Alpha 1-Antitrypsin-Deficiency–Related Emphysema

Alan F. Barker, M.D.

Abstract: ***Background:*** **A congenital cause of emphysema resulting from alpha 1-antitrypsin (A1AT) deficiency affects 1 in 2500 individuals and could account for emphysema in 2 percent of all persons with emphysema. Individuals aged 30 to 45 years with chronic shortness of breath and coughing could have A1AT deficiency.**

Methods: **Using the key words "alpha 1-antitrypsin deficiency," "chronic obstructive pulmonary disease," and "emphysema," the MEDLINE files were searched from 1985 to the present. Data from articles published before 1985 were accessed from cross-reference of the recent articles.**

Results and Conclusions: **Unlike smoker's emphysema, A1AT deficiency is panacinar, appears in middle-aged patients, and is more severe at the lung bases. Chronic bronchitis, mucous hypersecretion, and liver disease, as well as a family history of emphysema, are associated conditions. Clinical management includes the avoidance of smoking and atmospheric pollution. Also available is purified, functional human A1AT in quantities large enough for intravenous replacement or augmentation therapy. Future treatment for the disease includes synthetic elastase inhibitors and an aerosolized formulation of A1AT, which is currently under investigation. (J Am Board Fam Pract 1992; 5:489-93.)**

Emphysema is the result of progressive and irreversible destruction of the alveolar wall. Treatment of emphysema can be improved by a sharper definition of the clinical entity, clearer insight into its etiology and pathogenesis, and implementation of treatment programs motivated by such basic insights into the disease process. One such advance has been the discovery and characterization of a congenital form of emphysema associated with a specific protein deficiency — alpha 1-antitrypsin (A1AT)-deficiency emphysema. This review focuses on this less familiar form of emphysema that highlights the pathophysiology of the much more common smoking-related emphysema.

Methods

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Pathophysiology

The protein A1AT is a naturally occurring antiprotease, which protects connective tissue against degradation by a variety of proteolytic enzymes that normally occur in the body. As part of the inflammatory response, neutrophils, as well as damaged and dying cells, release proteases into the intracellular milieu. To a point, this inflammatory response is beneficial, and the influx of neutrophils to tissue helps protect it by destroying invading organisms or by barricading them against healthy tissue. Normally the inflammatory response is a well-regulated process in which the proteolytic enzymes released as part of the inflammatory response are balanced by the antiproteases also found in the tissues. If, as in the case of A1AT-deficiency emphysema, tissue levels of antiprotease are too low to offer adequate protection, the destructive inflammatory responses run to extremes.

A1AT deficiency was discovered in the 1950s with the application of the then-innovative electrophoresis methods to the study of trypsin inhibitors in human serum. Eventually A1AT was isolated and purified in the early 1960s, when serum protein electrophoresis revealed a marked reduction in the alpha 1-globulin band.

Considerable work has been done since the pioneering research by Laurell and Eriksson[1-3] to characterize the biochemical defect expressed as

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A1AT deficiency. Researchers have learned a great deal about the structure and function of the A1AT protein itself.[4,5] Their findings have made possible a therapy for A1AT-deficiency emphysema based upon augmentation or replacement of the insufficient or abnormal A1AT protein in affected individuals.[6]

The A1AT macromolecule, a single, relatively small polypeptide chain (molecular weight 47 to 52 kd), consists of 394 amino acid residues. The molecule has a single reactive site, at position 358. The rest of the A1AT molecule maintains a fixed conformation necessary to allow the methionine at position 358 to interact with the substrate and A1AT to function as a protease inhibitor. The methionine found at position 358 of the A1AT molecule is readily oxidized by exposure to free radicals and oxidants found in cigarette smoke, as well as by a variety of atmospheric pollutants.

Normal A1AT in serum is 1.2 to 2.0 g/L (120 to 200 mg/dL). On the basis of epidemiologic data, however, serum concentrations of 0.8 g/L (80 mg/dL) or less are taken to indicate clinical A1AT deficiency (Table 1). The phenotype can be identified by isoelectric-focusing gel analysis at serum pH 4 to 5. Radial immunodiffusion kits are now commercially available. Manufacturers of these commercial diagnostic kits differ somewhat in their standards for normal serum levels. Currently there are no international standards for normal levels; however, researchers at the National A1AT-Deficiency Registry sponsored by the National Heart, Lung and Blood Institute are developing them. For the purposes of research or specialized diagnostic tests, several other methods have been applied: monoclonal antibody testing specific for individual variants, restriction endonuclease analysis of genomic

Table 1. Serum Concentrations of Alpha 1-Antitrypsin (A1AT).

A1AT Level (g/L)*	Phenotype	Risk for Emphysema
1.2–2.0	MM	None
1.0–1.5	MZ	None
0.9–1.2	MS	None
0.8–1.0	SS	None
0.25–0.6	SZ	Unknown
0.15–0.5	ZZ	At risk
0–0.15	Null-Null	At risk

*To convert each value to mg/dL, multiply by 100.

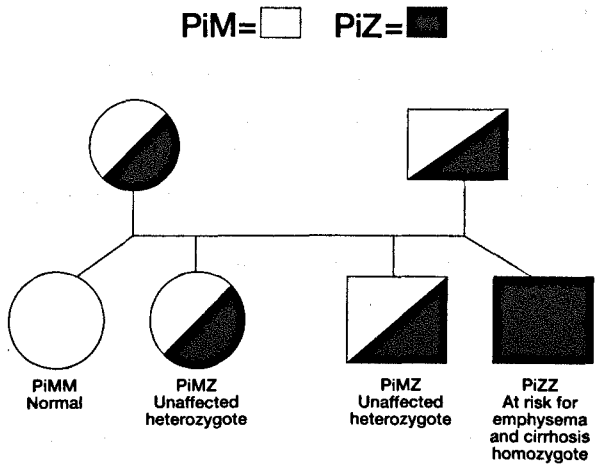

Figure 1. Example of how two unaffected parents (heterozygotes with no evidence of emphysema) have a one in four chance of having one child with A1AT deficiency, PiZZ. In any one family the proportion of affected children will be different.

DNA, and oligonucleotides that hybridize to specific regions of A1AT gene. Homozygous normal (protease inhibitor or PiMM) or heterozygous normal-deficient (PiMZ) or normal-null alleles (MO) produce no detectable disease (Figure 1), although serum concentrations of A1AT can be reduced. Patients with the phenotypes PiZZ (most common in the United States), PiSZ, Pi Null-Null, and PiZ-Null are almost certain ($P > 0.95$) to have serum A1AT levels of 0.15 to 0.50 g/L (15 to 50 mg/dL), which is 16 percent of normal. Patients with the phenotype PiSS have serum A1AT levels of 0.80 to 1.0 g/L (80 to 100 mg/dL) (52 percent of normal). Given the observation that the threshold of protection is approximately 0.80 g/L (80 mg/dL) (40 percent of normal), there is a strong likelihood that persons with the phenotypes of PiZZ and Pi Null-Null will develop A1AT-deficiency emphysema. For clinical purposes, the fine detail of the biochemical analyses can be reduced to the categories normal, deficient, and null.

Prevalence

The prevalence of emphysema in the United States is 9.1 per 1000 for all ages, but for persons aged 65 to 74 years, the prevalence of emphysema is 45.6 per 1000.[7] Approximately 2 percent of all emphysema cases in the United States are associated with A1AT deficiency.[8] In persons aged 35 to 50 years, the prevalence of A1AT-deficiency emphysema among individuals

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with obstructive lung disease is undoubtedly higher.

The frequency of PiZZ is 1 in 3500 to 1 in 1670, with racial and ethnic variability; the frequency of PiZZ in North America is approximately 1 in 2850. European ancestry is frequent; African-Americans and individuals of Asian descent are rarely affected.[9]

An estimated 80,000 to 100,000 persons in the United States are affected by the autosomal recessive disorder that results in insufficient serum concentrations of A1AT.[10] Carrying the trait does not invariably lead to disease. The disparity between the number of people carrying the trait and the number of people who eventually develop emphysema suggests that we have yet to explain fully the pathogenetic mechanisms that underlie A1AT-deficiency emphysema. A study of blood donors in St. Louis showed several individuals with A1AT deficiency and normal lung function, a finding suggesting that the method of identification (screening patients with obstructive lung diseases versus all individuals) will produce different clinical pictures.[11]

Diagnosis of A1AT-Deficiency Emphysema

The symptoms and signs of A1AT-deficiency emphysema closely resemble those of chronic obstructive pulmonary disease caused by cigarette smoking. As one would expect, 98 percent of all emphysema patients report dyspnea, increasing on exertion and becoming more severe with progression of the disease. Chronic productive cough is reported by 51 percent of patients (chronic bronchitis in 34 percent and episodes of paroxysmal cough in 17 percent). Pneumonia develops in 20 percent of patients, and reactive airways (i.e., wheeze or significant increase in forced expiratory volume in 1 second [FEV_1] in response to inhaled β-adrenergic bronchodilators) are observed in 20 percent of patients.[12]

Despite the great sophistication of modern diagnostic tests, problems remain in the clinical assessment of A1AT-deficiency emphysema patients. The clinical course of the disease is often erratic. There can be wide variability in average decline in FEV_1.

Family and personal histories give some indication of diagnosis.[13] In severe A1AT-deficiency emphysema, signs and symptoms develop early or in midlife, unlike other forms of emphysema (notably emphysema associated with smoking), which commonly develop later in life. A1AT-deficiency emphysema, unlike the smoker's emphysema, is panacinar and ordinarily more severe in the lung bases. A chest radiograph shows bibasilar bullae. In smoker's emphysema the bullae are in the upper lobes. In about one-half the cases, the onset of A1AT-deficiency emphysema is accompanied by chronic bronchitis. Excess proteases can induce bronchial secretory cell metaplasia, hence the mucous hypersecretion. Liver disease can also be associated with A1AT deficiency. Finally, of course, a family history of emphysema is a strong indicator of the congenital form of the disease. If these details of personal and familial histories are sufficient to raise clinical suspicion, an A1AT assay should be ordered. By convention, 35 percent of normal is taken to be pathognomonic of the A1AT-deficiency disorder. The normal two- or threefold increase in A1AT concentration in response to the inflammatory response and acute infection is blunted.[12]

Management of A1AT Deficiency and Emphysema

The most important feature in the clinical management of A1AT-deficiency emphysema is avoidance of cigarette smoking. Additional helpful steps to reduce the neutrophil burden include avoiding second-hand smoke, dusty workplaces, and atmospheric pollution. Moderate regular exercise is advisable to maintain good respiratory health. Bronchodilators can be beneficial to improve or stabilize pulmonary function. Bronchial hyperresponsiveness often accompanies emphysema because of airway inflammation. Although the administration of bronchodilators could have little effect on the signs and symptoms of emphysema itself, bronchodilators can offer considerable relief in managing the hyperreactive airways. Purely symptomatic therapy using bronchodilators is often inadequate in the treatment of emphysema, however, because the loss of alveolar function is not reversible. Corticosteroids by aerosol or administered systemically are adjunctive measures to reduce the inflammatory response. The administration of oxygen might help in advanced stages of the disease.

Until recently, little could be done to inhibit the disease process itself. That purified, functional human A1AT is currently available in quan-

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tities sufficient for continuous therapy in a large number of patients now makes it possible to augment deficient or absent A1AT.[14,15] Therapy for emphysema therefore has been directed toward blunting the progress of the disease and offering symptomatic relief. Therapy is indicated for patients whose lung function is abnormal, especially if function is deteriorating. Patients whose FEV_1 is less than 80 percent but more than 30 percent of the predicted response are good candidates for A1AT replacement and augmentation therapy. There is no lower limit of pulmonary function, however, and the American Thoracic Society advises that treatment plans be formulated on a patient-by-patient basis. Even in late stages of disease, with drastically reduced lung function (e.g., FEV_1 less than 30 percent of predicted response), A1AT replacement or augmentation therapy can offer therapeutic benefit. A1AT administration will safely augment serum levels into a protective range,[15] but studies of functional efficacy have not been done.

Replacement or augmentation therapy guidelines have been developed by the American Thoracic Society for the treatment of congenital A1AT-deficiency emphysema.[16] Serum A1AT must be less than 0.8 g/L (80 mg/dL). Smoking-related emphysema disqualifies a patient for A1AT replacement or augmentation therapy. Patients younger than 18 years are not considered candidates for A1AT replacement or augmentation therapy; there is no upper age limit. A1AT replacement or augmentation therapy is not indicated for the treatment of other possible A1AT-deficiency diseases. The presence of liver disease in conjunction with emphysema, however, does not disqualify the patient.

A1AT is administered by intravenous infusion at a dose of 60 mg/kg of body weight at an infusion rate of 0.08 mL/kg/min. Present guidelines recommend weekly infusions. The goal of treatment is to reach a nadir A1AT serum level of at least 0.8 g/L (80 mg/dL). Research has suggested that 250 mg/kg every 4 weeks may be as effective as 60 mg/kg every week.[17]

Although knowledge of the biochemistry of the disorder has advanced, comparatively little is known about the natural history of A1AT-deficiency emphysema and about the experience of patients with the disease. Consequently, the National Heart, Lung and Blood Institute has established a National A1AT-Deficiency Registry of patients older than 18 years who have serum A1AT concentrations below 0.8 g/L (80 mg/dL) and who have the phenotypes PiZZ, PiZ-Null, Pi-Null-Null most commonly associated with A1AT-deficiency emphysema. Thirty-four centers have now been established throughout the United States, and three are in British Columbia, Canada. A total of 1000 patients have had A1AT-deficiency emphysema diagnosed and have been registered between 1989 and May 1992.

The Future of A1AT Replacement or Augmentation Therapy

In the future, A1AT from additional natural sources and recombinant DNA technology could reduce the cost of therapy and increase its availability. The A1AT molecule itself can be altered (valine substituted for methionine) to lengthen the half-life in the body without adversely affecting its activity. Synthetic elastase inhibitors might also be developed.

Perhaps the most encouraging development in A1AT replacement or augmentation therapy, however, is the administration of A1AT by the inhalation route. An aerosolized formulation of A1AT is being investigated that would permit more convenient and effective treatment. Inhaled droplets of A1AT can provide topical treatment to the emphysematous lung. Chemically active A1AT might pass through alveolar epithelium to increase A1AT levels, increasing resistance to neutrophil elastase. In preliminary studies, A1AT in this formulation has proved safe and nontoxic.[18] Its clinical effectiveness is now being evaluated.

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