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ALPHA 1 ANTITRYPSIN IN CHRONIC LIVER DISEASES

by

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Alpha-1 antitrypsin (AAT) deficiency is one of the major causes of intrahepatic cholestasis in infancy. AAT is a glycoprotein synthesized by the liver and which functions as an enzyme inhibitor of trypsin, elastase, collagenase, chymotrypsin, plasmin and Hageman factor cofactor. AAT shows an extensive polymorphism. Using acid starch gel electrophoresis followed by immunochemical reaction, 24 alleles of the AAT gene have been identified, the inheritance of which is codominant. Phenotypes are designed by the initials Pi (protein inhibitor) followed by letters (1,2) referring to electrophoretic mobility. PiM is the predominant phenotype. Individuals with the PiZZ, PiPZ, PiSZ, show an increased incidence of cirrhosis and emphysema. The same holds true for the phenotype Pi - where there is little or no AAT. Depending on the frequency of the PiZ gene, the frequency of the PiZZ infants (where the AAT function is most impaired) in children with neonatal intrahepatic cholestasis is around 15-30% (3).

1. Effect of AAT deficiency

10-15% of children with the PiZZ phenotype seem to develop liver disease in infancy (2).

Average birth weight is about half a kilogram below normal.

In a prospective study (3) made in Sweden on 118 PiZZ infants, 100% showed obstructive jaundice (7% clinical jaundice, 3% subclinical) another 6% gave evidence of liver disease (hepato and splenomegaly, umbilical bleeding). Later on, at three and six months of age, 41% showed biochemical evidence of liver disease. Since strict criteria were adopted for the upper limit of hepatic enzymes, the real incidence of liver involvement is probably higher. No other pathogenic factors were recognized. Later on, most of these children were clinically well. However, portal hypertension may occur, and effectively occurred in one child at the age of six. The prognosis is still uncertain. Patients who do have a subclinical obstructive jaundice may develop cirrhosis.

Since AAT deficiency is rarely found in young adult cirrhotics, with no history of neonatal cholestasis, it is assumed that the prognosis of patients who show only biochemical signs of liver disease is good. In late adulthood, the danger of developing, in addition to

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emphysema, a liver cirrhosis and/or a liver cancer is about 10-15% (4). Ericksson found six hepatomas amongst nine cirrhotics registered as PiZZ. According to Morin *et al.*, (5) heterozygotes are probably not predisposed to cirrhosis and liver cancer. Conversely, a recent paper from Clerc *et al.*, (6) presents the results of AAT phenotype determination in 11 African patients suffering from primary liver cancer. Two of them were of the MM type, the other nine belonged to the MZ type. This result is impressive since this phenotype is rare in the population of Ivory Coast where the study was done (1 out of 900 in a recent survey). These results would indicate that the Z trait is a major genetic factor of risk for primary hepatocellular carcinoma.

2. Pathological changes

In PiZZ children with clinical evidence of liver disease, the constant pathological finding is the presence of PAS positive amylase resistant globules in hepatocytes. However, they may be few and difficult to identify during cholestasis. This accumulation of globules is at present interpreted as the result of an impaired secretion of AAT by the liver cell. The primary structure of the Z phenotype would lack an asparagine residue and thus would not allow the fixation of sialic acid at this site; the secretion of AAT would then be slowed down and the protein would accumulate within the cell. Fibrosis seems to be associated with the development of portal hypertension and cirrhosis. Bile-duct proliferation is observed at the beginning of the disease. Bile ducts are less easy to find as the age of the patient increases.

3. Laboratory detection

Antitrypsic activity of serum and Pi phenotype determination by two dimensional immunoelectrophoresis (where the first electrophoretic run is operated in starch gel) are the key tests for establishing the AAT deficiency. Recently, the technique of immuno-fixation has been successfully used. Conventional liver function tests are useful for the detection of liver impairment.

4. Mechanism of pathological liver changes

This mechanism is at present unknown. It can be hypothesized that either 1) accumulation of AAT in liver cells is deleterious *per se* or 2) that AAT functional deficiency operates by liberating the activity of endogenous proteolytic enzymes. AAT was shown to enter macrophages presumably to inhibit proteolytic enzymes. Thus, in AAT deficiency, macrophages activated during inflammation would have a higher destructive activity.

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