Review

The Clinical Implications of the Alpha 1- Antitrypsin Deficiency

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ABSTRACT Alpha1-antitrypsin deficiency, one of the three most common potentially lethal genetic disorders among whites, an autosomal recessive genetic disease, leads to early-onset panacinar emphysema, increased lung cancer risk, chronic liver disease and skin disorders. It has recently been studied the causal relationship of alpha1-antitrypsin deficiency (mainly the Z allele) to inflammatory bowel disease, but also to the increased incidence of extraintestinal manifestation, the most frequent being the cutaneous, articular and hepatic ones, as well as its relation to fibromyalgia.

KEYWORDS alpha1-antitrypsin deficiency, genotype, morbidity

Alpha 1-antitrypsin deficiency, described for the first time in 1963, is one of the 3 most common genetic defaults with lethal potential among whites people (the other two are cystic fibrosis and Down syndrome), and is more frequent in north Europeans and Caucasians. The genetic default affects 1 in 3000-5000 individuals, it has autosomal recessive transmission, and the result is a lower level of alpha 1-antitrypsin in serum and pulmonary tissue, and an increase in neutrophil elastase activity, targeting structural proteins especially from the lungs (1). The morbidity and mortality rates are unknown.

Not all patients with homozygous deficit develop symptomatic emphysema or cirrhosis, but for those who do develop the symptoms, the mortality rate is high. Generally, the white race is the most affected, and the gendre repartition is equal. The enzymatic deficiency can represent a cause of neonatal jaundice, it may cause hepatic cirrhosis or liver failure in children and it is the primary cause for liver transplant at that age. The hepatic implication can be assigned to a certain sequence of the alpha-1-antitrypsin gene deficit. Usually, alpha 1-antitrypsin deficiency leads to symptomatic emphysema in the fourth decade of life for smokers, and later in non-smoker patients and rises the risk for pulmonary neoplasm (2).

The alpha-1-antitrypsin deficiency gene, located on chromosome 14, region 14q32.1, consists of an untranslated exon followed by 4 translated exons. So far, there were identified at least 130 alpha-1-antitrypsin deficiency alleles. Patients with two deficient alleles are, generally, considered to be at risk and those with one deficient allele are considered as people with a lower risk to develop symptoms. The alpha-1-antitrypsin production is controlled by a pair of genes from Protease inhibitor (Pi) locus, having been identified almost 24 versions of the alpha-1-antitrypsin and all of them are inherited as codominant alleles. Most frequent alleles are M (PiM 90%) and homozygous individuals MM have a high level of alpha 1-antiprotease (serum level 20-53 μmol/L or 150 - 350 mg/dl).

Deficient alleles Z or S, that presented with the substitution of only one base have been identified in patients with serum levels of alpha 1-antitripsine substantially reduced. Most frequent forms of alpha 1-antitrypsine deficiency are correlated with Z alleles or PiZ homozygous (ZZ), the homozygous ZZ phenotype being considered the most severe phenotype leading often to pulmonary or hepatic involvement. The serum level of the protein in these patients is 3,4 - 7 μmol/L (10 - 15% of normal serum level). Serum levels higher than 11 μmol/L seem to be beneficial. The emphysema develops in patients (but not in all of them) with serum levels lower than 9 μmol/L. The SZ and SS phenotypes can lead to severe pulmonary problems, especially to smokers. The variation of the deficient S allele was located in exon 3 causing the substitution of glutamine with valine in codon 264, and the variation of the deficient Z allele was located in exon 5 and causes the substitution of glutamine with lysine in codon 342. In the serum of the patients with homozygous phenotype ZZ was found only 15% of normal alpha 1-antitrypsine level, while in patients with SS phenotype were found approximately 60% of normal levels. The null alleles were characterized as having proteins undetectable to isoelectric focalization and

serum concentrations lower than 30 mg/dL (5.5 μmol/L) by immunoturbodimeric evaluation.

The others genotypes associated with severe alpha 1-antitrypsine deficiency include PiSZ, PiZNull and PiNull. S gene is more frequent among Spanish or Portuguese individuals, and Z gene in north and west Europeans. Patients with PiSZ phenotype present a risk to develop emphysema, 20-50% higher compared to MM homozygous patients. The serum levels of alpha 1-antitrypsine in these patients is 75-120 mg/dL. Patients with the null gene for alpha 1-antitrypsine will not produce the protein and will present a higher risk to develop emphysema (100% by the age of 30). No patient with the null gene develops liver involvement due the production and low accumulation of the protein in endoplasmic reticulum of the hepatic cells. The null gene is less frequent among alleles associated with alpha 1-antitrypsine deficiency. Carriers or heterozygous (MZ, MS or M/Null) have serum levels of approximately 35% of normal level, but do not develop the disease (3).

The guidelines of the World Health Organization recommend the screening for the deficit of alpha 1-antitrypsin at least once for all patients suffering from chronic obstructive pulmonary disease and for all adults and children with asthma (4,5). The evaluation methods are represented by the isoelectric focusing, immunoturbidimetric evaluation and real-time polymerase chain reaction (PCR) for the detection of the Z and S deficient alleles (6). The major biochemical activity of the alpha 1-antitrypsin molecules is illustrated by the inhibition of several proteases derived from neutrophile (trypsin, elastase, proteinase 3, cathepsin G).

Therefore, this acute-phase protein is better defined as alpha 1-antiprotease. It is synthesized by hepatocite and after the release from the liver it circulates and spreads in the alveolar and interstitial fluids. Its main function in the lungs is to inactivate the neutrophilic elastase, an enzyme released during the phagocytosis of the alveolar organisms or particles. alpha 1-antiprotease represents almost 95% of all antiproteases active in alveolus and the neutrophilic elastase is considered to be the protease highly responsible for alveolar damage (7). In healthy people, alpha 1-antiprotease has a defending function preventing the distruction of the alveolar wall. Individuals having a genetic disorder of the alpha 1-antitrypsin do not release the enzyme by the liver, serum and alveolar levels of the protein are low and the

alveolar antiprotease protection is also decreased. The lack of protease-antiprotease balance leads to the unlimited lysis of the elastine and of the collagen from the alveolar walls followed by progressive emphysema (7). The apoptosis of the alveolar cells can play an important role in the pathogenesis of the lung emphysema. Recent evidence suggests that alpha 1-antiprotease can inhibit the apoptosis of the alveolar cells and additionally protects against the emphyzema in the absence of the neutrophilic inflammation. Smoking accelerates the beginning of the symptomatic disease with approximately 10 years through the increase of the number of neutrophile (and neutrophile elastase) in alveoli and through the inactivation of the small quantity of existing antiprotease. Other factors that can precipitate the start of the disease or accentuate its symptoms include: infections, dust and smoke exposure, conditions which may recruit neutrophils in the alveoli.

The results of recent studies indicate that individuals carrying the alpha 1 antitrypsin deficiency allele might have an increased risk of developing lung cancer, especially squamous cell carcinoma and bronchialveolar carcinoma. An unsolved paradox of the lung cancer is the fact that although the majority of the patients smoke, just a small part of the long term smokers develop this type of cancer. In addition, smoking, apart from its well-known role of a risk factor for lung cancer, favors the appearance/emergence of CPODincluding emphysema şi chronic bronchitis. CPOD does not only increase the risk of lung cancer at smokers and nonsmokers, but it also participates as an additional risk factor for its emergence. Both diseases are strongly associated with smoking and have familiar aggregation. Homozygotic individuals for the deficiency gene of alpha1-antitrypsin (8) or the heterozygotic ones (carrier of alpha1AD) are inclined to develop BPCO. However, it has not been clearly stated/settled whether the individuals having alpha 1-antitrypsin deficiency and the carriers have an augmented risk of lung cancer. Patients suffering from this type of cancer, smokers or nonsmokers, have a bigger probability of possessing the alpha 1 antitrypsin deficiency allele than the white population of the USA. Similarly, it has been acknowledged that the likelihood of the squamous cell carcinoma and bronchialvolar carcinoma patients to be carriers is more increased. The destruction of the pulmonary tissue due to the lack of balance between neutrophilic elastase and alpha 1-

antitrypsin represents a condition which promote the development of lung cancer.

Two mechanisms have been proposed in order to ascertain the implication of this genetic deficiency in increasing the risk of developing pulmonary neoplasm. The first one, the indirect mechanism, the carrier status of the the alpha 1 antitrypsin deficiency allele might be the indirect cause or a paraneoplastic marker for lung cancer. Individuals with different degrees of pulmonary damage can have a long exposure period to air pollutants, in this way increasing the absorption and improving the action of the carcinogens found in the smoke of a cigarette. Secondly – the direct mechanism: specific changes/alterations of the Pi gene lead to lung cancer. The Pi genes, whose domains are studied in the present, are polymorphic. The changes corresponding to Z and S alleles are found at the level of 3 and 5 exons. What is really interesting is that within the Ib exon of the Pi gene, there are two binding sites capable of interaction with c-jun (AP1) producing proto-oncogenes. The combination's function of the Pi and/or c-jun(AP1) mutation remains to be studied. For smokers with pulmonary neoplasm detailed study shows that passive smoking and undiagnosed lung disease are significant risk factors. There was a close association between the presence of disease at these patients and alpha1-antitrypsin deficiency, suggesting that it may be a link between Pi locus and c-jun proto-oncogene. It is also possible that the role of Pi alleles deficiency differ in smokers than non-smokers to develop lung cancer. In conclusion, genes encoding markers for organ and tissue specific products (eg, proteases and protease inhibitors) and their interaction with various environmental factors have not been adequately studied in lung cancer etiology and newer studies suggest that carriers of defective alleles of alpha 1 - antitrypsin may be at increased risk for developing lung cancer with squamous cell and bronchoalveolar carcinoma (9).

Clinical expression of alpha 1-antitrypsin deficiency of lung, liver and skin damage has a considerable variability of severity and clinical manifestations. Alpha 1-antitrypsin deficiency is related to about 3% of cases of chronic obstructive pulmonary disease and is responsible for early onset emphysema at non-smoking individuals (10). Ten of the twenty percent affected in the neonatal period develop significant liver injury and panniculitis characterized by acute inflammatory infiltrates and fat necrosis is a rare skin complication of

alpha 1-antitrypsin deficiency (11-12). There are indications that deficient heterozygous may develop chronic liver disease even if serum levels of alpha 1-antitrypsin are almost normal, especially in combination with other risk factors such as alcohol abuse or chronic viral hepatitis. People with these mutations have an increased risk for developing cryptogenic cirrhosis and primitive hepatocellular carcinoma (13,14). Determination of alpha 1-antitrypsin phenotype will probably be recommended for all patients with chronic liver disease, especially if liver function deteriorates faster than expected, even if serum levels of alpha 1-antitrypsin is normal. Liver biopsy remains the gold standard for establishing the presence of alpha 1-antitrypsin deposits in the liver (14,15).

Etiologic role of alpha 1-antitrypsin deficiency especially for Z alleles in chronic inflammatory bowel was recently studied for its involvement in the development of extra intestinal manifestations (16). Thus, ulcerative colitis can present a variety of extra intestinal manifestations, most commonly skin, joint and liver. In these, appear a leukocytoclastic vasculitis clinically manifested in purpuric spots or bleeding edema, eye or respiratory tract haemorrage i and autoimmune hemolytic anemia. Systemic corticosteroids and azathioprine lead to significant extra intestinal manifestations. Patients with alpha 1-antitrypsin deficiency and ulcerative colitis have a severe systemic vasculitis with multiorgan damage. alpha 1-antitrypsin deficiency testing in patients with ulcerative colitis can detect individuals at increased risk for severe extra intestinal manifestations (17).

It was reported the case of two Spanish sisters with alpha 1-antitrypsin deficiency and fibromyalgia who received a treatment with alpha 1-antitrypsin achieving a rapid, progressive and constant control of symptoms of fibromyalgia for about 6 years. Because of the commercial crisis of this preparation, both patients had their treatment interrupted for the next 5 years (each for 4-6 months consecutively). There was a striking recurrence of the symptoms of fibromyalgia, which disappeared in the administration of alpha 1-antitrypsin infusion (18-19).

In conclusion, alpha 1-antitrypsin deficiency affects 1 in 3000-5000 individuals, being one of the three most common life-threatening genetic disease in the white population leading to early onset panlobular emphysema, increased risk of lung cancer, chronic liver disease and skin

damage. Moreover, it has recently been studied the etiologic role of alpha 1-antitrypsin deficiency especially of Z alleles in chronic inflammatory bowel disease as well as increased incidence of a variety of extraintestinal manifestations and a possible link with fibromyalgia.

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