

ALPHA-1-ANTITRYPSIN DEFICIENCY ASTHMA AND ALLERGY

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SUMMARY: The biochemistry, genetics and pathology of alpha-1-anti-trypsin deficiency are reviewed. The geographical distribution in Europe of more current phenotypes M, SZ is discussed. Two cases of alpha-1- anti-trypsin are presented one homozygotic ZZ non-smoker without any respiratory pathology and one heterozygotic SZ heavy smoker with a severe chronic obstructive pulmonary disease and reversibility to Beta-2-mimetics suggesting asthma. The relationship between alpha-1-antitrypsin and asthma is discussed and general measures of treatment or prevention suggested.

Key words: Alpha-1-anti-trypsin - COPD - Allergy - Asthma.

INTRODUCTION

The first report of alpha-1-antitrypsin was published in 1963 by LAURELL and ERIKSON followed by new papers in 1965, 1976, 1986 (8, 15, 16, 17, 18). Alpha-1-Antitrypsin is the major serum inhibitor of serine proteinases. This protein is a 54-KDa glycoprotein coded on chromosome 14 at 932,1 and his gene consists of four translated exons. The active site consist of a methionine serine (Met 358 ser 359) amino acid sequence responsible for the specificity against serine proteinase. Alpha-1-antitrypsin is made essentially in hepatocytes but macrophages can also produce this protein. The gene for Alpha-a-1-antitrypsin is polymorphic with over hundred variants (1, 6, 8, 12, 15, 18, 21, 22, 28, 32, 34, 36, 37, 48, 54, 56, 41, 49).

THE SERPIN FAMILY

Alpha-1-antitrypsin is the archetypal member of the serine proteinase inhibitor (SERPIN) superfamily. This SERPIN family includes other members alpha-1-antichymotrypsin, C1esterase inhibitor, antithrombin, and plasminogen activator inhibitor. These serpins are important payers in the control of proteinases involved in inflammation and in the complement, coagulation and fibrinolytic cascades (34,35,36).

The serpin family is characterized by more than 30% sequence homology with alpha-1-antitrypsin and stability of tertiary structure (34, 35, 36).

The polymerization of serpins is not restricted to mutants of alpha-1-antitrypsin and may cause various diseases, emphysema or cirrhosis for alpha-1-antitrypsin, thrombosis for antithrombin, angioedema for C1 inhibitor and dementia for neuroserpin. Due to the homology of structures the polymerization of alpha-1-antitrypsin (56) may be considered as a paradigm for the serpinopathies (33, 34, 35, 36, 37) and physiologic or pathologic processes that affect one member of the serpin superfamily may be extrapolated to another (34, 35). Polimerization is due to the mutant form of alpha-1-antitrypsin namely Z and less, S variants. Alpha-1-antitrypsin levels are reduced in the lung of patients with alpha-1-antitrypsin deficiency and the fraction available to protect the lung is less effective to inhibit neutrophils elastase than normal M alpha-1-antitrypsin (9, 10, 24, 25, 39, 45). The inhibitory activity of Z alpha-1- antitrypsin is functionally reduced because Z variant favours the spontaneous transformation of alpha-1-antitrypsin monomeric forms in to loop-sheet polymers. Within the lung (45, 56) this conformational transition inactivates alpha-1-antitrypsin as a proteinase inhibitor further reducing the levels of alpha-1-antitrypsin available to protect the alveoli (56). On the other hand the polymers are chemoattractants for human neutrophils explaining the great number of neutrophils found in broncho alveolar lavages from patients with Z alpha-1-antitrypsin deficiency (45, 56).

GENETICS AND PHENOTYPES

Alpha-1-antitrypsin is coded for as chromosome 14 at q 32.1 and the gene consists of four translated exons. The

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active site consists of a critical methionine-serine (Met 358 Ser 359) amino acid sequence that gives the protein its specificity against serine proteinases, mainly neutrophil elastase, interacting specifically with the ser 173-His41-Asp 88 triad of the active site of the enzyme (6, 11, 12, 21, 27, 56). Alpha-1-antitrypsin is a polymorphic gene with over 100 variants (6, 11, 12, 21, 27). The majority of mutations do not affect the function of the protein but may alter its charge and hence its isoelectric point. This results in a series of bands corresponding to the diverse variants distinguishable by isoelectric focussing of serum proteins at acid (1.4.0-5.01) pH. The variants are named by letters according to their mobility on the gel. These moving towards the anode ahead of the normal M type are afforded letters below M and those moving slower than normal are given letters above M in the alphabet. The protein is inherited as a codominant gene and the phenotype reflects this inheritance. MM is a homozygous normal. SS or ZZ are homozygous abnormal and MS or MZ are heterozygous for the deficient S or Z genes (6, 11). The current variant is labelled Pi M, it accounts for approximately 95% of the alleles in subjects of northern European descent (5, 11, 56). The phenotype M has its own variants. M1, M2, M3 that can be identified by characteristic band patterns (6,56). S and Z alleles are other common variants. The S alleles M1 Val 213 + glu 264 codes for 60% of the protein produced by the M allele and which is present more in the population of southern Europe, mainly in Iberian Peninsula (5, 50, 51). The reduced amount of protein produced by this allele is the result of molecular instability in the endoplasmic reticulum and the increased catabolism (58). The function of Pi S is only slightly diminished in report to normal (23, 25, 56, 58). The Z allele codes for 10 to 20% of the protein produced in the M allele and is present in around 3% of the northern European population. The gene is transcribed normally but the point mutation (GAG-AAG) changes the amino acid at position 342 from glutamic acid to lysine with consequent slight reduction in association rate with neutrophil elastase and a resultant increase in mobility of the active site that facilitates spontaneous protein polymerisation within the hepatocyte (58). The S and Z variants are more usually present as heterozygotes in combinations with the more common M allele. The heterozygotes have a slightly reduced serum concentration of alpha-1-antitrypsin depending on the association MS or MZ (2, 4, 6, 12, 25, 28, 29, 34).

LABORATORY DIAGNOSIS

In practice a serum electrophoresis must be done in all the respiratory patients, either rhinitis, asthma or COPD. When the global percent and absolute value of alpha-1

fraction is low (less than 1.5%) a quantification of alpha-1-antitrypsin in serum by radial immunodiffusion (40, 41, 42) or other method, can detect most heterozygotes (around 90%) and all deficient homozygotes with the rare exception of functionally inactive but quantitatively normal variants, Pi F allele (34, 56). However the heterozygotes can have normal serum concentration due to non specific increase of alpha-1-antitrypsin as an acute phase protein response (29, 34, 56).

When a decrease is confirmed by at least two consecutive assays the next phase is to determine the phenotype of the protein by isoelectric focussing. Null genes, not transmitted to produce secreted alpha-1-antitrypsin cannot be detected by isoelectrophoresis due to the absence of the gene product in series. The most rare alleles can be identified only by family studies or by direct genotyping (6, 34, 56).

LIVER PATHOLOGY

The Z mutation results in the accumulation of alpha-1-antitrypsin as inclusions in the rough endoplasmic reticulum of the liver. These inclusions predispose the ZZ homozygote to neonatal hepatitis cirrhosis and hepatocellular carcinoma (15, 16, 17, 57). The liver disease associated in the Z forms of alpha-1-antitrypsin results from the overload of abnormal Z alpha-1-antitrypsin within the endoplasmic reticulum of hepatocytes (4, 12, 16, 17). The accumulation of abnormal protein starts in utero and is characterized by the accumulation of alpha-1-antitrypsin in the periportal cells. Around 70% of ZZ alpha-1-antitrypsin homozygote infants have a raised serine alanine aminotransferase in the first year of life but remains abnormal only in 15% of Z homozygotes by 12 years of age (33, 34, 35, 36, 57), serum bilirubin is raised in around 10% of Z homozygote infants but usually falls to normal by six months of age (15, 16, 17, 33). Some infants present cholestatic jaundice or liver disease but these symptoms usually resolve by second year of life some children progress to juvenile cirrhosis (15, 16, 17). The risk of death from liver disease in Pi Z children during childhood is around 2-3% with greater risk for boys (33). All adults with the Z allele of alpha-1-antitrypsin have slowly progressive hepatic damage that is often subclinical and evident only as a minor degree of portal fibrosis. Up to 50% of the ZZ alpha-1- antitrypsin homozygote patients can present clinically evident cirrhosis and occasionally with hepatocellular carcinoma (33, 34, 57).

EPIDEMIOLOGY

The most common causes of intermediate deficiency are the MS and MZ genotypes presented in Southern and Northern European populations (5).

The greatest frequency of the S allele occurs in Portugal and Spain attaining rates of 152 per 100.000 inhabitants in North of Portugal and 115 in South. In Spain rates vary between 149 in Galician border with Northern Portugal and 100 per 100.000 in Catalunya and Cantabria (5, 50, 51). Globally S-alpha-1-antitrypsin (Glu 264 val) is found in up to 28% of southern Europeans (5, 34, 50, 51). S alpha-1-antitrypsin gives plasma levels of alpha-1 antitrypsin that are 60% of the normal M allele but it is not generally associated with pulmonary lesions (37).

The Z allele is more common in northwest Europe with frequency declining from West to East and from North to South (6, 34). The Z variant (Glu 342 Lys) results in a more severe deficiency with plasma alpha-1-antitrypsin levels of 10% of the normal M allele and around 60% in the MZ heterozygotes, 50% from the M allele and 10% from the Z allele (33). Double heterozygotes SZ must present alpha-1-antitrypsin levels around 40%, 30% from the S allele and 10% from the Z allele (34).

MS heterozygotes have a reduction of around 10% and MZ heterozygotes around 40%. SZ double heterozygotes are rare and have a reduction around 60% of alpha-1-antitrypsin level. These subjects may have an increased risk for COPD or asthma if they are smokers (1, 9, 10, 14, 24, 26). A study done in Iberian Peninsula does not found a relationship between SZ phenotype and COPD (3). In a recent study from Denmark (13) there was an increased risk for asthma chronic bronchitis or emphysema in MZ heterozygotes but only for first degree relatives of ZZ COPD patients suggesting that other genetic or environment factors play a role (1, 2, 7, 28, 29, 30, 37, 47, 52, 57, 59, 60).

CLINICS

Alpha-1-antitrypsin plays a central role in the protection of the lungs against proteolytic attack, acting as an inhibitor of proteinases. Genetic deficiency, when marked (ZZ homozygotes) leads to basal panlobular emphysema of early onset (33, 34, 35). Clinically the respiratory disease associated with alpha-1-antitrypsin deficiency usually causes progressing dyspnea leading in the late stages to "cor pulmonale" and polycythemia. Chest radiographs typically show bilateral basal emphysema with scarce basal pulmonary vessels in contrast with the vascularization of upper lobes which is relatively normal (34). High resolution computed tomography is the most accurate method of assessing the distribution of panlobular emphysema and for monitoring progress of pulmonary disease. Lung function tests are typical for emphysema with a reduced ratio of forced expiratory volume in the first second (FEV1) to forced vital capacity (FVC),

air trapping with increased ratio residual volume total lung capacity and low gas transfer factor (34). The onset of respiratory disease clinically relevant can be delayed until the sixth decade in non-smokers even with a marked (ZZ homozygotes) alpha-1-antitrypsin deficiency. In absence of triggering factors, mainly tobacco, these subjects can have a normal lifespan. The more marked forms of lung disease are characteristically seen in PiZ alpha-1-antitrypsin homozygote patients but a Pi SZ and P1 MZ individuals also can have a slightly greater risk of pulmonary emphysema (1, 2, 3, 7, 29, 39, 46, 54, 55).

Most patients with alpha-1-antitrypsin deficiency have chronic bronchitis. Bronchiectasis are frequent, between 25% to 50% in different studies (56).

Tobacco smoking has a devastating effect in subjects with alpha-1-antitrypsin deficiency but many subjects, mainly heterozygotes MS or MZ retain their correct lung function until old age even if they smoke. Although the overall prognosis in non-smokers with alpha-1-antitrypsin deficiency remains good a proportion of these subjects decrease lung function in middle age (1, 2, 7, 11, 12, 22, 26, 29, 30, 31, 37, 46, 48, 51).

LUNG FUNCTION

The rate of decline of lung functions in ZZ genotype subjects who are lifelong non-smokers is highly variable (27). It is possible that other genetic factors influence the clinical course in ZZ homozygotes. It has been recently suggested that polymorphism in the endothelial nitric oxide synthase (NOS) gene contributes to the development of COPD in ZZ homozygotes (25, 27, 38).

ALPHA-1-ANTITRYPSIN AND ASTHMA

The relationship of asthma with alpha-1-antitrypsin deficiency has been reported as soon as 1969-1970 by FAGERHOL and ourselves (19, 40, 41). Many patients have demonstrable reversibility to beta-2 agonists and anticholinergics agents. Using standardized criteria, reversibility suggesting asthma is present in 65% of the patients (56). Abnormalities of alpha-1 antitrypsin could aggravate asthma by the effect of proteases released not only by neutrophils but also by mast cells in the course of asthmatic inflammation or the absence of an immunostatic effect of alpha-1 antitrypsin (4). The propensity of abnormal alpha-1 antitrypsin phenotypes to cause asthma is suggested by the increased methacholine bronchoreactivity in MS and to a lesser degree MZ, heterozygotes from both asthmatic and non asthmatic families (30, 31, 47, 60). A signifi-

cant decrease of the functional efficiency of alpha-1 protease inhibitor of the M1M1, M1M2 and M2M2 phenotypes can also be important in the inflammatory pathogenesis of asthma (20).

Alpha-1-anti-trypsin deficiency is not very common in asthma and in our experience only other 8 cases, aside of the patients here reported, have been confirmed, however without genetic study. One COPD family from Southern Portugal (Alentejo) where family nicknames are currently given was appropriately named "Catarrh".

PREVIOUS STUDIES

After the initial reports of LAURELL and ERICKSON (15, 30, 32) we start studying alpha-1-antitrypsin concentrations in respiratory diseases in 1968 and published the first results in 1970 (41). These results have been presented to the European Congress in 1970 (40) and 1971 (42). 146 patients with asthma or COPD where the alpha-1 fraction was decreased in cellular acetate eletrophoresis were studied. In 54 out of 146 cases alpha-1-antitrypsin concentration was decreased in radial immunodiffusion. 2 out of 20 cases of COPD have a deficiency of alpha-1-antitrypsin (10%). In asthma 2 out of 126 have a significant decrease of alpha-1-antitrypsin (1,6%). 1 case of alpha-1-antitrypsin in rhinitis without asthma or COPD was also been found. These cases are probably the first Portuguese cases of alpha-1-antitrypsin deficiency and after the paper of FAGERHOL (19) the previous year, one of the first reports of asthma with alpha-1-antitrypsin deficiency (40, 41, 42).

CLINICAL CASES

2 patients with confirmed alpha-1-AT deficiency and allergic diseases and complete identification of phenotype have been studied. Genetic studies have been done in the Genetics section of J. Chaves Clinical Pathology Clinic.

Case 1: C.J.J. 62 male heavy smoker during 30 years, complaints of cough, sputum from 7 years, dyspnea in the last few years. Previously treated with fluticasone salmeterol + thyotropium. Objective examination respiratory sounds diminished. PFR 300 l/mn (normal 550±100) reversibility by salbutamol - 400 l/mn CT: Centro-lobular emphysema mainly in superior lobes. Hyperinsuflation. Electrophoresis decrease of alpha-1 fraction (0,6% of 6,9) alpha-1 antitrypsin 64,5. Genetic study genotype SZ mutations GLU 342 lys and GLU 264 val.

Case 2: C.M.C. 40, female, non-smoker, story of rhinitis and urticaria without lower respiratory symptoms. Objective examination normal. Lung function normal.

On electrophoresis alpha-1 fraction was 0,6% of 7.45/l. Alpha-1 antitrypsin assay 25- Genotype PI ZZ mutation GLU 342 lys. Thyroid auto antibodies increased TG: 72,3 TPO: 1.673

DISCUSSION

The patients presented exemplify the diversity of clinical presentation of alpha-1-anti-trypsin deficiency. The homozygotic ZZ patient who theoretically will have the more severe form of alpha-1-anti-trypsin deficiency with chronic obstructive pulmonary disease and eventually hepatic disease had only chronic urticaria associated with an auto immune thyroiditis. Physical examination, lung function, imagiology were normal as well as hepatic echography and hepatic laboratory evaluation. An healthy behaviour and complete abstinence of tobacco must explain that for the time going this patient is going well. The relationship with urticaria and thyroid auto-immunity is probably coincidental. The second patient one relatively rare form of ZS heterozygoty was an heavy smoker during a large period and presented marked obstructive lung disease however with reversibility to beta-2-mimetics and paroxystic dyspnea pointing out to a diagnosis of asthma. The association of alpha-1-antitrypsin deficiency and asthma has been reported for the first time in 1969-70 (19, 40, 41) and more largely discussed in the last few years (6, 11, 30, 31, 47, 49). In this case the tobacco consumption can be the trigger for a more severe form of pulmonary obstructive diseases either COPD or asthma (6, 11, 31, 47, 49).

PREVENTION AND THERAPY

Tobacco smoke has a devastating effect in patients with alpha-1-antitrypsin deficiency. Warning of these effects is essential and prevention of the effect of tobacco mandatory (1, 8, 9, 10, 12, 14, 22, 24, 25, 26, 27, 4, 55, 58).

Otherwise treatment is the current treatment for COPD and asthma including bronchodilators, beta-2-mimetics or anticholinergics and inhaled steroids exacerbations should be prevented by antibiotherapy (1, 2, 14, 22, 29, 37, 48, 54). Preventive vaccination with bacterial lysates is controversial but still currently and largely used in most European countries (43, 44).

Protection of the lung could be attained in more severe cases by administration or alpha-1-antitrypsin administered by intravenous infusion or by inhalations. The efficacy of augmentation therapy has been controversial for many years but recent trials support his beneficial effect on the decline of lung function (13, 23, 24, 53, 61).

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Press Releases

FREQUENT INFECTIONS MAY BE A SIGN OF IMMUNODEFICIENCY

MILWAUKEE — Children who get frequent infections, such as ear infections, sinusitis or pneumonia, may have a more severe condition called immunodeficiency, according to the American Academy of Allergy, Asthma & Immunology (AAAAI).

Patients who have immunodeficiency have infections that usually do not go away without using antibiotics and often recur within one or two weeks after antibiotic treatment is completed. These patients frequently need many courses of antibiotics each year to stay healthy. There are several forms of immunodeficiency and while some are very severe and life-threatening, many are milder but still important enough to cause recurrent or severe infections.

"People with immunodeficiency get the same kinds of infections that other people get—ear infections, sinusitis and pneumonia", said Jordan Orange, MD, PhD, FAAAAI, Chair of the AAAAI's Primary Immunodeficiency Diseases Committee. "The difference is that their infections occur more frequently, and are often more severe, and have a greater risk of complications".

Allergist/immunologists often use the frequency of the use of antibiotics to mark the frequency of significant infections. General guidelines for determining if a patient may be experiencing too many infections are:

- The need for more than four courses of antibiotic treatment per year in children or more that two times per year in adults.
- The occurrence of more than four new ear infections in one year after four years of age.
- The development of pneumonia twice over any time.
- The occurrence of more than three episodes of bacterial sinusitis in one year or the occurrence of chronic sinusitis.
- The need for preventive antibiotics to decrease the number of infections.
- Any unusually severe infection or infections caused by bacteria that do not usually cause problems in most people at the patient's age.

■ **When to see an allergy/asthma specialist:** If your child has any of these conditions, consult with an allergist/immunologist for more information on recurrent infections, immunodeficiency, proper diagnosis and treatments.

The AAAAI's *How the Allergist/Immunologist Can Help: Consultation and Referral Guidelines Citing the Evidence* provide information to assist patients and health care professionals in determining when a patient may need consultation or ongoing specialty care by the allergist/immunologist. Patients should see an allergist/immunologist if they: have chronic or recurrent infectious rhinosinusitis.

Have any of the following warning signs:

- Eight or more new infections within one year.
- Two or more serious sinus infections within one year.
- Two or more months on antibiotic with little or no effect.
- Two or more pneumonias within 1 year.
- Failure of an infant to gain weight or grow normally.
- Recurrent deep skin or organ abscesses.
- Persistent thrush in mouth or elsewhere on skin after age 1 year.
- Need for intravenous antibiotics to clear infections.
- Two or more deep seated infections.
- A family history of immune deficiency.

To find an allergist/immunologist in your area or to learn more about allergies and asthma, call the AAAAI's Physician Referral and Information Line at (800) 822-2762 or visit the AAAAI Web site at www.aaaai.org.