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Review Article

The Association of Alpha-1 Antitrypsin Deficiency and Arterial Aneurysms: An Update and Review

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Abstract

Alpha-1 antitrypsin deficiency (AATD) is an autosomal codominant genetic disorder caused by mutations in the *SERPINA1* gene. It results in reduced circulating levels of alpha-1 antitrypsin (AAT), a serine proteinase inhibitor (PI) primarily produced by hepatocytes. The most common deficient alleles are PI*S and PI*Z, with PI*ZZ homozygotes having the most severe deficiency and highest risk for lung and liver disease. While AATD is well established as a cause of early-onset emphysema and liver cirrhosis, emerging evidence suggests a potential association with the formation of arterial aneurysms. The pathophysiological rationale for this association centers on protease-antiprotease imbalance and potential extracellular matrix degradation of elastin in arterial vessel walls. Several studies have reported increased frequencies of AATD alleles in patients with abdominal aortic aneurysms and intracranial aneurysms compared to the general population, with some demonstrating statistically significant associations. Additionally, patients with the PI*ZZ genotype have been shown to have larger aortic diameters, greater aortic stiffness, and reduced distensibility compared to controls. However, the evidence is inconsistent, as several large studies have failed to demonstrate significant associations between AATD and aneurysm formation. Overall, current evidence suggests an association of AATD with the development of arterial aneurysms. However, it is also clear that the presence of AATD alone is not sufficient to increase the risk of developing new-onset arterial aneurysms.

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Introduction

Alpha-1 antitrypsin (AAT) is a serine proteinase inhibitor (PI) primarily produced by hepatocytes.[1] It is also synthesized in the intestine and the lungs and is an acute-phase protein.[2] AAT plays a major role in preventing tissue damage by inhibiting proteolytic enzymes, mainly neutrophil elastase. Moreover, AAT also acts as an anti-inflammatory agent.[2]

AAT is encoded by the *SERPINA1* gene located on the long arm of chromosome 14. Over 150 alleles of *SERPINA1* have been identified, and each allele is assigned a letter code based on electrophoretic mobility. The normal genotype is composed of two normal alleles conventionally called the "M" allele. This results in the normal genotype, PI*MM.[2] Alpha-1 antitrypsin deficiency (AATD) is the result of mutations to these alleles and is inherited in an autosomal codominant pattern. The most common deficient alleles are single-nucleotide polymorphisms. These include allele S (a substitution of valine for glutamic acid at residue 264) and allele Z (a substitution of lysine for glutamic acid at residue 342). In contrast, null alleles are usually the result of an early stop codon, and patients with these mutations have no detectable AAT.[3]

Patients with AATD can be classified according to their genotype as heterozygous, PI*SZ, or homozygous, when both alleles are the same, PI*SS or PI*ZZ. Individuals who carry two copies of the Z allele have very low AAT and are at very high risk of lung disease. Those with the SZ combination have an intermediate risk for lung disease only in the presence of smoking exposure.[4] Individuals with an MS (or SS) combination usually produce sufficient amounts of AAT to protect their lungs and, therefore, do not have an increased risk of AATD-related lung disease.[2] However, people carrying MZ alleles have a slightly increased risk of experiencing impaired lung or liver function.[5]

Although the risk is increased by modifiers such as smoking[6] and alcohol use,[7] large studies have reported that MZ allele carriers have a significantly increased risk for lung and liver disease compared to non-carriers. A study on 422,506 non-carriers, 138 PI*ZZ, 864 PI*SZ, 1,014 PI*SS, and 17,006 PI*MZ individuals suggested that liver fibrosis/cirrhosis incidence was elevated in PI*SZ (adjusted odds ratio [OR] = 3.1 [1.1–8.2], $P = 0.027$) and in PI*MZ participants (OR = 1.7 [1.2–2.2], $P = 0.001$). ORs were adjusted for age, sex, body mass index, alcohol consumption, and diabetes mellitus.[5] Also, the same study showed that PI*MZ individuals displayed a moderately increased OR for emphysema (adjusted OR = 1.6 [1.3–1.9], $P < 0.0001$).[5]

Although genotypes are helpful in predicting disease severity, phenotypes are often more clinically useful. Phenotypes are identified by measuring concentrations of AAT variants in the blood, which helps confirm blood levels and monitor the effects of therapy.

Keywords: Alpha-1 antitrypsin deficiency; Aneurysm; SERPINA1; Proteinase inhibitor; Abdominal aortic aneurysm; Arterial aneurysm.

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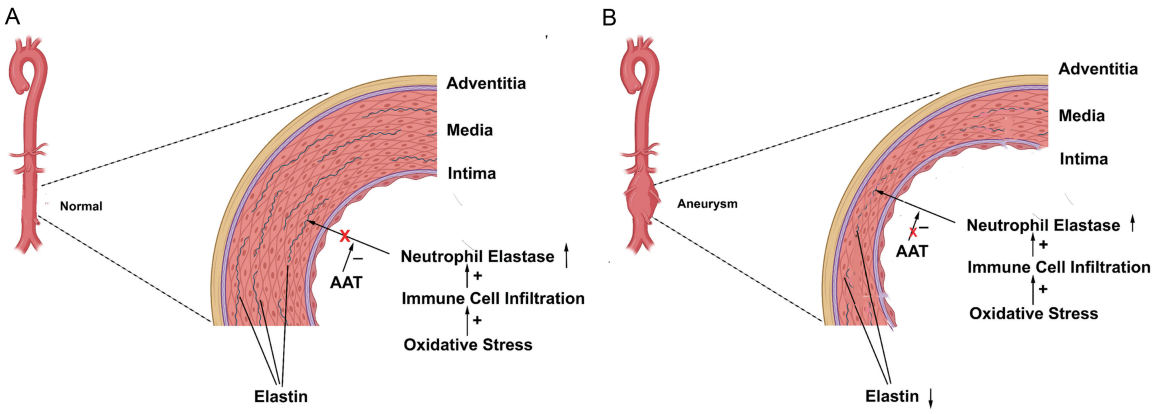

Fig. 1. Proposed mechanism of aneurysms associated with AATD. An aneurysm results from ECM (primarily elastin) degradation, oxidative stress, and immune cell infiltration. (A) In a healthy individual, AAT inhibits serine proteases, such as neutrophil elastase. (B) When AAT is deficient, neutrophil elastase is not inhibited, leading to elastin degradation and increased susceptibility to aneurysm formation. Created with BioRender. AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; ECM, extracellular matrix; ↑, increase.

Patients who have only normal alleles are referred to as MM, with normal AAT levels (20 to 53 μmol/L), 100%. Patients with the SZ phenotype have a deficiency of plasma AAT, with levels below 23 μmol/L.[8] Patients with ZZ have typical levels of AAT of less than 7 μmol/L.[8] In addition to these phenotypes, some rare patients have defects resulting in the absence of detectable (null) AAT protein in the plasma.[8] They have a higher risk for severe lung disease, while liver disease is not typically associated. Another rare phenotype, dysfunctional, is associated with normal protein levels but a non-functional protein. Like the null phenotype, these cases develop severe lung disease, but not liver disease. That is because mutations in *SERPINA1* are responsible not only for the deficiency of circulating PI but also for the accumulation of misfolded abnormal PI in the liver. This accumulation leads to hepatic damage.[3]

AATD is a multisystem and phenotypically heterogeneous disorder[9,10] that mainly affects the lungs and the liver. The clinical manifestations of AATD result from low serum AAT levels and AAT accumulation inside hepatocytes. AAT is normally produced in the endoplasmic reticulum and secreted by the Golgi complex from the hepatocytes into the blood. Mutation of the *SERPINA1* alleles leads to the misfolding of AAT. The rate at which misfolded AAT is produced and accumulates in polymers versus the hepatocyte degradation of misfolded AAT influences the clinical presentation.[2]

PI*SS produces misfolded AAT at a slow rate, with part being secreted into the blood and part being degraded inside the hepatocytes. Thus, the clinical presentation of PI*SS will be the result of low levels of AAT and will translate mainly into lung symptoms due to unbalanced proteolytic damage by neutrophil elastase.[3]

On the other hand, PI*ZZ leads to severe AATD. In these patients, there is rapid production of misfolded AAT. Around 70% is degraded within the hepatocytes, 15% is secreted into the blood, and 15% forms polymers that are either degraded, secreted, or remain in the liver. The polymers that accumulate in the liver cause endoplasmic reticulum stress. This leads to either cell death or propagation of cellular stress that can eventually lead to liver cirrhosis. These remaining misfolded polymers inside the hepatocytes are periodic acid–Schiff positive and resistant to diastase, and are the histologic hallmark of AATD.[3]

Because elastin is also an important structural component of arterial vessels, it is possible that deficient or misfolded AAT might result in detrimental effects on arterial vessels in addition to the well-characterized pulmonary and hepatic phenotypes. The aim of this report is to review the clinical evidence for an association of AATD with arterial aneurysms.

Epidemiology of AATD

AATD is a condition that occurs worldwide, but its prevalence varies among different populations. The worldwide prevalence of the S or Z allele and one copy of the M allele in each cell (MS or MZ) has been reported to be 2.4%. A large European cohort showed that the prevalence of COPD in individuals with PI*ZZ is as high as 57%.[11] Clinically significant liver fibrosis can be present in up to 35% of these patients.[3] Also, hepatic involvement has been described in the literature, although the prevalence is unclear.[12]

AATD is more prevalent among individuals of European ancestry and relatively less common among individuals of Asian and other ancestries. Mean gene frequencies of PI*S or PI*Z in Central Europe are as high as 3%, compared to 1% in East Asia. It has been reported that approximately 557,475 individuals in the United States have PI*SS, PI*SZ, or PI*ZZ, while worldwide more than 3.3 million people are estimated to have allele combinations associated with AATD.[13]

Proposed pathogenesis of aneurysms associated with AATD

An aneurysm, defined as a localized dilation of all three layers of an artery, occurs in the setting of vascular smooth muscle cell death, degradation of the extracellular matrix (ECM), oxidative stress, and immune cell infiltration (Fig. 1). The ECM is mainly composed of elastin, which is produced by vascular smooth muscle cells. Degradation of elastin can lead to dilation and rupture. The ECM is mainly degraded by serine proteinases and metalloproteinases. Serine proteinases degrade the ECM directly, breaking down elastin, and indirectly induce apoptosis of vascular smooth muscle cells. In this context, it has been hypothesized that AATD could increase the risk of the formation of vascular aneurysms due to increased proteolytic injury to the ECM in the vascular wall.[14]

Clinical evidence linking AATD and aneurysms

There have been several studies on the association between AATD and aneurysms (Table 1).[15–19] A large study evaluated

Table 1. Alpha-1 antitrypsin phenotypes and their association with arterial aneurysms

Author (y) (Ref.)	Study population; control subjects	Aneurysm type	PI*MM	PI*MS	PI*SS	PI*MZ	PI*SZ	PI*ZZ	Outcomes
Cohen (1990)[15]	47 patients with AAA; general population	AAA	40 (85%)	2 (4%)	–	5 (11%)	–	0	PI*MZ significantly higher in patients with AAA compared to the general population (P = 0.026)
		Control	95%	3–4%	–	3–4%	–	2–3%	
St Jean (1996)[18]	173 patients with AAA; 72 patients with IA; 192 US whites of mixed European heritage	AAA	156 (90%)	12 (6.94%)	–	5 (2.89%)	0	–	PI*Z allele was eight times higher compared to the control (P = 0.014), but not significant after correcting for multiple comparisons.
		IA	67 (93.1%)	1 (1.39%)	–	3 (4.17%)	1 (1.39%)	–	
		Control	181 (94.27%)	8 (4.17%)	–	2 (1.04%)	0	–	
Schievink (1996)[16]	100 patients with IA; 904 general population	IA	83 (83%)	9 (9%)	0	7 (7%)	–	1 (1%)	PI*MS and PI*MZ (16%) are more common in IA patients compared to controls (7%), OR 2.56 (95% CI 1.32–4.75; P = 0.005). PI*ZZ frequency higher in IA compared to control, OR 67 (95% CI 2–363.3; P = 0.015)
		Control	839 (92.8%)	38 (4.2%)	2 (0.2%)	25 (2.8%)	–	0	
Schardey (1998)[19]	126 patients with AA; 300 population from Germany	AA	104 (82.5%)	9 (7.1%)	1 (0.7%)	4 (3.1%)	0	–	The percentage of PI*MM was lower in patients with AA compared to controls (P < 0.001).
		Control	279 (93%)	10 (3.3%)	0	8 (2.6%)	1 (0.3%)	–	
Pini (2021)[17]	138 patients with AAA; Italian population	AAA	116 (84.06%)	16 (11.59%)	1 (0.73%)	3 (2.17%)	–	–	Pi*S deficiency allele frequency was higher in AAA (6.5%) compared to the control (2.5%), P < 0.01
		Control	§						

§PI*S frequency in the Italian population was 2.5%, and PI*Z frequency was 1.3%. AA, aortic aneurysm; AAA, abdominal aortic aneurysm; CI, confidential interval; IA, intracranial aneurysm; OR, odds ratio; PI, proteinase inhibitor.

the frequency of AAT-deficient alleles in patients with vascular aneurysms and included 47 patients with abdominal aortic aneurysm (AAA). They showed that the PI*MZ genotype was significantly more frequent in their sample with AAA compared to the general population.[15] Another study compared the AAT genotype distribution in 100 patients with intracranial aneurysms that involved the anterior cerebral artery complex, the internal carotid artery complex, the middle cerebral artery complex, or the vertebrobasilar artery complex to the general population. The rates of PI*MS and PI*MZ in patients with intracranial aneurysms were significantly higher than in the general population, with an OR of 2.56 (95% confidence interval [CI] 1.32–4.75; $P = 0.005$). Also, 1% of the patients with intracranial aneurysms had the PI*ZZ phenotype compared to the expected 0.015% in the general population, with an OR of 67.0 (95% CI 2.0–363.3; $P = 0.015$).[16] These results suggest a positive association of PI*Z with the presence of aneurysms. Both of these earlier studies used isoelectric focusing gels to determine AAT genotypes. However, neither measured the serum AAT levels or serum markers of inflammation such as C-reactive protein.

A more recent study used PCR to compare the frequency of AAT genotype in 138 patients with AAA with that in the general population and correlated AAT and C-reactive protein levels in AATD versus the general population. They showed a statistically significant higher frequency of the PI*S deficiency allele, 6.5% versus 2.5%, in the patients with AAA compared to the general population.[17]

However, other studies have failed to show an increased frequency of AATD alleles in patients with aneurysms. A large study compared AAT allele frequency distribution in 173 patients with AAA and 72 patients with intracranial aneurysms to 192 controls. The pooled PI*Z and PI*S allele frequencies were found not to be increased in patients with AAA compared with controls, nor in patients with intracranial aneurysms compared to controls. However, in a subgroup analysis of patients with intracranial aneurysms, the frequency of the PI*Z allele was eight times higher compared to the control ($P = 0.014$) but was not significant after correcting for multiple comparisons.[18] Current clinical practice guidelines from the American Thoracic Society conclude that the evidence for a link between AATD and AAA is weak and do not recommend routine screening for AATD in patients with aneurysms.[20]

A study of 43 cases of hepatic artery aneurysm showed that one patient had AATD.[21] A retrospective study of 1,767 cases of liver-transplanted patients over 10 years in three centers found four cases of splenic artery aneurysm rupture. Out of these, three had the PI*Z deficiency allele. The relative risk for splenic artery aneurysm rupture in patients with AATD was 277, which was statistically significant ($P < 0.01$).[22] In general terms, chronic obstructive pulmonary disease has been recognized as a risk factor for thoracic aortic aneurysm development,[23] and portal hypertension, with or without cirrhosis, is associated with an increased 15% prevalence of splenic artery aneurysms.[24]

AATD patients with PI*ZZ have also been reported to have significantly larger aortic diameters, greater aortic stiffness, and less aortic distensibility compared to controls.[25] In another study with a larger number of patients with AATD, 50 PI*ZZ and one PI*SZ, these results were reinforced, as there was a significant positive correlation between aortic diameter and age ($r = 0.43$; $P = 0.0016$). This correlation was not seen in the control group, suggesting a correlation with decreased AAT levels.[26]

Besides vascular aneurysms, AATD also seems to increase the risk of atrial septal aneurysm. A study of thirty patients with atrial septal aneurysm revealed that PI*M3M3 was significantly higher in patients with atrial septal aneurysm compared to controls (OR 6.68, 95% CI 2.09–21.4, $P = 0.001$).[27] M3 is an M allele variant resulting from glutamic acid at position 400 being replaced by aspartic acid due to a single nucleotide change (adenosine to cytosine at codon 1200).[27]

Conclusions

Given that protease–antiprotease imbalance and ECM degradation could predispose affected individuals to vascular wall weakness, there is a plausible pathophysiological rationale for a potential association.

Studies on the association of PI*ZZ with the development of arterial aneurysms described above had some highly significant statistics. However, several studies comparing affected individuals to those with the normal PI*MM genotype have reported contradictory results. Overall, expert opinion favors an association between AATD and arterial aneurysms. However, it is also clear that AATD alone is not sufficient for the development of new-onset vascular diseases. It seems most likely that AATD is just one of a number of cofactors that increase the risk of the development of new-onset arterial aneurysms. Therefore, the data are insufficient to recommend routine screening for AATD in patients with aneurysms and vice versa.

No studies have specifically evaluated whether augmentation therapy affects aneurysm formation or progression in AATD patients. Future well-designed studies incorporating comprehensive genotyping, standardized aneurysm phenotyping, and adequately powered cohorts are needed to determine the risk associated with specific AAT genotypes for the development of arterial aneurysms.

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Conflict of interest

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Author contributions

Review concept (GYW), information collection and drafting of the manuscript (MDSS), and revision of the manuscript (GYW, MDSS). All authors have approved the final version and publication of the manuscript.

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