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Alpha-1 antitrypsin deficiency

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Summary

Objective: To review the topic of alpha-1 antitrypsin (AAT) deficiency.

Method: Narrative literature review.

Results: Much work has been carried out on this condition with many questions being answered but still further questions remain.

Discussion and Conclusions: AAT deficiency is an autosomal co-dominantly inherited disease which affects the lungs and liver predominantly. The clinical manifestations, prevalence, genetics, molecular pathophysiology, screening and treatment recommendations are summarised in this review.

Introduction

AAT deficiency is a genetic disorder that affects an approximated 3.4 million individuals worldwide, when individuals with the ZZ, SZ or SS phenotype are included (1). This condition is clinically characterised by early-onset emphysema and liver disease.

AAT deficiency was first documented by Laurell and Eriksson in 1963 (2). They carried out a painstaking review of 1500 serum protein electrophoresis gels in which the band for the α 1 was absent. Three out of five of these patients developed emphysema at a young age. Since that time much work has been done on AAT deficiency elucidating the genotypes and the phenotypes of the condition, the clinical variation in symptoms and signs, the method of diagnosis and of screening and the possibilities for treatment. Many questions have been answered but with these many more questions surface.

Prevalence of AAT deficiency

AAT deficiency is a genetic cause of Chronic Obstructive Pulmonary Disease (COPD). The frequency of AAT deficiency can only be estimated. In one study of 965 patients with COPD who were screened for AAT deficiency 1.9% were shown to have the disease (3). Extrapolating from the National Health Information Survey in the USA which estimates that 3.1 million Americans have emphysema this would suggest that in 59,000 of these patients the emphysema is caused by AAT deficiency. Under-recognition of AAT deficiency is a problem. When given a questionnaire addressing the number of doctors seen for symptoms attributable to AAT deficiency and the onset of AAT deficiency-related symptoms the 300 patients studied reported a mean delay between first symptom and initial diagnosis of the disorder of 7.2 years

(4). The delay in initial diagnosis was shown in this study to be associated with adverse outcomes for the patients in relation to psychosocial effects. Other consequences include slowed opportunities to offer specific counselling and therapy. More recently this delay has decreased slightly to a mean of 5.6 years (5) demonstrating still further room for improvement.

Clinical Manifestations

The clinical disease associated with AAT deficiency can present in a number of ways but the most frequent organs affected are the lung and the liver. In the lung, emphysema is the most common manifestation. The emphysema associated with AAT deficiency tends to be early in onset (i.e. in the fourth and fifth decades), panacinar in pathology and disproportionate in its effect on the lung bases (compared to the more apical distribution in AAT replete patients) (6-8). Evidence for the association of bronchiectasis with AAT deficiency is mixed. Larsson originally noted bronchiectasis in 11.3% of 246 patients with the ZZ phenotype (9). The NHLBI registry reported bronchiectasis in only 2% of 1129 participants (10) and in a case-control study Cuvelier and colleagues recorded no excess frequency of AAT deficiency in patients with bronchiectasis compared with those without bronchiectasis (11). A more recent study characterising the computed tomographic phenotype of patients with AAT deficiency found that clinically significant bronchiectasis occurred in 27% of the patients studied, greater than previously recognised (12).

After the lung the liver is the next most commonly affected organ in AAT deficiency. In a Swedish population-based screening study of 200,000 neonates, 22 (18%) of 120 babies with the Z allele had evidence of some liver dysfunction over follow-up to the age of 6 months, including obstructive jaundice (12%) and minor

abnormalities (7%) (13). When liver dysfunction is present the risk of progressing to liver cirrhosis was estimated to be 50%; 25% died within the first decade of life and 2% developed cirrhosis later in childhood (14). Larsson's study followed 246 patients with the Z mutation for up to 11 years and found liver disease in 12.2% (cirrhosis in 11.8%, neonatal hepatitis in 0.4%, and hepatoma in 3.3%) (9). Finally Eriksson's analysis of 38 post-mortem examinations from among 58 decedents with expected AAT deficiency in Malmo, Sweden observed cirrhosis in 34% (n=14), in whom cirrhosis was suspected during life in 64% (15). The established association of Z mutation AAT deficiency with liver disease has lead to the recommendation for screening all neonates, children and adults with unexplained liver disease for this condition (16). Low AAT levels can lead to a diagnosis of AAT deficiency, but there is no correlation between AAT level and risk of liver disease. The risk of cirrhosis in SZ patients is now established. The S variant is known to have an increased susceptibility to polymerization, although this is marginal compared with the more conformationally unstable Z variant (17). There has been speculation that the two may interact to produce cirrhosis, but this has never been demonstrated experimentally.

Panniculitis is a skin condition associated with AAT deficiency. This condition however is not frequent with an occurrence of about 1 in 1000 patients with AAT deficiency (18).

Vasculitis is another of the less frequently occurring diseases associated with AAT deficiency. An over-representation of abnormal AAT phenotypes in people with antiproteinase 3 antibody-positive (i.e., c-ANCA-positive) vasculitis in case series has established an association between the two conditions. Specifically, prevalence of the Z allele among c-ANCA positive individuals was 5.6-17.6%, which exceeds by

threefold to ninefold the prevalence in healthy people (16, 19). The ATS/ERS statement also recommends testing for all adults with c-ANCA-positive vasculitis.

The precise risk of developing emphysema in people with the ZZ phenotype is not known. Tobin et al assessed the risk of developing emphysema in ZZ siblings of index cases (20). They found that emphysema was present radiographically in 90% of smokers compared with 65% of non-smokers. A Swedish study found that in adults homozygous for the Z allele only 29% of never smokers and 10% of ever smokers were healthy (21). The remainder had lung disease. Findings from post-mortems reported in the same study and of CT studies reported by Parr et al suggest that only 14-20% of Z homozygotes were free of COPD (22). The most common cause of death in patients with AAT deficiency is respiratory failure (accounting for 50-72% of deaths) followed by liver cirrhosis (10-13%) (23, 24). The observed overall yearly mortality rate ranges from 1.7% to 3.5% (9, 23-26). Factors found to be associated with increased mortality include older age, lower education, lower FEV1 predicted, lung transplant, and not receiving augmentation therapy (23). In another study only age and CT assessment of proportion of emphysema predicted respiratory and all-cause mortality (24).

There is also an association of the Z allele of AAT with asthma (27, 28), pancreatitis (29) and vascular aneurysms (30, 31). Associations with some neuropsychological conditions have also been suggested. AAT S or Z polymorphisms were shown to be present in 25% of persons with anxiety disorder and 42% of persons with bipolar disorder compared to 10% of a control group without pre-existing affective disorder (32). A recent study comments on how low serum AAT in family

members of individuals with autism correlates with PiMZ genotype (33) and another study suggests a link between the Z allele and “intense creative energy” (34).

Genetics

AAT deficiency is an autosomal co-dominant condition. The AAT protein is encoded by the SERPINA1 gene, previously known as the protease inhibitor (PI) gene, the locus for which is located on chromosome 14q32.1 (35-39). This gene for AAT has been cloned and sequenced (40, 41). The SERPINA1 gene is 12.2kb in length with seven exons and six introns.

The SERPINA1 gene or PI locus is highly polymorphic with approximately 123 single nucleotide polymorphisms (SNPs) listed (42). Differences in speed of migration of different protein variants on gel electrophoresis has been used to identify the PI phenotype, and these differences in migration relate to variations in protein charge resulting from amino acid alterations **(figure 1)** (43). The M allele results in a protein with a medium rate of migration; the Z form of the protein has the slowest rate of migration. Some individuals inherit null alleles that result in protein levels that are not detectable. Individuals with a Z pattern on serum isoelectric focusing are referred to as phenotype PIZ (encompassing both PIZZ and PIZnull genotype variants). The S variant occurs at a frequency of 0.02-0.03 and is associated with mild reductions in serum AAT levels. The Z variant is associated with a severe reduction in serum AAT levels. The most common alleles are the M variants with allele frequencies of greater than 0.95 and normal AAT levels.

The Z allele (Glu342Lys) causes the most severe plasma deficiency and is most prevalent in southern Scandinavia and the northwest European seaboard, with gene frequencies reducing toward the south and east of the continent (44, 45). In contrast, the S allele (Glu264Val) causes only mild plasma deficiency and is most

common in southern Europe and becomes less frequent as one moves northeast. The frequencies of the Z allele in the United States are similar to the lowest frequencies in Europe, but the S allele is more common than in northern Europeans. AAT deficiency is infrequent in the Asian, African and Middle Eastern populations (1) .

Even in patients with severe AAT deficiency, the development, manifestations and progression of COPD are highly variable, which suggest that modifier genes, environmental exposures, and the combined effect of gene and environmental factors may be relevant to disease expression. The altered AAT protein is the product of a single gene, but the disease phenotype is probably a result of many genes. Genetic modifiers of lung disease in AAT deficient individuals may also provide insight into COPD unrelated to AAT deficiency.

The AAT protein, that the SERPINA1 gene gives rise to, is 52 kDa and includes 394 amino acids with the active site of the enzyme inhibitor at methionine 358. It is an antiprotease. Initially labelled “antitrypsin” it was later found to have a much higher affinity for the protease neutrophil elastase (NE). In its activity inhibiting NE, AAT plays a pivotal role in the delicate protease-antiprotease balance.

The molecular defect in the Z allele is a substitution of a lysine for a glutamic acid at position 342 due to a single base alteration in the gene. The low protein levels result from polymerisation of the protein within the hepatocyte endoplasmic reticulum, with subsequent reduction in serum levels due to intracellular accumulation (46). In ZZ homozygous patients the plasma AAT level is of 10% of the normal M allele and 60% in the MZ heterozygote (50% from the M allele and 10% from the Z allele).

Molecular pathophysiology

The AAT molecule is an acute phase glycoprotein (47). This is synthesised and secreted mainly in the liver by hepatocytes (48, 49) but also synthesised by and secreted from macrophages (50), intestinal (51) and bronchial epithelial cells (52). It not only inhibits pancreatic trypsin (53) but also it many other proteinases including neutrophil elastase, cathepsin G (54) and proteinase 3 (55).

Crystal structures have shown that AAT is composed of three β sheets (A-C) and an exposed mobile reactive loop that presents a peptide sequence as a pseudosubstrate for the target proteinase (56-61). The critical amino acids within this loop are the PI-PI' residues, methionine serine, as these act as "bait" for neutrophil elastase (62). After docking, the enzyme cleaves the P1-P1' peptide bond of AAT and the proteinase is inactivated by a mousetrap action that swings it from the upper to the lower pole of the protein in association with the insertion of the reactive loop as an extra strand in β-sheet A (63-68). This altered product of the AAT bound to its substrate is recognised by hepatic receptors and cleared from circulation (69). The conformational change that underlies the clinical disease of AAT deficiency interferes with the processing of this altered protein in the hepatocyte. **(Figure 2)**

Molecular Pathology of the Liver Disease

Current evidence tells us that the liver disease in Z variant AAT deficiency is caused by an accumulation of the abnormal protein in the liver rather than a plasma deficiency. Strong support is provided by the fact that null alleles, which produce no AAT, are not associated with cirrhosis (70). In addition to this, overexpression of ZAAT in animal models results in liver damage (71, 72).

The presence of the Z mutation causes a conformational change in the AAT molecule. The β sheet A opens leaving it susceptible to interaction with another AAT molecule to form a dimer or following interaction with further AAT molecules to form a polymer (57, 73-75). These polymers get trapped in the endoplasmic reticulum. The experimental proof of this was in work from Lomas et al showing polymer formation when the purified plasma ZAAT is incubated under physiological conditions (74). These polymers were also found in inclusion bodies in the liver of a Z heterozygotic patient (74, 76) and in hepatic cell lines expressing the Z variant (77). In work on *Xenopus* oocyte cells, blocking the polymerisation with point mutations was shown to increase secretion of mutants of AAT (78). The Z mutation causes most of the unstable protein to form polymers.

The method by which the hepatocytes deal with the polymers has been the source of much study. Trimming asparagine linked oligosaccharides target ZAAT polymers into an efficient non-proteosomal disposal pathway (79-81). The proteosome pathway has been shown to be important in some hepatic (82) and extrahepatic mammalian cell lines (83, 84). Retained ZAAT stimulates an autophagic response in the hepatocyte (85, 86).

The endoplasmic reticulum has a very important role in protein folding and the handling of misfolded proteins. Specific signalling pathways (87) and effector mechanism have evolved to deal with the temporal and developmental variation in the ER load. The upstream signal that activates these pathways is referred to as ER stress and is defined functionally as an imbalance between the load of proteins facing the ER and the organelle's ability to process that load. The cellular response to ER stress has four main functional components: ER overload response (EOR), the unfolded

protein response (UPR) (88), a decrease in protein synthesis, and programmed cell death (89).

There is a great heterogeneity of liver disease in ZAAT patients. Experimental work shows effects with an increase in temperature, concentration of the substrates for polymerisation (73, 74) and genetic factors (90, 91). Results regarding temperature vary in different studies. One study shows no increase in intracellular ZAAT in response to raised temperatures (92) but further work in a *Drosophila* model of AAT deficiency show a clear temperature dependence of polymerisation in vivo (93).

Cigarette smoking is the most important factor in the development of the lung disease associated with AAT deficiency (94, 95). It is in the lung that the imbalance in the protease antiprotease balance is seen to have a major effect. In the case of Z variant AAT deficiency there is less AAT in the lung (96). The AAT that is present is 5 times less effective than normal AAT (97-100). The residual AAT is susceptible to inactivation by oxidation of the P1 methionine residue by free radicals from leukocytes or direct oxidation by cigarette smoke (54, 101-103). The Z AAT also favours the formation of polymers in the lung (104). ZAAT deficient patients have excess neutrophils in lavage fluid (105) and in tissue sections of the lung (106) possibly related to the chemoattractant effect of an excess of leukotriene B4 (LTB4) and interleukin (IL) -8 (107, 108) and the polymers themselves (109). These circumstances of unopposed proteolytic enzyme activity and an increase in inflammatory conditions cause the trademark emphysema of this disease.

Screening

Recommendations for screening for AAT deficiency have been clarified with publication of the American Thoracic Society /European Respiratory Society

statement on diagnosis and management of the condition (16). The four main benefits of early detection of AAT deficiency are 1. smoking prevention/cessation 2. minimizing the hazards of occupational respiratory pollutants 3. allowing opportunities to receive augmentation therapy and 4. the potential for family planning and guided genetic counselling/testing (110). Symptomatic individuals may require life-long therapy, and early detection may reduce the clinical and economic burdens of progressive lung deterioration (111).

Smoking cessation advice has proven to be effective in patients with AAT deficiency. Follow-up of the original patients from the 1970s AAT deficiency screening program in Sweden who are now 30 years of age has shown that smoking is less common in them than in control subjects (112). Further studies showed that following screening the subsequent provision of information and advice prevented the majority of affected adolescents from smoking (113, 114).

It is perceived that knowledge of AATD diagnosis should aid affected individuals in their occupational choices, allowing them to avoid exposure to environmental agents (e.g. avoiding careers in steel-manufacturing.)

Augmentation therapy is available and will be discussed in more detail in the next section. Early diagnosis with screening programs allows this to be instigated while lung function is preserved.

The impact of diagnosis through screening has multiple implications for the individual. There is a psychological impact of the diagnosis which can be positive for patients satisfied to have found a reason for their symptoms but may be negative with concerns for the future. The ethics of screening family members raises a challenge especially in respect to minors who have the decision made for them. The

consequences of a confirmed diagnosis of AATD include possible discrimination for example by employers and insurers.

Screening with genotyping is recommended. AAT levels may be less expensive but establishing the genotype gives more information about the likelihood of developing clinical consequences of the disease.

Treatment of AAT deficiency

As AAT deficiency results in COPD the medical therapy for COPD also applies to AAT deficiency. These have been outlined in previous published guidelines of the ATS, BTS and the GOLD guidelines (115-117). Most patients with AAT deficiency and obstructive lung disease find symptomatic benefit from bronchodilators even though objective bronchodilator responsiveness may be lacking. Those with proven bronchial hyperreactivity may be given an inhaled steroid with the presumption that a decrease in bronchial inflammation may reduce the loss in FEV_1 over time. A study has suggested benefit of inhaled steroids in some patients with AAT deficiency-related lung disease, although it is not clear which patients benefit (118). Antibiotics are recommended for treatment of exacerbations triggered by bacterial infections. Portable oxygen is recommended for those who desaturate with exercise but otherwise long-term oxygen therapy is only recommended for those with severe hypoxaemia. This should be prescribed in concordance with the ATS and ERS criteria (115, 116). Oral steroids can be cautiously considered in patients with a clear asthmatic component to their disease and long term use should be avoided. Co-morbidities that accompany COPD outside the setting of AAT deficiency should always be borne in mind. These include depression, anxiety and malnutrition.

Pulmonary rehabilitation can offer benefit; improving endurance, reducing dyspnoea and reducing number of hospitalisations (119).

Treatment specific to AAT deficiency is centred on AAT augmentation therapy. There are four potential treatment options (1) intravenous human plasma-derived augmentation therapy, (2) augmentation therapy by inhalation, (3) recombinant AAT augmentation therapy, and (4) synthetic elastase inhibition.

Intravenous human plasma-derived augmentation therapy

Since the early 1980s intravenous administration of purified human AAT concentrate was shown to increase lung levels of AAT in AAT deficient patients (96, 120). Patients receiving once weekly IV doses increased the antineutrophil elastase capacity in lung epithelium lining fluid by 60-70%. A purified preparation was manufactured and shown to be biologically active (121-123) and this lead to the US Food and Drug Administration approval in the United States in 1988. Randomised placebo-controlled trials evaluating the effect of IV AAT replacement therapy in attenuating the development of emphysema are lacking with only one published (124). Recommendations on the use of augmentation therapy is based on the ATS/ERS guidelines (16).

Decline in FEV_1 has been shown to be lower in patients treated with iv augmentation therapy compared with untreated patients (125, 126). In comparing the different degrees of functional impairment, a significant effect of the treatment was demonstrated only in the group of patients with an initial FEV_1 of 31-65% predicted. This non-randomised study showed that weekly infusion of human AAT in patients with moderately reduced lung function may slow the annual decline in FEV_1. In a similar study from the NHLBI Registry the mortality rate was lower in those

receiving augmentation therapy as compared with those not receiving therapy and mean FEV_1 decline was only slowed in the subgroup of patients with moderate emphysema. The only randomised trial was small with only 58 patients. The number of patients limited the only significant finding to being an attenuation in the loss of lung density in the treated group (124).

Augmentation therapy by inhalation

Aerosol application of AAT in patients with AAT deficiency increases AAT concentration and anti-elastase activity in the lower respiratory tract in a dose-dependent fashion (127). Preliminary data suggest that one or twice daily administration of aerosolized AAT may produce sustained anti-elastase protection of the lungs.

Recombinant AAT augmentation therapy and synthetic elastase inhibition

A number of recombinant forms of AAT have been developed as well as recombinant secretory leukoprotease inhibitor (128) and several synthetic low molecular weight elastase inhibitors are being evaluated but their clinical efficacy and safety have not been reported.

In summary the available studies indicate a lowered overall mortality and a slower rate of FEV_1 decline in augmentation therapy recipients with FEV1 values of 35-65% of predicted.

Lung transplantation may be recommended for some patients with end-stage lung disease. Due to limitations on available donor lungs single lung transplant is more common despite the fact that outcome has been shown to be better in patient

who receive double lung transplant. Approximately 12% of all lung transplant operations for emphysema are due to AAT deficiency (129). Five year survival rates following lung transplant is approximately 50% with bronchiolitis obliterans being the major cause of death post-transplant (130).

Lung volume reduction surgery

Lung volume reduction surgery (LVRS) improves exercise capacity and relieves dyspnoea in patients with usual emphysema but the story is less clear in AAT deficiency. One study showed a benefit to bilateral LVRS in AAT deficient patients with emphysema but functional measurements (except 6 minute walk test) returned to baseline at 6 to 12 months (131). LVRS was not recommended in the ATS/ERS guidelines for management of AAT deficiency in their 2003 statement.

Future Research

A large volume of research continues in the field of AAT deficiency. Three examples are in the field of candidate modifier genes, anti-inflammatory proteins and potential synthetic antiproteases. Although the gene responsible for the conformational change in AAT has been identified variations in the presentation of patients strongly suggests the role for candidate modifier genes. An example of a potential modifier is Selenoprotein S / SEPS1. This selenoprotein has been shown to decrease manifestations of ER stress in an in vitro model of Z-variant AAT deficiency (132).

Other anti-inflammatory therapies will continue to be investigated in this disease. Recent work showed that bronchoalveolar lavage (BAL) fluid from patients with AAT deficiency containing free neutrophil elastase had increased cathepsin B

and matrix metalloproteinase-2 (MMP2) activities compared with BAL fluid from healthy volunteers. AAT augmentation therapy to AAT-deficient individuals reduced cathepsin B and MMP-2 activity in BAL fluid in vivo. Furthermore, AAT-deficient patients had higher levels of secretory leukocyte peptidase inhibitor (SLPI) and lactoferrin after AAT augmentation therapy suggesting a novel role for AAT inhibition of NE-induced upregulation of MMP and cathepsin expression both in vitro and in vivo (133).

Conclusion

AAT deficiency is an under diagnosed disease causing much morbidity and mortality in those affected. Much has been elucidated about the genetics and the molecular pathophysiology and potential therapies of this condition. Further research continues to investigate the varying presentations between different patients with AAT deficiency and the full effect of AAT and the body's response to it.

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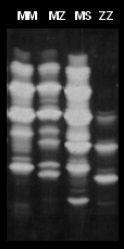

Figure 1. Diagnostic AAT isoelectric focussing gel. A Sebla Hydragel 18 AAT isoelectrofocussing gel showing migration of four different AAT isoforms - MM, MZ, MS and ZZ.

Figure 2: In Z variant AAT deficiency accumulation of the abnormal protein in the endoplasmic reticula of hepatocytes leads to the liver disease of AATD. Decreased AAT enters circulation and arrives in the lung leading to decrease in the antiprotease activity in the lung due to a lower concentration and a higher amount of inactive AAT. This leads to increased protease activity and the destructive process which leads to emphysema.