α1-Antitrypsin level in patients with spontaneous pneumothorax

Stężenie α1-antytrypsyny u chorych na samoistną odmę opłucnową

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Słowa kluczowe: samoistna odma opłucnowa, antyproteaza, stężenie.

Abstract

Introduction: α1-Antitrypsin deficiency is an under-recognized condition with long diagnostic delays between the first symptoms and diagnosis, and there is evidence that patients with suggestive symptoms may see many physicians before an exact diagnosis is made. An increased incidence of serum α1-antitrypsin deficiency has been reported in patients with spontaneous pneumothorax.
Aim of the research: To evaluate α1-antitrypsin level in subjects with spontaneous pneumothorax.
Material and methods: Thirty-nine patients with the diagnosis of spontaneous pneumothorax and 100 age- and sex-matched control subjects were included in the study. α1-antitrypsin concentrations were determined by nephelometry. Serum qualitative Z antitrypsin variant was analyzed using commercial ELISA kits and α1-antitrypsin phenotyping was carried out by means of isoelectric focusing.
Results: Spontaneous pneumothorax occurred in 29 patients for the first time; 10 patients had recurrent pneumothorax. There were no significant differences in age and lung function comparing the patients with and without α1-antitrypsin deficiency. α1-Antitrypsin level was significantly higher in patients with spontaneous pneumothorax (1.53 ±0.23 g/l) than controls (1.34 ±0.31 g/l) ($p = 0.03$).
Conclusions: Elevated serum α1-antitrypsin level in patients with pneumothorax may show the need to inhibit the activity of proteases that are important for lung damage.

Streszczenie

Wstęp: Niedobór α1-antytrypsyny jest często niedostatecznie rozpoznawany. Okres między pojawieniem się pierwszych symptomów a diagnozą jest wydłużony. Są dowody, że chorzy z jednoznacznymi objawami odwiedzają wielu lekarzy, zanim zostanie postawiona właściwa diagnoza. U chorych na samoistną odmę opłucnową zauważa się częstsze występowanie niedoboru α1-antytrypsyny w surowicy.
Cel: Ocena stężenia α1-antytrypsyny u chorych na samoistną odmę opłucnową.
Materiał i metody: Badaniem objęto 39 pacjentów, u których zdiagnozowano samoistną odmę opłucnową, a grupa kontrolna obejmowała 100 osób dobranych pod względem wieku i płci. Stężenie α1-antytrypsyny określono metodą nefelometrii. Analizę wartościową wariantu genu Z dla antytrypsyny wykonano przy użyciu testów ELISA, a fenotypowanie α1-antytrypsyny przeprowadzono metodą ogniskowania izoelektrycznego.
Wyniki: U 29 chorych samoistna odma opłucnowa wystąpiła po raz pierwszy, natomiast 10 chorych miało nawracającą odmę opłucnową. Nie zaobserwowano istotnych różnic pod względem wieku i funkcji płuc pomiędzy pacjentami z niedoborem α1-antytrypsyny a tymi, u których taki niedobór nie występował. Stężenie α1-antytrypsyny było znacznie wyższe u chorych na samoistną odmę opłucnową (1,53 ±0,23 g/l) niż w grupie kontrolnej (1,34 ±0,31 g/l) ($p = 0,03$).
Wnioski: Zwiększone stężenie α1-antytrypsyny we krwi u chorych na odmę opłucnową może wskazywać na konieczność hamowania działania proteaz, które są istotne dla uszkodzeń płuc.

Introduction

α1-Antitrypsin (AAT) deficiency is a genetic disorder that predisposes individuals to the development of liver and lung disease [1, 2].

The AAT protein is encoded by the protease inhibitor (PI) locus located on chromosome 14q32.1 and inherited in an autosomal recessive way [3, 4]. The primary AAT function is to inhibit neutrophil elastase. In severe deficiency, anti-elastase protection in the lung interstitium and alveolar space is markedly decreased to about 15–20% of normal levels, similar to the decrease in plasma levels. The PI locus is high-

ly polymorphic, and approximately 100 variants have been identified [1, 3]. Normal serum levels (1–2.5 g/l) of AAT are associated with the M allele [3]. Most of the AAT deficiency-related pathologies are linked to the Z allele, and in clinical practice, 96% of patients with AAT deficiency have a ZZ genotype. The remaining 4% carry mostly SZ, MZ, and other rare genotypes associated with this deficiency [4].

Aim of the research

The aim of this study was to analyse and compare the rates of AAT deficiency in patients with spontaneous pneumothorax and healthy controls. Thus early identification of this genetic disorder allows preventive measures to be taken, the most important of which is the avoidance of smoking (including the inhalation of second-hand smoke) and exposure to environmental pollutants. Early detection also allows careful lung function monitoring and augmentation therapy and specific counselling for these patients' family members [1, 3].

Material and methods

Subjects

The patients with spontaneous pneumothorax for this retrospective study were recruited from the Hospital of Lithuanian University of Health Sciences. For 29 patients spontaneous pneumothorax was diagnosed for the first time, while for 10 patients it was recurrent. The control group was formed from healthy persons who underwent a prophylactic health check-up. Smoking history was calculated in pack-years as the product of tobacco use (in years) and the average number of cigarettes smoked per day/20 (years × cigarettes per day/20). The study design was approved by the Regional Ethics Committee, and all the studied subjects gave their informed consent.

Sample collection and evaluation

Blood samples were drawn in serum tubes, clotted at room temperature (~22°C) for 30–60 min, and centrifuged for 15 min at 4000 rpm. Serum samples were immediately frozen at –70°C for further analysis. Serum concentrations of AAT were determined by nephelometry (Dade Behring Marburg GmbH, Germany) according to the manufacturer's instructions. The presence of the Z allele was checked by enzyme-linked immunosorbent assay (ELISA) kits (Euro-Diagnostica/Wieslab, Sweden), qualitative method according to prepared standard guidelines for the product. AAT phenotyping was carried out by isoelectric focusing (LKB Multiphor II and LKB Macrodrive 5 Constant Power Supply, Amarcham Pharmacia Biotech, Piscataway, NJ, USA) as described previously [5].

Statistical analysis

Statistical analysis was performed using the SPSS 14.0 program. Quantitative variables were expressed as means with standard deviations (SD). The differences among means were analyzed for their statistical significance with the Kruskal-Wallis test. A p value of less than 0.05 was considered significant.

Results

The demographic data of the studied patients are shown in the Table 1. Spontaneous pneumothorax occurred in 29 patients for the first time; 10 patients had recurrent pneumothorax. Three patients (7.7%) with spontaneous pneumothorax had AAT deficiency: 2 severe (ZZ and SZ phenotypes) and 1 moderate (MZ phenotype). The patient with AAT deficiency in the control group had moderate AAT deficiency (MZ). There were no significant differences in age or lung function comparing the patients with and without AAT deficiency. These data could be explained by the relatively young age of the patients with AAT

Table 1. Main characteristics of studied individuals

Variable	Spontaneous pneumothorax (n = 39)	Controls (n = 100)	Value of p
Age [years]	33.2 ±3.2	35.5 ±4.5	> 0.05
Male/female, n (%)	25(64)/14(36)	59 (59)/41(41)	> 0.05
FVC (% predicted normal)	90 ±10	102 ±12	> 0.05
FEV1 (% predicted normal)	88 ±18	95 ±10	> 0.05
Smoking status, n (%):			
Smokers	14 (36)	25 (25)	
Ex-smokers	2 (5)	8 (8)	
Never smokers	23 (59)	67 (67)	> 0.05
AAT deficiency genotype, n (%)	3 (7.7)	1 (1)	> 0.05

Data are presented as mean ± SD unless otherwise stated

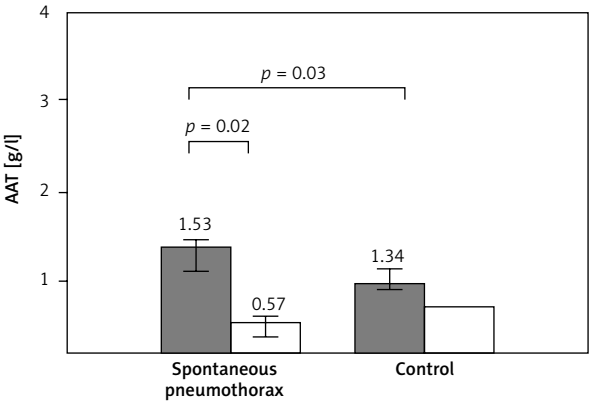

Figure 1. Serum AAT concentration in subjects without AAT deficiency (filled bar) and with AAT deficiency (not filled bar)

deficiency to develop lung obstruction. The patients with ZZ and SZ genotypes had recurrent pneumothorax (second). Computed tomography of the chest in the patients with the SZ and ZZ phenotypes showed bullous emphysema despite their young age (34 and 37 years, respectively) and good lung function.

The mean serum AAT level in the subjects without AAT deficiency was significantly higher in the patients with spontaneous pneumothorax than the controls (1.53 ±0.23 g/l vs. 1.34 ±0.31 g/l, $p = 0.03$) (Figure 1). As expected, a significant difference in the serum AAT concentration between AAT-deficient and AAT-non-deficient patients with spontaneous pneumothorax was found ($p = 0.02$) (Figure 1).

Discussion

An important finding of our study is that 7.7% of patients with spontaneous pneumothorax had AAT deficiency phenotypes including severe deficiency-related ZZ and SZ phenotypes. Based on the results of this study, we have made a presumption that AAT deficiency could result in a higher risk of the development of spontaneous pneumothorax. Because of a low incidence rate of the ZZ phenotype [4, 6] in the general population, we presume that there is a slight chance for such disorders to manifest concurrently in the same patients. To date, only a few case reports of spontaneous pneumothorax with AAT deficiency have been reported [7–9]. Daniel and Teba reported spontaneous pneumothorax to be observed in a patient with an abnormally low level of AAT [7]. However, some studies involving patients with simple spontaneous pneumothorax failed to prove AAT deficiency to be present in these patients [10, 11]. These differences in the results could be explained by a varying frequency of the Z allele in the general population.

Previous studies performed by others in the general population of Lithuania [12] reported from moderate to high prevalence of Z alleles when compared to other Northern Europe countries. The prevalence of the Z deficiency allele in Latvia, followed by southern Norway, Denmark, southern of Sweden, Estonia and Lithuania, is exceptionally higher than in most other countries worldwide [3, 12, 13]. In COPD patients case control studies demonstrated an even higher increase in the prevalence of AAT deficiency allele Z, compared with the healthy control group, with an OR for the MZ phenotype between 1.5 and 5 [13–15]. The case-detection program of 2,137 COPD patients in Spain revealed 7 cases of ZZ deficiency (0.37%) [13]. In another program undertaken in Italy, the detection rate for ZZ was 6.4% [12]. This is probably related to the sample composition consisting of several individuals with different types of chronic respiratory diseases.

To date, the mechanisms of spontaneous pneumothorax have not been elucidated; therefore, protease-antiprotease imbalance could be a possible part of disease pathogenesis. In our study, 3 patients with spontaneous pneumothorax had AAT deficiency: the serum AAT level in the patients carrying the ZZ, SZ, or MZ allele was 0.33 g/l, 0.55 g/l, and 0.83 g/l, respectively. The AAT deficiency phenotypes in patients with spontaneous pneumothorax could indicate a lack of antiprotease activity. However, we found that the AAT level was significantly higher in the patients with spontaneous pneumothorax without AAT deficiency than in the controls and was even similar to the level in COPD patients reported in other studies [16]. One study of 32 patients with spontaneous pneumothorax presented similar results [11]. The authors showed that the AAT level in the patients with spontaneous pneumothorax was higher than in the healthy controls [11]. The net impact of AAT on the lungs seems to be the result of context-dependent (i.e., AAT phenotype) and contrasting protective and inflammatory effects in the respiratory system [1, 3]. On the one hand, elevated serum AAT levels can reflect a beneficial shift in the protease-antiprotease balance, the cornerstone of the pathophysiological pathway mediating the effect of severe AAT deficiency on lung tissue [3]. On the other hand, elevated serum AAT can also reflect low-grade inflammatory processes in the lungs [2], which are considered a risk factor for alveoli damage. Our study had some limitations: the level of systemic inflammatory markers was not measured, and this could have an impact on our results. Nevertheless, an important message of our study is that a higher AAT level determined in the patients with spontaneous pneumothorax could point to the significance of protease-antiprotease imbalance in the pathogenesis of pneumothorax. The elevated AAT level in the patients with pneumothorax may show the need to inhibit the activity of proteases that are important for lung damage.

The prevalence of AAT deficiency in Lithuania has not been reported, but it could be estimated to be sim-

ilar to that in other European developed countries, i.e., 1 : 3000–5000 [6, 16]. This might signify that more than 900 ZZ subjects remain undiagnosed. For some patients the first manifestation of AAT deficiency may be spontaneous pneumothorax [17]. Therefore, an early diagnosis of this genetic condition could prevent or at least slow down the development of AAT deficiency-related complications including the development of COPD. Despite a small number of the patients with AAT deficiency, the results of the present study could support the general concept of targeted screening for AAT deficiency in patients with spontaneous pneumothorax.

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