



Alpha1-antitrypsin deficiency and asthma

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Purpose of review

The aim of the article is to highlight the association between α 1-antitrypsin deficiency (AATD) and asthma.

Recent findings

AATD is one of the most common and underrecognized autosomal disorders associated with an increased risk of developing liver and lung diseases. An association between α 1-antitrypsin and asthma has been suggested, especially with severe forms of this disease. Many studies have shown an increased prevalence of asthma in the α 1-antitrypsin-deficient population overtime (4–38%). The biological mechanism underlying these two conditions and able to bind them has not yet been well investigated. As α 1-antitrypsin is the main inhibitor of the serine proteinase and it is an important anti-inflammatory protein with pronounced immunomodulatory activities, it can be hypothesized that the link between AATD and asthma might be represented by the elastase/antielastase imbalance and the proinflammatory effect that occurs because of the reduction of this protein.

Summary

There is a strong need for further researches to better understand the molecular mechanisms binding AATD and asthma. It is also recommendable to screen for AATD, late-onset asthma patients, and/or those with not fully reversible airways obstruction.

Keywords

α 1-antitrypsin, α 1-antitrypsin deficiency, α 1-antitrypsin polymers, asthma, neutrophil asthma, phenoendotyping asthma, severe asthma

INTRODUCTION

α 1-Antitrypsin deficiency (AATD) is one of the most common and underrecognized autosomal disorders associated with an increased risk of developing liver and lung diseases.

α 1-Antitrypsin (AAT) is a serine-proteinase inhibitor that plays a crucial role in protecting the connective tissue, including the one in the bronchial walls, from damages caused by proteinases and, in particular, by neutrophilic elastase. It is also an important anti-inflammatory protein with pronounced immunomodulatory activities [1,2].

AAT is mainly produced by hepatocytes from where it spreads through the systemic circle to the organs and tissues needing protection. It is also produced in small quantities by macrophages, monocytes, circulating neutrophils, and alveolar macrophages. Recently, it has been documented that it can also be synthesized by respiratory cells such as bronchial epithelial cells [3–5,6*].

This protein is codified by the highly polymorphic SERine Proteinase INhibitor 1 gene, located on

the long arm of the chromosome 14 [7,8]. This gene has more than 100 different allelic variants that produce different amounts of AAT. The most

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KEY POINTS

- Prevalence data show an increase in asthma cases in the population with AATD.
- The elastasis/antielastasis imbalance and the loss of inflammatory and immunomodulatory properties could represent the biological mechanisms able to bind AATD to asthma.
- Screening for AATD in asthma with late administration and/or airways obstruction not fully reversible to acute bronchodilator should be encouraged.

frequent normal allelic variant associated with normal serum level is the protease inhibitor (PI)*M. The most clinically relevant allelic deficient variants are PI*S and PI*Z. PI*Z is the most prevalent variant, responsible for severe disease. Although individuals with PI*ZZ alleles have only 10% normal serum levels, which is responsible for severe manifestations of AAT deficiency, PI*SS ones have around 60% of normal AAT serum levels and are associated with less severe disease [9–15].

The severity of the PI*Z is because of a point mutation (Glu342Lys) in the protein's active region, making it less functional than the normal one and prone to polymerization. Polymerization of the protein leads to its accumulation in the endoplasmic reticulum of the producing cells, triggering the endoplasmic reticulum-associated protein degradation (ERAD), the unfolded protein response, and the proinflammatory response. Accumulation of polymers in the endoplasmic reticulum and the inflammatory response cause direct damages to the hepatocytes. The sequestration of the polymers in the endoplasmic reticulum, apart from damaging the hepatocytes and promoting, in association with inflammatory response, the onset of liver disease, determines a protein deficiency in the systemic circle [16]. AATD in patients homozygous for the Z allele is so severe that it favors the development of pulmonary emphysema, especially in smokers, even at young age. AATD related to the Z allele variant is alone responsible for 1–2% of all forms of pulmonary emphysema [9,17].

The S-mutated form is retained within the hepatocytes as the Z one, but most of the misfolded proteins are eliminated by the ERAD, and a part is correctly refolded and secreted. Nevertheless, this variant results in lower circulating plasma levels of AAT, which may fail to effectively inhibit neutrophil elastases.

Soriano *et al.* [18] showed that AATD affects approximately one in 2000–5000 individuals

worldwide. Some studies estimate that the frequency of PI*Z and PI*S alleles where more than 18 000 (0.1%) and 1.2 million (0.7%) population, respectively, in 97 countries worldwide, with the highest prevalence in Latvia (PI*S around 31.3/1000 population and PI*Z around 45.1/1000 population) [19,20]. In Europe, the prevalence of AATD is estimated to be 23.73 per 100 000 in all age groups and 29.36 per 100 000 in people above 30 years, whereas the frequency of homozygous AATD is 0.01–0.02% [21]. PI*Z has a frequency gradient of presentation decreasing from north to south Europe, whereas PI*S has an inverse distribution, from 10% in southern Europe (mainly Spain) to 5% in the north [22].

Whether pulmonary emphysema and liver disease are the conditions most frequently associated with AATD, AATD has shown to be associated with other conditions, such as panniculitis, vascular disease, and systemic vasculitis [23–26].

PREVALENCE DATA

An association between AATD and asthma has also been suggested, especially with severe forms of this disease.

Many studies have shown an increased prevalence of asthma in the AATD population over-time (4–38%). In 1978, Larsson *et al.* [27] documented a 4% prevalence of asthma in a study with 246 Swedish patients diagnosed with AATD between 1963 and 1977. In the following years, Tobin *et al.* [28], Janus *et al.* [29], and Eden *et al.* [30] found, in smaller populations, higher prevalence of asthma in their case-series and case-control studies: 11, 34, and 22%, respectively [28–30]. McElvaney *et al.* [31], during a study aimed to characterize the patients registered in the National Heart, Lung and Blood Institute Registry of AATD, reported an asthma prevalence of 31% in a group of 1129 AATD patients.

In the following two decades, several studies showed variable asthma prevalence in AATD patients: Piitulainen's *et al.* [32] documented 15% of asthma prevalence in 98 PiZZ Swedish patients; Eden *et al.* [33] estimated a 21–38% of asthma prevalence in a deep analysis of the National Heart, Lung, and Blood Institute Registry with an overall population of 1052 AATD patients.

A few years later (2006), Eden [34] found an asthma prevalence of 17% in a group of 458 AATD patients in a study specifically aimed at estimating the prevalence of asthma and atopy among AATD patients from the Alpha-1 Foundation Research Registry. Furthermore, in these last two studies, Eden verified that asthma signs and symptoms in AATD patients were common and associated with a greater loss of lung function. The progressive loss of lung

function was also observed by Demeo *et al.* [35] in a family-based cohort study, originally aimed at finding risk factors for chronic obstructive pulmonary disease (32% of asthma prevalence in 378 AATD severe patients). Finally, in more recent years, Kelbel *et al.* [36], in an observational study of 500 patients with severe AATD, found a 46% prevalence of asthma and allergic diseases. Among them, 55 were diagnosed as affected by AATD. This suggests that AATD is still now an underdiagnosed risk factor [36,37]. Moreover, Aiello *et al.* [38] recently showed that atopy is more prevalent among asthmatic patients with AATD compared with the ones without (74 and 48%, respectively), endorsing Eden's finding of 1997 that atopy is frequently associated with AATD and might predispose the individuals to the development of asthma.

Conversely, many studies have shown an increased prevalence of AATD in patients affected by asthma (5–20%). Miravittles *et al.* [39] documented a 19.8% of AATD prevalence in 111 asthmatic patients enrolled in a cross-sectional study. On the other hand, Von Ehrenstein *et al.* [40] documented a lower prevalence of AATD (4.9%) in a survey conducted among 338 children with asthma. Similar results were reported in 2006 by two cross-sectional studies, conducted by Van Veen *et al.* [41] and Montealegre *et al.* [42], which found a prevalence of 4.9% among 122 patients, and 11.4% among 119 asthmatic children admitted in a major ED department in Ponce (Puerto Rico), respectively [41,42]. Similarly, Eden reported a year later, a 10.5% prevalence of AATD among 284 poorly controlled asthmatic patients enrolled in a cross-sectional study [43]. Suárez-Lorenzo *et al.* [44] documented a 22.4% prevalence of patients with at least one deficient allele *al* among 648 asthmatic patients.

All in all, prevalence data indicate that asthmatic patients with AATD, compared with those without AATD, have more severe disease with lack of bronchodilators reversibility, higher corticosteroids consumption for symptoms management [45], lower control of the asthmatic disease with a poor respiratory function and faster decline, and a worst prognosis [31,33–35,40,46,47]. This suggests that AATD may be a risk factor for developing asthma and worsening its course [48].

For all these reasons, the World Health Organization in 1997, the American Thoracic Society in 2003, and the European Respiratory Society in 2017 recommended the search for AAT genetic deficit in asthmatic patients whose spirometry fails to return to normal after bronchodilator therapy and in those with late-onset asthma characteristics frequently linked to the most severe forms of the disease [7,15,49].

MECHANISMS INVOLVED IN THE CORRELATION BETWEEN α 1-ANTITRYPSIN DEFICIENCY AND ASTHMA

Although the association between AATD and asthma is sufficiently well documented, the biological mechanism underlying the two conditions and binding them has not yet been well investigated. As AAT is the main inhibitor of the serine proteinase and it is an important anti-inflammatory protein with pronounced immunomodulatory activities [1,2], it can be hypothesized that the link between these two conditions might be represented by the Elastase/Antielastase imbalance and by the proinflammatory effect that occurs because of a reduction of a protein with important antiinflammatory and immunomodulatory effects.

The imbalance between elastase and antielastase, in fact, could lead to an excess of this protease in the airways of asthmatic patients, as shown by the significant increase of neutrophil elastase in the induced sputum of some asthmatic patients [50]. This increase in asthmatic patients is correlated with airway inflammation and with forced expiratory volume in 1 second decline [19,50,51].

The excess of neutrophil elastase implies several biological consequences. Mainly its unopposed proteolytic activity contributes to the degradation of the extracellular matrix (ECM), especially elastin. ECM and, in particular, elastic fibers that play a crucial role in the tissues' mechanical and elastic properties are well represented in the airways wall (both in central and distal ones) and in the lung parenchyma. Such degradation in airway walls and their alveolar attachments decreases both mechanical stability and elasticity of the bronchial walls promoting airway collapse, especially in exhalation and, consequently, airflow obstruction [52,53]. This alteration of the connective tissue in the short term period may sustain an increase of bronchial hyper-responsiveness, whereas in the long period, with subsequent airway remodeling, the decline of lung function, and asthma progression [54].

Furthermore, the loss of antiprotease protection, mainly against neutrophilic elastase, leads to macrophage activation with excessive production of neutrophil chemotactic factors such as IL-8 and LTB₄. This triggers the vicious cycle of neutrophil inflammation in response to the elastase–anti-elastase imbalance. Finally, lung epithelia and macrophages can express higher AAT levels in response to airway inflammation. An analysis of sputum proteome shows, in fact, that SERPINA 1 is upregulated in asthma [50]. In Z homozygous patients, this may generate increased levels of polymerized AAT, thereby inducing endoplasmic reticulum stress, along with the release of proinflammatory cytokines

and the activation of macrophage proteases in the airways, that is, type of inflammation that could impact disease progression [12].

Therefore, from a biological point of view, it may be interesting to consider the imbalance between elastase and antielastase as an element able to link AATD and asthma and promote asthma evolution.

Loss of inflammatory and immunomodulatory properties

The AAT is an antiinflammatory protein that, under physiological conditions, can reduce inflammatory processes by regulating the chemotaxis processes of neutrophils mediated by IL-8 and soluble immune-complexes. The formation of the AAT-IL-8 complex, in fact, blocks the binding to the receptor of CXC chemokine receptor 1 chemokines exposed on the cell membranes of neutrophils, inhibiting the cytoskeletal reorganization [55,56].

The AAT deficiency, on the contrary, may increase neutrophil inflammation. It has been shown, in fact, that the neutrophil cell population and its chemotactic index are markedly developed in the lungs of patients with severe forms of AATD [57].

Additionally, the AAT also reduces the activity of the alveolar macrophages by binding the leukotriene factor LTB₄, a powerful neutrophil chemo-attractant released in presence of neutrophil elastase [58] and inhibiting the production of TNF- α and metalloprotease-12.

AAT immunomodulatory activity also involves the eosinophils and drives the downregulation of other proinflammatory cytokines, such as IL-6, IL-1 β , IL-32, and the upregulation of antiinflammatory ones such as IL-10, IL1 β Ra, and TGF- β .

Among other mechanisms, AAT also has important interactions with the adaptive immunity mechanisms, affecting the proliferation of Th1, Th2, and Th17 cells and enhancing the T-regulatory cell production [23,59]. It has also been described an AAT action on the dendritic cells, preventing their maturation through the antigen presentation process and on B-lymphocytes proliferation through the downregulation of the B-cell-activating factor [60].

Finally, it has been documented the role of AAT in reducing the caspase3-mediated cell apoptosis [61].

Thus, in AATD patients, the combination of the reduced AAT-related immunomodulatory activity and the lower expression of antiinflammatory factors could lead to a condition of chronic airways' inflammation, a potential biological link between these two conditions.

The enhancement of the activity of other proteases, such as metalloprotease-9 and cathepsins, involved in the remodeling processes of ECM is among the main inflammatory mechanisms related to the neutrophilic elastase in absence of AAT [62,63].

The Z-allele variant can also promote inflammation through the production of AAT polymers. The allele Z variant of the AAT is, in fact, characterized by a point mutation (Glu342Lys) right in the active site of the protein that makes it less functional and prone to polymerization. These polymers are retained in the endoplasmic reticulum, causing increased cellular stress, caspase activation, and cell death [3]. The subsequent release of polymers outside the cells acts as an inflammatory factor, increasing the neutrophils' inflammation mediated by IL8 [64]. As bronchial epithelial cells are also able to synthesize, accumulate and secrete the polymeric form of the Z protein, thus promoting the onset of neutrophil inflammation in the airways [6[¶]], it could be postulated that the neutrophil inflammation induced by the local production of polymers of the Z variant of the protein may represent another biological mechanism linking these two conditions.

Neutrophil inflammation in the airway could help to explain the lower control of the disease, the greater decline in respiratory function, and the worse prognosis of asthmatic patients with AATD compared with those without this genetic deficiency as the neutrophilic inflammation phenotype is less susceptible to the therapy currently available for the treatment of asthma.

CONCLUSION

Although the association between AATD and Asthma is well established and the statements of the main scientific societies recommend the search for AATD in asthmatic patients with obstruction not fully reversible and late-onset asthma (both characteristics frequently associated with the most severe forms of disease), the biological mechanisms binding these two conditions have not been sufficiently investigated at the moment. However, it could be hypothesized that the link between the two diseases is the protease/antiprotease imbalance following AATD and the proinflammatory effect that occurs in the presence of a deficiency of a protein that has an important anti-inflammatory and immunomodulatory effect. Further studies are necessary to confirm these two hypotheses.

Therefore, there is a strong need to perform molecular studies aimed at characterizing the relationship between asthma and AATD to ensure the execution of patient-targeted genotyping and, in

Table 1. Asthma characteristics suggestive for AATD screening**Characteristics of asthmatic patients to be screened for AATD**

Late-onset asthma

Corticosteroids unresponsive

Nonfully reversible airways obstruction

AATD, α 1-Antitrypsin deficiency.

future perspective, to identify new molecular targets and specific therapeutic strategies.

PRACTICAL PROSPECTIVES

Asthmatic patients with late-onset asthma and neutrophilic airway inflammation that do not respond to corticosteroid therapy, showing no full reversibility to acute bronchodilator administration and/or persistent airway obstruction because of faster and relevant airway remodeling, should undergo AAT determination (Table 1). Therefore, AAT assessment should be considered as part of the phenoendotyping process of severe asthma to find new 'treatable traits' for the management of the disease.

All patients with asthma and AATD should undergo a strict follow-up regimen to promptly diagnose the early development of emphysematous disease with chronic obstructive pulmonary disease and, therefore, asthma and COPD overlap.

We aim these patients should be included in randomized control trials to verify the hypothesis AAT replacement therapy can be effective in lung functional decline control, asthma exacerbations reduction, and quality-of-life improvement.

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