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ORIGINAL ARTICLE

The patient profile of individuals with Alpha-1 antitrypsine gene mutations at a referral center in Brazil

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ABSTRACT

Objective: The clinical, functional, radiological and genotypic descriptions of patients with an alpha-1 antitrypsin (A1AT) gene mutation in a referral center for COPD in Brazil. **Methods:** A cross-sectional study of patients with an A1AT gene mutation compatible with deficiency. We evaluated the A1AT dosage and genotypic, demographic, clinical, tomographic, and functional characteristics of these patients. **Results:** Among the 43 patients suspected of A1AT deficiency (A1ATD), the disease was confirmed by genotyping in 27 of them. The A1AT median dosage was 45 mg/dL, and 4 patients (15%) had a normal dosage. Median age was 54, 63% of the patients were male, and the respiratory symptoms started at the age of 40. The median FEV1 was 1.37L (43% predicted). Tomographic emphysema was found in 77.8% of the individuals. The emphysema was panlobular in 76% of them and 48% had lower lobe predominance. The frequency of bronchiectasis was 52% and the frequency of bronchial thickening was 81.5%. The most common genotype was Pi*ZZ in 40.7% of participants. The other genotypes found were: Pi*SZ (18.5%), PiM1Z (14.8%), Pi*M1S (7.4%), Pi*M2Z (3.7%), Pi*M1I (3.7%), Pi*ZMnichinan (3.7%), Pi*M3Plowell (3.7%), and Pi*SF (3.7%). We did not find any significant difference in age, smoking load, FEV1, or the presence of bronchiectasis between the groups with a normal and a reduced A1AT dosage, neither for 1 nor 2-allele mutation for A1ATD. **Conclusions:** Our patients presented a high frequency of emphysema, bronchiectasis and bronchial thickening, and early-beginning respiratory symptoms. The most frequent genotype was Pi*ZZ. Heterozygous genotypes and normal levels of A1AT also manifested significant lung disease.

Keywords: Alpha-1 antitrypsin; Emphysema; Alleles.

INTRODUCTION

Alpha-1 antitrypsin deficiency (A1ATD) is a rare genetic disease that is related to the development of early emphysema and liver disease. Epidemiological studies estimate that A1ATD affects 1 in every 2,000 to 5,000 individuals born alive.[1] The only Brazilian study reporting on the prevalence of A1ATD estimates that 2.8% of patients with chronic obstructive pulmonary disease (COPD) have this deficiency.[2] The Platino study showed that, in the city of São Paulo, 15.8% of individuals aged 40 years or older had COPD,[3] which indicates that there is probably a large number of patients with undiagnosed A1ATD.

Alpha-1 antitrypsin (A1AT), a highly pleomorphic glycoprotein, has more than 100 identified alleles, and its main function is to inhibit several proteases.[4,5] Its variants are inherited by codominance, and they are classified according to the protease inhibitor (PI) system.[6,7] The phenotypes that have the highest risk of developing pulmonary emphysema are those associated with low A1AT production, the most common being the Z mutation. However, other mutations, such as S, I, Mmalton, Mnichinan, Plowell and Null, can lead to low dosages of A1AT.[6] The production of a dysfunctional protein can also occur, as in Pittsburgh and F mutations. The most common mutated alleles that occur with normal A1AT serum levels are the M variants, which still do not have a defined clinical significance.[4,6,7]

A1AT is produced primarily in the liver and, through the bloodstream, it reaches the lungs, where it performs its antielastolytic function.[4] When it is deficient, pulmonary emphysema occurs due to an imbalance in the protease-antiprotease ratio, which makes it incapable of protecting the lungs from the elastolytic action of neutrophil elastase,[8] among other aggressions, such as smoking and environmental exposures, leading to accelerated lung damage.

Its diagnosis is made through examining the clinical patterns of the disease and the corresponding laboratory changes. When there is evidence of reduced A1AT serum levels, genotyping should be performed in order to identify their variants.[4,5,9] However, A1AT is an acute phase protein, and its levels may be increased in situations of inflammation, thus a diagnosis of A1ATD cannot be not excluded even with a single normal dosage.[4]

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To date, we do not have a clinical, radiological and functional description of patients with A1ATD in Brazil. Although the A1AT dosage is recommended to be checked routinely in patients with COPD, as suggested by the World Health Organization (WHO), the examination is rarely done due to unawareness, the unavailability of the test, and its high cost to the health system. Knowledge about these characteristics in a Brazilian population of patients can allow for a systematic screening criteria to be designed for individuals with high pretest probability for positive screening,[10] saving costs associated with the generalized screening for all patients with COPD.

The primary objective of this study was the clinical, functional, radiological and genotypic characterization of A1ATD in a referral center specialized in respiratory diseases in Brazil, and to enable the design of a protocol for systematically tracking patients with COPD. We also compared the normal and altered A1AT dosage groups, and the groups with genotypes associated with one and two allele mutations for A1ATD.

METHODS

Study design

A cross-sectional study with patients that have a mutation in the A1AT gene, who were treated at the COPD Outpatient Clinic of the Pulmonary Division of the Hospital das Clínicas at the Faculdade de Medicina of the Universidade de São Paulo (HC-FMUSP), and who were diagnosed until February 28, 2015. It was approved by the Research Ethics Committee of the HC-FMUSP under Resolution Number 1,291,260.

Patients

Clinical and laboratory criteria were established in order to perform the genotyping of A1AT gene mutations in patients treated at the COPD outpatient clinic. These include: a low A1AT serum dosage; the early onset of emphysema (under 45 years of age); emphysema in non-smokers; disproportionate emphysema to smoking load; emphysema in patients with cases of A1ATD in the family; and bronchiectasis of an unknown cause.

All patients older than 18 years of age with an A1T1 gene mutation compatible with A1T1D that was identified by genotyping were included in the study. Patients without a A1T1D diagnosis confirmed by genotyping, those with mutations in the A1AT gene that were not compatible with the deficiency, and those who never performed spirometry with a bronchodilator test and computed tomography (CT) were excluded.

Clinical and demographic data

The data collected were obtained at the time of the medical consultation or by consulting the A1ATD patients' medical records. The data included: age, gender, body mass index (BMI), SpO_2, age of onset of respiratory symptoms, history of alcoholism and smoking, smoking load, comorbidities (described in the patient chart), dyspnea (ranked by the modified Medical Research Council - mMRC), number of exacerbations reported by the patient in the last year (according to GOLD recommendations),[11] current treatment, and evaluation for a lung transplant.

Chest computed tomography and lung function tests

For this study, the following were considered: the most recent chest tomography, spirometry with a bronchodilator test and plethysmography performed by the patient. For the diagnosis of COPD, the GOLD-recommended criteria were used. [11]

The spirometry reference values used were those established by Pereira et al.,[12] where the absolute and percentage of predicted post-bronchodilator (BD) values of forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1), as well as the FEV1/FVC ratio were collected. For the bronchodilator response, criteria described in 2002 by the Guidelines for Pulmonary Function Testing of the Brazilian Society of Pulmonology and Tisiology (FEV1 post-BD ≥ 200 mL of pre-BD and ≥ 7% of predicted and/or post-BD FVC ≥ 350 mL of pre-BD) were used.[13] Pre-BD values of total lung capacity (TLC), residual volume (RV) and pulmonary diffusion (DLCO) were recorded from plethysmography with predicted values from Neder et al.[14]

Liver Disease Evaluation

The patients were considered to have liver impairment, if they presented changes in the evaluation exams at any time during the follow-up consultations, investigated by: aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-GT and bilirubin dosages.

ALPHA-1 ANTITRYPSIN DOSAGE AND GENOTYPING

The A1AT dosage was performed by a blood plasma analysis after centrifugation, using an immunoturbidimetric method. Normal A1AT value levels were considered to be ≥ 83 mg/dL, according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[4] If the patient had performed more than one test, the lowest value was considered. Genotyping was performed by a polymerase chain reaction (PCR) using a peripheral blood sample analysis that was collected on filter paper. The DNA was extracted from the dried blood and the sample was subjected to the sequencing of exons 2, 3, 4 and 5 of the SERPINA1 gene in order to identify the polymorphisms. Direct sequencing of the PCR products was performed from the BigDye™ Terminator V.3.0 kit (Applied Biosystems, Warrington, England), and the samples were applied to the Genetic Analyzer DNA sequencer (Applied Biosystems, Tokyo, Japan).

Statistical analysis

The collected data were analyzed using the Statistical Package for Social Sciences (SPSS) program, version

21.0, and were reported as absolute numbers, proportions, means and medians, standard deviation and interquartile ranges. The analysis of non-normal distribution numerical variables was compared between two groups by the Mann-Whitney test. For categorical variables, Fisher's exact test was used. Numerical variables of non-normal distribution were correlated through Spearman's Rho test. P-values of <0.05 were considered to be statistically significant.

RESULTS

Using the established clinical criteria, 43 patients with suspected A1ATD were selected from a population of 531 patients undergoing follow-up care at the COPD clinic in 2014. Of the total selected, 1 patient did not undergo genotyping and 15 participants presented a normal A1T1 gene after genotyping and, therefore, were excluded from the study. Thus, a total of 27 patients with A1ATD were included in the study, having a diagnosing accuracy level of 62.8%, after clinical and laboratory suspicion, and a prevalence of 5.1% in our COPD clinic population (Figure 1).

As Table 1 shows, the median A1AT dosage in study participants was 45 mg/dL, and 4 individuals (15%) had normal levels (≥ 83 mg/dL). The median age of the participants was 54 years old. Sixty three percent were male and had a median BMI of 23.7. The median age at the onset of respiratory symptoms was 40 years old. Ten individuals (37%) were non-smokers, 52% were former smokers, and 11% were active smokers. Five individuals did not present comorbidities, and the most prevalent comorbidities were gastroesophageal reflux disease (22%), systemic arterial hypertension and dyslipidemia (both 19%) and rhinitis (22%). The most frequent respiratory diseases were bronchiectasis (52%), asthma (19%) and tuberculosis (15%).

The evaluation of pulmonary function showed an obstructive pattern in the majority of patients, with a reduced median of FEV1 predicted values (43%), FEV1/FVC (0.47) and pulmonary diffusion (59.5% of the predicted value), and important air entrapment seen in the increase in residual volume (169% of the predicted value) (Table 2). In 70% of individuals, FEV1 was less than 60% of the predicted values. A bronchodilator response was present in 12 patients (44.4% of the individuals), and most of it was FVC.

As for the tomographic findings, emphysema was found in 21 individuals (77.8%), 16 were panlobular, and 10 had a lower lobe prominence (respectively: 76.2 and 47.6% of the individuals with emphysema). Of the six participants without emphysema, two individuals had the Pi*ZZ genotype, two individuals had Pi*SZ, and in two individuals the Pi*M1Z genotype was found, with all of them having bronchial thickening, and four of them having bronchiectasis. Bronchiectasis was found in 52% of the participants, bronchial thickening in 81.5% and mosaic perfusion in 44% (Table 3).

Genotypic analysis showed that the most commonly found genotype was Pi*ZZ (40.7% of patients) (Table 4). This genotype shows a median A1AT dosage of 20.0 mg/dL. All of the participants had altered dosages (<83 mg/dL), and in general presented a more severe pulmonary disease with a median FEV1 of 37% of the predicted value. Only 36% were smokers.

Genotypes with a heterozygous Z allele were the most frequent, then Pi*ZZ, with Pi*SZ (18.5% of patients) and Pi*M1Z (14.8% of patients) being the most common. The presence of a history of smoking in the non-Pi*ZZ genotypes was high, reaching 100% in most of them, and there was also a high frequency of bronchiectasis. It was observed that the 4 individuals with a normal A1AT dosage do not have the Z allele (Table 4).

In the study, eight participants had liver impairment (29.6%), and all of them had a homozygous or heterozygous Z allele. In the Pi*ZZ genotype, 45% of the individuals had liver function impairment, and in Pi*M1Z, 50% of the individuals had this alteration (Table 4).

Bronchiectasis was found in 52% of the participants: in 4 (36%) with the Pi*ZZ genotype, but these alterations

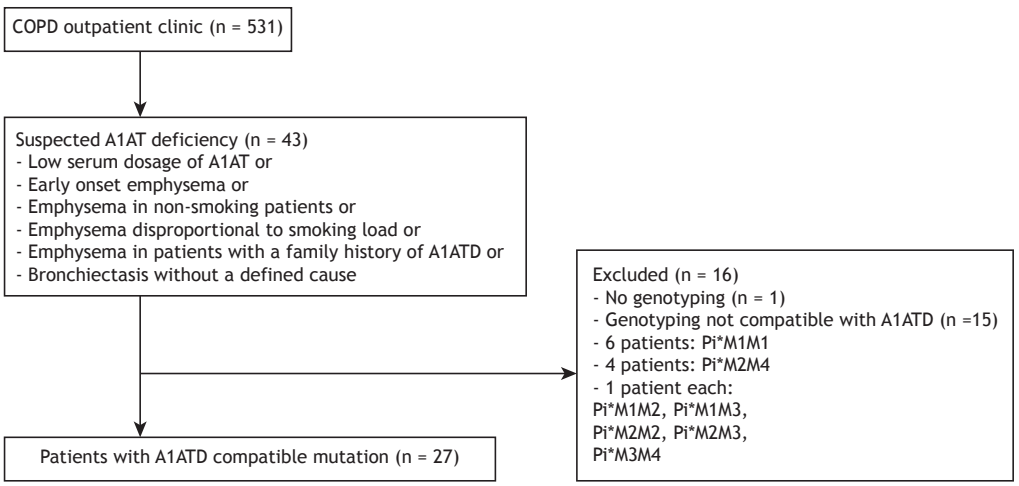

Figure 1. Flowchart of the patients included in the study.

Table 1. Dosage of alfa-1 antitrypsin and demographic characteristics of the patients with a mutation of the alpha-1 antitrypsin gene.

Variables	Population of patients confirmed with the A1AT gene mutation (n = 27)
A1AT serum level- mg/dL Median (interquartile range)	45 (20-81)
A1AT serum level - n (%) Reduced (< 83 mg/dL) Normal (≥ 83 mg/dL)	23 (85) 4 (15)
Age (in years) Median (interquartile range)	54 (42-59)
Age at onset of respiratory symptoms (in years) Median (interquartile range)	40 (25-48)
BMI - kg/m^2 Median (interquartile range)	23.7 (20.6-27.8)
Gender - n (%) Male/female	17 (63)/10 (37)
Alcoholism - n (%) Non-alcoholic Ex-alcoholic Active alcoholic	25 (92) 1 (4) 1 (4)
Smoking - n (%) Non-smoker Ex-smoker Active smoker	10 (37) 14 (52) 3 (11)
Smoking load- packs/year Median (interquartile range)	28.5 (24-37)
Bronchiectasis - n (%) Yes/no	14 (52)/13 (48)
Asthma - n (%) Yes/no	5 (19)/22 (81)
Allergic rhinitis - n (%) Yes/no	6 (22)/21 (78)
Pulmonary tuberculosis - n (%) Yes/no	4 (15)/23 (85)
Systemic arterial hypertension - n (%) Yes/no	5 (19)/22 (81)
Diabetes mellitus - n (%) Yes/no	1 (4)/26 (96)
Dyslipidemia - n (%) Yes/no	5 (19)/22 (81)
Gastroesophageal reflux disease - n (%) Yes/no	6 (22)/21 (78)
Depression - n (%) Yes/no	4 (15)/23 (85)
Osteoporosis - n (%) Yes/no	1 (4)/26 (96)
Past history of cancer - n (%) Yes/no	3 (11)/24 (89)

A1AT: alfa-1 antitrypsin; BMI: body mass index.

were more frequent in the genotypes Pi*SZ (60%) and Pi*M1Z (75%), as well as in all individuals of the Pi*ZMnichinan, Pi*M1S and Pi*SF genotypes (Table 4). Of the individuals with bronchiectasis, four had no emphysema on the tomography, and only one individual had a history of previous pulmonary tuberculosis. The presence of bronchiectasis is not associated with A1AT dosage (p=0.52), age (p=0.79), or smoking (p = 1.00), but it is associated with males (p=0.046).

The four individuals with a normal A1AT dosage had a median dosage of 101.5 mg/dL and had the following genotypes: Pi*M1S, Pi*M1I and Pi*M3Plowell. All of the patients had a diagnosis of COPD, with tomographic emphysema, a history of smoking, a median smoking rate of 28 packs/year, and two patients presented concomitant bronchiectasis. The median FEV1 of these patients was 1.01L (31.5% of the predicted value).

Table 5 shows the characteristics of the group with a normal and altered A1AT dosage, and shows no statistically significance difference between age, smoking load, FEV1 and the presence of bronchiectasis. An analysis of the groups with one A1ATD mutated allele

Table 2. Pulmonary function measurements in patients with a mutation of the alpha-1 antitrypsin gene.

Functional variables	Median (n = 27)	Interquartile range
FEV1 - L	1.37	1.00-2.05
FEV1 - % predicted	43	32-67
FVC - L	3.03	2.52-3.45
FVC - % predicted	71	62-96
FEV1/FVC	0.47	0.39-0.75
TLC - L	6.15	5.3-7.7
TLC - % predicted	118	91-129
RV - L	3.00	2.2-4.8
RV- % predicted	169	128-231
DLCO - % predicted	59.5	31.8-81.5

FEV 1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; DLCO: pulmonary diffusion.

Table 3. Tomographic characteristics in patients with a mutation of the alpha-1 antitrypsin gene.

Tomographic characteristics	Frequency (%) (n = 27)
Emphysema	21 (77.8%)
Panlobular	16 (59.2%)
Prevalence in upper lobes	4 (14.8%)
Prevalence in lower lobes	10 (37%)
No predominance	7 (25.9%)
Bronchial thickening	22 (81.5%)
Bronchiectasis	14 (52%)
Mosaic perfusion	12 (44%)
Bubbles	7 (26%)
Cysts	1 (4%)

Table 4. Mutations in the alpha-1 antitrypsin gene found with their frequency, clinical, laboratory, and lung function characteristics (n=27).

Genotype	Frequency n (% of the total number of study subjects)	Median A1AT dosage in mg/dL	Number of individuals with A1AT serum level > 83 mg/dL n (% of the same genotype)	FEV1 Median in L (% of predicted)	Current or previous smoking n (% of the same genotype)	Number of patients with BQT n (% of the same genotype)	Number of patients with liver disease n (% of the same genotype)
Pi*ZZ	11 (40.7%)	20.0	0	1.36 (37%)	4 (36%)	4 (36%)	5 (45%)
Pi*SZ	5 (18.5%)	58	0	1.37 (43%)	4 (80%)	3 (60%)	0
Pi*M1Z	4 (14.8%)	79.5	0	1.88 (73%)	2 (50%)	3 (75%)	2 (50%)
Pi*M2Z	1 (3.7%)	76	0	3.02 (103%)	1 (100%)	0	0
Pi*ZMnichinan	1 (3.7%)	27	0	1.28 (43%)	1 (100%)	1 (100%)	1 (100%)
Pi*M1S	2 (7.4%)	106	2 (100%)	1.01 (31.5%)	2 (100%)	2 (100%)	0
Pi*M1I	1 (3.7%)	111	1 (100%)	0.67 (19%)	1 (100%)	0	0
Pi*M3Plowell	1 (3.7%)	88	1 (100%)	1.37 (48%)	1 (100%)	0	0
Pi*SF	1 (3.7%)	81	0	2.05 (58%)	1 (100%)	1 (100%)	0

A1AT: alfa-1 antitrypsin; FEV1: forced expiratory volume in one second; BQT: bronchiectasis.

versus two mutated alleles also showed no statistically significant difference for age, FEV1, smoking load and the presence of bronchiectasis, but the difference between the A1AT dosage, which was higher in the alleles with only one mutation, was statistically significant. This result highlights that, even at normal or near normal dosages, such as those observed in the presence of a single allele for A1ATD, pulmonary disease may be present in a severe form at an early age, despite a similar smoking load.

The clinical evaluation showed that 44.4% of individuals had dyspnea with a mMRC greater than

or equal to 2, more than one exacerbation had manifested in 59.3% of them in the last year, and 18.5% presented SpO2 lower than 92% in ambient air, and are users of home oxygen therapy. There was no statistically significant association between mMRC and normal versus altered A1AT dosage, which reinforces the findings that the group of patients with a normal dosage exhibited a similar disease severity to that of the altered dosage group.

Two individuals with a Pi*ZZ genotype are receiving A1AT replacements. The evaluation for lung transplants was performed in 7 patients (26%), with 4 of them being contraindicated, one of them being followed, one being evaluated, and one being release after an evaluation of the transplant.

DISCUSSION

The present study presented the genotypic analysis and the clinical, radiological and functional evaluations of 27 individuals with a mutation in the A1AT gene in a Brazilian referral center. This study is relevant because of its genotypic analysis of mutations that are not frequently evaluated in other studies, as well as the fact that it used genotyping on individuals with normal serum levels, but who had a high clinical suspicion for A1ATD.

The diagnosis of A1ATD was confirmed in 64.3% of the cases in which it was suspected. We found a prevalence of 5.1% of A1ATD in our COPD outpatient clinic. In a recent study, Russo et al. found that 2.8% of patients with COPD in Brazil had A1ATD,[2] which is an alarming finding considering the low frequency of this diagnosis in clinical practice and the small number of articles published on A1ATD in the Brazilian population.[2,15] Our country has a vast racial diversity, miscegenation and European immigration from countries where the frequency of alleles involved with A1ATD is high.

In our data, we observed that a majority of individuals were male, with a positive history of smoking, and the onset of symptoms present at an early age of 40, which is similar to other studies,[4,16] where 40.7% of their participants had the Pi*ZZ genotype. The individuals of this genotype presented low A1AT dosages, reduced FEV1 values, which connotes advanced lung disease, and a lower percentage of a history of smoking when compared to the other genotypes. Bronchiectasis was found in 36% of the individuals with this genotype, and 2 subjects did not have tomographic emphysema. Other genotypes found in our population, in order of frequency, were: Pi*SZ, Pi*M1Z and Pi*M1S. And the other genotypes had one individual each: Pi*M2Z, Pi*M1I, Pi*ZMnichinan, Pi*M3Plowell and Pi*SF. Many of these genotypes are cited in the literature as not causing clinically significant disease,[4,17,18] especially when there is only one allele with a mutation in the A1AT gene. However, in our study, we found that they had a reduced FEV 1 and a high prevalence of COPD and bronchiectasis. It is probable that the individuals' history of smoking contributed to the onset of lung disease, but the severity of the disease, characterized by low FEV 1 values, may not be justified only by the smoking.

Four individuals had normal A1AT dosages and were heterozygous for A1AT gene mutations. Despite the normal dosage, they had a FEV 1 and frequency of bronchiectasis similar to that of the altered A1AT dosage group. There was also no difference between the amounts of smoking load of these groups, suggesting that smokers with normal A1AT, but with a compatible genotype for an A1AT mutation, are at risk for more rapid loss of lung function. These data demonstrate, for the first time in the national population, the extreme importance of performing A1AT genotyping when there is high clinical suspicion, even when there are normal A1AT dosages.

The presence of bronchiectasis in 52% of our sample was higher than that reported in other studies,[21,22] with 26% being in a study with a greater number of participants.[22] The high frequency of bronchiectasis in our study is not justified by the high incidence of tuberculosis in our country, since only one individual with bronchiectasis presented a history of tuberculosis. Another relevant finding is the high prevalence of bronchial thickening and mosaic perfusion, which brings attention to airway involvement in these patients.[23,24] And the very presence of individuals with bronchiectasis in the absence of emphysematous lesions in four patients should be emphasized, given that it is speculated that bronchiectasis occurs due to a distortion effect of the parenchyma because of

Table 5. Characteristics between the groups with normal and altered alpha-1 antitrypsin dosage, and genotypes with 2 alleles for alpha-1 antitrypsin deficiency and 1 allele for alpha-1 antitrypsin deficiency.

Variable	Normal A1AT dosage (n = 4)	Altered A1AT dosage (n = 23)	p-value	Genotypes with 2 alleles for A1ATD (n = 18)	Genotypes with 1 allele for A1ATD (n = 9)	p-value
A1AT dosage mg/dL (median)	101.5	30.0	< 0.001*	22	81.5	< 0.001*
Age	44	54	0.41*	54	47	0.24*
FEV1 % predicted (median)	31.5	43	0.11*	43	53	0.68*
Smoking load packs/year (median)	28	28.5	0.59*	28.5	29.5	0.80*
Bronchiectasis n (%)	2 (50%)	12 (52%)	1.00$	8 (47%)	6 (60%)	0.70$

A1AT: alfa-1 antitrypsin; A1ATD: alfa-1 antitrypsin deficiency; *Mann-Whitney test; FEV1: forced expiratory volume in one second; $Fisher's exact test.

emphysema, which is not justified in the patients who do not have emphysema. [25]

Our main limitations include the fact that we performed a cross-sectional analysis of a small sample of unicentric medical records. Nevertheless, our sample reflects the rarity of the disease and, because it includes a small population with regular outpatient follow-up, the percentage of missing data was minimal.

The main take away from our study is the characterization of A1ATD in Brazil. By knowing the characteristics of our population, we can systematize a screening process in individuals with a high probability of A1ATD for future studies. Thus, it will be possible to reduce the costs of a generalized screening process for all patients with COPD,[4] in a country with such severe economic limitations.

The characterization of A1ATD in our study showed that the most frequent genotype found was Pi*ZZ. Individuals with a mutation in the A1AT gene in only one allele and a normal A1AT serum dosage also presented significant lung disease. A high frequency of emphysema, bronchiectasis and bronchial thickening, low median values of FEV1 and A1AT, and an early onset of respiratory symptoms were found.

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