Research Article

Liver disease in alpha-1 antitrypsin deficiency

The purpose of this review of alpha1-antitrypsin (AAT) deficiency is twofold. First, it will present some of the features of this condition; and second, it will provide a current, annotated list of references for those who wish to read more than this space will permit. In part, the motivation for this review is that current medical and even subspecialty textbooks are not current, and often not accurate, in their descriptions of the deficiency. Many individuals with AAT deficiency remain clinically healthy, or have minimal disease. Thus, people who have recently discovered that they have AAT deficiency should neither be unduly alarmed nor inappropriately unconcerned their diagnoses.

AAT deficiency is the most prevalent potentially lethal hereditary disease of Caucasians. Individuals with AAT deficiency have an increased risk of early onset, severe pulmonary emphysema[1] and for liver disease.

Discovery of AAT deficiency by Laurell & Eriksson in 1963[2] provided a foundation for current thinking about the pathogenesis of pulmonary emphysema.[3,4] Although AAT deficiency has become one of the best understood genetic disorders at a molecular and protein level, many questions about the clinical disease remain unanswered. Current American and International research projects should provide answers to some of these questions in the future.

Biochemistry of AAT

Serum was shown to inhibit trypsin nearly a century ago. A specific trypsin-inhibitory protein was isolated from the alpha-globulin region of human serum in 1962, and was named alpha-antitrypsin. Following the recognition that this protein also inhibits a number of other proteases, it has also been named alpha-protease inhibitor. When used in a clinical context, the original terms "alpha-antitrypsin" and "alpha-antitrypsin deficiency" are used most often, to respect the investigators who discovered the protein and its deficiency. Details about the biochemistry of AAT have been reviewed.[5]AAT is synthesized by hepatocytes and to a lesser extent by monocytes and other cells. Most of the circulating AAT is synthesized by the liver.

Function

It is now thought that inhibition of human leukocyte elastase is the major function of AAT. Leukocyte elastase is a serine protease found within granules of neutrophils and monocytes. This enzyme has a number of biologically important activities; for example, it is probably very important in killing bacteria,[6] in digesting injured tissue during wound healing, and in allowing neutrophils and monocytes to exit from the vasculature and penetrate tissues to reach sites of inflammation. However, if its activity is uncontrolled, it can injure a variety of structural components of normal tissues, and uncontrolled leukocyte elastase may also be pro-inflammatory.[7–9] Deficiency of AAT removes a major control mechanism for leukocyte elastase, and this deficiency can allow leukocyte elastase to injure the delicate gas-exchanging region of the lung, eventually leading to pulmonary emphysema.

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AAT deficiency

The synthesis of AAT is controlled by a pair of genes at the protease inhibitor (Pi) locus. The genes are inherited as co-dominant alleles (products of both genes can be found in the circulation). Many abnormal variants have been very well characterized; they result from point mutations in the gene, and most commonly have one or two amino acid substitutions when compared to the normal protein. Some of these changes result in little (or rarely, no) AAT in the circulation.[10,11]

Heterozygotes and individuals with the S variant usually do not have "normal" circulating levels of AAT. However, in this discussion the term "AAT deficiency" will be reserved for individuals with severely diminished AAT levels ($<11\mu M$).

Variant types of AAT

More than 75 different genetic variants of AAT are now recognized,[10,11] but many of these are quite rare. AAT in the serum can be characterized by phenotyping, which is accomplished by isoelectric focusing of serum. DNA for AAT (most often in white blood cells) can also by typed by genotyping, which is accomplished by allele-specific amplification. The most common variants of AAT will be discussed below. The remainder is beyond the scope of this review, but most are described in the excellent review by Brantly.[10]

Genetic transmission

Individuals with AAT deficiency have two deficient alleles for the protein. Thus, the deficiency is inherited as an autosomal recessive condition. Brothers and sisters of deficient individuals have a 25% chance of also having the condition. Children of deficient individuals can be expected to be heterozygotes ("carriers") for the deficiency. These children have only a small risk of being AAT deficient, and this risk is present only if the partner of the deficient individual is a carrier. Phenotyping or genotyping are necessary to reliably detect carriers, since AAT levels of normals and carriers overlap to some extent.

The normal M alleles

The normal M alleles represent by far the largest group of AAT alleles. They result in normal amounts, and normal functionality, of AAT in the blood. The M1, M2, and M3 alleles differ only subtly from one another, and the differences are not clinically important.

The Z variant

By far the most prevalent type of clinically important AAT deficiency is classified as phenotype Pi Z. In these individuals,

isoelectric focusing reveals only an abnormally migrating Pi Z type AAT. These individuals may be either Pi ZZ homozygotes or Pi Znull heterozygotes, since no AAT attributable to the null genes can be found in the circulation. Genotyping is necessary to distinguish between these two possibilities, although family studies of the pattern of inheritance of low AAT levels may be helpful.

The Z variant has two amino acid substitutions when compared to the most prevalent normal type of AAT. It is subtly abnormal as an inhibitor of leukocyte elastase.[12] However, the most striking abnormality in affected individuals is that circulating levels of the protein are only 10-15% of normal. When livers of these individuals are examined, the hepatocytes contain an abnormal accumulation of AAT.[13] The Pi Z type of AAT is secreted abnormally slowly by both hepatocytes and monocytes. This abnormality is thought to cause the deficiency. The exact cause of the abnormal secretion of Pi Z type AAT is a matter of current investigation. One of the amino acid substitutions (Glu6Lys) may result in mis folding of the AAT, leading to intracellular accumulation and intracellular degradation of the abnormal protein.[14] The structural alteration in the Z variant appears to allow "loop-sheet polymerization" of the molecule, during which the reactive center loops of one molecule become inserted into an opening in the A sheet of another molecule.[15,16]

The S variant

The S variant has a single amino acid substitution (Glu6Val) when compared with the most prevalent normal type of AAT. The S mutation is not associated with intracellular accumulation of the protein, and the S protein inhibits elastase normally. The amounts of the S protein that reach the circulation are slightly lower than normal, because of intracellular degradation of the AAT before it is secreted.[17] The S allele is slightly more prevalent than the Z allele among U.S. Caucasians, and it is much more prevalent in the Iberian peninsula and neighboring countries. Individuals with the Pi S phenotype do not appear to be at increased risk for lung or liver disease.

Common heterozygotes

Pi MS individuals have one normal allele and one S allele. They have nearly normal, and occasionally normal, levels of AAT. They do not appear to be at increased risk for lung or liver disease. Pi MZ individuals have one normal allele and one allele for the Z variant. They usually have decreased levels of AAT in their circulation; however, since they are capable of mounting an acute phase response, their levels can fall within the normal range (particularly if they are ill or are taking oral contraceptives). The livers of Pi MZ heterozygotes show mild intracellular accumulation of the protein. There appears to be minimal excess risk of lung or liver disease in Pi MZ heterozygotes, although studies have not consistently shown that there is no increased risk.[18–22] For more information, see the excellent review by Hutchison.[23] It seems to be advisable to offer a great deal of reassurance to Pi MZ heterozygotes regarding their own risk of developing lung or liver disease, but to counsel them about the risk of genetic transmission of the deficient allele.

Pi SZ individuals have one allele for the S variant and one for the Z variant (the classical deficiency variant). They have AAT levels that range from approximately 1/3 to 1/2 of normal. Pi SZ heterozygotes are more common than Pi Z (AAT deficient) individuals in American populations. The livers of Pi SZ heterozygotes show mild accumulation of AAT. Studies of the risk of disease in Pi SZ heterozygotes have reached variable conclusions;[24,25] this issue is

discussed in Hutchison's review.[23] Based upon the studies published to date, it seems most appropriate to state that these individuals have little, and probably no, increased risk of clinically significant lung or liver disease. It again seems advisable to offer these individuals reassurance regarding their own risk, but to counsel them regarding the risk of transmission of the Z allele.

Lung and liver disease in AAT deficiency

Pulmonary emphysema

As noted above, AAT normally provides an important defense against attack on the normal structural components of the lung parenchyma by leukocyte elastase. Thus, deficiency of this inhibitor increases the risk that leukocyte elastase will injure alveolar walls when it is released from inflammatory cells in the lower respiratory tract. Over many years, the cumulative effect of this injury is alveolar septal destruction and airspace enlargement, which presents clinically as pulmonary emphysema.

Pulmonary emphysema was described as a complication of AAT deficiency by Eriksson in 1964.[1] In the classic description of AAT deficiency,[23,26] patients have:

a. Insidious onset of progressive shortness of breath between ages 25 and 40.

b. Increasing dyspnea and increasing evidence of airflow obstruction as the disease progresses.

c. Chest radiographic abnormalities including hyperinflation and symmetrical loss of parenchymal vascularity and

d. Chest radiographic abnormalities most marked in the lung bases, and commonly associated with bullae. About half of the patients have chronic or episodic productive cough.

Interestingly, however, only a very small fraction of all individuals with AAT deficiency have been diagnosed. In the United States and the United Kingdom, the fraction is approximately 5%. In Sweden and Denmark up to approximately 25% of deficient individuals have been diagnosed. There is reason to believe that many of those who have escaped diagnosis have either:

A. No lung disease; or

B. Mild or atypical disease. This most interesting "hidden" population of individuals with AAT deficiency is further discussed below.

When lung disease becomes established, lung function impairment tends to be progressive in severity. In British and American studies, the range of decline in FEV1 tends to be between 51 and 100ml/year (with a large variability) in the absence of intervention.[23,26] This rate is in the range of 1.5 to 3 times the normal rate of lung function decline.

Liver disease:

Ten to 20% of infants with AAT deficiency have neonatal hepatitis with cholestatic jaundice; others may have abnormal liver enzymes, hepatomegaly, or both.[27] A very small proportion (1-2%) of children with AAT deficiency die from cirrhosis in childhood. In the remainder, liver abnormalities tend to diminish or disappear,[28,29] although mild hepatomegaly or mild elevations in liver enzymes may persist.

Adults with AAT deficiency have a significant risk of cirrhosis and hepatoma in middle to late life.[30] The exact risk for individual patients

is difficult to determine, however, and this risk probably should be given little emphasis when counseling patients who currently have no clinically detectable liver abnormalities.

The liver disease appears to be related to chronic stress on hepatocytes resulting from the burdens of accumulated intracellular AAT and the increased requirement for intracellular protein degradation.[10,14]

Variability in severity of clinical disease

The extent of lung and liver disease in AAT deficiency varies strikingly. An interesting paradox is that adults with severe lung disease often do not have liver disease, and vice versa. While some patients with AAT deficiency develop end-stage lung disease in the third to fifth decades of life, many others escape clinically-important lung disease into mid to late life.[31–33] Many individuals ascertained through non-standard means escape significant lung disease.

Cigarette smoking clearly has an adverse effect on the course of lung disease. Asthma, repeated pulmonary infections, and as-yet unidentified additional familial factors also appear to be associated with a more severe course of lung disease.[31]

The prognosis for newly-identified individuals with little or no lung disease is not known. However, many may escape significant lung disease, especially if they do not smoke. It is prudent to follow such individuals with periodic lung function testing, at least until continued research clarifies their prognosis. Ongoing research may provide further information about the natural history of lung disease in these individuals.

Liver disease

The severity of clinically-apparent liver disease is highly variable. A minority of infants and children are affected, as noted above.[29,34] Only 1-2% of children have a severe course, with death from cirrhosis (or requirement for liver transplantation) in childhood. Only some adults with AAT deficiency eventually develop cirrhosis and/or hepatocellular carcinoma.[30,35] The risk for adult liver disease increases with age. The reason for the variability in severity of liver disease is the subject of ongoing research.[36,37]

Treatment of AAT deficiency

A major goal in the management of patients with AAT deficiency is the prevention of lung disease, or reduction in the rate of progression of any lung function impairment that is already present. It is important to realize that, under normal conditions, few inflammatory cells are found within the lung parenchyma. Therefore, the potential for lung injury in AAT deficiency may be small in the absence of other pro-inflammatory stimuli (smoking, asthma, respiratory infections, etc.). A mainstay of management is to reduce the number of inflammatory cells in the lung. A specific treatment, "augmentation" therapy, is also now available in many countries, to increase circulating levels of AAT.

Smoking cessation

This should be the first priority in management of AAT deficiency. Lifelong nonsmokers can be told that if they continue to refrain from smoking they will have a good chance of avoiding serious lung disease. Once they have been informed about their diagnosis and about the very serious consequences of continuing to smoke, most current smokers are successful in quitting.

Aggressive treatment of asthma

Asthma is now increasingly recognized as an inflammatory disease of the airways. Inflammatory cells (particularly neutrophils) accumulate in and around the airways, and increase the burden of leukocyte elastase in the lower respiratory tract. There is evidence that asthma can lead to permanent lung injury in patients with AAT deficiency. Thus, aggressive treatment of asthma may reduce the long-term impact of AAT deficiency on lung function.

It may be prudent to treat even mild asthma in patients with AAT deficiency with inhaled corticosteroids [such as triamcinolone (Azmacort), flunisolide (Aerobid), or fluticasone (Flovent)]. Inhaled cromolyn sodium (Intal) may also help to reduce airway inflammation and hyper reactivity. A theophylline preparation may be used as a second-line bronchodilator. Systemic corticosteroids may be appropriate during exacerbations of asthma, to suppress airway inflammation (as well as to relieve symptoms).

Early and aggressive treatment of respiratory infections: AAT deficient patients with severe lung disease often have a history of repeated respiratory infections.[31] Even minor respiratory infections probably warrant broad-spectrum antibiotic coverage.

General supportive care: When lung disease is severe, patients may require supplemental oxygen and home health care. Motorized carts may help in allowing patients to retain mobility. Pulmonary rehabilitation programs and support groups have been very helpful for many patients.

Augmentation therapy

Prolastin, which is a concentrated preparation of human 1-proteinase inhibitor (AAT) manufactured by Bayer Corporation, is now available for intravenous administration to AAT-deficient patients. Prolastin is prepared from pooled human plasma that has been screened for the hepatitis B surface antigen and for antibodies to the human immunodeficiency virus. As an additional precaution against transmission of infectious agents, the product is heated for 10 hours at 60^0C.[38] For further protection, administration of hepatitis B vaccine is recommended prior to therapy.

In Pi Z individuals, once-weekly intravenous infusion of Prolastin maintains circulating levels of AAT that are thought to be adequate for protection of the lung parenchyma.[39–43] Infusions increase levels of AAT in broncho-alveolar lavage fluid, and the AAT recovered from the broncho-alveolar lavage is functionally active. Prolastin infusions appear to substantially correct the biochemical deficiency in Pi Z individuals.

While Prolastin has been shown to be "biochemically efficacious," it has been more challenging to demonstrate that it alters the clinical course of AAT deficiency. Data from a large North American registry of patients with AAT deficiency showed that augmentation was associated with a statistically significant diminution in the rate of decline of lung function among individuals with moderately impaired lung function, and with a lower mortality. While encouraging, this study suffered from the flaw that treatment was not randomized. Thus, true treatment effects could have been confounded by other variables in the study population, such as socioeconomic status or access to medical care. A European study, also not randomized, showed a similar effect of augmentation therapy on slowing the rate of decline of lung function. A Danish-Dutch randomized, controlled

trial showed a strong trend toward a lowering of the rate of decline of lung function in the augmented group, but the difference did not quite reach statistical significance at the 0.05 level in the modest number of subjects studied. In summary, intravenous augmentation is a logical approach to specific treatment of AAT deficiency, and clinical studies have shown promise for the treatment. Definitive proof of its efficacy has not been demonstrated, largely because of the logistical difficulties and expense associated with a large, long-term clinical trial having an appropriate randomized, double-blind clinical trial.

Prolastin is a biological product, and some risks of infusion might be expected. In the initial studies, only 4 episodes of self-limited fever were observed in 507 infusions.[40] Since its release, the product has had an excellent safety record. In particular, there has been no documented transmission of infection, and no evidence of immunologic reactions.

Prolastin has been approved for once-weekly intravenous infusion of 60mg of active product per kilogram of body weight. A once-monthly infusion of larger amounts has also been shown to be safe and to have nearly equivalent biochemical effectiveness.[44] The latter regimen would be more convenient and may offer some cost savings on disposable IV supplies. This convenience must be balanced against the suboptimal circulating AAT levels in the week prior to the succeeding dose. Other dosing schedules have been used in clinical practice; however, weekly administration is the only schedule that has been approved for United States patients by the FDA. Full prescribing information can be found in the package insert for Prolastin.

Prolastin can be administered in the physician's office or in a facility where intravenous infusions are routinely given for other indications. Home administration is the option chosen by the majority of patients. In the United States, Prolastin is only available through Bayer Direct, which distributes the product directly to patients.

Prolastin is usually not recommended for individuals with normal lung function. It should be reserved for those with phenotypes Pi Z, Pi Znull, Pi null or other phenotypes with equally severe deficiency. It should not be given to individuals who do not have AAT deficiency or to individuals with mildly deficient phenotypes. Further guidelines can be found in a statement by The American Thoracic Society regarding the approach to individuals with AAT deficiency.[45]

Augmentation by inhalation: Several biologicals manufacturers have shown interest in providing augmentation of AAT directly into the lung by the inhaled route. There is some logic to support this route, and such an approach could allow sparing of this expensive product. Early, small clinical studies have appeared to show that this route is safe, and that augmentation by this route may reduce airway inflammation. Current studies are determining the optimal device for delivery of protein into the deep lung, which may be a particular challenge in individuals with airways disease. Normally, the airway epithelial barrier to protein movement is quite tight, so delivery into the interstitial space of the lung may be challenging by this route. The future of augmentation by inhalation awaits the completion of randomized, controlled clinical trials.

Lung transplantation

Lung transplantation is becoming a viable option for some patients, although the combined experience is still relatively small. As experience with the new surgical techniques (particularly single lung transplantation) increases, lung transplantation may become more attractive to AAT deficient patients with end-stage lung disease. Liver transplantation Successful liver transplantation has been reported. This may be an option for carefully-selected individuals with end-stage liver disease.

Future prospects

AAT delivered by inhalation, genetically engineered AAT, and other inhibitors of leukocyte elastase are in early stages of clinical trials. Even under the most optimistic timetable, these alternatives will not be available for a number of years. Some animal experiments have begun to demonstrate the feasibility of gene therapy and gene repair. Obviously, these therapies must be shown to be absolutely safe before they could be recommended for this condition.

Acknowledgements

None.

Conflict of interest

Author declares that there is no conflict of interest.

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