M: Male.

Table 5. The patients' characteristics with α1-antitrypsin deficiency and polymorphism, part 2.

Patients	Predicted DL_{CO} (%)	sPAP on echo (mmHg)	6MWD (m)	Min SaO_2 (%) on 6MWD	α1-AT levels	Genotype of α1-AT polymorphism
Case 1	83	25	560	97	1.69*	PiMS
Case 2	90	25	520	96.8	0.69	PiMM
Case 3	61	20	656	98	0.72	PiMM
Case 4	72	30	620	96	0.84	PiMM
Case 5	34	40	160	82	0.80	PiMZ
Case 6	102	30	450	95	0.71	PiMM
Case 7	81	35	456	96	0.84	PiMZ
Case 8	89	30	400	95	0.77	PiMM

*Case 1 had a normal α1-AT level but PiMS polymorphism.
α1-AT: α1-antitrypsin (normal reference range: 0.9–2.0 g/L).
DL_{CO}: Diffusing capacity of the lungs for carbon monoxide.
Echo: Echocardiography.
SaO_2: Oxygen saturation.
sPAP: Systolic pulmonary arterial pressure.
6MWD: Six-minute walk distance.

Table 6. The comparison of the frequency of α1-antitrypsin polymorphism in interstitial lung disease cases with the normal population.

Genotype of α1-AT polymorphism	Healthy population	Study subjects with ILDs	P-value
PiMM	1164	100	
PiMZ	9	2	0.15
PiMS	7	1	0.44
Total	1203	103	

α1-AT: α1-Antitrypsin.
ILD: Interstitial lung disease.

the α1-AT-deficient subjects, one had rheumatoid arthritis and one had granulomatosis with polyangiitis. However, α1-AT polymorphisms were not detected in either of them.

In the widely cited study of Geddes et al. (18), patients with rheumatoid arthritis complicated by fibrosing alveolitis were found to be more likely to have abnormal α1-AT phenotypes than healthy controls. They found a marked increase in the prevalence of the MZ phenotype among patients with cryptogenic fibrosing alveolitis (CFA). Hubbard et al. (19) compared the α1-AT phenotypes of 189 patients with CFA to 189 age-, sex-, and community-matched controls. In their report, CFA was not associated with abnormal α1-AT phenotypes. Consistently, none of the 25 IIP patients in the present study had α1-AT deficiency and/or polymorphism.

Mota et al. evaluated α1-AT deficiency and/or polymorphism in 27 patients with granulomatosis with polyangiitis (20). They could not observe α1-AT deficiency compared with the control group while abnormal α1-AT phenotypes were detected in 5 patients. We detected AT deficiency in 1 patient with granulomatosis with polyangiitis (0.9%). Abnormal α1-AT phenotypes were not observed in any patient with granulomatosis with polyangiitis.

Barnes et al. (9) examined the role of neutrophil elastase in SSc typified by vascular dysfunction, tissue fibrosis, and inflammation. They found that relative deficiency in serum α1-AT levels in SSc could have important and pathogenically relevant effects since elastase has proinflammatory and profibrotic roles. They concluded that elastase inhibitors available in clinical practice could serve as potential therapeutic options in SSc. In this first trial showing an association between α1-AT polymorphism and SSc, 33 SSc subjects were studied and their serum α1-AT levels were found significantly lower than those of the control group. Similarly, we studied 31 SSc cases and detected α1-AT deficiency in 3 and α1-AT polymorphism in 2.

Sarcoidosis has not been related to α1-AT previously. However, we detected α1-AT deficiency in two subjects and α1-AT polymorphism in one with sarcoidosis. To our best knowledge of the literature in English, this is the first report documenting a possible relation of sarcoidosis with α1-AT deficiency and/or polymorphism.

Simsek et al. (8) determined the prevalence of α1-AT deficiency in a healthy Turkish population. They documented 0.7% PiMZ and 0.6% PiMS genotypes. In the present study, although α1-AT polymorphism in ILD patients was more frequent than in the normal population, the difference was not statistically significant. We did not document any homozygote polymorphism in the study subjects, either.

Some subjects with α1-AT polymorphism may have normal serum levels of α1-AT. In other words, serum α1-AT level ranges of various phenotypes of α1-AT may overlap. Zorzetto et al. (21) reported that the majority of individuals showing α1-AT levels within the range of 0.93–0.73 mg/dL had PiMS and PiMZ genotypes. However, in our study, we observed these genotypes in 2 out of 7 patients with low α1-AT levels (0.90–0.72 mg/dL) with a frequency of 43% lower than that reported by Zorzetto et al. This difference may be due to the limited number of cases with α1-AT deficiency in our study group. α1-AT levels in individuals with the PiMZ genotype were also given in the range of 0.90–2.10 mg/dL by the American Thoracic Society and European Respiratory Society document (22). These data can explain the normal α1-AT level found in a patient with the PiMZ genotype in our study.

The relationship between α1-AT deficiency and chronic obstructive lung disease is well studied; however, the relationship of ILDs with parenchymal destruction and α1-AT deficiency has not been investigated. Investigating protease and antiprotease balance can lead to further treatment opportunities because pathogenesis is not clear in ILDs. No research has been reported including all ILDs to date. Once the pathologic mechanism is understood, similarly to COPD patients (23), a feasible α1-AT

replacement could be a life-saving option for patients with ILDs with very limited armamentarium in current practice.

We herein report the first study addressing α1-AT deficiency and polymorphism in a variety of ILDs including IIP and other ILDs. Our findings have shown that low levels of α1-AT are found in collagen vascular disease, mainly SSc-related ILDs, and sarcoidosis, but not in IIP subjects. Large-scale studies are warranted in such patients.

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