

Chapter 2

Pathophysiology of Alpha-1 Antitrypsin Lung Disease

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Abstract

Alpha-1 antitrypsin deficiency (AATD) is an inherited disorder characterized by low serum levels of alpha-1 antitrypsin (AAT). Loss of AAT disrupts the protease–antiprotease balance in the lungs, allowing proteases, specifically neutrophil elastase, to act uninhibited and destroy lung matrix and alveolar structures. Destruction of these lung structures classically leads to an increased risk of developing emphysema and chronic obstructive pulmonary disease (COPD), especially in individuals with a smoking history. It is estimated that 3.4 million people worldwide have AATD. However, AATD is considered to be significantly underdiagnosed and underrecognized by clinicians. Contributing factors to the diagnostic delay of approximately 5.6 years are: inadequate awareness by healthcare providers, failure to implement recommendations from the American Thoracic Society/European Respiratory Society, and the belief that AATD testing is not warranted. Diagnosis can be attained using qualitative or quantitative laboratory testing. The only FDA approved treatment for AATD is augmentation therapy, although classically symptoms have been treated similarly to those of COPD. Future goals of AATD treatment are to use gene therapy using vector systems to produce therapeutic levels of AAT in the lungs without causing a systemic inflammatory response.

Key words Alpha-1 antitrypsin deficiency, Alpha-1 antitrypsin, Chronic obstructive pulmonary disease (COPD), Emphysema, Neutrophil Elastase

1 Introduction

Alpha-1 antitrypsin deficiency (AATD) is an underrecognized codominantly inherited disorder best known for its physiological effects on the lungs. It was first identified by Laurell and Eriksson approximately 50 years ago when they noted an absence of the alpha-1 band on serum protein electrophoresis [1, 2]. AATD is characterized by reduced amounts of alpha-1 antitrypsin (AAT), a 52-kDa serine protease inhibitor (SERPIN) that is secreted primarily by hepatocytes, although lung and gut epithelial cells, monocytes, and macrophages are secondary sources. AATD is the only genetic risk factor for chronic obstructive pulmonary disease (COPD) and often presents between the ages of 20 and 50 with nonspecific symptoms such as dyspnea, bronchitis, wheezing, and cough [2, 3].

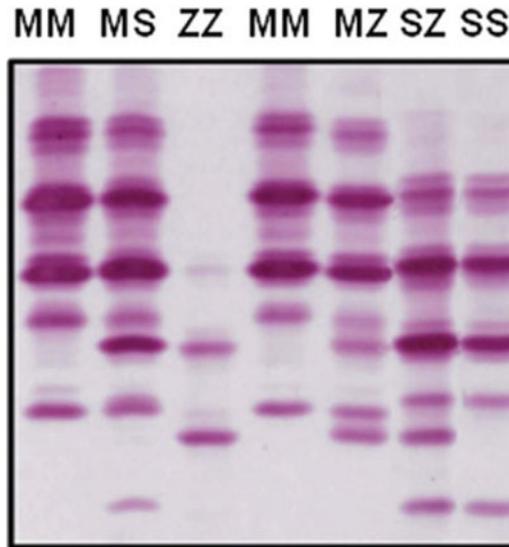


Fig. 1 Qualitative detection of common AAT phenotypes using isoelectric focusing to observe migration rates. Original figure was modified to not include an additional part of image. *Source* [7]

AAT is encoded by the protease inhibitor (PI) locus of the *SERPINA1* gene on chromosome 14q32.1 and is composed of 394 amino acids with its active site at methionine 358. The normal plasma concentration of AAT ranges from 0.9 to 1.75 g/L (15–30 $\mu\text{M/L}$) with a half-life of 3–5 days. Approximately 123 naturally occurring genetic variants of AAT have been discovered [3–6]. Genetic variants are named depending on speed of migration on an isoelectric focusing (IEF) gel (Fig. 1). For example, the wild-type allele “M” has a medium rate of migration. The two most common mutant alleles of AAT are “Z” (Glut342Lys), accounting for over 90% of disease-causing alleles, and “S” (Glu264Val). The “Z” allele in particular is associated with a severe reduction in plasma AAT levels (to about 5 $\mu\text{M/L}$) and has the slowest rate of migration on an IEF gel [4, 8, 9].

Due to the many genetic variants of AAT, patients can be classified into four distinct phenotypes: (1) normal: variants of the M phenotype that are prevalent in 99% of the worldwide population and present with normally functioning AAT and plasma levels of $\geq 20 \mu\text{M/L}$; (2) deficient: a mutant phenotype, frequently of the S and Z variants, prevalent in $<1\%$ of the worldwide population and associated with plasma AAT levels $<20 \mu\text{M/L}$; (3) null: a phenotype found in $<0.1\%$ of the worldwide population characterized by no detectable AAT in plasma, truncated protein or unstable proteins that are degraded before secretion, and (4) dysfunctional: a phenotype found in $<0.1\%$ of the worldwide population characterized by normal amounts of AAT in plasma that do not function

correctly and lead to decreased elastase inhibitory activity [6, 10–13]. It is important to note that not all individuals with severe phenotypes such as PI*Z develop disease [14].

2 Epidemiology

Worldwide, it is estimated that more than 3.4 million people have AATD and that there are 116 million carriers of AATD alleles [6]. Affected individuals are commonly white Northern European or of Iberian descent. The incidence of AATD in white newborns is similar to that of cystic fibrosis. Women and men are affected in equal numbers, but men are at greater risk for lung deterioration. Symptomatic individuals have a high mortality rate due to airflow obstruction from lung disease [15–17].

In the USA, it is estimated that 100,000 individuals have AATD, with a prevalence of 1 case per 3000–5000 people [17]. However, only 10% or less of this population is correctly diagnosed [14]. This is supported by an investigation in St. Louis that found only 4% of patients with AATD had been identified and by polls of patients with AATD who reported seeing at least three clinicians before a diagnosis was made [18].

3 Pathophysiology

AAT is composed of three β -sheets and eight or nine α -helices. It expresses a secretion signal that targets it to the endoplasmic reticulum (ER) for folding and glycosylation before it is exported. Proteinase binding cleaves the reactive loop of AAT, which inserts into AAT's β -sheet, trapping the protease and inhibiting it. In a process called "loop sheet polymerization," the tertiary structural change from amino acid mutation results in molecular linkage as the reactive center of one AAT can bind to a gap in the β -sheet of another [19, 20]. The structure of loop sheet polymers of AAT has been elucidated by crystallization [21].

The most common mutation in AAT is the Z mutation, which occurs when there is a substitution of lysine for glutamic acid at position 342. Of the mutated AAT, 15% fold effectively, 15% form polymers, and 70% are degraded by the ER stress response in hepatocytes [1]. In a subset of patients, ER stress and accumulation of AAT in the liver leads to neonatal hepatitis, hepatic cirrhosis, and hepatocellular carcinoma.

After release into the circulation, it is currently believed AAT is internalized into the lungs via clathrin-mediated endocytosis [22]. There, the major function of AAT is to maintain the protease–anti-protease balance. In patients with AATD, the protease–antiprotease balance becomes skewed due to the degradation of mutant AAT by

ER stress, leaving proteases such as matrix metalloproteases, proteinase 3 (PR3), and cathepsins uninhibited [19]. Neutrophil elastase (NE) is the most important protease that AAT inhibits. When left unchecked, NE causes the destruction of lung matrix components, alveolar structures, and blood vessels. Mutant AAT has approximately 5 times less antiproteolytic activity against NE than normal AAT [20]. Furthermore, inhibition of matrix metalloproteases is important to prevent the degradation of the extracellular matrix. Another protease that AAT inhibits, matriptase, is involved in the activation of epithelial sodium channels. When AAT inactivates the catalytic domain of matriptase, it inhibits the epithelial sodium transport, which results in improved mucociliary clearance in patients with COPD.

AAT plays an essential role in reducing levels of cellular apoptosis in the lungs by inhibition of TNF-alpha, caspase-3, and intracellular cysteine protease. AAT also prevents hemolysis of red blood cells by binding to secreted enteropathogenic *Escherichia coli* proteins, thereby suppressing bacterial proliferation and lung infection in rat models [23].

Another important role of AAT is the attenuation of the neutrophil chemotactic response, a potent cause of inflammation. AAT forms an opposing gradient concentration to interleukin (IL)-8, a ligand for CXCR1 and an important chemokine, so that neutrophils move down an AAT concentration gradient and up an IL-8 gradient. A loss of AAT results in a disrupted concentration gradient and an increased neutrophil chemotactic response. AAT can also bind to soluble immune complexes in order to prevent increased neutrophil chemotactic response [23]. In patients with AATD, unimpeded IL-8 promotes a series of cellular events that contributes to approximately 31% of the neutrophil chemotaxis in the sputum of patients with COPD. Furthermore, alveolar macrophages in patients with AATD release an increased amount of leukotriene (LT) B₄. LT_{B4} is released when uninhibited NE binds to alveolar macrophages and is estimated to contribute to 47% of neutrophil chemotaxis in the sputum of patients with COPD. Patients with a PI*Z phenotype may create AAT polymers that are chemotactic for human neutrophils and cause heightened inflammation by stimulating myeloperoxidase release and neutrophil adhesion, resulting in interstitial neutrophilia [24].

Reactive oxygen species (ROS) produced by neutrophils via the NADPH oxidase enzyme complex are eliminated by AAT through uncertain mechanisms [23]. While ROS is important for killing microbes, release of these free radicals into extracellular space can cause extensive lung damage and inflammation. AAT may prevent asthma and other allergic diseases that cause inflammation by inhibiting IgE-dependent and calcium ionophore-induced histamine release from mast cells [23]. AAT also decreases plasma TNF-alpha levels, induces IL-1 antagonists and inactivates the cytotoxic

properties of α -defensins, reducing inflammation reactions [3, 4] Finally, AAT may modify inflammatory signaling pathways such as the cyclic adenosine monophosphate (cAMP)-dependent pathway, responsible for elevating leukocyte production, and inhibit pro-inflammatory cellular signaling [23].

4 Clinical Presentation

For the purpose of this chapter, severe AATD refers to individuals with a form of PI*Z, PI*null and some PI*SZ genotype variants [6]. Severe AATD predisposes patients to COPD, an obstructive disease that leads to early-onset pulmonary emphysema. Emphysema is commonly classified according to forced expiratory volume in 1 s (FEV₁) [13]. It is estimated about 1% of patients with COPD have severe AATD [17]. Individuals with severe AATD are classified as those who have an antitrypsin serum concentration below 35% of mean value or the threshold of 11 μ M/L [13, 20]. Patients with AATD most frequently present with dyspnea, but may also present with cough, wheezing, phlegm production, and bronchial hyperresponsiveness [2, 25].

AATD-associated emphysema is predominantly panacinar emphysema and found in the basal region of the lung, compared to more classical COPD emphysema found in the apical region of the lung. A chest CT (Fig. 2) will display this emphysematous change in the base, along with a loss of lung parenchyma and hyperlucency [27]. Emphysema develops as a result of unopposed NE, due to the breakdown of structures necessary for ventilation beyond terminal bronchioles. This leads to enlargement of airspaces and destruction of alveolar walls [28, 29]. Alveolar wall destruction reduces the elastic recoil of the lungs and impairs

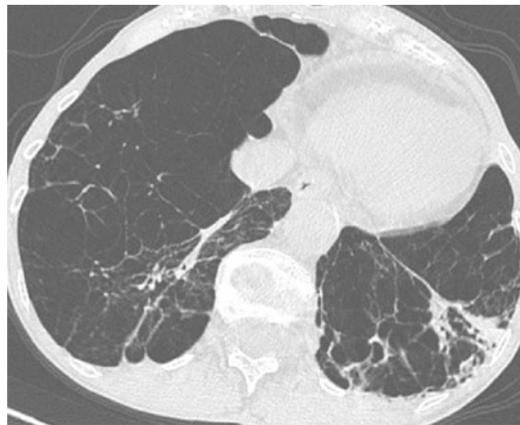


Fig. 2 An AATD associated panlobular emphysema displaying a loss of lung parenchyma. *Source* [26]

their ability to provide traction to small intrapulmonary airways and the pressure needed to inflate bronchi and extrapulmonary airways. Consequently, the airways collapse and obstruction occurs [29, 30].

In a study of patients with severe AATD, most patients had pulmonary function tests that revealed an FEV₁ of 50% predicted or lower and a registry of patients with severe AATD had an FEV₁ of $43 \pm 30\%$ predicted [31, 32]. FEV₁ is a measure of airway obstruction—specifically, it is the measure of the volume of air that can be exhaled in 1 s following a deep inhalation (normal range is 80–120% predicted). PI*ZZ individuals have an annual FEV₁ decline of 23–316 mL. Predictors for accelerated rate of FEV₁ decline include exposure to cigarette smoke, male sex, 30–44 years of age, and an original FEV₁ of between 35% and 79% of expected value [24]. A low FEV₁ is an important risk factor for death in individuals with severe AATD because it implies that patients have severe airway obstruction, progressive lung disease, and emphysema (Fig. 3). Emphysema is the most common cause of death in these individuals, killing approximately 58–72% of the population [34]. Along with a decreased FEV₁, most patients with severe AATD present with an increased functional residual capacity (FRC) [20]. The increased FRC is a consequence of the severe airway obstruction and the subsequent air trapping.

Cigarette smoking is the major risk factor for AATD individuals to develop emphysema [13]. Other risk factors include a history of asthma, chronic bronchitis, and pneumonia. Cigarette smoking is a major risk factor because it contains oxidants that are capable of converting the active site methionine 358 to methionine sulfoxide. This conversion inactivates AAT and reduces its affinity for NE by 2000-fold. In addition, cigarette smoke impairs lung elastase synthesis and recruits inflammatory cells that contribute to the NE

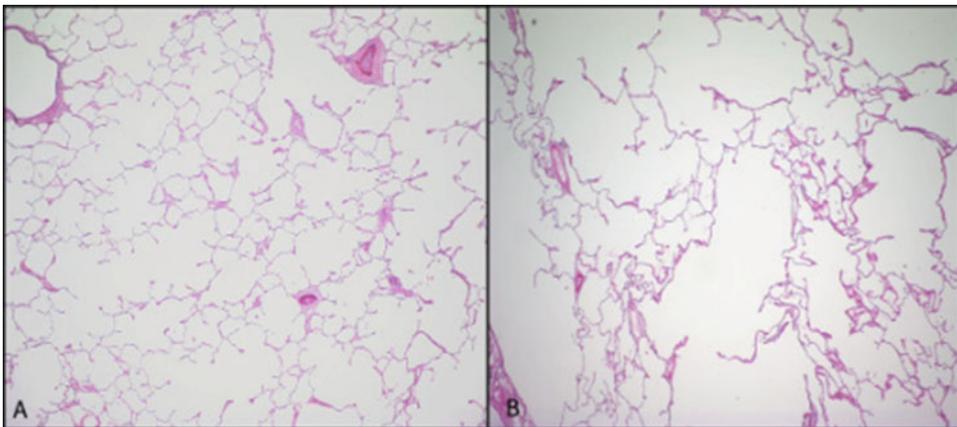


Fig. 3 (a) histological section taken from normal lung; (b) histological section taken from emphysematous lung. Source [33]

load [13]. Smokers and ex-smokers have significantly reduced FEV₁, increasing the risk of airflow obstruction and the development of emphysema [35]. Smokers and ex-smokers who have over 100 cigarettes in their lifetime have worse airway symptoms compared to nonsmokers. In fact, 30% of AATD patients who smoke tend to have significant phlegm and 48% wheeze regularly compared to 13% and 26% of nonsmokers respectively [27]. In addition, Larsson et al. reported that the median onset of dyspnea in smokers with severe AATD was 40 years, compared to 53 years in nonsmokers [36]. The mean life expectancy for smokers with severe AATD is 48–52 years, but this age significantly increases to 60–68 years in nonsmokers [3].

Severe AATD may also lead to bronchiectasis [37]. Bronchiectasis, or the pathological dilation of airways, occurs when the bronchial tree is obstructed due to inflammation, resulting in the destruction of ciliated epithelium by the host immune response. This leads to impaired mucociliary clearance, causing subsequent inflammatory responses and repeat lung infections with persistent inflammation. Over time, bronchi will lose their ability to move air into and out of the lungs as tissue damage extends to the muscle layers [38]. Currently there is debate about whether bronchiectasis is a symptom of AATD because large population based bronchiectasis registries have not shown significant differences between AAT allele frequencies compared to control populations [39]. However, some studies have shown that up to 40% of patients with AATD are affected by bronchiectasis, and in one study by Parr et al. 95% of individuals with severe AATD had a diagnosis of bronchiectasis [27, 37]. A diagnosis of bronchiectasis can be confirmed by a CT scan.

5 Diagnosis

AATD is a widely underdiagnosed and underrecognized disease by clinicians. The diagnostic delay, or time interval between first symptom and initial diagnosis, is estimated to be 5.6 years, with a median time as long as 8 years. Generally younger individuals have shorter diagnostic delays than older individuals [15, 40]. Contributing factors to underrecognition and diagnostic delay are an inadequate awareness of the disease by healthcare providers, a failure to implement evidence-based recommendations and the belief that testing for AATD is not warranted because of the lack of effective and available therapies [14]. It is currently recommended for physicians to test for AATD if any of the following features are found in a patient [13]:

- Emphysema in a patient 45 or younger.
- Emphysema in a nonsmoker or in the absence of a risk factor.

- Emphysema with prominent basilar changes on a chest x-ray.
- A family history of emphysema, bronchiectasis, liver disease or panniculitis.
- Clinical findings of panniculitis or unexplained liver disease.
- Anti-proteinase 3-positive vasculitis.

As previously stated, individuals with severe AATD are classified as those who have an antitrypsin serum concentration below 35% of mean value or the threshold of 11 $\mu\text{M}/\text{L}$ with a severe deficient phenotype [20]. Both quantitative and qualitative laboratory testing are typically done to confirm diagnosis of AATD.

Qualitative testing includes radial immunodiffusion and nephelometry, although both tests overestimate serum AAT concentration. Radial immunodiffusion is a technique used to quantitatively estimate antigens and nephelometry is a technique used to determine levels of blood plasma proteins. Threshold levels of 80 mg/dl and 50 mg/dl have been used for radial immunodiffusion and nephelometry, respectively, instead of 11 $\mu\text{M}/\text{L}$ [13].

Quantitative testing occurs at the phenotyping and genotyping levels. Phenotyping is done using IEF gels that identify AAT alleles based on their migration patterns. A drawback to phenotyping is it cannot be used to identify those patients with PI*null alleles due to the lack of production of the AAT protein [17]. Genotyping is done by purifying genomic DNA and conducting polymerase chain reaction (PCR), followed by a restriction enzyme digestion and electrophoresis. Melting curve analysis can also be performed after PCR [12, 41].

6 Current Therapy

Treatment of the symptoms of AATD is similar to that of COPD. Pharmacologically, bronchodilators such as long-acting beta-2-agonists with long-acting anticholinergic tiotropium and inhaled corticosteroids can be applied to maximize airflow and provide relief for acute respiratory distress. Antibiotics can be given if a bacterial airway infection that is exacerbating inflammation is suspected [9, 20, 42].

The only FDA approved therapy for AATD is augmentation therapy, or protein replacement by weekly intravenous infusions to restore serum AAT to a therapeutic level of 11 $\mu\text{M}/\text{L}$ [4]. This therapeutic level is similar to those found in patients with PI*MZ, a phenotype with little risk for developing significant COPD. Intravenous augmentation therapy has also been shown to reduce mortality and FEV₁ decline [42]. Inhaled therapy is an additional augmentation therapy that is under consideration because it can

potentially inhibit airway elastase and reduce elastase-dependent inflammation and damage.

AATD is an attractive target for gene therapy because it is a single gene disorder with a relatively short coding sequence and AAT is predominantly found in plasma and extracellular places. Multiple vector systems have been developed to deliver the gene, such as retroviruses, recombinant adenovirus (rAV), and recombinant adeno-associated virus (rAAV) [43]. The most promising of the gene therapies is rAAV, which is capable of inducing therapeutic levels of AAT and is not likely to develop an inflammatory response [44]. Typically, the rAAV vector is delivered via the liver or airway. A novel approach to gene therapy for AATD is to direct small DNA fragments to the liver where they will replace the abnormal DNA sequence of the *SERPINA1* gene [44]. This approach has not yet been tested for efficacy and safety.

Finally, for patients with AATD who progress to end-stage lung disease and therapy is ineffective, lung transplantation (LT) is an option. LT usually only occurs unilaterally due to lack of donors even though a double lung transplant has a better outcome [13]. Another surgical option is lung volume reduction surgery (LVRS). LVRS consists of removing a portion of an emphysematous lung so that the remaining portion can stretch within the thorax. The smaller lung will have more elastic recoil, causing an increase in FEV₁. Additionally, LVRS significantly decreases oxygen consumption and energy expenditure by respiratory muscles because oxygen consumption in emphysematous lungs is increased due to impaired respiratory mechanics [45].

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