

# Lack of awareness for alpha-1 antitrypsin deficiency: A single-center retrospective study

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## ABSTRACT

**INTRODUCTION** Alpha-1 antitrypsin deficiency (A1ATD) is a genetic condition that predisposes to COPD and to liver disease, although in some cases patients might present with different pathological features such as bronchiectasis, severe uncontrolled asthma anti-neutrophil cytoplasmic antibody (ANCA) angitis, etc. Although A1ATD is one of the commonest hereditary diseases in adulthood, more than 60 years from its first recognition, it is still an underrecognized disease.

**METHODS** In this study we have used data from the laboratory of a hospital specialized in respiratory diseases in Athens, Greece, 'Sotiria Chest Hospital'. All tests sent from two departments (1st Respiratory Medicine Department of the University of Athens and the 4th Respiratory Medicine Department) between January 2014 to June 2023 were collected and the reason which led to the A1AT levels measurement was recorded. Among 55866 patients (both outpatients and hospitalized) which had visited the two aforementioned departments during the study period, measurement of A1AT levels was performed in 194 patients (0.003%).

**RESULTS** In all, 83 patients (42.8%) were tested due to the presence of emphysema, 72 (37.1%) due to bronchiectasis, 14 (7.2%) due to severe uncontrolled asthma, and 25 (12.9%) for other causes.

**CONCLUSIONS** The extremely low proportion of awareness in the investigation of A1ATD is probably related to the underdiagnosis of the disease.

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## KEYWORDS

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## INTRODUCTION

A1ATD is a genetic condition that predisposes to COPD and to liver disease (i.e. cirrhosis and hepatocellular carcinoma) while in some cases patients may present with bronchiectasis without clinical etiology, vasculitis syndromes (anti-proteinase 3-positive vasculitis, necrotizing panniculitis), and/or a family history of the above<sup>1</sup>. According to epidemiological studies A1AT deficiency affects approximately 1 in 2000 to 1 in 5000 individuals<sup>2</sup>. It is widely known that although A1ATD is one of the commonest hereditary diseases in adulthood, more than 60 years from its first recognition, it is still an underrecognized condition<sup>1</sup> and it is believed that only 0.35–4% of the A1AT individuals are diagnosed. Accordingly, it is estimated that in Greece approximately 4000 patients are suffering from A1ATD deficiency and identified cases should range from 9 to 100. A recent cohort collecting cases from numerous centers all over the country detected 45 diagnosed patients, a number

very comparable to the cohorts of other studies<sup>3</sup>. The long diagnostic delays between the first symptom and initial diagnosis and the frequent need for affected individuals to see multiple healthcare providers before initial recognition, cause delays in offering them appropriate augmentation treatment which is known to delay disease progression<sup>4</sup>.

In a recent study Riley et al.<sup>5</sup> have reported testing patterns and disparities for alpha-1 antitrypsin deficiency (A1ATD) and have shown a very low uptake of 5.6% of alpha-1 antitrypsin measurement in the clinical setting among patients with chronic obstructive pulmonary disease, despite guidelines recommending broader testing. Those authors stated the importance of increasing awareness among healthcare professionals to perform more often testing for A1AT deficiency.

## METHODS

We performed a retrospective cohort study of people tested

**Table 1. Characteristics of patients tested for A1ATD according to the main reason which led to testing**

Main reason for testing	All (N=194) n (%)	Emphysema (N=83) n (%)	Bronchiectasis (N=72) n (%)	Asthma (N=14) n (%)	Other (N=25) n (%)	p
Age (years), median (IQR)	59.0 (49.0–69.3)	61.0 (54.0–68.0) <sup>§</sup>	63.5 (54.2–72.0)*	55.5 (36.5–68.0)	47.0 (35.5–67.5)* <sup>§</sup>	<b>0.002</b>
Gender (male)	115 (59.3)	51 (61.4)	44 (61.1)	6 (42.9)	14 (56)	0.214
<b>Smoking status</b>						<b>0.035</b>
Never smokers	45 (23.2)	10 (12)	19 (26.4)	6 (42.9)	10 (40)	
Ever smokers	149 (76.8)	73 (88)	53 (73.6)	8 (57.1)	15 (60)	
A1AT levels (mg/dL), median (IQR)	158 (133–196)	161 (133–209)	161 (138–209)	150 (136–166)	149 (131–212)	0.716
A1ATD detected	14 (7.2)	6 (7.2)	3 (4.2)	0 (0)	5 (20)	0.394

A1AT: alpha-1 antitrypsin. A1ATD: alpha-1antitrypsin deficiency. Bold indicates statistical significance.\*<sup>§</sup> Indicates statistically significant difference between groups. IQR: interquartile range.

for A1ATD from the records of two respiratory medicine departments of a hospital specialized in respiratory diseases in Athens, Greece. Tests sent to the hospitals' laboratories between January 2014 to June 2023 were collected. Patients' demographics and the reasons which led the physicians to prescribe the measurement of A1AT levels were also recorded.

From a database of 55866 patients which had visited the 1st University Respiratory Medicine Department of the University of Athens and the 4th Respiratory Medicine Department (both situated in 'Sotiria' Chest Hospital in Athens, Greece, during the period January 2014 to June 2023), measurement of A1AT levels was performed in 194 patients (0.003%).

## RESULTS

The normal range of values of our laboratory regarding A1AT levels is 90–200 mg/dL. From these patients, 83 (42.8%) were tested due to the presence of emphysema, 72 (37.1%) due to the presence of bronchiectasis of unknown cause, 14 (7.2%) were tested for severe uncontrolled asthma, and 25 (12.9%) for other causes (most commonly CT abnormalities and/or unspecified airflow limitation). A1AT levels did not differ regarding the cause of measurement. Although no differences between groups were observed in the patients' gender, patients tested due to the presence of emphysema and bronchiectasis were significantly older compared to those tested for severe difficult-to-treat asthma or other causes. Furthermore, patients tested due to the presence of emphysema and bronchiectasis were more frequently smokers compared to those tested for other reasons,  $p=0.002$ . Finally, low A1AT levels indicating A1ATD were observed in 14 (7.2%) patients. The results are presented in Table 1.

## DISCUSSION

In our study, we observed that even in a specialized hospital, physicians are not familiar with performing testing for A1AD deficiency. Although GOLD report suggests that all COPD patients should be tested for A1AT deficiency at least once in their lives<sup>6</sup>, low disease awareness has been recognized as the main reason for the underdiagnosis of this disease<sup>7,8</sup>. The percentage of 0.003% of prescribing the test in patients from a hospital specialized in respiratory diseases is extremely low. Lack of awareness of A1ATD, unclear results, expense, lengthy testing that necessitates referral to a specialist, and the belief that testing will not affect clinical care, have all been blamed for the guidelines' non-implementation<sup>9</sup>. However, even in a specialized hospital where the test is available, has no economic cost for the patient, and results are available in a few days, physicians still fail to perform measurement of the A1AT levels. Furthermore, instead of using the broad ATS and World Health Organization recommendations, clinicians still perform the measurement in a small minority of patients mainly with emphysematous lesions and rarely by taking into account other possible manifestations of the disease to guide a more directed screening approach<sup>10</sup>.

Our observations are in accordance with the study of Riley L et al.<sup>5</sup> showing that A1ATD continues to have low uptake in the clinical setting despite the GOLD recommendations suggesting a broader screening. Even in a specialized hospital in which the test is widely available and free of charge, still the absence of awareness leads to a very low frequency of performance of the measurement reflecting the main cause which leads into the underdiagnosis of the disease.

## Limitations

Our study has some limitations. First, we have searched the

measurements performed in our hospital laboratory during a specific period of time including the years of the pandemic during which there was a significant decrease in the number of patients visiting the hospital for respiratory diseases other than COVID-19. Furthermore, the low proportion of patients which have undergone A1AT measurement has been calculated using the number of patients who have visited the hospital for any respiratory disease and not specifically for diseases which could be manifestations of A1ATD such as COPD, bronchiectasis, or asthma. However, having in mind that COPD is one of the commonest causes of morbidity while bronchiectasis and asthma are very common diseases among the population of patients with respiratory symptoms, the number of patients tested for A1ATD in our cohort is still extremely low, indicating a lack of awareness even among respiratory medicine physicians for disease detection.

## CONCLUSIONS

There is a great unmet need for education of respiratory physicians regarding the importance of early diagnosis and treatment of the disease in order to perform a wider screening which will lead to a wider detection of the patients with A1ATD and allow early initiation of treatment.

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## CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for disclosure of Potential Conflicts of Interest and none was reported.

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## ETHICAL APPROVAL AND INFORMED CONSENT

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## DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

## PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

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