Evaluation of Alpha-1 Antitrypsin Level in the Serum of Children With Idiopathic Bronchiectasis

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Abstract- Bronchiectasis is a clinical syndrome characterized by chronic cough, sputum production, recurrent respiratory infections, and permanent bronchial dilation. The association between the level of alpha-1 antitrypsin (AAT) and bronchiectasis is controversial. In this study, we aimed to investigate this association in children with idiopathic bronchiectasis. The study was conducted on 20 patients with idiopathic bronchiectasis as the case group (mean age 15.9±2.1) and 20 healthy individuals as the control group (mean age 14.9±2.6). Serum AAT level was measured using nephelometric analysis (g/L). Other criteria including sex, parent consanguinity, number of hospitalizations, age of the first symptom were evaluated in both groups related to AAT level. The mean serum level of AAT in the case and control groups were 1.3±0.29; 1.5±0.59, respectively, with statistical significance (P=0.001). There was a significant difference between the two groups in the AAT level distribution, according to AAT normal range (P=0.01). The case group had a more positive attitude toward consanguinity than the control group (66.7% versus 33.3%; P<0.001). The results showed that 80% of patients had the first symptom of disease under one year of age, 6.6% 1-5 years, 6.6% 5-10 years, and 6.6% in more than ten years old. In the case group, 53.3% had a history of medical hospitalization for one time, 26.7% two times, while 20% of the patients had no medical hospitalization. Decreased AAT serum level and high consanguinity rates may be considered as two risk factors for idiopathic bronchiectasis occurrence in children.

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Introduction

Bronchiectasis is one of the most important chronic respiratory diseases characterized by abnormally and permanently dilated pulmonary airways (1). It is associated with a persistent cough, sputum production, recurrent chest infection, and malaise (2,3). The prevalence of bronchiectasis is not well defined and is underestimated in developing countries (4). Bronchiectasis is caused by some infectious lung diseases, including tuberculosis and pneumonia, and also by allergic bronchopulmonary aspergillosis (ABPA), airway damages, decreased mucociliary clearance, and primary or secondary immunodeficiency (5,6). Alpha-1 antitrypsin deficiency (AATD) is also considered as one of the causative agents of bronchiectasis (2).

Alpha-1 antitrypsin (AAT) is the prototype of the endogenous protease inhibitor (Pi) of serine proteases coded by the serine-protease inhibitor (SERPINA1) gene and is mainly secreted in the serum by the hepatocytes. AAT acts as an inhibitor for neutrophil elastase, which has a role in cellular matrix digestion, and its deficiency is associated with cellular matrix damages. AATD is a rare autosomal-codominant hereditary disease with a prevalence of 1-5 cases out of 10,000 (7). AATD increases the risk of lung and liver diseases, granulomatosis with polyangiitis, and panniculitis. It is mainly diagnosed by quantification of the serum level of AAT.

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Few studies have evaluated the association between AATD and bronchiectasis. This association has been confirmed by some studies, while other investigations have failed to show it. An abnormal AAT protein may predispose one to bronchiectasis through some mechanisms. The "Z" isoform of AAT may polymerize in the lung and act as a chemoattractant for neutrophils, which can then release inflammatory mediators and elastase that induces airway damage (8). Another indirect mechanism for AATD associated bronchiectasis is that anomalous AAT may predispose one to non-tuberculous mycobacteria (NTM) infection, which can secondarily cause bronchiectasis (9).

In the current study, we aimed to assess the AAT level in patients with idiopathic bronchiectasis compared with healthy subjects to know whether the AAT level could affect the occurrence of bronchiectasis.

Materials and Methods

The study was conducted on 20 patients diagnosed with idiopathic bronchiectasis who referred to Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran, and 20 healthy controls. Idiopathic bronchiectasis was diagnosed in patients by a chest high resolution computed tomography scan. The study was approved by local Ethics Committee of Shiraz University of Medical Sciences with the code of IR.SUMS.REC.1396.S812 on December 30, 2017. The written consent form was obtained from all participants.

5 ml whole blood was taken from all participants in the sterile collection tube and the samples were sent to laboratory within 24 h; then, the serums were separated from the blood by centrifugation. Alpha-1-antitrypsin serum level was measured by quantitative nephelometry assay and Mininephᵀᴹ human α-1 antitrypsin kit (MININEPH, Birmingham, UK); the values were expressed as gram per liter (g/L). The reference value of 0.629-0.1.696 g/L was considered normal, and the value below 0.629 g/L was regarded deficient.

Statistical analysis

SPSS software, version 18 (SPSS Inc, Chicago, Illinois), was used for statistical analysis. Kolmogorov-Smirnov test was used to check the normal distribution of the variable. The normality test indicated that the variables had a normal distribution. The mean age and mean AAT level were compared between the case and control groups using the *t*-test, while sex and consanguinity rates and AAT level regarding the normal range were compared between the groups using the *Chi*-square test.

Results

This study included 40 participants categorized into two groups; the case group included 20 patients with idiopathic bronchiectasis, with a mean age of 15.9±2.1 years. Of them, 12 (60%) were female, and 8 (40%) were male. The control group included 20 healthy subjects with a mean age of 14.9±2.6 years. Among these participants, 11 (55%) were female, and 9 (45%) were male. There was no significant difference between the case and control groups in sex and mean age (*P*>0.05; Table 1).

Table 1. Characteristics of the patients with bronchiectasis and healthy controls

		Patients (n=20)	Control (n=20)	*P*
Age (Mean±SD)		15.9±2.1	14.9±2.6	0.3
Sex	**Female**	12(60%)	11(55%)	0.85
	Male	8(40%)	9(45%)	
Consanguinity	**Yes**	15 (75%)	7 (33.3%)	0.001
	No	1 (5%)	13 (92.9%)	
AAT (%)	**≤0.629**	1(5%)	0	
	0.629-1.696	18 (90%)	11 (55%)	0.01
	≥1.696	1 (5%)	9 (45%)	
AAT (Mean±SD)		1.26±0.35	1.51 ± 0.59	0.001

AAT: alpha-1 antitrypsin

As to consanguinity, 15 (75%) subjects in the case group showed positive consanguinity; in contrast, 7 (33.7%) individuals in the control group had positive consanguinity, with a significant difference (*P*=0.001; Table 1).

In the case group, the serum level of AAT in one patient (5%) was below the normal range (0.629-1.696), and in 18 (90%) patients, a normal amount of AAT level

was reported, whereas the AAT level was within the normal range and higher than normal range in 11(55%) and 9 (45%) healthy subjects, respectively (Table I). There was a significant difference between the two groups regarding the distribution of the AAT level (P=0.01; Table 1).

The mean serum level of AAT was 1.26±0.35 in the case group and 1.51±0.59 in the control group, with a significant difference (P=0.005). In the case group, 80% of patients had the first symptom of the disease in less than one year of age, 6.6% in 1-5-year-old ones, 6.6% in 5-10 years of age, and 6.6% in more than ten years of age. In the case group, 53.3% had a history of medical hospitalization for one time, 26.7% two times, and 20% of patients had no medical hospitalization. The correlation between the age and AAT level was analyzed using Pearson correlation test and no significant difference was seen in this regard (P>0.05).

Discussion

Bronchiectasis is defined as a disorder associated with irreversible dilation of a part of the bronchial tree caused by destruction of the muscle and elastic tissue airway dilation. AATD is one of the causative agents of bronchiectasis due to its inhibitory effect on the neutrophil elastase, which digests several components of the cellular matrix in the lung. However, the association between bronchiectasis and AATD remains unclear. The results of this study showed that AAT serum levels were lower in patients with bronchiectasis compared with normal individuals. Few studies investigated the AAT level among patients with bronchiectasis. Consistent with our study, Greulich *et al*., showed a decreased level of AAT in patients with respiratory diseases, especially those with a history of COPD, emphysema, and bronchiectasis (10). Similar to our findings, Badawy *et al.*, reported that only 5% of patients with bronchiectasis had low AAT level (11). Other studies evaluated the incidence of bronchiectasis among those suffering from AATD. In a study performed by Filipa *et al*., on 114 patients with AATD, 29.8% of patients showed evidence of bronchiectasis with lower AAT serum levels (12). Similarly, Parr et al. examined 74 patients with AAT deficiency and found that 70 (95%) had bronchiectasis changes on their CT scan (13). Conversely, a rare occurrence of bronchiectasis was reported in patients with AATD in some studies. Lonni *et al*., on 1258 bronchiectasis patients enrolled from different European countries, found only eight cases of AATD (0,6%) (14). In contrast with our findings, all the bronchiectasis patients had a normal serum level of AAT (between 0.9 and 1.8 g/L), while there was a lower value in only two Pi-MZ subjects (0.7 and 0.85, respectively) (14).

Consanguinity is considered one of the causative factors for bronchiectasis occurrence (15). Our findings showed a high frequency of consanguinity among patients with bronchiectasis versus healthy control. Similar to our study, Satırer *et al*., reported 59.4% positive consanguinity within bronchiectasis patients and considered it in the etiology of bronchiectasis (16). Karadag *et al*., also reported that 42.6% of the parents of patients with bronchiectasis were either first- or second-degree relatives (17). In addition, in a study performed by Doğru *et al*., 37.2% of idiopathic bronchiectasis cases were positive for the consanguinity of parents (18). The higher rate of consanguinity in our study group may suggest that hereditary factors are implicated in the development of idiopathic bronchiectasis in our population, which needs further studies.

The result of this study showed that 80% of patients with bronchiectasis had the first symptoms of disease in less than one year. Most studies reported that bronchiectasis developed early in infants by the effect of some risk factors, including meconium ileus on presentation, respiratory symptoms, pulmonary infection (especially with P. aeruginosa), and gas trapping on the CT scan. In some studies, the clinical data have indicated that bronchiectasis occurs in preschool-age children (19). In another study performed by Kim et al., the mean age at onset was seven years and seven months, and bronchiectasis occurred before five years of age in 39 (42%) patients (20). Given that in the current study, bronchiectasis occurred in 80% of children aged under one year, clinicians should be aware of the possibility of bronchiectasis when they see common initial presenting symptoms including chronic cough, recurrent pneumonia, fever, and dyspnea regardless of their age. Some studies have proposed that free neutrophil elastase activity at three months of age increases the probability of persistent bronchiectasis at both 12 months and three years of age. AAT can inhibit its activity by binding to the extracellular neutrophil elastase activity. In this study, we hypothesized that a decreased level of AAT in patients with bronchiectasis might be related to the increase in elastase activity and early onset of the disease. However, it needs to be confirmed by genotyping of patients for AATD.

The results of the present study will be supported by the general concept of targeted screening for AAT deficiency among patients with bronchiectasis, with a large population of bronchiectasis patients. The current

study only quantified the level of AAT in the serum of the participants and failed to assay the genotype of individuals for AAT; this should be considered in future studies.

In conclusion, the present study showed decreased AAT serum levels in patients with bronchiectasis; it can be considered as a possible cause for disease occurrence. Parent consanguinity could influence an individual risk for bronchiectasis development.

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