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The role of alpha-1-antitrypsin protein in the pathogenesis of abdominal aortic aneurysm

Agata W. Dżeljilji[1], Joanna Chorostowska-Wynimko[1], Dariusz Szewczyk[2], Wojciech Popiołek[2], Artur Kierach[3], Piotr Andziak[2, 4]

[1]1st Department of Lung Diseases, National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland
[2]Department of General and Vascular Surgery, Central Clinical Hospital of the Ministry of the Interior, Warsaw, Poland
[3]Kierach Clinic, Tychy, Poland
[4]2nd Department and Chair of General, Vascular and Oncological Surgery, Medical University of Warsaw, Poland

Abstract

Alpha-1-antitrypsin is a potent antiprotease playing an important role in maintaining protease-antiprotease balance. It protects the structures of extracellular matrix against destruction by proteolytic enzymes. Loss of elasticity occurs when increased protease activity is accompanied by qualitative impairment or reduced concentrations of antiproteases. Alpha-1-antitrypsin deficiency is a risk factor for obstructive lung disease, including emphysema, liver and kidney disorders and, less often, follicular panniculitis, granulomatosis with polyangiitis (previously Wegener's granulomatosis). Literature also emphasises the role of AAT in the development of aortic aneurysms, and results of biochemical studies support this theory. Aortic aneurysm is an important clinical problem, unceasingly associated with high mortality. For this reason, it is exceptionally important to identify its risk factors. Studies on the relationship between AAT and development of AAA (abdominal aortic aneurysm) have been conducted since the 1990s. Due to the development in molecular diagnostic techniques, new reports on the topic appeared over the last decade.

Key words: abdominal aortic aneurysm, alpha-1-antitrypsin

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Introduction

Abdominal aortic aneurysm (AAA) is defined as widening of the aorta by at least 50% compared to its normal diameter. Another definition describes AAA as distention of the aorta by > 3 cm.

It usually occurs after the age of 55 and is 4–8 times more common in men than in women, with its prevalence estimated at 4–7.6%.

Aneurysm is a symptom of a defect in the intima media of the vascular wall, the main component of which is elastin. In a normal aorta, the number of elastin layers is significantly reduced in the subrenal region, which may explain the most frequent localisation of aneurysms. Elastin is not synthesised in an adult aorta and its half-life is estimated at 50–70 years. The process of tissue aging alone does not lead to pathological arterial dilatation, it occurs as a result of uncontrolled destruction by proteolytic enzymes. Another mechanism involves mutations leading to production of abnormal connective tissue proteins that act as a scaffold for collagen and elastin, e.g. fibrilin-1 mutation in Marfan syndrome.

Pathogenesis of aneurysm-like lesions is difficult to establish, as they often coexist with atherosclerosis [1]. Proteolytic processes, augmented by chronic inflammation, antiprotease deficiency, and haemostasis, play a significant role in their development. The main proteolytic enzyme of fibrinolysis — plasmin, activates extracellular matrix metalloproteinases (MMP), which break down aortic wall components.

Address for correspondence: Agata W. Dżeljilji, 1st Department of Lung Diseases, National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland, e-mail: nosearmy85@gmail.com

Histopathological sections show fragmentation of the elastin fibres, increased metalloproteinase activity, and inflammatory reaction in the tunica intima and adventitia [2–4]. The above-described data demonstrate the complexity of this issue and indicate the need for further investigation.

There are well-established factors that influence the development of AAA, such as: atherosclerosis, smoking, COPD, arterial hypertension, age > 50 years, and genetic predispositions. Much less is known about phenomena leading to progression of aortic lesions: inflammation, remodelling of connective tissue scaffolding and oxidative stress, as well as protease-antiprotease imbalance and the role of alpha-1-antitrypsin. The impact of excessive destruction or insufficient rebuilding of the extracellular matrix in response to inflammation among patients with aneurysms remains speculative.

Significance of AAT

Excessive proteolysis causes destruction of elastic and collagen fibres, resulting in vascular wall remodelling. Disruption of protease-antiprotease balance occurs when increased activity of proteolytic enzymes is accompanied by quantitative or qualitative deficiency of antiproteases [5].

Neutrophil elastase is the main factor responsible for increased proteolysis under deficiency of alpha-1-antitrypsin (AAT), the strongest protease inhibitor [6].

Alpha-1-antitrypsin, also known in the literature as alpha-1-antiprotease, owes its name to a historical hypothesis indicating trypsin (a serine protease) as its main antagonist. It is currently known, that the scope of AAT action is significantly broader. Its physiological activity is based on antiprotease properties against proteolytic enzymes, especially neutrophil elastase, as well as proteinase 3, myeloperoxidase, cathepsin G, serine proteases (tripsin, kallikrein 7 and 14, urokinase, granzyme B, triptase, chymase, matriptase), cysteine proteases (caspase 1 and 3, calpain I) and metalloproteinase ADAM-17 (TACE, tumour necrosis factor-alpha-converting enzyme) [7]. Alpha-1-antitrypsin protein is coded by the SERPINA 1 gene located on the long arm of chromosome 14 (4q32.1). It is highly polymorphic and the multitude of mutations results in a significant number of variants of the product (i.e. AAT). Over 130 of them have been identified to date. Normal, fully functional AAT protein is produced by variant M of the SERPINA 1 gene. Thus, normal genotype, occurrence of two proper M alleles is designated as PiMM. PiZ and PiS variants are most common in the Caucasian population. Severe inherited AAT deficiency occurs among individuals homozygous for PiZZ system, with heterozygous PiSZ system, or persons with null mutation, which determines a total lack of AAT production (PiNull/Null, PiZ/Null) [8]. It is thought, that severe homozygotic AAT deficiency (PiZZ) in Europe is more common in Scandinavian countries (allele frequency 2.3%) than in the south of the continent (allele frequency 1.0%) — 1 in 4727 Caucasian neonates on average. Poland is one of the few European countries that does not have full data on the prevalence of AAD [9–17].

It has been possible to perform full diagnostics of alpha-1-deficiency in Poland since 2010. Also, National Registry of Patients with AAT Deficiency is in operation [18].

Relationship between AAT protein and development of AAA

The occurrence of familial cases and greater predilection for the disorder among men point to genetic background of AAA [19, 20]. Biochemical data support the theory of excessive extracellular matrix proteolysis. Increased activity of neutrophil elastase, an imbalance between AAT antiprotease and neutrophil elastase, was observed among patients with abdominal aortic aneurysms. However, initial reports on reduced AAT protein concentrations were not unequivocally confirmed in later studies [21, 22].

The first reports come from 1990, when Cohen et al. [23] showed more frequent occurrence of PiMZ AAT phenotype among patients, who developed abdominal aortic aneurysm. Also, the study by Schardey et al. [24] demonstrated greater prevalence of a rare PiMV phenotype. The PiV allele is exceptionally rare and its biological activity has not been fully determined to date. Pini et al. [25] conducted molecular diagnostics of AAT deficiency among 138 patients with AAA. Presence of deficient alleles was confirmed in 20 of them, including 16 PiMS, 1 PiSS, 1 PiMZ. A rare variant of AAT was also identified in two patients. The authors compared their results with data estimates for Italian population, demonstrating significantly more frequent occurrence of deficient PiS alleles in the AAA group (7.8% vs. 2.2%, $p < 0.001$), as well as lack of significant differences for PiZ (1.1% vs. 1.3%, $p > 0.05$). According to the authors, noted differences point to the role of AATD in the pathogenesis of AAA.

Elzouki and Eriksson [26] also suggested a possible role of PiS in this disorder, presenting a case of a patient with AAA and deficit PiSZ genotype. Concurrently, no relationship was demonstrated between severe AAT deficiency caused by PiZZ genotype and increased risk of AAA development. Autopsy of 30 individuals homozygous for PiZZ and 120 patients with normal PiMM variant failed to corroborate statistically significant

dependence between AAA development and PiZZ genotype (p=0.027). Results of studies by Ramsbottom et al. published in the same year demonstrated significantly more frequent occurrence of PiMZ and PiZZ genotypes among patients diagnosed with abdominal aortic aneurysm [27]. Concordant results of Elzouki and Eriksson [26], Ramsbottom [27], and Pini [25] indicate the involvement of PiS variant in the pathogenesis of AAA in contrast to the results obtained by Cohen et al. [23], who observed such relationship for PiZ only.

Over the last decade, intense studies were conducted devoted to the analysis of human proteome, including investigations focused on identification of differences in protein profiles among patients with AAA compared to healthy subjects. Significantly higher expression of AAT was demonstrated in comparison with the control group ($p<0.05$) [28]. Increased serum AAT in patients with AAA may indicate the necessity for inhibition of proteases responsible for change in the structure of vascular wall.

Biological activity of AAT protein is also an important issue. It is determined not only by its concentrations in blood or tissues, but also by its structure. The above-mentioned studies analysed mainly the quantitative aspect of the problem. Besides AAT, 24 other proteins were identified. Since the control group consisted of patients without atherosclerosis, selected proteins may be associated with evolution of atherosclerotic plaques. Moreover, due to AAT being an acute-phase protein, the scope of its function as a biomarker in vascular pathology requires further investigation.

Since patients with AATD are at an increased risk of vascular disease, studies on vessel elasticity are also of interest. Booms et al. [29] observed a tendency towards significantly lower blood pressure among men with AATD compared to those presenting PiMM phenotype, which, according to authors, has a strong causal relationship with reduced arterial elasticity. Absence of a similar relationship in the group of studied females seems to corroborate this hypothesis in the context of known influence of estrogens on vascular wall tension. However, Elzouki et al. [30], who examined pulsatile change in vessel diameter based on ultrasound examination together with blood pressure measurements, demonstrated no differences between men heterozygous for PiZ and the control group with PiMM. On the other hand, the study confirmed less frequent occurrence of ischaemic heart disease among patients with AAA and heterozygous variant of PiZ AAT compared with AAA and proper AAT structure ($p = 0.03$). The same research team showed also significantly reduced elasticity of abdominal aorta among male patients homozygous for PiZZ compared to men with PiMM ($p = 0.025$). As in other studies, no such relationships were found for females ($p = 0.17$) [31]. It seems that the above-described phenomena may be interpreted as early vascular changes, supporting the predilection of individuals with AATD for vascular disease.

Analysis of literature from 2003 yielded a weak relationship between AATD and AAA. According to the statement of the American Thoracic Society and European Respiratory Society, AATD does not constitute the main genetic determinant for development of AAA, although its role in this process has not been completely excluded. Results of studies and biochemical background point to disruption of AAT protein structure and function as a possible risk factor for development of AAA. Also, joint guidelines by the American Thoracic Society and European Respiratory Society emphasise the need for further studies on this issue [32].

Summary

Growing knowledge of biochemical processes and progress in the field of genetics enabled ongoing research on the role of abnormal AAT variants in the pathogenesis of AAA. Available literature data is inconclusive. Proteomic studies demonstrated increased expression of AAT protein among patients with AAA compared to the profile found in healthy subjects.

Significantly more frequent occurrence of deficient AAT phenotypes among patients with AAA has yet not been unequivocally corroborated, although some studies convincingly point to the possible role of impaired PiS AAT protein in the pathogenesis of the disorder. However, some studies led to discovery of new, previously unknown variants of AAT protein, showing that it is highly polymorphic. Reports of abdominal aortic aneurysm development in patients homozygous for PiZZ variant of AAT are rare and most likely associated with the influence of other factors.

Despite several decades of research, the aetiology of AAA remains unclear. Obtained evidence does not exclude the role of AAT — one of the most potent antiproteases, in the pathogenesis of AAA. Considering the properties of AAT and available literature data, further research seems reasonable.

Conflict of interest

None.

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