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Research Article

# Alpha 1 Antitrypsin Deficiency: Characterization of Patients in a Tertiary Hospital

**Joana Vilaça[1]*, Sofia Brandão Miranda[1]*, Maria Ventura Nogueira[1], Diana Oliveira[1] and Filipa Neiva[1]**

*Gastroenterology Unit, Pediatric Service, Hospital de Braga, Portugal*

**Joana Vilaça and Sofia Brandão Miranda contributed equally to this work and should be considered as first authors.*

## Abstract

### Introduction

AAT deficiency (AATD) is an autosomal recessive disorder characterized by decreased or dysfunctional AAT production. It is associated with lung, liver, and, less commonly, skin disease. In pediatric populations, hepatic manifestations are more common. The goal of this study is to characterize the pediatric population with AATD at a Level III hospital.

### Materials and Methods

A retrospective study was conducted to evaluate the pediatric population with pathogenic variants in the SERPINA 1 gene at a Level III hospital. The entire pediatric population aged 0-18 years in 2022 was selected, with the exception of those with AATD but no identified genotype. Data analysis was performed using IBM SPSS, version 23.

### Results

72 patients were included, mostly male (n=42, 58.3%), with a mean age of diagnosis of 61.63 months (SD=50.33). AAT values varied between 11 and 109, with a mean of 59.60 (SD=18.05). The most frequent genotype was MZ (n=27, 38.0%), followed by SZ (n=20, 28.2%). The most common reasons for measuring AAT and subsequent diagnosis were asthma and preschool-age sibilant wheezing, comprising 54.4% of the total. Patients with the ZZ genotype had significantly lower AT values compared to patients with the MS (p=0.034), MZ (p<0.001), and SS (p=0.001) genotypes. Patients with the SZ genotype showed significantly lower values compared to patients with the MZ genotype (p=0.002).

### Conclusion

The ZZ genotype has a high risk of liver and lung disease, and it is essential to alter environmental factors in order to change the natural course of the disease.

**Keywords:** Alpha 1 antitrypsin deficiency; Genotype; Pediatric age

***Corresponding authors:** Sofia Brandão Miranda, Paediatric Department, Hospital de Braga, Braga, Portugal, Tell: +351 926702396; E-mail: asofiabmiranda@gmail.com

Joana Vilaça, Paediatric Department, Hospital de Braga, Braga, Portugal, Tell: +351 916566764; E-mail: joana.gvilaca@gmail.com

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## Introduction

Alpha-1-antitrypsin (AAT) is a glycoprotein encoded by the SERPINA1 gene, located on the long arm of chromosome 14 (14q31-32). It is a protease inhibitor (Pi) that inhibits the proteolytic action of enzymes. AAT is primarily produced in the liver, but it is also produced to a lesser extent in macrophages and the bronchial epithelium. It reaches the lungs through circulation, where it performs its main function of inhibiting proteolysis [1].

Alpha-1 Antitrypsin Deficiency (AATD) is an autosomal codominant disorder characterized by decreased production or dysfunctional production of alpha-1 antitrypsin (AAT). This disorder is associated with lung, liver, and, more rarely, skin disease. In pediatric age, hepatic manifestations are predominant. In this age group, AATD is the most frequent genetic cause of liver disease and the second leading cause of liver transplantation, after biliary atresia. AATD is one of the most prevalent hereditary genetic disorders worldwide, with a frequency in Europe comparable to that of Cystic Fibrosis (occurring in approximately 1 in every 2000-4000 individuals) [2,3].

In Northern Europe, the Z allele is predominant, while in the Iberian Peninsula, variants with the S allele are more common. There is currently a lack of consistent data on the prevalence of AATD in Portugal. However, it is estimated that the prevalence of the five main phenotypic classes of PIS and PIZ deficient alleles (PIMS, PIMZ, PISS, PISZ, and PI*ZZ) in Portugal is 1 in every 3.8 individuals. The S allele has a decreasing frequency from North to South in the country, while the Z allele has the highest prevalence in the North and the lowest in the center [4].

The aim of this study is to characterize the pediatric population with AATD in a level III hospital.

## Materials and Methods

### Study design, setting and population

A retrospective study was conducted to evaluate the pediatric population with pathogenic variants in the SERPINA 1 gene at a level III hospital. The study included the entire pediatric population aged 0-18 years in 2022. The population with AATD but without an identified genotype was excluded from the study.

### Data collection and procedure

Data was collected between September and November of 2022. SERPINA1-genotype, AAT value, age at diagnosis, reason for diagnosis and the presence of hepatitis.

### Data handling and statistical analyses

Data analysis was performed using IBM SPSS, version 23. An exploratory data analysis was carried out in order to verify if the quantitative variables presented a normal distribution, analyzing the asymmetry and kurtosis values, the results of the Shapiro-Wilk tests and the graphs. Since the variables did not present a normal distribution, parametric and non-parametric tests were performed and, when similar results were obtained, the results of the parametric tests were presented (Fife-Schaw, 2006).

For the descriptive analysis of variables, absolute (n) and relative (%) frequencies are presented for qualitative variables and means (M), standard deviation (SD), median (Mdn) and interquartile range (AIQ) for quantitative variables.

To analyze differences between three or more categories in relation to quantitative variables, ANOVA was used, when using parametric tests, and the Kruskal-Wallis test, when using non-parametric tests. In this last test, when statistically significant differences were found, pairwise comparisons were used, with Bonferroni correction to identify differences between groups. As effect size measures, the eta squared (η2) is presented in both tests.

To analyze the association between two qualitative variables, the chi-square test was used. However, since the percentage of cells with an expected count less than 5 was greater than 20%, the Fisher Test result is reported. As a measure of effect size, Cramer's V (φc ) is presented.

## Results

The sample consisted of 72 patients, with the majority being male (n = 42, 58.3%) and an age at diagnosis ranging from 0 to 192 months, with a mean of 61.63 months (SD = 50.33). The AAT value ranged from 11 to 109mg/dL, with a mean of 59.60 (SD = 18.05). In terms of genotypes, the most frequent was MZ (n = 27, 38.0%), followed by SZ (n = 20, 28.2%) (Table 1).

| Genotype | n (%) |
|---|---|
| MZ | 27 (38.0) |
| SZ | 20 (28.2) |
| ZZ | 11 (15.5) |
| SS | 6 (8.5) |
| MS | 6 (8.4) |
| Mheerlen | 1 (1.4) |

**Table 1:** Descriptive measures related to genotype.

The most common reasons for measuring AAT and subsequently diagnosing AATD were asthma and sibilant wheezing in preschool age children, accounting for 54.4% of the total. This was followed by recurrent respiratory infections, in 16.2% of cases. Other reasons included family screening (11.7%), chronic hypertransaminases (10.3%), neonatal cholestasis (5.9%), and recurrent pneumothorax (1.5%) (Table 2).

The results of the analysis of differences between genotypes in terms of age at diagnosis and AAT value are presented in (Table 3).

| Reasons for AAT measure | n (%) |
|---|---|
| Asthma | 13 (19.1) |
| Neonatal cholestasis | 4 (5.9) |
| Elevation of transaminases | 7 (10.3) |
| Family history | 8 (11.7) |
| Recurrent respiratory infections | 11(16.2) |
| Recurrent pneumothorax | 1 (1.5) |
| Sibilant wheezing of preschool age children | 24 (35.3) |
| No data | 4 |

**Table 2:** Reasons for AAT measure.

There were statistically significant differences in terms of AAT value, $\chi2\ (4) = 34.24$, $p < 0.001$, $\eta2 = 0.50$. Pairwise comparisons, with Bonferroni correction, revealed that patients with the ZZ genotype had significantly lower AAT values than patients with the MS ($p = 0.034$), MZ ($p < 0.001$), and SS ($p = 0.001$) genotypes. Additionally, patients with the SZ genotype had significantly lower values compared to patients with the MZ genotype ($p = 0.002$). On the other hand, there were no statistically significant differences between genotypes regarding age at diagnosis, $F\ (4, 64) = 0.49$, $p = 0.740$, $\eta2 = 0.03$.

| | MZ (*n* = 27) | SZ (*n* = 20) | ZZ (*n* = 11) | SS (*n* = 6) | MS (*n* = 5) | p |
|---|---|---|---|---|---|---|
| **Age at diagnosis** *(M, DP)* | 66.89 (51.10) | 60.10 (49.36) | 55.36 (56.56) | 42.67 (36.10) | 81.60 (72.70) | 0.740[a] |
| **AAT** *(Mdn, AIQ)* | 68.00 (13.00) | 54.50 (18.00) | 29.00 (11.00) | 72.50 (6.00) | 69.00 (15.00) | < 0.001[b] |

**Table 3:** Relationship between genotype and age at diagnosis and serum AAT value.

a ANOVA; b Teste de Kruskal-Wallis

Only 13.7% (n = 7) of the sample had chronic hepatitis. When analyzing the association between the existence of chronic hepatitis and genotype, a statistically significant association was found (Fisher's test, $p = 0.017$). There were significantly more cases with chronic hepatitis and the ZZ genotype (57.1%) compared to those without (7.1%), as presented in (Table 4).

| **Chronic hepatitis** | | | | |
|---|---|---|---|---|
| | No hepatitis (n = 42) n (%) | Hepatitis (n = 7) n (%) | p | φc |
| **Genotype** | | | 0.017 | 0.53 |
| MZ | 20 (47.6) | 2 (28.6) | | |
| SZ | 10 (23.8) | 0 (0.0) | | |
| ZZ | 3 (7.1) | 4 (57.1) | | |
| SS | 5 (11.9) | 0 (0.0) | | |
| MS | 4 (9.5) | 1 (14.3) | | |

**Table 4:** Association between chronic hepatitis and genotype.

## Discussion

The aim of this study was to characterize the Portuguese pediatric population with AATD at a level III hospital. Our research found that there are still few studies on AATD in pediatric age, possibly because manifestations at this age have only recently been discussed.

In previous studies, men have been found to be more affected by AATD than women, which may lead to men being tested for AATD more frequently than women [5]. This fact is in line with our study, in which there is a predominance of males, with 58.3% of the cases.

The median age at diagnosis in this study was 61.63 months (5.13 years), which is higher compared to other studies. For example, a French study reported a mean age at diagnosis of 1.8 years ±3 SD, and a Turkish study reported that 84% were diagnosed before 2 years of age [5].

In our study, the most frequent genotype was MZ, accounting for 38% of cases, followed by SZ, with 28.2%, and the least frequent was ZZ, with 15.5% of cases. This frequency is similar to that found in a Portuguese study from 2018 [4].

There is a significant variability in the age of onset of respiratory symptoms, which rarely appear before 25 years of age. Although asthma/wheezing and recurrent respiratory infections are not common manifestations of AATD in children, these were the main diagnostic reasons in this study. This may be explained by the fact that the measurement of AAT is requested in these specific conditions. On the other hand, spontaneous pneumothorax may be the first manifestation of AATD, and in our sample, we had a case of an adolescent with spontaneous recurrent pneumothorax that led to the diagnosis of AATD. The presentation of AATD with hepatic manifestation is less common, possibly because cholestasis and elevation of transaminases most often manifest earlier in ZZ genotypes, which is also the least frequent genotype in our study [4-6].

Serum levels of AAT are lower in children than in adults [4-6]. Different alleles determine different percentages of protein production, and therefore, there are expected serum levels for each phenotype [7].Children with the MZ genotype have higher AAT values than those with the SZ genotype, and these have higher values than those with the ZZ genotype [4,7]. This is similar to our results, in which patients with the ZZ genotype had significantly lower AAT values than those with the MZ genotype ($p < 0.001$). Additionally, patients with the SZ genotype had significantly lower values compared to those with the MZ genotype ($p = 0.002$).

In this study, there were significantly more cases of chronic hepatitis in patients with the ZZ genotype (57.1%) compared to the other genotypes, which is similar to what is described in the literature [4,6].

There is a relationship between the presence of the ZZ genotype and the presence of chronic hepatitis, with 30-40% of these individuals having liver disease, even if they are asymptomatic [4,5]. This study has several limitations. Firstly, it is a retrospective study on a disease for which there is currently no national pediatric guideline for current practice. Therefore, data were not collected systematically or designed for research purposes, which explains the missing data. Secondly, AATD is an underdiagnosed disease, which introduces the risk of selection bias and potential overestimation of disease severity.

## Conclusion

The natural history of patients with AATD is very variable and highly dependent not only on the AAT variant detected but also on genetic polymorphisms that can modulate its expression. Environmental factors such as tobacco smoke exposure, pollution, exposure to fumes and dust, obesity, alcohol consumption, and viral infections with hepatic tropism can also alter the natural history of these patients. It is essential to invest in prevention, alerting patients to these risk factors. Early diagnosis allows for family screening and genetic counseling in case of another pregnancy. Prospective studies are needed to understand the evolution of patients with AATD and how preventive and therapeutic measures can alter the course of the disease.

## Statement of Ethics

The study complies with the guidelines for human studies and was conducted in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all participants and the study protocol was approved by the local Hospital Human Ethics Committee.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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