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Alpha One Antitrypsin Deficiency: A Pulmonary Genetic Disorder

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1. Introduction

Alpha one antitrypsin protein (A1AT), is encoded on the SERPINA1 (serpin peptidase inhibitor, clade A, member 1 gene), (OMIM 107400), located on chromosome 14q32.1 and functions as inhibitor of the enzyme neutrophil elastase. People with a low serum level of this protein are described as having the alpha-1-antitrypsin deficiency (A1ATD), (OMIM #613490), one of the most common heritable disorders. Having this disorder can predispose an individual to a variety of clinical diseases, with the lungs and the liver being the two organs most commonly affected. The A1AT protein is synthesized mainly in the liver by hepatocytes, secreted into the blood stream, and acts as an inhibitor of neutrophil elastase released primarily in the lung during inflammation. The most common allele for the SERPINA1 gene is named M (Middle), which encodes a normal A1AT protein identified in the middle on an isoelectric focusing gel. Over 120 allelic variants have been discovered and are named based on their position and movement on isoelectric gels, A-L if they exhibit faster migration than M, and N-Z if the proteins migrate more slowly. Rare mutations are often named after the discoverer or location of discover (Mmalton, Lowell, etc). A patient's genotype is notated as PI*Allele-Allele, and so patient homozygous for the wild-type A1AT protein is noted as being PI*M-M.

The most common allelic variation causing clinical disease is the Z protein, manifesting most often in the setting of the genotype PI*Z-Z. This mutated protein spontaneously misfolds and then polymerizes with other misfolded A1AT proteins, becoming trapped in large quantities in the endoplasmic reticulum of liver hepatocytes. This results in liver inflammation and fibrosis, and can lead to clinically significant cholestasis and cirrhosis. Not all allelic variants of A1ATD cause liver damage, however, as some encode truncated proteins which do not misfold or polymerize. Rare null mutations have also been discovered due to point mutations that introduce a premature stop codon within the DNA sequence. Patients with the genotype PI*Null-Null do not develop liver disease because they do not synthesize mutated protein, but are at extremely high risk for the development of lung disease because of their inability to inhibit neutrophil elastase.

In the case of the Z allele, the trapped protein is ineffectively secreted into the blood stream, resulting in a low serum concentration of A1AT. The mutated protein also has a reduced functional activity, making it a less effective inhibitor of neutrophil elastase. Without an appropriate level of functional A1AT in lung tissue, neutrophil elastase is free to break down elastin, a critical component of lung structure, which is thought to be the major

mechanism leading to lung damage and the development of emphysema. The lung injury is worsened in the setting of chronic tobacco use, making smoking cessation paramount in the management of people with the deficiency.

Clinical disease associated with the A1AT deficiency is highly variable, suggesting that many genetic modifiers and environmental exposures play a role in the disease expression. The typical symptoms of pulmonary disease include exertional shortness of breath, wheezing, and chronic cough. The cornerstone of disease management is ensuring total smoking abstinence in all patients, as smoking is associated with a much higher rate of decline in lung function in patients with A1AT deficiency. Replacement therapy with purified A1AT protein given intravenously has been approved in several countries as treatment of the deficiency state, and can prevent decline in lung function. Though many studies support its use and clinical benefit, true randomized placebo controlled studies have been limited in size and scope.

2. History of the disorder

In 1962 at the University of Lund, Sweden, Dr. Carl-Bertil Laurell (1919-2001) was examining the serum protein electrophoresis strips of patients with chronic obstructive pulmonary disease, when he noted an absence of the alpha-one band in a small group of patients. Dr. Sten Eriksson was a resident at the University hospital at the time and assisted Laurell in the study because of his previous experience with protein chemistry. Together, they discovered five cases that formed the basis of their first report of alpha one- antitrypsin deficiency. Three of the five patients in their report developed emphysema at an early age, leading to the conclusion that there must be an association between pulmonary disease and the alpha-one band deficiency (Laurell & Eriksson 1963).

It was later discovered that the major function of the alpha 1-antitrypsin protein was to inhibit the enzyme neutrophil elastase, a protease released by neutrophils in the lungs during inflammation. Neutrophil elastase was shown to induce experimental emphysema in animals. (Senior, et al. 1977). These findings lead to the first hypothesis describing the pathogenesis of lung disease, that an imbalance of proteases and anti-proteases could result in an unregulated destruction of critical components of lung structure, namely elastin, leading to the development of clinical lung disease. This hypothesis continues to be central to the understanding of lung disease pathogenesis to this day, and helps explain why patient deficient in A1AT, which could not regulate neutrophil elastase, would be predisposed to emphysema development.

Work by Dr. H. L. Sharp described the association between alpha one antitrypsin deficiency and liver disease in 10 children in 1969 (Sharp et al., 1969). Sharp discovered intracellular inclusions in the liver hepatocytes of A1ATD individuals, and further work found these inclusions to be polymers of the mutant Z allele of the A1AT protein. Evidence for A1ATD was also supported from the results of a large epidemiologic study published in 1976 by Sveger in Sweden (Sveger, 1976). After screening 200,000 infants for A1ATD he identified 127 infants and found that 14 developed cholestatic jaundice in infancy. These studies established the role of A1AT in liver disease pathogenesis.

3. Genetics

Alpha-1-antitrypsin deficiency has been described as an autosomal co-dominant disorder or as an autosomal recessive disorder. Patients who are heterozygote for the enzyme deficiency have roughly half the serum concentration of A1AT compared with normal individuals, and

homozygote have a very low serum concentration of enzyme. This pattern of enzyme levels has led many authors to describe the inheritance pattern as autosomal co-dominant, (see DeMeo's review on the genetics of A1ATD as one example (DeMeo & Silverman, 2004)). Heterozygotes have only a small increased risk for developing clinically significant disease, while homozygotes are at a much higher risk for developing disease, leading other authors to describe the deficiency as having autosomal recessive inheritance (see Alpha-1 antitrypsin deficiency page on the National Center for Biotechnology Information website as an example). We prefer to describe the inheritance pattern as autosomal co-dominant, as this highlights the fact that heterozygotes for the deficiency are at an increased risk for clinical disease when compared with the general population, especially in the setting of external risk factors for lung disease (e.g. smoking). Another important characteristic of the deficiency is its variable clinical expressivity. Some homozygotes for the deficiency do not develop impairment in the lung function and never develop symptoms related to the disease (Seersholm & Kok-Jensen 1998). Incomplete penetrance and variable clinical phenotype (expressivity) is one of the reasons why population studies estimating the number of individuals with the deficiency are much higher than the actual number of people who have been diagnosed. For unclear reasons, A1ATD is rarely tested for despite guidelines that recommend otherwise for clear patient types. Complicating A1ATD diagnosis is the continued low rate of diagnosis and management of Chronic Obstructive Pulmonary Disease (COPD).

More than 120 mutations in the SERPINA1 gene have been identified, although many do not cause a defect in the serum protein or function or relevant clinical disease (US National Library of Medicine August 2009). The allele most common to the general population is the M allele, and the most clinically relevant variants are the S and Z alleles. People with the PI*Z-Z genotype make up at least 95% of deficient individuals who present with clinical disease, and PI*M-Z heterozygotes on very rare occasion have any symptoms. The Z allele is caused by a glutamic acid to lysine substitution at position 342. A more common allelic variant is the S protein, caused by a glutamic acid to valine substitution at position 264. This protein is successfully degraded before accumulating in the liver and does not cause liver disease. PI*S-S individuals are not thought to be at risk for pulmonary disease, however the compound heterozygotes PI*S-Z or PI*S-null are at an increased risk for developing pulmonary symptoms. Null alleles are due to mutations that introduce an early stop codon, which prevents complete transcription of the gene. Patients who are homozygote for the null mutation (PI*null-null), or heterozygote with Z (PI*null-Z) are at the highest risk for developing severe pulmonary symptoms (Stoller & Aboussouan, 2005).

The Z allele occurs mainly within one haplotype, meaning that other genetic material surrounding the allele is similar, and suggests a single relatively recent origin in Caucasians (Cox et al., 1985). Its high frequency in southern Scandinavia and estimated origination date of approximately 2000 years ago suggests that the mutation originated in the Viking population and was spread across Europe by Viking raiders. Using the pooled epidemiological data on 75,390 individuals, researchers estimated the prevalence of both the Z and S mutation in 21 countries. With this information, they created a topographic map of the mutation prevalence, depicting how the mutation may have spread. The ZZ phenotype shows highest prevalence in the southern Scandinavian Peninsula, Latvia, and Denmark, and progressively decreases towards the South and the East of Europe. The S allele has its highest prevalence in the Iberian Peninsula, which includes modern day Portugal, and Spain, as well as Southern France and gradually decreases towards the North, South and

East of the continent. The S mutation appears to have originated within the Portuguese population, but its date of origin is unknown. It is assumed that both mutations were introduced to North America by mass migration.

Most Common Phenotypes and likely Pulmonary Consequences of A1AT alleles

| Allele | Concentration of A1AT (micromoles/L) | COPD risk |
|--------------|--------------------------------------|--------------------------|
| Pi-MM | 20-53 | General population |
| Pi-MS | 20-48 | Very low/ gen population |
| Pi-SS | 15-33 | Low |
| Pi-MZ | 12-35 | Low |
| Pi-SZ | 9-19 | Variable |
| Pi-ZZ | 2.5-7 | High |
| Pi-Z-null | <2.5 | Very high |
| Pi-null-null | none | Very high |

Fig. 1. Common alleles of the SERPINA1 gene (adapted from Hogarth & Rachelefsky, 2008)

4. Epidemiology

There is an estimated 1.1 million people with severe A1ATD and 116 million carriers in the world (Luisetti & Seersholm, 2004). Although previously considered a disease of Caucasians, recent data shows that A1ATD exists in all racial subgroups worldwide including African blacks, Arabs and Jews in the Middle East, as well as people from central, far east and south east Asia (de Serres, 2002). Determining the number of people in the United States with emphysema primarily due to A1ATD can be made by taking the estimate of the number of Americans with COPD (3.1 million), and the estimate that about 1.9% of patients with emphysema are likely due to A1ATD (Lieberman et al., 1986). This results in an estimate that at least 59,000 individuals in the United States have severe symptomatic COPD due to A1ATD. Large screening studies have also been undertaken, including the classic prevalence study done by Sveger, where 200,000 neonates were screened at birth in Sweden (Sveger 1974). The results demonstrated 1 in 1575 live births were homozygous for the Z mutation (PI*ZZ). A similar study undertaken in Oregon, USA screened 107,038 newborns and found the prevalence of the ZZ phenotype in that population to be 1 in 5097 (O'Brien et al., 1978). Among 20,000 healthy blood donors tested in St. Louis, Missouri in the United States, 1 in 2857 were homozygous for the Z mutation. With this information, the researchers estimated a total prevalence of 700 individuals in St. Louis with the deficiency, however they were only able to locate 28 (4%) after contacting local doctors (Silverman, et al., 1989). Estimates from Central and Southern Africa based on limited data from screening studies estimated that 1 in 15 Africans are S carriers. Our own data on carrier rate in Americans of African Descent demonstrate 1 in 18 are S carriers. Epidemiologic data not only highlight that prevalence of the deficiency is high, but reinforce that the disease is significantly under diagnosed in most populations.

5. Pathophysiology

The SERPINA1 gene, previously known as the PI (protease inhibitor) gene, is located between 14q31.1-32.3 on the human genome, and encodes A1AT, which is a 52-kD glycoprotein composed of 394 amino acids. The active site is a single peptide bond, Met358-

Ser359. The protein is primarily synthesized and secreted by hepatocytes, but also in mononuclear cells, intestinal and lung epithelial cells. A1AT is an acute phase reactant with a normal concentration in serum of 20-53 micromole/L. Alpha one antitrypsin is a member of the serpin family of protease inhibitors, which regulate important proteolytic enzyme cascades including the coagulation cascade, complement cascade, and plasmin inhibition (Crowther et al., 2004). Serpins not only inhibit proteases but cause a conformational change in their structure readying them for destruction. A1AT's mechanism of inhibition has been likened to a mouse-trap. When neutrophil elastase attacks A1AT enzyme, it binds and then cleaves its reactive center loop, which causes a spring-like movement within the A1AT molecule to fling the elastase molecule across itself, inhibiting its function and altering its structure so it can be destroyed (Huntington et al., 2000).

5.1 Pulmonary pathophysiology

The prevailing theory describing the pathogenesis of emphysema in A1AT deficient individuals is of an imbalance in protease and anti-protease enzymes in lung tissue. Neutrophil elastase is released during inflammation and leads to an uncontrolled proteolytic attack on elastin, which is left unchecked by the low concentration of alpha one antitrypsin (Gadek et al., 1981). Furthermore, the circulating Z allele of A1AT has been shown to have a less functional active site, making the small amount of mutant protein a functionally ineffective inhibitor of neutrophil elastase (Ogushi et al., 1987). Elastin is the backbone of lung structure, and a critical component of the lungs ability to recoil. It is thought that elastin's destruction leads to lung hyperinflation and obstruction, leading to development of emphysema.

More recently, studies have shown that the mutated protein can form polymers within the lungs, similar to the polymerization occurring in the liver, and become chemoattractants for neutrophils resulting in excessive inflammation. Polymers of the mutated A1AT protein have been identified in the bronchial alveolar lavage fluid of individuals with the PiZZ phenotype (Mulgrew et al., 2004). These findings have led to a possible evolutionary explanation for why alpha-one anti-trypsin deficiency became so prevalent in many populations. The argument for the selective advantage of being a carrier is that a less regulated pulmonary inflammatory response to an external noxious stimulus (e.g. infection) would lead to higher chances of recovery. Prior to the discovery of antibiotics for respiratory infections, the mortality rate from these illnesses was high. A more robust and unregulated inflammatory response in the lungs could have provided a survival advantage to the carriers (Lomas, 2006). In the modern antibiotic era, and the advent of mass-produced external noxious stimuli (smoking, pollution), this mutation does not appear to have a theoretical selective advantage anymore.

How cigarette smoke accelerates the decline of lung function in A1ATD has also been studied. When the methionine amino acid in the active site of A1AT protein is oxidized by cigarette smoke, the kinetics of neutrophil elastase inhibition is reduced (Ogushi et al., 1991). Newer experimental data shows A1AT may have other roles in the lung epithelium besides inhibiting neutrophil elastase. A1AT has recently been found to block the cigarette smoke mediated release of TNF-alpha and MMP-12 in alveolar macrophages (Churg et al., 2007). In cellular studies, A1AT has also been found to inhibit apoptosis through direct inhibition of activated Caspase-3 (Petrache et al., 2006). The link between A1AT and apoptosis has led to new theories of emphysema development as both an inflammatory disorder and accelerated lung aging process.

5.2 Liver pathophysiology

People with the alpha one antitrypsin deficiency develop liver damage by a completely different mechanism. After being synthesized in hepatocytes, the mutated A1AT alleles bind together to form large polymers that result in inflammation and fibrosis. Liver disease caused by A1ATD has become the prototypical disease in a new category of diseases, termed the conformational diseases. Also included in this category of diseases are Alzheimer's and other forms of neurodegenerative dementias, which are caused by the aggregation of proteins in neurons (Carrell & Lomas, 2002). People with the P1*ZZ mutation of A1AT have a high concentration of the mutated alpha-one antitrypsin allele in the endoplasmic reticulum of liver cells. The Z mutation allows the protein to undergo a spontaneous structural change, which opens up the main sheets of the molecule and bind to the reactive center in the next molecule. These interactions can result in the formation of long polymers of mutated proteins (Lomas et al., 1992). The large protein structures aggregate in liver cells, which is thought to lead to inflammation, fibrosis and cirrhosis by a still unclear mechanism. The reason why some people with ZZ allele genotype do not develop clinically relevant liver disease is also not clear.

6. Clinical manifestations

A1ATD is often unrecognized despite the high prevalence of lung disease in the United States and the world. Alpha-1-related lung disease presents with common respiratory symptoms including dyspnea, decreased exercise tolerance, wheezing, cough, excess sputum production, frequent lower respiratory tract infections, and a history of suspected allergies and/or asthma (Needham & Stockley, 2004). These symptoms are often ascribed to other diseases for years prior to the correct diagnosis of alpha one antitrypsin deficiency. A 1994 mail survey found that on average it took 7.2 years after symptom onset before the diagnosis was made, and 44% of people saw three different physicians before a diagnosis was made (Stoller et al., 1994). A similar survey repeated in 2003 found the mean time to diagnosis was 5.6 years, however, the delay was more pronounced in older and female patients (Stoller et al., 2005). Since the diagnosis of A1ATD requires one simple blood test, clearly more effort needs to be made to educate both physicians and the public of the disease and the importance of a diagnosis.

There is significant variability in the age of symptom onset in people with A1ATD, and some smokers and non-smokers may never develop symptoms. This highlights the variability in disease penetrance among deficient individuals, and makes accurate descriptions of the common symptoms and other clinical characteristics of deficient individuals difficult to obtain. Most of the clinical characteristics and other features of the deficiency are obtained by studying large registries of patients with the disease. These data sets are often flawed by ascertainment bias. Most of the patients in the large A1ATD registries presented initially to a doctor with concerning pulmonary symptoms, eventually leading to a diagnosis of A1ATD. These patients are then referred to a specialist who will enroll them into the registry, and are termed index cases. Less often, asymptomatic individuals who are diagnosed after a family screening are enrolled (non-index cases). This was true of the large group of 1129 A1AT deficient individuals in the National Heart, Lung and Blood Institute Registry (McElvaney et al., 1997). 72% of the enrollees were index cases, receiving a diagnosis of the A1ATD after developing concerning pulmonary symptoms, and 20% were non-index cases, diagnosed by screening following an investigation of family members of individuals with A1ATD. In that registry, the remaining smaller percentage of

people were diagnosed after they were discovered to have abnormal chest radiograph findings, abnormal pulmonary function tests, liver abnormalities, or other blood testing. therapy with the purified A1AT protein.

6.1 Pulmonary clinical manifestations

The NHLBI registry data provides the best clinical picture of the typical patients diagnosed with this deficiency. 97% of them had the P1*ZZ mutation, and most were diagnosed in the third or fourth decade of life. The most common symptom in this group was shortness of breath on exertion (83%). Other common symptoms included wheezing during an upper respiratory illness (75%), wheezing without upper respiratory illness (65%), recent lung infection (67%), and chronic productive cough (49%).

Pulmonary function testing of individuals in the NHLBI registry demonstrated a pattern consistent with emphysema: the median Forced Expiratory Volume in one second (FEV1) was 47% of predicted, the ratio of the FEV1/FVC (Forced Vital Capacity) was 43% of predicted, and the DLCO (which represents the amount of destruction in alveoli-capillary units) was 50% of predicted. These numbers highlight a common feature of people with A1ATD: the airflow obstruction (represented by low FEV1 and low FEV1/FVC) seen on pulmonary function testing seems to be out of proportion to the lifetime quantity of cigarettes they have smoked. Also in the NHLBI registry, 28% of people showed significant bronchodilator responsiveness (i.e., reversibility) of their airflow obstruction on pulmonary function tests during their initial visit, which is a characteristic of people with asthma (Eden et al., 2003). With these common symptoms and pulmonary function test characteristics, it is easy to see why patients with A1ATD are often misdiagnosed as having only uncomplicated asthma, emphysema or COPD.

In contrast to the above registry data, a study with high level of non-index cases (e.g. siblings of affected individuals) found that far fewer of this population had typical pulmonary symptoms of A1ATD (Seersholm & Kok-Jensen, 1998). After a mean follow-up of 8 years, only 46% of the non-index case patients reported symptoms of shortness of breath, 27% reported wheezing, and 14% reported a chronic cough. Also in this group, their average FEV1 was 100% of predicted, and their FEV1/FVC = 0.79, essentially normal pulmonary function tests.

Classically, severe A1ATD causes panlobar emphysema with lower lobe predominance on radiologic imaging studies (Guenter et al., 1968). However, with high-resolution chest CT scanning, bronchiectasis has also been found to be a common feature of patients with A1ATD. In a study of 74 people with the P*ZZ phenotype, 70 subjects had bronchiectasis changes on CT scan. 27% of the study participants were felt to have clinically significant bronchiectasis, which was described as 4 or more airway segments with bronchiectasis plus symptoms of regular sputum production (the most common symptom of people with bronchiectasis) (Parr et al., 2007).

Multiple studies have measured the rate of decline in lung function among patients with A1ATD using the forced expiratory volume in one second (FEV1) as a marker of lung disease progression. This measure is used regularly to quantify the severity and progression of patients with COPD and asthma. For non-smokers with normal levels of A1AT, the rate of FEV1 decline is around 20-30 mL/year. The decline in the FEV1 among a group of A1ATD patients who never smoked was 67 mL/year, was 54 mL/year in ex-smokers, and was 109 mL/year in current smokers (Alpha-1-antitrypsin deficiency study group, 1998). The first two numbers are not statistically significantly different, however the third is

significant, which highlights the extreme importance of smoking cessation in all people with A1ATD. The difference in the rate of decline of FEV1 between A1ATD and normal patients highlights the principle of augmentation therapy with replacement alpha-one protein. Mortality in people with A1ATD is most frequently due to respiratory failure, followed by liver cirrhosis. The observed yearly mortality rate ranges between 1.7-3.5%. Factors associated with increased mortality include older age, lower education, lower FEV1, history of lung transplant, and people who were not receiving augmentation therapy with the purified A1AT protein (Stoller et al., 2005).

6.2 Liver clinical manifestations

A1ATD has a strong association with liver disease, leading to a recommendation that all individuals of any age with unexplained liver dysfunction should undergo testing for the deficiency. In the Swedish population screening study by Sveger, of 200,000 people, 18% of the 120 people found to be homozygote for the Z mutation had some evidence of liver dysfunction (Sveger, 1974). This included obstructive jaundice in 12%, and minor abnormalities in others. Among those with liver dysfunction, the risk of developing cirrhosis is high. It is possible that younger individuals more often have liver dysfunction because their hepatocytes are less well equipped to handle the polymerized A1AT proteins. In a small autopsy series of patients with A1AT disease, cirrhosis was observed in 34% of patients, and hepatocellular carcinoma was observed in 34% of those with cirrhosis (Eriksson, 1987).

6.3 Necrotizing panniculitis

Panniculitis is an uncommon skin disorder with a strong association with A1ATD. It is characterized by painful, cutaneous nodules at the sites of trauma, often on the trunk, back and thighs. On biopsy, areas of fat necrosis are interspersed with areas of normal tissue. The skin necrosis is felt to develop because of unopposed proteolysis, and augmentation therapy has been described as causing a rapid resolution of the disease (Dowd et al., 1995).

7. Testing for disease

Guidelines published by the American Thoracic Society and European Respiratory Society in 2003 have helped clarify who should undergo testing for A1ATD (American Thoracic Society, 2003). The guidelines divided people into categories for whom testing is recommended, those for whom testing could be discussed and considered, and those for whom testing was discouraged. For the following group of people testing should be recommended. These include: adults with emphysema, chronic obstructive pulmonary disease, or asthma with incompletely reversible airflow obstruction, people of all ages with otherwise unexplained liver disease, or adults with necrotizing panniculitis. In the following group of people testing could be considered and discussed: adults with bronchiectasis without an obvious etiology, adults with anti-proteinase 3-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis, formerly known as "Wegener's Granulomatosis"), adolescents with airflow obstruction on pulmonary function tests.

When family history is considered, the following recommendations were made. There is a strong recommendation for testing all siblings of an individual with A1ATD. There is also a recommendation to consider testing in the following situations: individuals with a family history of emphysema or liver disease, or anyone with a family history of A1ATD or A1ATD heterozygote. The 2003 guidelines recommended against routine population screening except

in the following circumstances - if the prevalence of A1ATD is greater than 1 in 1500 the population, smoking is prevalent, and adequate genetics counseling services are available.

Nephelometry or Rocket Immunodiffusion can measure serum levels of A1AT and is a reasonable screening test for the deficiency. However, this method is subject to errors because the protein is an acute phase reactant and rise with inflammation. The gold standard for diagnosis is "Phenotyping" of the protein is done via isoelectric focus gel analysis, which can only be performed at a few specialized laboratories within the United States. DNA Analysis of genotype is done to probe for the common S and Z genes. A1ATD testing can be done via serum and whole blood draw from the vein, but can also be done via a single finger-stick of blood placed onto a card that is mailed into a central lab for testing. A combination of measuring the serum A1AT concentration and performing a PCR based assay to identify S and Z alleles will accurately identify 96% of individuals as compared to the more difficult gold standard isoelectric focusing (Snyder, 2006).

8. Treatment

The corner stone of alpha one antitrypsin management is smoking cessation and smoke avoidance in all individuals with the deficiency. Guidelines for the management of the chronic airflow obstruction (COPD) have been published elsewhere (GOLD guidelines, ATS guidelines, etc.) Augmentation therapy is utilized to increase serum and lung epithelial lining fluid (ELF) levels of A1AT through the weekly intravenous infusion of purified human A1AT protein (Wewers et al., 1987).

It is FDA approved to treat for adult patients with A1ATD (protein concentration < 11 micromoles/dL) and evidence of air flow obstruction. The treatment can be very costly because it involves life-long regular infusions of a blood product, and it is not available worldwide. The treatment was approved based on two factors, that there is biochemical equivalence between exogenous replacement protein and protein found in normal human serum, and there is normalization of serum protein levels in deficient individuals who are receiving replacement. Many non-randomized prospective studies have demonstrated the effectiveness of augmentation via reduction in the annual rate of decline of lung function. Well-designed and adequately powered randomized trials have been limited to date. A recent meta-analysis of published human studies demonstrated augmentation therapy does reduce the annual rate of lung function decline (as measured by FEV₁) in A1ATD individuals (Chapman et al., 2009).

8.1 Future therapies

Ongoing work in areas of inhaled therapy, longer half-life protein, recombinant forms, small molecule chaperone inhibitors to increase liver secretion and gene transfer therapy continue. These studies and fields are all in various stages of development.

9. Conclusion

Alpha1- antitrypsin deficiency is a not uncommon disease, which is not limited to the European and Caucasian American population, but now affects all ethnic groups. Effective treatments for this disease, including smoking cessation, management of COPD/emphysema and other complications, and augmentation therapy with purified A1AT protein is well established. However, the disease remains under-diagnosed, and

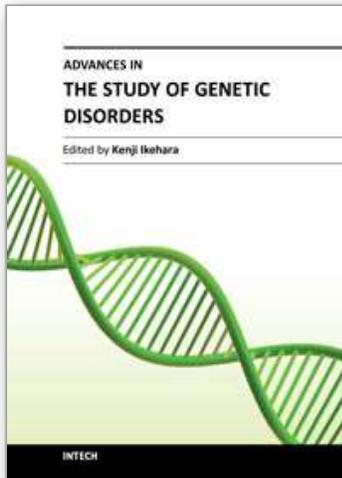
many times patients are diagnosed years after symptoms have developed. Future work to improve education among healthcare professionals to improve rates of diagnosis, as well as improved disease specific treatments are important steps in making this disease a more treatable illness.

10. References

- Alpha-1-antitrypsin deficiency study group. (1998). Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. *Am J Respir Crit Care Med*, Vol. 158, No. 1, (July 1998). pp. 49-59.
- American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med*, Vol. 168, No. 7, (October 2003). pp. 818-900.
- Blanco, I., de Serres, FJ., Fernandex-Bustillo, E., Lara, B., & Miravittles, M. (2006). Estimated numbers and prevalence of PI*S and PI*Z alleles of alpha 1-antitrypsin deficiency in European countries. *Eur Resp J*, Vol. 27, No. 1, (January 2006). pp. 77-84.
- Carrell, RW. & Lomas, DA. (2002) Alpha 1-antitrypsin deficiency - a model for conformational disease. *NEJM* Vol. 346, No. 1 (January 2002), pp. 45-53.
- Chapman, KR., Stockley, RA., Dawkins, C. Wilkes, MM., Navickis, RJ. (2009). Augmentation therapy for alpha1-antitrypsin deficiency: a meta analysis. *COPD*, Vol. 6, No. 3, (June 2009). pp. 177-18
- Churg, A., Wang, X., Wang, RD., Meixner, SC. Pryzdial, EL., & Wright, JL. (2007) Alpha1-antitrypsin suppresses TNF-alpha and MMP-12 production by cigarette smoke-stimulated macrophages. *Am J Resp Cell Mol Bio*, Vol. 37, No. 2 (August 2007), pp. 144-151
- Cox, DW., Woo, SL., & Mansfield, T. (1985). DNA restriction fragments associated with alpha 1-antitrypsin indicate a single origin for deficiency allele PI Z. *Nature*, Vol. 316, No. 6023, (July 1985). pp. 79-81
- Crowther, DC., Belorgery, D., Miranda, E., Kinghorn, KJ., Sharp, LK., & Lomas, DA. (2004) Practical genetics: alpha1-antitrypsin deficiency and the serpinopathies. *Eur J of Human Gen*, Vol. 12, No. 3 (March 2004). pp. 167-172
- de Serres, FJ. (2002). Worldwide racial and ethnic distribution of alpha1-antitrypsin deficiency. *Chest*, Vol. 122, No. 5 (November 2002). pp. 1818-1829.
- DeMeo, DL, & Silverman, EK. (2004). Alpha1-Antitrypsin deficiency - 2: Genetic aspects of of alpha1-antitrypsin deficiency: phenotypes and genetic modifiers of emphysema risk. *Thorax*, Vol. 59, No. 3, (March 2004). pp. 259-264
- Dowd, SK., Rodgers, GC., & Callen, JP. (1995). Effective treatment with alpha-protease inhibitor of chronic cutaneous vasculitis associated with alpha1-antitrypsin deficiency. *J Am Acad Dermatol*, Vol. 33, No. 5 pt 2, (November 1995). pp. 913-916.
- Eden, E., Hammel, J., Rouhani, FN., Brantly, ML., Barker, AF., Buist, AS., Fallat, RJ., Stoller, JK., Crystal, RG., & Turino, GM. (2003). Asthma features in severe alpha1 antitrypsin deficiency: experience of the National heart , Lung, and Blood Institute Resistry. *Chest*, Vol. 123, No. 3, (March 2003). pp. 765-771.
- Eriksson, S. (1987). Alpha 1-antitrypsin deficiencny and liver cirrhosis in adults: an analysis of 35 Swedish autopsied cases. *Act Med Scand*, Vol. 221, No. 5, pp. 461-67

- Gadek, JE., Fells, GA., Zimmeran, RL, Rennard, SI., & Crystal, RG. (1981). Anti-elastase of the human alveolar structures: implications for the protease-antiprotease theory of emphysema. *J Clin Invest*, Vol. 68, No. 4 (October 1981), pp.889-898
- Guenter, CA., Welch, MH., Russell TR, Hyde, RM., & Hammarsten, JF. (1968). The pattern of lung disease associated with alpha1-antitrypsin deficiency. *Arch Int Med*, Vol. 122, No. 3 (September 1968). pp. 254-257
- Hogarth, KD., & Rachelefsky, G. (2008). Screening and Familial Testing of Patients for Alpha1 Antitrypsin Deficiency. *Chest*, Vol. 133, No. 4 (April 2008). pp. 981-988
- Huntington, JA., Read, RJ., Carrell RW. (2000). Structure of a serpin-protease complex shows inhibition by deformation. *Nature*, Vol. 407, No. 6806 (October 2000). pp. 923-926
- Laurell, CV., & Eriksson A. (1963) The electrophoretic alpha 1-globulin pattern of serum in alpha 1-antitrypsin deficiency. *Scandinavian Journal of Clinical Laboratory Investigation*, Vol. 15, pp. 132-40
- Lieberman, J., Winter, B., & Sastre, A. (1986). Alpha1-antitrypsin Pi-types in 965 COPD patients. *Chest*, Vol. 89, No. 3 (March 1986). pp. 370-73.
- Lomas, DA. (2006). The selective advantage of alpha 1-antitrypsin deficiency. *Am J Respir Crit Care Med*, Vol. 173, No. 10 (May 2006), pp. 1072-1077
- Lomas, DA., Evans, DL., Finch, JT., & Carrell, RW. (1992). The mechanism of Z alpha1-antitrypsin accumulation in the liver. *Nature*, Vol. 357, No. 6379, (June 1992), pp. 605-607.
- Luisetti, M., & Seersholm, N. (2004). Alpha1 antitrypsin deficiency: 1. Epidemiology of alpha1 antitrypsin deficiency. *Thorax*, Vol. 59, No. 2, (February 2004). pp. 164-169.
- McElvaney, NG., Stoller, JK., Buist, AS., Prakash, UB., Brantly, ML., Schluchter, MD., & Crystal, RD. (1997). Baseline Characteristics of Enrollees in the National Heart, Lung and Blood Institute Registry of Alpha-1 Antitrypsin Deficiency. *Chest*, Vol. 111, No. 2, (February 1997). pp. 394-403.
- Mulgrew, AT., Taggart, CC., Lawless, MW., Greene, CM., Brantly, ML., O'Neill, SJ., McElvaney, NG. (2004). Z alpha1-antitrypsin polymerizes in the lung and acts as a neutrophil chemoattractant. *Chest*, Vol. 125, No. 5 (May 2004), pp. 1952-57
- Needham, M. & Stockley, RA. (2004). Alpha1-antitrypsin deficiency - 3: clinical manifestations and natural history. *Thorax*, Vol. 59, No. 5, (May 2004), pp. 441-445
- O'Brien, ML., Buist, NR., & Murphey (1978), WH. Neonatal screening for alpha 1-antitrypsin deficiency. *J Pediatr*, Vol. 92, No. 6 (June 1978). pp. 1006-1010.
- Ogushi, F., Fells, GA., Hubbard, RC., Straus, SD., & Crystal, RG. (1987). Z-type alpha1-antitrypsin is less competent than M1-type alpha1-proteinase inhibitor as an inhibitor of neutrophil elastase. *J Clin Invest*, Vol. 80, No. 5 (November 1987), pp.1366-1374
- Ogushi, F., Hubbard, RC., Vogelmeier, C., Fells, GA., & Crystal, RG. (1991) Risk factors for emphysema. Cigarette smoking is associated with a reduction in the association rate constant of alpha1 antitrypsin for neutrophil elastase. *J Clin Invest*, Vol. 87, No. 3 (March 1991), pp. 1060-1065.
- Online Mendelian Inheritance in Man (July 2010). "MIM ID #613490: Alpha-1-Antitrypsin Deficiency. Available from <http://www.ncbi.nlm.nih.gov/omim/613490>, created 7/20/2010, accessed 3/14/2011
- Online Mendelian Inheritance in Man (September 2010). MIM ID *107400: Serpin Peptidase Inhibitor, Clade A, Member 1; Serpina1. 3.14.2011. Available from <http://www.ncbi.nlm.nih.gov/omim/613490>. Accessed 3/14/2011

- Parr, DG., Guest, PG., Reynolds, JH. Dowson, LJ. & Stockley, RA. (2007). Prevalence and Impact of Bronchiectasis in alpha 1-antitrypsin deficiency. *Am J Respir Crit Care Med*, Vol. 176, No. 12, (December 2007). pp. 1215-1221.
- Petrache, I., Fijalkowska, I., Medler, TR., Skirball, J., Cruz, P., Zhen, L., Petrache, HI., Flotte, TR., & Tudor, RM. (2008). Alpha1-anti-trypsin Inhibits Caspase-3 Activity, Preventing Lung Endothelial Cell Apoptosis. *Am J of Path*, Vol. 169, No. 4 (October 2006), pp. 1155-1166.
- Seersholm, N. & Kok-Jensen, A. (1998). Clinical features and prognosis of life time non-smokers with severe alpha1 antitrypsin deficiency. *Thorax*, Vol. 53, No. 4 (April 1998). pp. 265-268.
- Seersholm, N., & Kok-Jensen A. (1998). Clinical features and prognosis of life time non-smokers with severe alpha1 antitrypsin deficiency. *Thorax*, Vol. 53, No. 4, (April 1998). pp. 265-268.
- Senior, RM., Tegner, H., Kuhn, C., Ohlsson, K., Starcher, BC., & Pierce, JA. (1977). The induction of pulmonary emphysema with human leukocyte elastase. *Am Rev Respir Dis*, Vol. 166, No. 3, (September 1977). pp. (469-475)
- Sharp, HL., Bridges, RA., Krivit, W., & Freier, ER. (1969). Cirrhosis associated with alpha1-antitrypsin deficiency: a previously unrecognized inherited disorder. *J Lab Clin Med*, Vol. 73, No. 6, (June 1969). pp. 934-939
- Silverman, EK., Miletich, JP, Pierce, JA. Sherman, LA., Endicott, SK., Broze, GJ. & Campbell, EJ. (1989). Alpha1-antitrypsin deficiency: high prevalence in the St. Louis area determine by direct population screening. *Am Rev Respir Dis*, Vol. 140, No. 4 (October 1989). pp. 961-66
- Snyder, MR., Katzmann, JA., Butz, ML., Wiley, C., Yang, P., Dawson, DB., Halling, KC., Highsmith, WE., & Thibodeau, SN. (2006). Diagnosis of alpha1-antitrypsin deficiency: an algorithm of quantitation, genotyping and phenotyping. *Clin Chem*, Vol. 52, No. 12, (December, 2006). pp. 2236-2242
- Stoller, JK., & Aboussouan, LS. (2005). Alpha1-antitrypsin deficiency. *Lancet* , Vol. 365, No. 9478, (June 2005). pp. 2225-2236
- Stoller, JK., Sandhaus, RA., Turino, G., Dickson, R., Rodgers, K. & Strange, C. (2005). Delay in diagnosis of alpha 1-antitrypsin deficiency: a continuing problem. *Chest*, Vol. 128, No. 4, (October 2005). pp. 1989-94.
- Stoller, JK., Smith, P., Yang, P. & Spray, J. (1994). Physical and social impact of alpha 1-antitrypsin deficiency: results of a mail survey of the readership of a national newsletter. *Cleve Clin J Med*, Vol. 61, No. 6, (Nov-Dec 1994). pp. 461-467.
- Stoller, JK., Tomashefski, J., Crystal, RG., Arroliga, A., Strange, C., Killian, DN., Schluchter, MD., & Wiedemann, HP., (2005). Mortality in individuals with severe deficiency of alpha1-antitrypsin. *Chest*, Vol. 127, No. 4, (April 2005). pp. 1196-1204.
- Sveger, T. (1976). Liver disease in alpha 1-antitrypsin deficiency detected by screening of 200,000 infants. *N Engl J Med*, Vol. 294, No. 24, (June 1976). pp. 1316-1321
- US National Library of Medicine, (August 2009) Genetics Home Reference, "SERPINA1" Available at <http://ghr.nlm.nih.gov/gene/SERPINA1>, Accessed 3/14/2011
- Wewers, MD., Casolaro, MA., Sellers, SE., Swayze, SC., McPhaul, KM., Wittes, JT., & Crystal, RG. (1987). Replacement therapy for alpha1-antitrypsin deficiency associated with emphysema. *NEJM*, Vol. 316, No. 17, (April 1987). pp. 1055-1062



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The studies on genetic disorders have been rapidly advancing in recent years as to be able to understand the reasons why genetic disorders are caused. The first Section of this volume provides readers with background and several methodologies for understanding genetic disorders. Genetic defects, diagnoses and treatments of the respective unifactorial and multifactorial genetic disorders are reviewed in the second and third Sections. Certainly, it is quite difficult or almost impossible to cure a genetic disorder fundamentally at the present time. However, our knowledge of genetic functions has rapidly accumulated since the double-stranded structure of DNA was discovered by Watson and Crick in 1956. Therefore, nowadays it is possible to understand the reasons why genetic disorders are caused. It is probable that the knowledge of genetic disorders described in this book will lead to the discovery of an epoch of new medical treatment and relieve human beings from the genetic disorders of the future.

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