PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

ORIGINAL ARTICLE

Alpha-1-antitrypsin deficiency in children: a 10-year case study from a tertiary hospital

Joana Carvalho Queirós[1], Rita Gomes[1], Bebiana Sousa[1], Júlia Vasconcelos[2], Ermelinda Santos Silva[3], and Maria Guilhermina Reis[4]*

[1]Serviço de Pediatria, Centro Materno Infantil do Norte; [2]Serviço de Imunologia Clínica; [3]Unidade de Gastroenterologia Pediátrica, Serviço de Pediatria, Centro Materno Infantil do Norte; [4]Unidade de Pneumologia Pediátrica, Serviço de Pediatria, Centro Materno Infantil do Norte. Unidade Local de Saúde de Santo António, Porto, Portugal

Abstract

Introduction and Objectives: Alpha-1-anti-trypsin (A1AT) is a glycoprotein mainly produced in the hepatocyte. A1AT deficiency is one of the most prevalent genetic disorders and the spectrum of it related diseases is quite wide. Severe A1AT deficiency predisposes individuals to Chronic Obstructive Pulmonary Disease (COPD) and liver disease. Our aim was to characterize clinically, biochemically and phenotypically a sample of pediatric A1AT-deficient (A1ATD) patients and to investigate whether there was any lifestyle change after diagnosis. Additionally, it was our goal to promote awareness to A1ATD among the medical community and to encourage the creation of a national pediatric registry and collaboration in the European registry. **Methods:** An observational retrospective study with analysis of the clinical records of all pediatric patients that had AAT measurement in our tertiary center between January 2010 and December 2019 and revealed levels < 93 mg/dl. **Results:** We enrolled 203 patients, 125 (61.6%) males. Median age at diagnosis was 2.93 years (IQR: 0.73-6.31). There was a family history in 18 patients (8.9%). The assessment of serum A1AT levels was motivated by: respiratory disease (121/203; 59.6%), liver disease (39/203; 19.2%), and family screening (6/203, 3%). The median serum A1AT concentration was 79 mg/dl (IQR: 68-85.4). Phenotyping in 47 patients (23.2%) revealed: MZ (12; 28.6%), MS (10; 23.8%) and ZZ (7; 16.7%). The prevalence of smoking exposure before and after diagnosis was 23.6% and 20.1%, respectively. Only 33% of patients underwent influenza vaccination after diagnosis. **Discussion:** In our sample, there was no significant change in the smoking exposure before and after diagnosis. It would be important to evaluate the impact of early diagnosis and the lifestyle changes on the long-term prognosis, as well as the creation of follow-up protocols in pediatric age. Larger, multicentric studies are needed to determine the real prevalence, the frequency of the main associated mutations, as well as the clinical consequences and follow-up approach required.

Keywords: Alpha-1-antitripsin deficiency. Pediatric age. Familiar history.

***Correspondence:**
Joana Carvalho Queirós
E-mail: joanarpcqueiros@gmail.com

Received: 01-12-2022
Accepted: 09-07-2024
https://pjp.spp.pt

Available online: 01-01-2025
Port J Pediatr. 2025;56(1):10-16
DOI: 10.24875/PJP.M24000460

Défice de alfa-1-antitripsina na população pediátrica: casuística de 10 anos de um hospital de nível III

Resumo

Introdução e Objetivos: O défice de A1AT apresenta um espetro clínico variável e a sua prevalência está subestimada, estando um curso um registo nacional. Caracterizar clínica, bioquímica e fenotipicamente uma amostra de doentes com défice de A1AT em idade pediátrica, promover a participação no registo nacional, e averiguar se houve alteração do estilo de vida após o diagnóstico. **Métodos:** Análise retrospetiva de todos os doentes pediátricos que realizaram doseamento sérico de A1AT no CHUP no período de janeiro/2010 a dezembro/2019 e que revelaram uma concentração < 93 mg/dl. **Resultados:** Incluídos 203 doentes, sendo 125 (61,6%) do sexo masculino. A idade mediana ao diagnóstico foi 2,93 anos (IQR: 0,73-6,31). Havia história familiar de défice de A1AT em 18 doentes (8,9%). O doseamento de A1AT foi motivado por: doença respiratória (121/203; 59,6%), doença hepática (39/203; 19,2%), e rastreio familiar (6/203, 3%). A concentração sérica mediana de A1AT foi 79 mg/dl (IQR: 68-85,4). A fenotipagem em 47 doentes (23,2%) revelou: MZ (12; 28,6%), MS (10; 23,8%) e ZZ (7; 16,7%). Em quatro doentes foi efetuada biópsia hepática e um foi submetido a transplante hepático. A prevalência de exposição tabágica antes e depois do diagnóstico foi de 23,6% e 20,1%, respetivamente. Apenas 33% dos doentes realizaram vacina antigripal após o diagnóstico. **Discussão:** A incidência de diagnóstico por rastreio familiar foi baixa e o genótipo foi avaliado numa minoria dos doentes. Destaca-se ainda a baixa redução da exposição tabágica após o diagnóstico. Seria importante avaliar o impacto do diagnóstico precoce e alteração do estilo de vida no prognóstico a longo prazo, bem como a criação de protocolos de seguimento em idade pediátrica.

Palavras-chave: Défice de alfa-1-antitripsina. Idade pediátrica. História familiar.

Keypoints

What is known

- A1AT deficiency is one of the most prevalent genetic disorders and the spectrum of it related diseases are quite wide, but it seems to be underdiagnosed in pediatric age.
- Severe A1AT deficiency predisposes individuals to Chronic Obstructive Pulmonary Disease (COPD) and liver disease.
- Lifestyle changes appear to have an important influence on the prognosis of the disease.

What is added

- Family screening accounted for only 3% of diagnoses, which contrasts with the expected prevalence and highlights significant underdiagnosis, even among families with a positive history of A1AT deficiency.
- The PiMZ phenotype was the most prevalent (28.6%) in this cohort, differing from previous studies in the Iberian Peninsula that identified PiMS as the most frequent phenotype.
- To encourage diagnosis and inclusion in the European register of the disease.

Introduction

Alpha-1-antitrypsin (A1AT) is a glycoprotein from the serine protease inhibitor superfamily. It is encoded in the PI locus of the *SERPINA1* gene on the long arm of chromosome 14 (14q31.32)[1,2,3]. A1AT is mainly produced in the hepatocytes, but is also synthetized by neutrophils, mononuclear phagocytes, lung epithelial cells and intestinal cells[1,4,5]. Under normal conditions the liver is capable of secreting 34 mg/kg of A1AT in 24 hours, but that may increase two- to five-fold in response to inflammatory, tumoral or infectious conditions[1].

The highly polymorphic A1AT gene is passed by simple mendelian inheritance in an autosomal codominant pattern through two alleles, meaning that affected individuals have inherited an abnormal A1AT gene from each parent[1,8]. More than 150 alleles of A1AT have been identified by isoelectrofocusing (IEF) and each has a letter code (A and Z)[1,5,8]. The set of variants is called the PI (protease inhibitor) system, and most have no clinical significance[1]. Normal alleles are present in more than 85 – 90% of individuals and are Pi*M. The most prevalent deficient alleles are designated PiS and PiZ[1,5,9].

A1AT deficiency is one of the most prevalent genetic disorders, and is most common in the adult population[5]. The estimated prevalence is around 1:2000 – 4000 people in Europe, but it seems to be underdiagnosed mainly in the pediatric age range[5,10]. Despite several studies having been carried out in the past decade, more epidemiological studies are needed to determine the real prevalence of this condition[10]. In 2018, Ruiz et al., reported a prevalence of 8.1% of the Z allele and 81.9% of the PiZZ phenotype in an adult

population of the Portuguese island of Madeira[22]. Nevertheless, to the best of our knowledge there are no epidemiological studies conducted in the Portuguese pediatric population.

The A1AT deficiency, together with other genetic characteristics, as well as certain environmental factors, predispose these individuals to a greater risk of developing disease (tobacco smoke to lung disease and alcohol to liver disease)[1,5]. Also, obesity was described in association with a higher risk of liver disease progressing to fibrosis and cirrhosis in adults with A1AT deficiency[23]. The spectrum of A1AT deficiency-related diseases is quite wide, and depends on the age at presentation. It is currently considered a systemic condition, with the lungs and liver being the most affected organs, and less commonly, the skin[5,9,13,14]. The main clinical manifestations of severe A1AT deficiency include severe liver disease in infancy and childhood, caused by polymer toxicity, and pulmonary emphysema occurring in adulthood, due to low serum A1AT concentration[1,5].

The accumulation of A1AT polymers in hepatocytes can lead to their injury and progression to cirrhosis may occur[2]. Although hepatic involvement is more frequent with advancing age, cholestatic jaundice or hepatitis may be seen in infants and young children[13,19]. Only 3% of cases are diagnosed due to hepatic manifestations, such as elevated transaminases[12]. Skin involvement is rare, although panniculitis and vasculitis may appear[5].

The diagnosis of A1AT deficiency is confirmed by laboratory tests that quantify serum A1AT levels[1]. Several tests are currently available, both quantitative and qualitative: serum A1AT assay is a quantitative test that quantifies the amount of protein circulating in the blood; A1AT phenotyping is a qualitative test that detects circulating variants; A1AT genotyping and *SERPINA1* gene sequencing are considered the ideal method for identifying specific mutations associated with A1AT deficiency[1,5]. In the event of clinical suspicion, the quantification of serum A1AT levels is recommended. The consensus of the American Thoracic Society and European Respiratory Society suggests the combination of a quantitative test and phenotyping as the gold standard for diagnosis[5,15]. If blood levels are lower than 110 mg/dL phenotyping should be performed to confirm the diagnosis[15].

According to the American Thoracic Society/European Respiratory Society, and extrapolating for the pediatric age range, the indications for serum A1AT levels are: early onset emphysema; emphysema in the absence of exposure to known risk factors; confirmed cases of A1AT deficit in the family; family history of respiratory pathology, such as emphysema, dyspnea, cough or bronchiectasis; family history of liver disease or panniculitis; individuals with chronic obstructive pulmonary disease (COPD); asthmatics whose respiratory function tests do not normalize after adequate treatment; or in the presence of liver disease of unknown origin[12,20].

After diagnosis, the initial approach should include a thorough clinical history and examination, focusing on the aforementioned organ systems that are most affected. Other auxiliary diagnostic tests should be performed depending on the clinical findings, as well as the age of the patient[5]. Respiratory function tests, such as spirometry, plethysmography and carbon dioxide diffusion capacity should be performed in the case of older children or adolescents[15]. Other examinations, such as arterial blood gas analysis, respiratory effort tests, chest x-ray and a computed tomography (CT) scan, can also be considered depending on the clinical setting[16]. Liver function tests and abdominal ultrasounds should be considered[1,5,10]. Serum liver assessment should include transaminases, as well as alkaline phosphatase, gamaglutamiltransferase (GGT), bilirubin, albumin, coagulation tests, platelets count, fat soluble enzymes, and alpha-fetoprotein[17]. Abdominal ultrasound identifies indirect signs suggestive of steatosis and cirrhosis, clarifying the need for further investigation[5]. Liver biopsy is not recommended as an initial test, but may be performed when there is an established liver lesion to better assess diagnosis and prognosis[17].

In regard to the management of these patients, the primary focus should be on promoting lifestyle modifications, including avoidance of tobacco exposure, adherence to a healthy diet, daily exercise and immunizations. In patients with respiratory symptoms, symptomatic treatment and respiratory kinesiotherapy should also be provided[1,5,10]. In patients with end-stage liver disease, liver transplantation is an option[23].

The follow-up depends largely on the clinical presentation and evolution. Individuals diagnosed during childhood may never show manifestations if they have never been exposed to tobacco, for example[5]. Respiratory function tests should be considered in late adolescence, as well as every two to three years. Liver evaluation with abdominal ultrasound and laboratory testing should also be performed at similar intervals[5,10].

Our aim was to characterize clinically, biochemically and phenotypically a sample of pediatric A1AT-deficient patients and to investigate whether there was any change in lifestyle after diagnosis. It was also our goal to promote awareness and to encourage the creation of a national pediatric registry and collaboration in the European registry.

Table 1. Sample baseline characterization

Total	203
Gender	
Male	125 (61.6%)
Female	78 (38.4%)
Age at diagnosis (years)	2.93 (0.75-6.31)
Time until diagnosis	2 (0-13) months
County of residence	
Porto	48 (23.6%)
Gondomar	35 (17.2%)
Vila Nova de Gaia	15 (7.24%)
Valongo	14 (6.9%)
Matosinhos	11 (5.4%)
Other	80 (39%)
Positive family history of A1AT deficiency	18 (23.4%)
Reason for A1AT measurement	
Respiratory disease	121 (59.6%)
Hepatic disease	39 (19.2%)
Family screening	6 (3.0%)
Unknown	37 (17.9%)
Serum A1AT levels (mg/dL)	79 (68.0-85.4)
Phenotype	47 (23.2%)
MZ	12 (28.6%)
MS	10 (23.8%)
ZZ	7 (16.7%)
SZ	6 (14.3%)
SS	1 (2.4%)
Other	6 (14.3%)

Data is presented as n, n (percentage) or median (IQR), as appropriate.
A1AT: alpha-1-antitrypsin.

Table 2. Auxiliary exams and therapeutic approach

Total	203
Serum measurements performed at diagnosis	
BT - Abnormal values (n = 84)	29 (14.3%)
GGT - Abnormal values (n = 120)	36 (17.7%)
ALT - Abnormal values (n = 128)	28 (13.9%)
Liver biopsy (total)	4 (2.0%)
Nuclear inclusions	1 (25%)
Spirometry (total)	24 (11.8%)
Abnormal	15 (62.5%)
Abdominal ultrasound	50 (24.6%)
Abnormal	15 (29.4%)
Supportive therapy	14 (6.9%)
UDCA	9 (64.3%)
Vitamins and UDCA	5 (35.7%)
Smoke exposure	
Prior to diagnosis	41 (23.6%)
After diagnosis	34 (20.1%)
Immunizations	
Influenza	61 (33.0%)
Pneumococcal	127 (62.6%)

Data is presented as n, n (percentage) or median (IQR), as appropriate.
BT: bilirubin; GGT: gamma-glutamyl transferase; ALT: alanine aminotransferase; UDCA: ursodeoxycholic acid.

Methods

Study design and sample

We conducted a retrospective study of patients under 18 years of age, diagnosed with A1AT deficiency in the biochemical laboratory of Centro Hospitalar Universitário de Santo António, between January 2010 and December 2019. We first analysed the laboratory records, and then we analysed the patients' clinical records.

Inclusion and exclusion criteria

All pediatric patients who underwent serum A1AT measurements by immunoturbidimetry in the aforementioned period were screened. The inclusion criterion was a A1AT serum level lower than 93 mg/dL. Patients who did not undergo a clinical observation and follow-up in our institution were excluded.

Definition of variables and data collection

Data were collected by assessing the electronic clinical files.

Demographic data (age at referral and diagnosis, sex and county of residence) and clinical variables (family history of A1AT deficiency; personal and family history of liver or respiratory disease; smoke exposure prior to and after diagnosis; and influenza and pneumococcal immunization) were collected. The reason behind the referral for consultation and the A1AT measurement (liver or respiratory disease, family screening, other or unknown) were also reviewed.

Regarding auxiliary examinations performed during follow-up time, we evaluated minimum and maximum serum levels of A1AT and, when performed, blood levels of bilirubin, gamma-glutamyltransferase (GGT) and alanine aminotransferase (ALT) at diagnosis, spirometry, abdominal ultrasound, liver biopsy and genotype/phenotype studies.

We also reviewed the need for support treatment (nutritional, vitamins and trace elements and ursodeoxycholic acid (UDCA)) and liver transplantation.

Ethics

This research complies with all the relevant national regulations, institutional policies and is in line with the tenets of the Helsinki Declaration. The study was approved by the Ethics Committee of Centro Hospitalar Universitário de Santo António and Instituto de Ciências Biomédicas Abel Salazar.

Statistical analysis

Statistical analysis was performed using IBM® SPSS® Statistics 25.0. Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as median and percentiles 25 and 75.

Results

The sample baseline characterization is described in table 1. A total of 203 patients were included, of whom 61.6% were male and 38.4% were female. The median age at diagnosis was 2.93 years (Interquartil range (IQR): 0.75 - 6.31). Most patients lived in Porto (23.6%) and were referred for a pediatric appointment by primary care facilities (26.8%). There was a family history of A1AT deficiency in 23.4% of patients, but this was not the reason for A1AT measurement in all. Serum A1AT measurement in the context of family screening was carried out in only 3.0% of patients. Other reasons included respiratory symptoms (59.6%), such as repeated airway infections, recurrent wheezing and asthma, and liver abnormalities (19.2%), such as unexplained elevation of transaminases and jaundice of unknown cause. The median serum A1AT levels in our sample was 79 (IQR: 68.0 - 85.4; minimum 6, maximum 89.8) mg/dL.

Table 2 describes the investigation and clinical approach in our sample during a median follow-up time of three years (IQR: 2 - 7). The median time until diagnosis was two months (IQR: 0 - 13). Serum measurements of BT, GGT and ALT were performed at diagnosis in 41.6%, 59.7% and 63.7% of patients, and were abnormal in 34.5%, 30.0% and 21.9% of cases, respectively. Spirometry was performed in 12%, with abnormal results in 63% of these. Concerning the liver study, abdominal ultrasound was carried out in 25% of patients, with abnormal results in 29%. Four patients underwent a liver biopsy and A1AT inclusions were found in one. Phenotype studies were conducted in 23.2% patients, with MZ, MS and ZZ being the most prevalent types (28.6%, 23.8% and 16.7%, respectively).

Fourteen (6.9%) patients needed supportive therapy with vitamins and/or UDCA. One patient had liver cirrhosis and underwent liver transplantation. The majority (62.6%) of patients were vaccinated against pneumococcal infection and approximately one third against influenza virus.

Discussion

A1AT deficiency is underdiagnosed in the pediatric age, thus although it is assumed to be common, its real prevalence is not known[10]. The clinical implications of this deficiency are not yet fully understood, especially in heterozygotic individuals. Underdiagnosis is likely to be a major limitation in the study of the disease impact in the pediatric age group[12]. Nevertheless, several countries have already taken the first step with the creation of national A1AT registries and Portugal has recently joined this group of countries. Although still at the early stages of implementation, it has been growing. However, data regarding the pediatric population are still scarce.

During the study period of ten years, 203 pediatric patients were diagnosed with this condition in one tertiary hospital located in northern Portugal. This reinforces the need to carry out epidemiological studies, especially in this age group. The distribution by municipalities is linked to our hospital's area of intervention. As expected, the municipality of Porto had the highest number of cases, 48 (23.6%), since it is the largest municipality in our hospital's area of influence, with the largest population and the easiest access to health care.

With regard to phenotype, the Pi*MZ was the most common, present in 28.6% of cases. These results differ from previous studies carried out in the Iberian Peninsula, which indicate that the Pi*MS phenotype is the most common[11,13,21]. This difference may stem from the fact that the study was carried out in the general population, including adults.

According to the literature, the Pi*ZZ phenotype is associated with a higher prevalence of pulmonary disease and, in these patients, A1AT values below 50 mg/dL are more common[20]. This phenotype was found in 16.7% of our sample. Despite the percentage being lower than expected[2], it was found that all of these patients had A1AT values lower than 50 mg/dL, with the highest levels in this group being 45 mg/dL.

The identification of individuals at risk may be performed by the presence of clinical manifestations or through family screening[5,11]. Furthermore, asthma is a very common finding amongst these individuals, although there is no well-established relationship between A1AT deficiency and asthma[17]. Likewise, serum levels of A1AT should be measured during the etiologic

study of bronchiectasis, although no causal relationship has been made so far[18]. A1AT deficiency predisposes individuals to the early appearance of chronic obstructive pulmonary disease, such as emphysema, and severe and prolonged exacerbations are common in these individuals[5,16]. The pediatric population is a very particular group since the vast majority of patients are identified during investigations for respiratory symptoms, mainly recurrent infections or chronic cough[5].

In our population, 59.6% of cases had respiratory symptoms, including repeated airway infections, recurrent wheezing and asthma. This is in line with the literature, as the most common consequence of A1AT deficiency is lung injury consequent to a lower protection against the action of the electrophilic protease in the lung tissue[1,7]. Since the hepatocyte is the main site of production of this protein, its lower activity will lead to the accumulation of the abnormal alpha-1-anti-trypsin in the hepatocyte, with consequent injury[5,12]. As expected, hepatic manifestations were the second most frequent reason for A1AT measurement (19.2% of cases), mainly due to the unexplained elevation of transaminases and jaundice of unknown cause. Despite this, in our sample, initial measurements of serum BT, GGT and ALT were carried out in only around 60% of patients. The fact that this was a retrospective study is an important limitation of this study. Furthermore, the lack of determination of the prevalence of obesity in our population is also an important limitation, as it may be overestimating the echographic alterations found (hepatic steatosis).

A positive family history is to be expected, since it is a genetic disease passed by autosomal codominant mendelian inheritance[1,8]. Nevertheless, a positive family history of A1AT deficiency was described in only 23.4% of our sample, a much lower percentage than that described in the literature[1,5]. Moreover, diagnosis by family screening was performed in only 3.0% of patients. These data, in conjunction with the high prevalence that appears to exist and the presence of disease even in heterozygotes, raises the question of whether A1AT measurement should be performed in asymptomatic children with a positive family history. Furthermore, since the presence or absence of disease manifestations also depends on environmental factors, early diagnosis can promote lifestyle changes to minimize some important risk factors. Although there are no clear recommendations in the pediatric age range, it is known that in the adult population, a positive family history is a criterion for AAT measurement.

There are no established protocols regarding the initial approach and follow-up for these patients. As such, a patient's clinical management should be individualized, according to their age, clinical manifestations and complementary test findings. In our sample, the median follow-up time was three years. Serum levels of bilirubin, GGT and ALT were measured at diagnosis in the majority of cases. The frequency of laboratory check-ups were also determined individually and according to previous findings and clinical evaluation. Spirometry and abdominal ultrasound tests were performed in 11.8% and 24.6% of our sample, respectively. Clinical presentation, progress and the individual clinician's experience, is therefore shown to be the principal impetus behind the follow-up of these patients, since there are no defined national or international protocols.

Smoking avoidance and the implementation of healthy lifestyle habits were reinforced in all newly-diagnosed children[1,10]. It has been proven that these measures can delay and minimize the impact of the disease on the quality of life of affected individuals[12]. In our sample, there was a non-significant decrease in smoke exposure after diagnosis. Similarly, these patients were also advised to have the annual influenza vaccine and anti-pneumococcal vaccine. However, the vaccination rate in our sample was only 33.0% and 62.6%, respectively. In our view, it would be interesting to run awareness campaigns in schools, primary health care facilities and even the media regarding the importance of these preventive measures, integrated in a broader prevention of OCPD.

We acknowledge a number of important limitations to our study. First, the retrospective nature of this study, the short follow-up period, and the fact that we report a single center's experience. Furthermore, our sample included only children living in northern Portugal. Despite these limitations, to our knowledge this is one of the first Portuguese studies that tried to characterize a sample clinically, biochemically and phenotypically, although there may have been a selection bias with the inclusion of more severe cases.

Larger, multicentric studies are needed to determine the real prevalence of this condition in Portugal, the frequency of the main associated mutations, as well as the clinical phenotypes and follow-up approach required for these patients. Furthermore, prospective studies would be essential to evaluate the impact of an early diagnosis on the prevention of complications and on the quality of life of these patients. The creation of a national register is essential for a better understanding of this condition and consequently an improvement of healthcare. In Portugal, it is hoped that this is a step in the process of integration into the European register.

Authors' contribution

J. Carvalho: Conceptualization, bibliographic research, writing-original draft, writing-review and editing. R. Gomes: Conceptualization, writing-original draft, writing-review and editing. B. Sousa: Conceptualization, writing-original draft, writing-review and editing. J. Vasconcelos: Validation, writing-review and editing. E. Santos-Silva: Patient's follow-up, validation, writing-review and editing. M. Guilhermina-Reis: Conceptualization, Patient's follow-up, validation, writing-review and editing.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Vidal R, Blanco I, Casas F, Jardí R, Miratvilles M. Diagnóstico y tratamiento del déficit de alfa-1-antitripsina. Arch Bronconeumol. 2006;42(12):645-59. https://doi.org/10.1157/13095974.
2. Martin JP, Charlionet R, Sesboué R, Ropartz C. Alpha1-antitrypsin deficiency. Lancet. 1976;307(7956):434. https://doi.org/10.1016/s0140-6736(76)90284-1.
3. DeMeo DL. Alpha-1 antitrypsin deficiency: genetic aspects of alpha-1 antitrypsin deficiency: phenotypes and genetic modifiers of emphysema risk. Thorax. 2004;59(3):259-64. https://doi.org/10.1136/thx.2003.006502.
4. Crowther DC, Belorgey D, Miranda E, Kinghorn KJ, Sharp LK, Lomas DA. Practical genetics: alpha-1-antitrypsin deficiency and the serpinopathies. Eur J Hum Genet. 2003;12(3):167-72. https://doi.org/10.1038/sj.ejhg.5201127.
5. Lopes AP, Mineiro MA, Costa F, Gomes J, Santos C, Antunes C, et al. Portuguese consensus document for the management of alpha-1-antitrypsin deficiency. Pulmonology. 2018;24:1-21. https://doi.org/10.1016/j.pulmoe.2018.09.004.
6. Janciauskiene SM, Bals R, Koczulla R, Vogelmeier C, Köhnlein T, Welte T. The discovery of α1-antitrypsin and its role in health and disease. Respir Med. 2011;105(8):1129-39. https://doi.org/10.1016/j.rmed.2011.02.002.
7. Bergin DA, Hurley K, McElvaney NG, Reeves EP. Alpha-1 antitrypsin: A potent anti-inflammatory and potential novel therapeutic agent. Arch Immunol Ther Exp (Warsz). 2012;60(2):81-97. https://doi.org/10.1007/s00005-012-0162-5.
8. Lomas DA. Alpha-1 antitrypsin deficiency: molecular pathophysiology. Thorax. 2004;59(6):529-35. https://doi.org/10.1136/thx.2003.006528.
9. American Thoracic Society/European Respiratory Society. Standards for the diagnosis and management of individuals with alpha1-antitrypsin deficiency. Am J Respir Crit Care Med. 2003;168:818-900.
10. Stoller JK, Aboussouan LS. Alpha1-antitrypsin deficiency. Lancet. 2005;365(9478):2225-36.
11. Piitulainen E, Tanash HA. The clinical profile of subjects included in the Swedish National Register on individuals with severe alpha 1-antitrypsin deficiency. COPD. 2015;12 Suppl 1:36-41.
12. Fernandes Fraga JFF, Sá A, Martins VM, Calvino J, Pereira AP, Quaresma M. Deficiência de alfa-1 antitripsina num grupo de crianças com patologia respiratória: experiência da consulta de Pediatria/Alergologia do hospital de Vila Real. Acta Pediátrica Portuguesa. (s.d.);42(3):99.
13. Sveger T. Liver disease in alpha-1 antitrypsin deficiency detected by screening of 200,000 infants. N Engl J Med. 1976;294:1316-21.
14. Stockley RA. Alpha1-antitrypsin: more than just deficiency. Thorax. 2004;59:363-4.
15. American Thoracic Society/European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003;168(7):818-900.
16. Camelier AA, Winter DH, Jardim JR, Barboza CE, Cukier A, Miravitlles M. [Alpha-1 antitrypsin deficiency: diagnosis and treatment]. J Bras Pneumol. 2008;34(7):514-27.
17. Cuvelier A, Muir JF, Hellot MF, Benhamou D, Martin JP, Benichou J, et al. Distribution of alpha1-antitrypsin alleles in patients with bronchiectasis. Chest. 2000;117(2):415-9.
18. Pulmonology Portuguese Society Bronchiectasis Study Group. Recommendations for aetiological diagnosis of bronchiectasis. Rev Port Pneumol. 2016;22(4):222-35.
19. Needham M, Stockley RA. Alpha 1-antitrypsin deficiency: clinical manifestations and natural history. Thorax. 2004;59(5):441-5.
20. Serra S, Banha G, Duarte P. Défice de alfa-1 antitripsina. A propósito de dois casos clínicos. Rev Port Pneumol (Engl Ed). 2008;14(2):295-302. https://doi.org/10.1016/s2173-5115(08)70261-6.
21. National Organization for Rare Disorders (NORD). Alpha-1 antitrypsin deficiency: affected populations. Accessed on June 1, 2021.
22. Ruiz M, Lacaille F, Berthiller J, Joly P, Dumortier J, Aumar M, et al. Liver disease related to alpha1-antitrypsin deficiency in French children: The DEFI-ALPHA cohort. Liver Int. 2019;39(6):1136-46. https://doi.org/10.1111/liv.14035.
23. Fromme M, Schneider CV, Trautwein C, Brunetti-Pierri N, Strnad P. Alpha-1 antitrypsin deficiency: a re-surfacing adult liver disorder. J Hepatol. 2022;76(4):946-58. https://doi.org/10.1016/j.jhep.2021.11.022.