Determination of Alpha-1 Antitrypsin Level in Patients with Severe Asthma

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Background: This descriptive study aimed to determine the serum level of alpha-1 antitrypsin (AAT) in patients with severe asthma.

Materials and Methods: The serum level of AAT was determined in 43 patients with severe asthma. Pulmonary function tests were performed and data were analyzed by SPSS version 19 software.

Result: The mean age of patients was 41±13.8 years (range 14 to 78 years). The AAT level was within the normal range (90–200 mg/dl) in 38 patients (88.4%) and less than normal in 2 patients (4.7%).

Conclusion: No association was observed between the serum level of AAT and lung function in severe persistent asthmatic patients. The prevalence of AAT deficiency was low in patients with severe persistent asthma. These results must be confirmed by further longitudinal investigations using larger cohort studies.

Key words: Severe asthma, Alpha-1 antitrypsin

INTRODUCTION

Asthma is a syndrome characterized by airflow obstruction that noticeably varies with or without treatment. Narrowing of the airways is usually reversible, but some patients with chronic asthma may suffer irreversible airflow obstruction. The increasing global prevalence of asthma and high health care costs have led to extensive researches about its mechanism and treatment. Bronchial asthma has a wide clinical spectrum ranging from a mild intermittent disease to one that is severe, persistent and difficult to treat, which can also be fatal in some cases (1).

The National Institute of Health Guidelines for the Diagnosis and Management of Asthma have characterized severe persistent asthma in untreated patients by several criteria: continual symptoms (also occurring frequently at night) that cause limitations in physical activities; frequent exacerbations; persistent airflow obstruction with forced expired volume in 1 sec (FEV1) less than 60% of the predicted value and peak expiratory flow (PEF) diurnal variability greater than 30% (2).

The AAT is a principal inhibitor of serum protease that is mainly secreted by hepatocytes and to a minor extent, by monocytes, pancreatic islets, lung alveolar cells and colonic enterocytes. Significant reductions in serum and tissue AAT levels in human beings are associated with chronic obstructive pulmonary disease (COPD) especially pulmonary emphysema and liver disease which can lead to cirrhosis, necrotizing panniculitis and vasculitis (3,4).

The AAT deficiency as an autosomal and co-dominant genetic disorder is characterized by decreased concentration and activity of the AAT in blood and tissues.
Although some degrees of the AAT deficiency are somewhat more common worldwide, its severe deficiency (the AAT serum levels less than 11µmol or 50 mg/dl) is a rare occurrence.

In a cohort study of 1052 subjects with AAT deficiency, researchers reported that signs and symptoms of asthma were frequent in AAT deficiency and may start at the age of most rapid FEV1 loss. In AAT deficiency, augmentation therapy cannot effectively prevent the loss of lung function in asthmatic patients as compared to non-asthmatic patients.

However, some reports about COPD show that AAT therapy had good results in some patients with COPD and AAT deficiency. According to these reports augmentation therapy improves lung function in subjects with AAT deficiency when adjusted for age, gender, smoking status and baseline FEV1 %. The beneficial effects were noted in ex-smoker subjects with FEV1 less than 50% of the predicted value. On the base of recent studies about asthma and its relation with AAT deficiency, the results could not distinguish the impact of asthma on the course of irreversible airflow obstruction in severe AAT deficiencies.

In this study, we determined the serum level of AAT in patients with severe asthma in order to show whether AAT deficiency is a risk factor of persistent airflow limitation in patients with asthma or not. If we find reasonable relation between the AAT level and asthma, we can improve treatment of severe asthma with AAT replacement therapy.

MATERIALS AND METHODS

This descriptive study was performed on patients with severe persistent asthma identified and treated in a hospital outpatient department between March 2011 and March 2012. The total number of participants enrolled was 43 and all of them were over 14 years of age. Candidates in this study had the following inclusion criteria: age over 14 years with the diagnosis of severe persistent asthma and symptomatic disease during the previous year. Each patient fulfilled the international Global Initiative for Asthma (GINA) classification criteria, with symptoms of episodic wheezing, cough and shortness of breath which responded to bronchodilators. The reversible airflow obstruction was documented in at least one previous pulmonary function study (persistent airflow obstruction with FEV1 and/or PEF less than 60% of the predicted value and PEF variability greater than 30% which were treated in outpatient clinic of Department of Pulmonology in Rasoul Akram Hospital). The exclusion criteria were as follows: current smoking or previous exposure, existence of respiratory disease besides asthma and co-existence of other diseases that might impress clinical data or respiratory function values (e.g. heart failure, anemia, systemic diseases). They were treated with inhaled corticosteroids and long-acting bronchodilators for more than one year. All patients were symptomatic and had at least one severe exacerbation during the last year requiring a course of oral corticosteroids. At the time of this study, patients were non-smokers and had been in clinically stable condition for at least one month.

During one day, lung function measurements and blood sampling were carried out and a short questionnaire was filled out. This questionnaire was used to assess patient characteristics such as: age, sex, smoking status, severity of symptoms, medication usage, duration of asthma and concomitant diseases. Pulmonary function tests were performed by using a spirometer and forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio were extracted. Then 10 ml of blood was drawn from each patient and transferred to the lab in cold box. The serum level of AAT was determined by immunoturbidimetric method using Roche COBAS INTEGRA 400 plus analyzer. In this experiment, the normal reference range was from 90 to 200 mg/dl for AAT level. The project was approved by the Ethics in Research Committee of the institution and all patients expressed their consent prior to their enrollment in this investigation.
**Analysis:**

Statistical analysis of continuous data was done by parametric Student's t-test or one sample as t-test, whenever appropriate. The correlations between categorical variables were studied using a parametric chi-square test or the nonparametric Fisher's exact test, depending on the distribution of the frequencies in a two-by-two table. The correlations between continuous variables were analyzed by means of the Pearson's and Spearman's correlation tests.

**RESULTS**

In this study, 43 patients (69.8% males, 30.2% females) were evaluated with severe asthma and a mean age of 41±13.8 years. The measured AAT level was normalized and is shown in Figure 1.

![Figure 1. The distribution of the AAT level in 43 asthmatic patients.](image)

The clinical characteristics, AAT levels, spirometry findings and demographic findings are listed in Table 1. After determination of the AAT level in these patients, we found that it was within the normal range (90 – 200 mg/ dl) in 38 patients (88.4%) and was less than normal in 2 patients (4.7%). In our study, there was no significant correlation between sex and AAT level (P=0.44), FEV1 and AAT level (P=0.33) or FEV1/ FVC and AAT level (P=0.94).

**DISCUSSION**

In this study, we chose a group of patients with severe persistent asthma based on step 4 of GINA classification; because we believed that if a relationship exists between AAT deficiency and asthma, it would be found most probably in this group of patients with persistent airflow limitation.

However, after data acquisition and analysis, it was observed that the AAT level in 88.4% of patients was within the normal range. It means that no association exists between serum level of AAT and lung function in patients with severe persistent asthma. The results of this study are in agreement with previously reported findings by Eden (17), who found no relationship between asthmatic features and accelerated decrease of lung function in patients with severe AAT deficiency. In addition, another study found no association between AAT phenotypes and lung function in severe asthmatic patients (12).

However, one investigation on asthmatic children observed that patients with severe AAT deficiency were susceptible to early decrease of lung function (18). Additionally, in a cohort study by Eden et al, it was shown that asthmatic features were prevalent in severe AAT deficiencies and symptoms appeared earlier (7). This finding is probably due to elevated levels of total serum immunoglobulin E (IgE) in these patients which can be responsible for the accelerated decrease of FEV1.

Considering the high number of asthmatic patients with persistent air-flow limitation, we expected to have a much higher prevalence of AAT deficiency (19). But our results indicated that AAT deficiency cannot be a risk

| Parameters                               | Results  |
|------------------------------------------|----------|
| Patients                                 | 43       |
| Age (year)                               | 41±13.8  |
| Sex                                      | 30 M, 13 F |
| FEV1                                     | 42.3±1.54 |
| FEV1/FVC                                 | 62.1±1.5 |
| Patients with normal level of AAT        | 38       |
| Patients with deficient level of AAT     | 2        |

Table 1. Demographic parameters and the serum level of AAT in asthmatic patients.
factor for development of persistent airflow limitation in asthmatic patients. Therefore, the efficacy of AAT replacement therapy would possibly be low for prevention of the lung function decline. Due to the limitations of this study (small sample size), our findings need to be confirmed by prospective longitudinal studies on a larger group of asthmatic patients.

In conclusion, we found that AAT deficiency cannot be a risk factor for persistent air-flow restriction in patients with asthma and the prevalence of AAT deficiency in patients with severe asthma was not considerable.

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