Alpha-1 antitrypsin deficiency and spontaneous pneumothorax: possible causal relationship

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Abstract

Background. *An increased incidence of serum alpha-1 antitrypsin deficiency has been reported in patients with chronic obstructive pulmonary disease, but has not been well proven in association with spontaneous pneumothorax. The aim of our study was to evaluate frequency of alpha-1 antitrypsin deficiency in subjects with spontaneous pneumothorax.*
Methods. *39 patients with the diagnosis of spontaneous pneumothorax and 100 age- and sex-matched control subjects were included in the study. Alpha-1 antitrypsin concentrations were determined by nephelometry, Serum qualitative Z antitrypsin variant was analyzed using commercial ELISA kits and alpha-1 antitrypsin phenotyping was carried out by means of isoelectric focusing.*
Results. *AAT deficiency phenotypes were detected in 3 (7.7%) patients with spontaneous pneumothorax, and only in 1 (1%) case in the control group. However, the observed differences did not reach statistical significance due to the considerable size disproportion between groups. The mean serum alpha-1 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. *Preliminary data confirm the clinical importance of alpha-1 antitrypsin deficiency phenotypes in patients with spontaneous pneumothorax and the need to screen them for alpha1-antitrypsin deficiency.*
Keywords: *spontaneous pneumothorax, alpha-1 antitrypsin, deficiency*

Rezumat

Deficitul de alfa-1 antitripsină și pneumotoraxul spontan: posibilă relație cauzală
Context general. *A fost raportată o incidență crescută a deficitului seric al alfa-1 antitripsinei la pacienții cu boală pulmonară obstructivă cronică, dar nu s-a dovedit asocierea acestei condiții cu pneumotoraxul spontan. Scopul acestui studiu a fost de a evalua frecvența deficitului de alfa-1 antitripsină la subiecții cu pneumotorax spontan.*
Metode. *Au fost incluși în studiu 39 de pacienți cu diagnosticul de pneumotorax spontan și 100 de subiecți de control, similari ca repartiție pe grupe de vârstă și sex. Concentrația de alfa-1 antitripsină a fost determinată prin nefelometrie. Varianta Z serică a antitripsinei a fost analizată cu teste comerciale ELISA iar fenotiparea s-a realizat prin focalizare izoelectrică.*
Rezultate. *Fenotipurile deficienței AAT au fost detectate la 3 pacienți (7,7%) cu pneumotorax spontan și numai la un caz (1%) din grupul de control. Cu toate acestea, diferențele observate nu au atins pragul semnificației statistice, din cauza disproporției importante între cele două grupuri comparate. Nivelul mediu seric al alfa-1 antitripsinei a fost semnificativ crescut la pacienții cu pneumotorax spontan (1,53 ± 0,23 g/l) decât la grupul de control (1,34 ± 0,31 g/l) (p=0,03).*
Concluzii. *Datele preliminare confirmă importanța clinică a deficitului de alfa-1 antitripsină la pacienții cu pneumotorax spontan, ca și nevoia de a-i testa pentru depistarea unui eventual deficit al acestei enzime.*
Cuvinte-cheie: *pneumotorax spontan, alfa-1 antitripsină, deficiență*

Introduction

Alpha-1 antitrypsin (AAT) deficiency is an autosomal codominant genetic disorder that predisposes individuals to the development of liver and lung disease[1, 2]. Alpha-1 antitrypsin deficiency is an under-recognized condition worldwide with only a small number of affected individuals detected, long diagnostic delays between initial symptoms and diagnosis, and evidence that patients with suggestive symptoms may see many physicians before an exact diagnosis is mad[3, 4].

The AAT protein is encoded by the protease inhibitor (PI) locus located on chromosome 14q32.1[3]. 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 highly 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 associate with this deficiency[4]. The aim of this study was to analyze 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].

Table I Main characteristics of studied individuals

Variable	Groups		P value
	Spontaneous pneumothorax (n=39)	Controls (n=100)	
Age, years	33.2±3.2	35.536.3±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: Smokers, n (%) Ex-smokers, n (%) Never smokers, n (%)	 14 (36) 2 (5) 23 (59)	 25 (25) 8 (8) 67 (67)	>0.05
C-reactive protein (mg/l)	8.3±2.2	6.6±1.8	>0.05
AAT deficiency genotype, n (%)	3 (7.7)	1 (1)	>0.05

Materials and methods

Subjects. The patients with spontaneous pneumothorax for this retrospective study were recruited from the Vilnius University Hospital Santariskiu Clinics, Hospital of Lithuanian University of Health Sciences, and Klaipeda University Hospital. For 29 patients spontaneous pneumothorax was diagnosed for the first time, for 10 patients it was recurrent. The control group was formed from healthy persons who underwent a prophylactic health checkup. 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 (year's × 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 minutes, and centrifuged for 15 minutes 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 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 by isoelectric focusing (LKB Multiphor II and LKB Macrodrive 5 Constant Power Supply, Amarcham Pharmacia Biotech, Piscataway, NJ, USA) as described previously[6]. ELISA test was performed to all patients. Phenotyping was performed only for patients with serum AAT deficiency or for patients with positive ELISA test results.

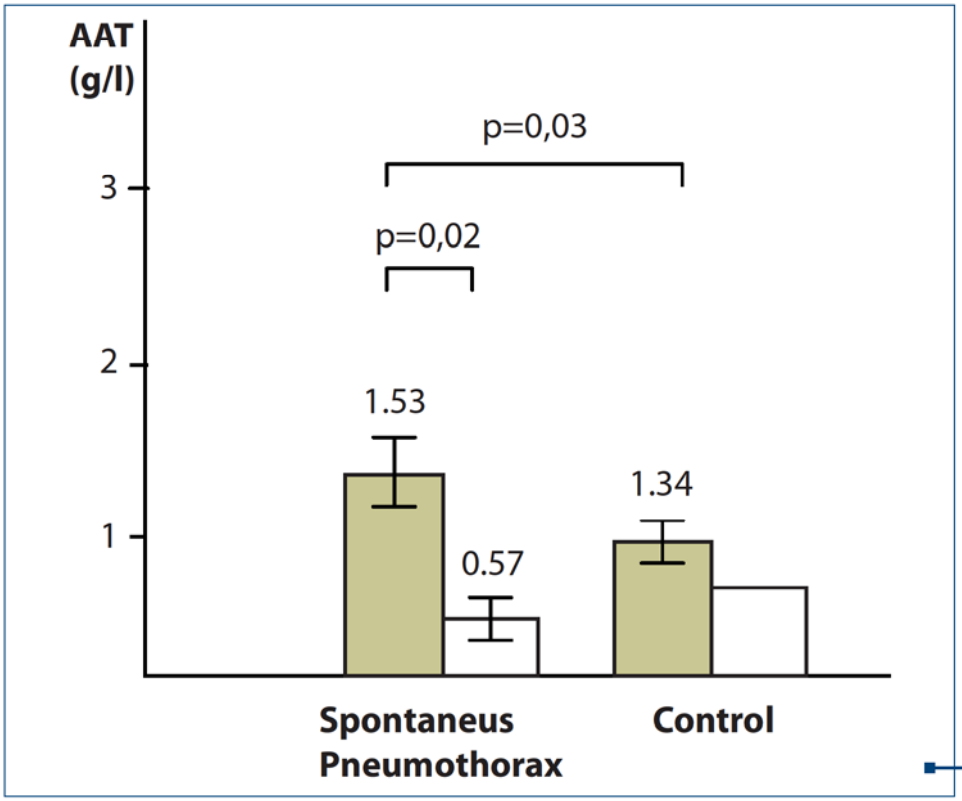

Figure 1. *Serum AAT concentration in subjects without AAT deficiency (filled bar) and with AAT deficiency (not filled bar)*

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 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 Table I. Spontaneous pneumothorax occurred in 29 patients for the first time; 10 patients had recurrent pneumothorax. These patients had distal acinar or paraseptal emphysema. 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 and lung function comparing the patients with and without AAT deficiency. These data could be explained by a relatively young age of the patients with AAT 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. Bacterial infections as causes of spontaneous pneumothorax were excluded because C reactive protein was not elevated in all patients.

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 versus 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-nondeficient patients with spontaneous pneumothorax was found (*P*=0.02) (Figure 1).

Discussion

An important finding of our study is that 7.7% 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, 5] 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 several case reports of spontaneous pneumothorax with AAT deficiency have been reported[14-16]. Daniel and Teba reported spontaneous pneumothorax to be observed in the patient with an abnormally low level of AAT[14]. However, some studies involving patients with simple spontaneous pneumothorax failed to prove AAT deficiency to be present in these patients[12, 13]. These differences in the results could be explained by a varying frequency of the Z allele in the general population.

Previous studies performed by other in the general population of Lithuania[8] 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[3,8,9]. In COPD patients case control studies demonstrated 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[9-11]. The case-detection program of 2,137 COPD patients in Spain revealed 7 cases of ZZ deficiency (0.37%)[9]. In another program undertaken in Italy, the detection rate for ZZ was 6.4%[10]. This is probably related to the sample composition consisting in several individuals with different types of chronic respiratory diseases.

To date, the mechanisms of spontaneous pneumothorax have not been elucidated yet; 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. 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 the results were similar to another study, where participated patients with COPD[7].

One study of 32 patients with spontaneous pneumothorax presented similar results[13]. The authors showed that the AAT level in the patients with spontaneous pneumothorax was higher than in the healthy control[13]. 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 could be estimated to 1:3000-5000[5, 7]. This might signify that that approximately 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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