Review Article

Alpha-1 antitrypsin deficiency: diagnosis and treatment*

Deficiência de alfa-1 antitripsina: diagnóstico e tratamento

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Abstract

Alpha-1 antitrypsin deficiency is a recently identified genetic disease that occurs almost as frequently as cystic fibrosis. It is caused by various mutations in the SERPINA1 gene, and has numerous clinical implications. Alpha-1 antitrypsin is mainly produced in the liver and acts as an antiprotease. Its principal function is to inactivate neutrophil elastase, preventing tissue damage. The mutation most commonly associated with the clinical disease is the Z allele, which causes polymerization and accumulation within hepatocytes. The accumulation of and the consequent reduction in the serum levels of alpha-1 antitrypsin cause, respectively, liver and lung disease, the latter occurring mainly as early emphysema, predominantly in the lung bases. Diagnosis involves detection of low serum levels of alpha-1 antitrypsin as well as phenotypic confirmation. In addition to the standard treatment of chronic obstructive pulmonary disease, specific therapy consisting of infusion of purified alpha-1 antitrypsin is currently available. The clinical efficacy of this therapy, which appears to be safe, has yet to be definitively established, and its cost-effectiveness is also a controversial issue that is rarely addressed. Despite its importance, in Brazil, there are no epidemiological data on the prevalence of the disease or the frequency of occurrence of deficiency alleles. Underdiagnosis has also been a significant limitation to the study of the disease as well as to appropriate treatment of patients. It is hoped that the creation of the Alpha One International Registry will resolve these and other important issues.

Keywords: alpha 1-antitrypsin; Emphysema; Pulmonary disease, chronic obstructive.

Resumo

A deficiência de alfa-1 antitripsina é um distúrbio genético de descoberta recente e que ocorre com freqüência comparável à da fibrose cística. Resulta de diferentes mutações no gene SERPINA1 e tem diversas implicações clínicas. A alfa-1 antitripsina é produzida principalmente no fígado e atua como uma antiprotease. Tem como principal função inativar a elastase neutrofílica, impedindo a ocorrência de dano tecidual. A mutação mais freqüentemente relacionada à doença clínica é o alelo Z, que determina polimerização e acúmulo dentro dos hepatócitos. O acúmulo e a conseqüente redução dos níveis séricos de alfa-1 antitripsina determinam, respectivamente, doença hepática e pulmonar, sendo que esta se manifesta principalmente sob a forma de enfisema de aparecimento precoce, habitualmente com predomínio basal. O diagnóstico envolve a detecção de níveis séricos reduzidos de alfa-1 antitripsina e a confirmação fenotípica. Além do tratamento usual para doença pulmonar obstrutiva crônica, existe atualmente uma terapia específica com infusão de concentrados de alfa-1 antitripsina. Essa terapia de reposição, aparentemente segura, ainda não teve a eficácia clínica definitivamente comprovada, e o custo-efetividade também é um tema controverso e ainda pouco abordado. Apesar da sua importância, não existem dados epidemiológicos brasileiros a respeito da prevalência da doença ou da freqüência de ocorrência dos alelos deficientes. O subdiagnóstico também tem sido uma importante limitação tanto para o estudo da doença quanto para o tratamento adequado dos pacientes. Espera-se que a criação do Registro Internacional de Alfa-1 venha a resolver essas e outras importantes questões.

Descritores: alfa 1-antitripsina, Enfisema; Doença pulmonar obstrutiva crônica.

Introduction

Alpha-1 antitrypsin (AAT) deficiency is a genetic disease that has numerous clinical implications and primarily affects the lungs and liver. It is likely that the first case described was that of woman in Alaska approximately 800 years ago; it might also have contributed to the premature death of Frédéric Chopin in 1849.[1]

The first formal report of the disease occurred a little more than 40 years ago, when Laurell, while reviewing tests in his laboratory, noticed the absence of the alpha-1 band in electrophoreses of serum proteins from 5 patients.[2] Subsequent investigations by Eriksson revealed that 3 of those patients presented early emphysema, and another had a family history of pulmonary emphysema.[2] Thus, the disease and of some of its principal characteristics began to be recognized. Since then, significant advances and standardization in the care of individuals with AAT deficiency have been described.[3,4] Novel diagnostic techniques have also been developed,[5] allowing the performance of large-scale epidemiological surveys—even allowing the genetic and pathophysiological bases of the disease to be studied.

Epidemiology

Epidemiological studies conducted worldwide have shown that AAT deficiency is nearly as common as is cystic fibrosis, affecting one out of every 2,000-5,000 individuals.[6] Recent evidence obtained through genetic mapping indicates that the PiZ allele probably appeared in the north of Europe 107-135 generations (3,210-4,070 years) ago, in the Neolithic period, although it might have appeared as recently as 66 generations (approximately 2,000 years) ago.[7] Although the deficiency allele designated PiS would have appeared earlier, the data are less precise; it is estimated to have appeared 279-470 generations (8,370-14,100 years) ago, probably in the Iberian Peninsula, due to its high incidence in this region.[7] It is believed that at least one of those alleles is present in 70,000-100,000 individuals in the United States, and that these figures are similar in Europe. It is estimated that the number of individuals with deficient variants is as high as 3.4 million.[8]

In the epidemiological study designated *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (PLATINO, Latin-American Project for the Investigation of Pulmonary Obstruction), designed for tracking cases of chronic obstructive pulmonary disease (COPD) and conducted in the city of São Paulo, it was found that 15.8% of individuals aged 40 or older had COPD, and that 12.5% of those individuals had never been exposed to tobacco smoke.[9] Based on these data, we can infer that COPD risk factors other than smoking, among which is AAT deficiency, are important in Brazil. Another study demonstrated that 2-3% of individuals with COPD present severe AAT deficiency.[10] According to the PLATINO study, there are 5 to 7 million individuals with COPD in Brazil. However, it is not known how many of those individuals have AAT deficiency or which is the most common deficiency allele. A study conducted in Brazil[11] found that 12.8% of the individuals studied were heterozygous for the S or Z allele or for the compound; however, the sample was not representative of the Brazilian population, since it included only individuals with cystic fibrosis.

Data from another study show that, in Spain, approximately 1.2 million (3%) of the 40 million inhabitants carry the Z allele, and that there are approximately 12,000 individuals who are homozygous for PiZZ and present concomitant severe AAT deficiency.[12] In the same study, the frequency of the main deficiency phenotypes was also estimated. The most prevalent would be PiMS (80%), followed by PiMZ (13%), PiSS (4.7%), PiSZ (1.6%), and PiZZ (0.1%). In addition, penetrance estimates indicated that there would be approximately 2,526 adults with COPD and 4,030 individuals (including children and adults) with chronic liver disease associated with the PiZZ phenotype in Spain.[12] These data can serve as a reference to estimate, rather imprecisely, the impact of AAT deficiency in Brazil.

Molecular aspects

The glycoprotein AAT is encoded in the SERPINA1 gene, locus Pi, located on the long arm of chromosome 14 (14q31-32). It is a member of the superfamily of serine protease inhibitors, and its principal function is to inhibit a series of enzymes, among which are trypsin, elastase, and protease-3. Despite the nomenclature, AAT has a greater inhibitory effect on neutrophil elastase than on trypsin.[6,13]

It is known that AAT deficiency is a genetic disorder with autosomal codominant inheritance, and more than 100 alleles, approximately 30 of which can have clinical implications, have been identified to date.[14] The variants are designated by letters of the alphabet, according to the protease inhibitor system, based on molecule migration velocity in an isoelectric pH gradient.[13] Based on serum levels of AAT and molecular function, the variants are classified into four groups[3]:

1) normal (normal serum AAT and normal function): M alleles
2) deficient (serum AAT less than one third of normal values): Z allele (the allele most often related to pulmonary disease), variant S, and rarer variants
3) null (undetectable serum level of AAT): QO alleles
4) dysfunctional (normal serum AAT but with reduced function): F and Pittsburgh alleles (among others)

Among all the variants related to clinical disease, mutation Z is the most common (approximately 95% of the cases) and results from the substitution of lysine for glutamic acid at position 342 of the SERPINA1 gene.[13] Table 1 shows the most common variants, as well as the mutations and the related clinical data.

Physiology of AAT

The AAT molecule is produced mainly in the liver (and, in smaller quantities, in macrophages and in the bronchial epithelium), and, through the circulation, it reaches the lungs, where it will perform its anti-elastolytic function.[3] The circulating fraction of AAT corresponds to approximately 40% of the total body levels of the protein; the remainder is found in the extravascular extracellular space, impregnating body tissues, such as the lungs, where it will take part in the tissue defense against elastolysis. Serum levels of AAT can increase in situations of inflammation, and it is therefore considered an acute phase protein.[4]

The inhibition mechanism occurs when an AAT molecule binds to a protease molecule, in a system comparable to a mousetrap.[15] In this inhibition process, one AAT molecule is destroyed for each protease molecule inhibited, resulting in a net loss of AAT molecules. However, under normal conditions, there is an excess of AAT in the lungs, which guarantees protection against the elastolytic effect of neutrophil elastase. In addition to acting as an antiprotease, AAT appears to serve an important anti-inflammatory function in the lungs.[16]

Pathophysiology

Polymerization

The substitution of lysine for glutamic acid at position 342 of the SERPINA1 gene configures protein Z.[6] The conformational changes originating from this mutation predispose the molecules to polymerization, which is irreversible, with conse-

Table 1 – Some of the most common alleles related to alpha-1 antitrypsin deficiency, mutations involved, and related clinical data.[13]

Alleles	Type of mutation	Associated disease(s)
Normal variants		
M (various subtypes)	Substitution (1 base pair)	None
Deficient variants		
S	Substitution (1 base pair)	Pulmonary
Z[a]	Substitution (1 base pair)	Pulmonary, liver
M$_{malton}$	Deletion (3 base pairs)	Pulmonary, liver
S$_{iiyama}$	Substitution (1 base pair)	Pulmonary, liver
Null alleles		
QO (subtypes)	Deletion or substitution	Pulmonary, eventually liver
Dysfunctional alleles		
Pittsburgh	Substitution (1 base pair)	Hemorrhagic diathesis
Z[a]	Substitution (1 base pair)	Pulmonary, liver

[a]The Z allele is a deficiency allele, and it is also dysfunctional.

quent accumulation of polymers within hepatocytes. Although this process can occur under normal conditions, factors such as high concentrations of protein Z, high temperatures, and changes in pH facilitate polymerization.[17] As a consequence of polymer formation, only approximately 15% of the molecules produced reach the circulation, leading to a reduction in serum levels. In addition to protein Z, other mutations give rise to proteins subject to this polymerization process, such as M_{malton} and others.[18]

Pulmonary disease

When serum levels of AAT are low or some AAT molecules are dysfunctional, the lungs are not protected against the elastolytic effect of neutrophil elastase or against other injuries. Therefore, AAT-deficiency-related pulmonary emphysema has been attributed to protease-antiprotease imbalance.[19] The resulting lesion would be a consequence of the increase in injury factors (smoking, infections, and, occasionally, occupational factors) or of the decrease in protective mechanisms (notably, serum levels of AAT), with the balance being shifted in favor of the occurrence of accelerated lung injury.[6]

In addition to the quantitative changes, such as low tissue levels of AAT, the most common mutation (Z) makes the AAT molecule approximately five times less efficient in inhibiting neutrophil elastase[20] and subject to polymer formation, which contributes to lung injury.[21] Smoking, in addition to potentiating lung injury, reduces the activity of the AAT molecule as an antiprotease by approximately 2,000 times,[20] making it an important, avoidable factor for the development of emphysema.

Patients with serum levels of AAT lower than 11 µmol/L (corresponding to 50-80 mg/dL in the tests commercially available) seem to be particularly subject to the development of emphysema; at the same time, individuals with serum levels higher than that seem to be at a significantly lower risk of developing emphysema.[22] Therefore, the idea of a "protective threshold" (serum AAT ≥ 11 µmol/L) arose.[3,6]

Liver disease

Unlike pulmonary disease, AAT-deficiency-related liver disease is not caused by the reduction in the serum levels of the enzyme, but by the accumulation of polymers within hepatocytes. Therefore, only the individuals with mutations that result in polymerization, such as S_{iiyama}, M_{malton}, and, especially, Z, can present liver disease.[17] The mechanism through which intracellular accumulation of polymers leads to liver injury, however, is still unknown.

After their formation, polymers accumulate in the endoplasmic reticulum of hepatocytes, where, under normal conditions, they are degraded by enzymes that function as "quality control" mediators. Liver disease, apparently, correlates with the result of the relationship between polymer formation and the capacity of the "quality control" cell system to degrade abnormally formed polymers.[23] There seems to be considerable individual variability in the degradation capacity of these polymers, which would explain why individuals with the same phenotype present varying degrees of liver disease.

Clinical manifestations

It has been shown that AAT deficiency is associated with the development of pulmonary disease and liver disease, as well as with diseases in other

Table 2 – Principal alpha-1 antitrypsin phenotypes, related serum levels, and associated risk of developing pulmonary or liver disease.[4]

Phenotype	Serum level of alpha-1 antitrypsin		Risk of emphysema[a]	Risk of liver disease[a]
	mg/dL	µmol/L		
MM	103-200	20-39	No increase	No increase
MS	100-180	19-35	No increase	No increase
SS	70-105	14-20	No increase	No increase
MZ	66-120	13-23	Possible slight increase	Slight increase
SZ	45-80	9-15	Slight increase	Slight increase
ZZ	10-40	2-8	High risk	High risk
Null	0	0	High risk	No increase

[a]When compared with the normal population.

organs and systems, although the last occur with less frequency. Nearly 80% of AAT-deficient patients are diagnosed on the basis of respiratory symptoms, compared with only 3% who are diagnosed on the basis of hepatic symptoms.[24] The recognition of AAT deficiency as the cause of pulmonary disease is important for the pulmonologist, since there can be a great delay between the onset of symptoms and diagnosis. In fact, in many patients, the recognition of mutations is achieved only very late and after appointments with different physicians; the interval between the onset of symptoms and the identification of the disease can be eight or more years.[25]

The phenotype most often related to pulmonary manifestations (96% of the cases) is PiZZ, which implies serum AAT concentrations at less than 20% of the normal values.[4] However, heterozygous individuals with mutation Z (or rarer mutations) can also be at increased risk for emphysema, depending on multiple factors, such as smoking, occupational exposure, and environmental exposure (Table 2).

The usual clinical presentation is similar to that of smoking-related COPD. The most prevalent symptoms are dyspnea upon exertion (84% of the patients), respiratory-infection-related wheezing (76%), wheezing in the absence of infections (65%), expectoration (50%), and chronic cough (42%).[26] A profile consistent with chronic bronchitis (productive cough for three months in two consecutive years) is seen in up to 40% of the patients.[3]

Pulmonary disease caused by AAT deficiency is clinically different from smoking-related COPD due to the fact that it has an earlier onset (fourth or fifth decade of life vs. sixth or seventh decade of life) and it is disproportionate to the tobacco intake.[6,24] At age 40, approximately 60% of nonsmokers with the PiZZ phenotype are symptomatic; ten years later, 90% already present manifestations. In smokers, the symptoms appear even earlier, approximately ten years earlier.[4] Respiratory disease exacerbations affect up to 50% of the patients, being more common in those with chronic bronchitis.[24]

The prevalence of bronchiectasis in individuals with AAT deficiency varies greatly. However, in the largest study sample to date, it was 26%, similar to what is observed in patients with COPD secondary to smoking.[27] When present, bronchiectasis is cylindrical or vesicular and is predominantly found in the lobes presenting the greatest degree of emphysema, although, in exceptional cases, it can precede the development of emphysema. The mechanism for the development of bronchiectasis remains a matter of debate, and it has even been suggested that this condition results from changes in the lung parenchyma.[28] Despite the controversy, it is recommended that AAT levels be determined in the etiological investigation of cases of bronchiectasis without definite cause.[3]

It has been suggested that there is a relationship between AAT deficiency and asthma, although such
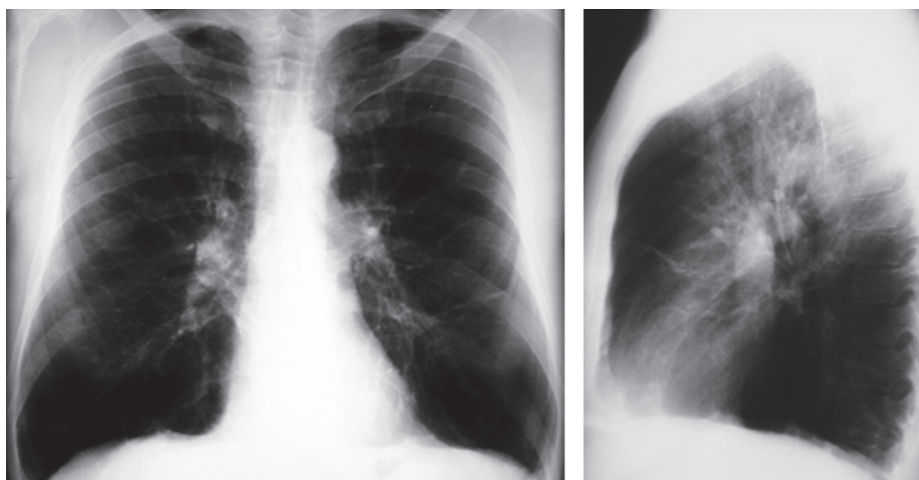

Figure 1 – Routine anteroposterior and lateral chest X-ray of a patient with pulmonary emphysema secondary to alpha-1 antitrypsin deficiency. Note the signs of hyperinflation and hypertransparency of the lung parenchyma clearly predominant in the lung bases.

a relationship has yet to be confirmed. In a study on the characteristics of asthma in patients listed in the North-American AAT Registry, 50% presented reversibility of airway obstruction in pulmonary function tests, and 22% met the criteria for the diagnosis of asthma (compared with 4.5% of the controls; p < 0.05).[29] Other studies, however, found no relationship between heterozygous phenotypes and clinical or functional changes in asthma patients.[30]

There seem to be a relationship between occupational exposure to particulate inhalants and the development of pulmonary disease in patients with the PiZZ phenotype.[31] An association between AAT deficiency and cancer, including lung cancer, has also been suggested.[32]

In relation to liver disease, AAT deficiency has been associated with neonatal cholestasis and early cirrhosis, which can evolve to hepatocellular carcinoma.[18] Other manifestations described as having a possible association with AAT deficiency are, among others, panniculitis and vasculitis related to antineutrophil cytoplasmic antibodies.[24]

Radiological findings

On routine X-rays (Figure 1), AAT deficiency is characterized by signs of hyperinflation, such as lowering and rectification of the hemidiaphragm, an increase in the anteroposterior diameter of the chest, and an increase in the retrosternal air space. Findings of decreased bronchovascular markings and hypertransparent areas, predominantly in the lung bases, are also suggestive of the disease. However, these alterations can also be diffuse.[3]

High-resolution computed tomography (HRCT) of the chest (Figure 2) is a method that is more sensitive for the detection of pulmonary disease than are routine X-rays, pulmonary function tests, or clinical profiles.[28] The characteristic pattern is panlobular
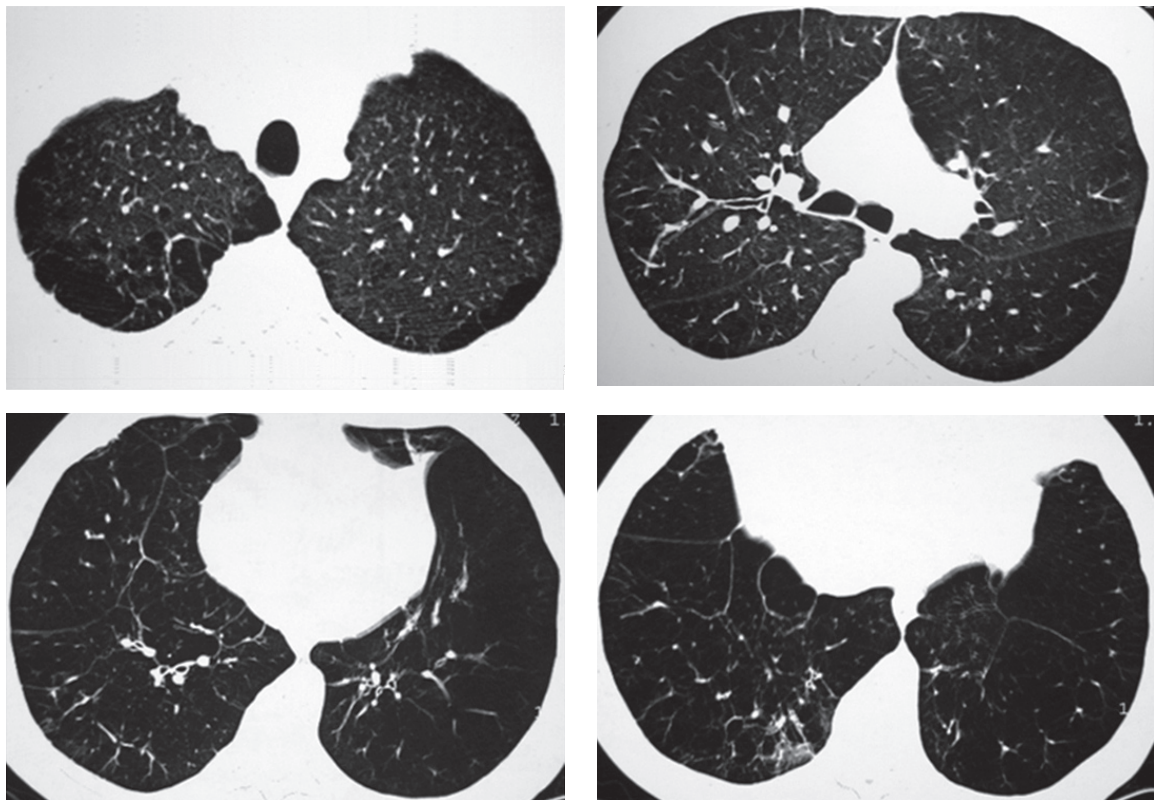

Figure 2 – High resolution computed tomography scan of the chest of a patient with alpha-1 antitrypsin deficiency. Note that the emphysema, although diffuse, is predominant in the lung bases. There is also slight thickening of the bronchial walls and a small focus of ground-glass opacity in the posterior segment of the right lower lobe.

emphysema, which represents a simplification of the lung architecture, with decreased attenuation of the lung parenchyma on X-rays and decreased blood vessel number and diameter. Tomographic alterations are also classically described as being predominant in the lung bases, although it is important to emphasize that, in up to 36% of the cases, they can extend to the lung apices and can occasionally present apical predominance. Bullae are less common than in smoking-related emphysema. Bronchiectasis can also be present.[3,28]

The degree of impairment observed on chest HRCT scans presents a favorable correlation with anatomopathological and pulmonary function findings, and, therefore, HRCT has been proposed as a method for the follow-up evaluation of the progression of emphysema. However, this application is limited by difficulties in the reproducibility of sequential tests, particularly those related to the intensity of inspiration, which directly influences the radiological density of the parenchyma.[28] At the moment, there is no formal recommendation regarding the need for tomographic follow-up evaluation of the disease, and the question of whether or not tomography is inedicated should be addressed on a case-by-case basis.[3]

Pulmonary function

The spirometric changes resulting from AAT-deficiency-related emphysema are the same described in smoking-related COPD: airflow obstruction, represented by a decrease in forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio and in FEV_1; and normal or decreased FVC. Full pulmonary function testing reveals increased residual volume and greater total lung capacity, as well as decreased diffusing capacity of the lung for carbon monoxide. Due to air trapping, pulmonary volumes, as measured by plethysmography, are typically greater than those measured by gas-dilution methods.[3] Some patients present significant variation in pulmonary function test results after bronchodilator use.[29]

The current recommendation is that, in the initial evaluation, full pulmonary function testing and arterial blood gas analysis be performed, and that, in the follow-up evaluation, simple spirometry be performed annually.[3] Patients treated with AAT

augmentation therapy require evaluations that are more frequent and detailed.[4]

Natural history

It is estimated that up to 20% of individuals with the PiZZ phenotype do not develop emphysema, even in autopsy studies.[6] Prior to the second decade of life, the most common manifestations are related to liver disease, and the development of pulmonary disease is rare.[33] One study found that the rate of FEV_1 decline ranged from 41-109 mL/year in patients presenting clinical manifestations[34]; this range, however, can be as large as 31-317 mL/year, depending on exposure to risk factors and on respiratory symptoms.[4] The authors found the following to be risk factors for more rapid progression: being a smoker; being male; being between 30 and 44 years of age; presenting FEV_1 between 35-79% of predicted; presenting bronchodilator responsiveness; and presenting low serum levels of AAT.[34]

Among the patients listed in the North-American AAT Registry, the 5-year mortality rate was 19%.[34] Respiratory insufficiency was the cause of death in 72% of the cases, compared with approximately 10% for liver cirrhosis. The risk factors for higher

Chart 1 – Clinical situations in which alpha-1 antitrypsin deficiency should be suspected and in which quantification of serum levels of alpha-1 antitrypsin is recommended.[3]

Early emphysema (age < 45 years)
Emphysema in the absence of exposure to known risk factors (smoking, occupational factors)
Emphysema predominantly in the lung bases
Case of alpha-1 antitrypsin deficiency confirmed in the family
Family history of emphysema, dyspnea and cough; bronchiectasis, liver disease, or panniculitis
All individuals with chronic obstructive pulmonary disease
Asthma patients whose spirometry results do not normalize despite appropriate treatment
Adults with bronchiectasis without definite cause[a]
Liver disease without definite cause
Necrotic panniculitis
Vasculitis related to antineutrophil cytoplasmic antibodies
Absence of alpha-1 band confirmed by electrophoresis of serum proteins

[a]Consider the determination of alpha-1 antitrypsin levels.

mortality were found to be advanced age, low level of education, low FEV$_1$, having undergone lung transplantation, and not receiving AAT augmentation therapy. However, chest HRCT has proven to be the best predictor of mortality in patients with AAT deficiency, being even better than pulmonary function parameters.[35] Others factors that modify the natural history of AAT deficiency, including genetic and enzymatic polymorphisms, are gradually being identified.[36]

Diagnosis

The diagnosis of AAT deficiency involves the recognition of clinical patterns of the disease and the identification of the corresponding abnormal laboratory test results.[4] In patients with clinical changes suggestive of AAT deficiency—such as early emphysema, family history of emphysema, and liver disease without definite cause—the disease should be included in the differential diagnosis; in these clinical situations, as well as when the α1 band is faint or absent in the electrophoresis of serum proteins, serum levels of AAT should be quantified (Chart 1).[3]

The quantitative tests commercially available, which employ radial immunodiffusion or nephelometry, tend to overestimate serum levels when compared with the purified standard test by the National Heart, Lung, and Blood Institute.[37] In addition, AAT behaves as an acute phase protein, and its serum levels can be falsely increased during inflammatory and infectious processes.[4] Nevertheless, determining the serum levels of AAT is essential to the diagnostic process, although it must be borne in mind that normal values vary according to the method used (Table 3).[3]

Although different serum concentrations of AAT can suggest certain phenotypes, evidence of low or undetectable serum levels of AAT should prompt phenotypic study in order to identify AAT variants (based on the motility of the molecules in an isoelectric pH[13] gradient) and confirm the diagnosis. Currently, in Brazil and in other countries, there are programs that offer simple methods for phenotypic determination through the collection of drops of blood with dry paper filter, which can be sent to a referral laboratory by mail. The materials required in order to perform these diagnostic methods can be easily obtained from the National Registry or from the local societies. Studies have demonstrated that phenotypic determination based on drops of blood on dry filter paper is feasible due to the fact that it is simple and affordable.[5]

The diagnosis of AAT, therefore, is confirmed when low serum levels are found concomitantly with a phenotype that is known to be related to the disease. Molecular-level diagnosis (genotyping), available in specialized laboratories, is an exceptional method for diagnostic confirmation in cases presenting discrepancies between the serum levels of AAT and the phenotype identified, being also recommended for the identification of rare variants and for the study of new variants.[4]

Treatment

Individuals with COPD secondary to AAT deficiency should receive the standard treatment recommended in the principal guidelines currently available, including bronchodilators, inhaled corticosteroids (when indicated), and pulmonary rehabilitation, as well as early and appropriate treatment of exacerbations.[38,39] In general, individuals with AAT deficiency present a normal immunological response, and vaccination is recommended (annually against influenza and every five years against pneumococci).[3] Smoking potentiates lung injury considerably, and smoking cessation should therefore be a fundamental objective of the treatment.[4]

A possible exception to nonspecific treatment of the pulmonary disease is lung volume reduction surgery, which, in patients with AAT deficiency, has shown less favorable results.[40] The benefits of this surgery seem to be less significant and more transitory. To date, there have been no recommen-

Table 3 – Methods available for determining serum levels of alpha-1 antitrypsin, as well as normal values and values considered "protective".[3]

Method	Normal ranges	Protective threshold
Purified standard test (NHLBI)[a]	20 to 53 µmol/L	11 µmol/L
Nephelometry	83-120 to 200-220 mg/dL	50 mg/dL
Radial immunodiffusion	150-200 to 350-400 mg/dL	80 mg/dL

[a]NHLBI: National Heart, Lung, and Blood Institute.

dations for lung volume reduction in this group of patients.[3]

Lung transplantation is another surgical option for patients with advanced pulmonary disease. Patients with AAT deficiency represent approximately 12% of all transplant recipients, with good functional results and mean five-year survival of approximately 50%.[41]

Alternative treatment of AAT deficiency

The specific treatment currently available for pulmonary disease secondary to AAT deficiency consists of periodic intravenous infusion of purified AAT from human plasma; such augmentation aims to raise the serum levels of AAT and, therefore, reconstitute the pulmonary defense against tissue elastolysis.[6]

Various formulations for clinical use, which differ as to the purification method used, are commercially available. Comparative studies have shown varying degrees of purity and in vitro activity.[42] However, the clinical implications of these differences have yet to be established.

Important points that should be considered regarding AAT augmentation therapy are efficacy in achieving certain outcomes (such as maintaining sufficient serum levels, delaying the decline in pulmonary function, and improving survival), safety, and cost-effectiveness.

Efficacy

The infusion of various AAT mixtures seems to meet the biochemical criteria of efficacy, and the anti-elastolytic activity of the molecules is maintained after intravenous administration.[43] In addition, it is possible to produce serum levels above the "protective threshold", which is considered a fundamental point of AAT augmentation therapy.[3] In 1987, one group of authors[44] obtained, through weekly infusion of 60 mg/kg of AAT, serum levels typically higher than 11 μmol/L (or 50 mg/dL, through nephelometry), considered the target level for effective protection of the lung parenchyma.

Weekly administration, however, can become troublesome for patients, especially since they might need to stay in the hospital for up to 4 h, from the preparation of the medication to the end of the infusion. An observational study revealed a decrease in the proportion of patients using weekly

infusions throughout the treatment period (from 51 to 33%).[45] In order to obtain a more comfortable dose schedule, studies have evaluated the pharmacokinetic profile of doses administered at greater intervals. In addition to weekly regimens of 50 or 60 mg/kg, regimens of 100 or 120 mg/kg every 14 days, regimens of 150 or 180 mg/kg every 21 days, and regimens of 250 mg/kg every 28 days have been tested.[46] Infusions of 50 or 60 mg/kg every 7 days and infusions of 100 or 120 mg/kg every 14 days maintained serum levels above the "protective threshold" in more than 85% of the interval between the doses (reaching 100% in the weekly regimen), and were considered appropriate. However, in order to achieve efficient serum levels (greater than 50 mg/dL) in the regimens with intervals of 21 and 28 days, higher doses of AAT would be necessary, which, in practice, would increase treatment costs. In a study conducted in Denmark,[47] the monthly infusion of 250 mg/kg resulted in insufficient serum levels on approximately 5 of the 28 days of each cycle.

There have been few studies on the clinical efficacy of AAT augmentation therapy, revealing the methodological difficulties involved (size of the sample necessary and, principally, cost).[3] In the first study published on this subject (in 1997), the authors[48] found that the FEV_1 decline was slower in patients who received AAT augmentation therapy than in those who did not (53 mL/year

Chart 2 – Minimum criteria necessary for recommending alpha-1 antitrypsin augmentation therapy according to the Spanish Society of Pulmonology and Thoracic Surgery.[4]

Age ≥ 18 years
Alpha-1 antitrypsin deficiency confirmed by serum levels ≤ 35% of the normal values
PiZZ phenotype or rare deficient variants
Abstinence from smoking for at least six months
Pulmonary emphysema confirmed by clinical profile accompanied by $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$
Confirmation of accelerated loss of pulmonary function in non-index cases[a]
Exclusion of associated immunoglobulin A deficiency
Patient's commitment to the treatment

FEV_1: forced expiratory volume in one second; and FVC: forced vital capacity. [a]Cases identified after investigation of the family history or screening.

vs. 74.5 mL/year; p = 0.02). Patients with an FEV_1 of 31-65% of predicted seemed to gain particular benefit.

A large observational study,[34] based on the North-American AAT Registry, showed a significant overall reduction in mortality among patients receiving AAT augmentation therapy. In the subgroup of patients with an FEV_1 of 35-49%, the decline in mortality was even more evident (relative risk of 0.21 for mortality in relation to those who were not treated; p < 0.001), and the reduction in loss of pulmonary function with the use of the treatment reached statistical significance.

In a cross-sectional study,[49] published in 2001 and involving the follow-up evaluation of 96 patients, it was shown that, in patients receiving AAT augmentation therapy, there was a reduction of approximately 15 mL (p = 0.019) in the annual decline in FEV_1, and, unlike in previous studies, this reduction was more evident in the patients with less intense obstruction (FEV_1 > 65%). The patients with a more rapid loss of pulmonary function presented the most expressive response, whereas those with an FEV_1 of 30-65% showed only a tendency toward a reduction.

There has been only one randomized controlled study on the efficacy of AAT infusion.[47] In that study, in which 56 patients were randomized to receive monthly infusions of AAT or placebo (albumin), the authors demonstrated no improvement in pulmonary function parameters, finding only a tendency (p = 0.07) toward a reduction in the progression of emphysema on the tomography scans of the patients who received the medication.

In addition to slowing the progression of emphysema, AAT augmentation therapy seems to have other beneficial effects, such as reducing the markers of bronchial inflammation.[16]

Safety

It has been shown that AAT augmentation therapy is well-tolerated. Most of the infusion side effects, such as headache, dizziness, nausea, and dyspnea, are mild or moderate. In addition, the frequency with which such effects occur is very low. Among patients listed in the North-American AAT Registry, there were an estimated 0.033 adverse events per patient/month, or approximately 2 events for each patient every five years of treatment. No contamination with the hepatitis virus or HIV was found.[45]

Cost-effectiveness and current recommendations

To date, only the biochemical efficacy of AAT augmentation therapy has been clearly confirmed, whereas the effect on relevant biological markers of the development of emphysema or the efficacy of AAT augmentation therapy on clinical and functional variables, as well as on variables of the progression of the disease, are still speculative. One of the main objectives of the International AAT Registry (see below) is to allow the design of comprehensive studies in order to answer these questions. Despite these limitations, AAT augmentation therapy has been approved in some countries, including Brazil. It is not surprising that the few studies available

Table 4 – Complementary tests and periodicity of performance recommended by the Spanish Society of Pulmonology and Thoracic Surgery for the follow-up evaluation of patients with alpha-1 antitrypsin deficiency receiving alpha-1 antitrypsin augmentation therapy.[4]

Test	Periodicity
Spirometry with bronchodilator	Every three months
Static lung volumes	Annually
Diffusing capacity of the lung for carbon monoxide	Annually
Arterial blood gas analysis and exercise tests	Dependent on the clinical profile and other test results
Hepatic function	Annually
Chest X-ray	Every six months or when new symptoms appear
High resolution tomography of the chest	In the initial evaluation; repeat only if justified by the clinical profile
Serologic testing for HIV and for hepatitis B and C	Routine use not recommended, since there is no evidence of transmission of viral agents (with AAT augmentation therapy)

demonstrate that this is a therapy whose cost-effectiveness is not highly favorable.[6,50] However, it is necessary to consider that AAT augmentation therapy is the only option of specific treatment available for such patients.

The benefits of AAT augmentation therapy seem to be more prominent in certain groups of patients, and international guidelines currently recommend that the use of AAT augmentation therapy be limited to patients with clinically established pulmonary disease that progresses despite optimal conventional therapy.[3,4] Patients with moderate airflow obstruction (FEV_1 of 35-60% of predicted) seem to gain more benefit from AAT augmentation therapy. However, it should be borne in mind that there is no consensus on whether or not AAT augmentation therapy is indicated; the authors of the British guidelines on COPD consider that, to date, there is insufficient evidence, and, therefore, they do not recommend AAT augmentation therapy.[51]

It has also been suggested that AAT augmentation therapy in indicated for individuals with AAT deficiency submitted to lung transplantation. During episodes of rejection or infection, in view of the increased elastolytic activity, AAT augmentation therapy can be considered.[3,52]

Chart 2 shows the minimum criteria recommended by the *Sociedad Española de Neumología y Cirurgia Torácica* (SEPAR, Spanish Society of Pulmonology and Thoracic Surgery) for indicating AAT augmentation therapy, and Table 4 shows the follow-up evaluation suggested by SEPAR for individuals with AAT deficiency receiving AAT augmentation therapy.[4]

New treatment perspectives

The use of intravenous AAT augmentation therapy has been limited by factors such as high cost, lack of proven efficacy, and inconvenient administration. Therefore, other forms of administration have been sought, as have therapies that do not involve exogenous AAT augmentation therapy, either by stimulating the endogenous production of the molecule or by using other drugs.[14]

Some studies suggest inhalation as an alternative form of AAT augmentation therapy, with greater ease of administration and reduction in the dose needed. The pulmonary deposition of aerosolized AAT particles is considered efficacious, with good tolerability and maintenance of the elastolytic activity.[53] It is believed that one or two daily doses, which would be convenient, have a satisfactory anti-elastolytic effect.[3] However, the distribution of the molecules within the lungs seem to vary, being subject to the heterogeneity of the disease.[54] In cases of more severe obstruction, there is reduced peripheral deposition of particles, which could have clinical implications.

Studies evaluating the stimulation of endogenous production of AAT using danazol, taking advantage of the fact that the AAT molecule behaves as an acute phase reagent, have not demonstrated any clinical efficacy of such treatment. Similarly, therapies aimed at reducing lung injury (antioxidants) or at promoting lung reepithelialization (all-trans-retinoic acid) have not provided benefits for patients.[14]

Therapies aimed at inhibiting polymerization, with reduced polymer accumulation in the liver and consequent increased serum levels of AAT, have been more promising. Researchers have been successfully developing specific peptides that bind with AAT molecules and cause in vitro inhibition of the polymerization process.[55]

Genetic therapies have also been the object of recent studies, involving the induction of normal AAT molecule production and the inhibition of mutant molecule production.[14] Normal genes have been successfully inserted, using viral vectors, into muscle and liver cells, as well as into the pleural space, resulting in sustained production of significant levels of AAT.[56] In a recent study,[57] which used clones of small interfering ribonucleic acid integrated into viral vectorsit was demonstrated that the production of AAT-Z was inhibited in mice. It was found that there was a reduction in the production and accumulation of molecules within hepatocytes three weeks later.

The international AAT registry

The Alpha One International Registry (AIR) was created in 1997, under the auspices of the World Health Organization, with the following objectives: to establish an international database including demographic description of the patients with AAT deficiency; to promote clinical and basic research for individuals with AAT deficiency and coordinate this activity; to collect, evaluate, and disseminate

information about all aspects of the disease; to provide support and increase lay knowledge about AAT deficiency; and to stimulate the prevention of the progression of the disease and its treatment.[58] Therefore, a database with the best standardization possible was created. Since its creation, the AIR has had member countries on various continents and has been growing every year. In Brazil, AIR activities began in 2005, under the auspices of the Brazilian Thoracic Society and with the technical and scientific support of the Spanish Registry of AAT Deficiency, which is linked to SEPAR.

Patients presenting AAT levels below the normal values (preferably confirmed by nephelometry) should be listed in the Brazilian section of the registry, after confirmation of the presence of a phenotype related to AAT deficiency. The Brazilian section of the registry provides diagnostic kits for phenotype determination, upon request by the physician.

Final considerations

To date, only the biochemical efficacy of AAT augmentation therapy has been adequately evaluated, and there are still no conclusive data regarding its clinical efficacy parameters or regarding biomarkers related to the development of pulmonary emphysema. The low prevalence of AAT deficiency, together with the general lack of cooperation from physicians regarding the international AAT registries, has made it impossible to develop new therapeutic alternatives more rapidly. With the creation and development of national and international AAT registries, this unfavorable scenario can be changed.

Acknowledgments

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