

## ALPHA -1- ANTITRYPSIN DEFICIENCY

### Deficijencija alfa-1-antitripsina

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#### **Review article**

#### **Summary**

Alpha-1-antitrypsin (A1AT) deficiency is the commonest genetic cause of liver disease in children and chronic obstructive lung disease in young adult smokers. The pathogenetic mechanisms are completely different. While low serum levels of A1AT cause reduced alveolar elasticity and subsequent emphysema, the liver disease in children with PiZZ phenotype is due to retention of abnormally folded A1AT in the hepatocytes. The symptomatic liver disease, however, develops in only 10-15% of children carrying the PiZZ phenotype and not in PiSS, PiNull and PiSZ phenotypes during childhood. The affected children have different degrees of severity of the liver involvement; approximately 25% will develop early cirrhosis necessitating liver transplantation, which represents the only effective treatment at present. A1AT deficiency is being increasingly recognised as a cause of liver disease in adults, where even a heterozygous state (PiMZ) may increase risks of developing hepatopathy in presence of other risk factors, such as chronic hepatitis B and C, alcohol abuse, autoimmunity or increased insulin resistance and steatohepatitis.

**Key words:** Alpha-1-antitrypsin deficiency, chronic liver disease, liver transplantation.

#### **Revijalni članak**

#### **Sažetak**

Alfa-1-antitripsin (A1AT) deficijencija je najčešći nasljedni uzrok oboljenja jetre kod djece, te hronične obstruktivne bolesti pluća kod pušača u srednjem životnom dobu. Njihovi patogenetski mehanizmi su kompletno različiti. Niski nivoi A1AT u serumu dovode do smanjene elastičnosti alveola i posljedičnog emfizema, dok je oboljenje jetre kod djece sa PiZZ fenotipom uzrokovano zadržavanjem abnormalno preklapljenog A1AT u hepatocitima. Oboljenje jetre sa kliničkim simptomima se razvija samo u 10-15% djece sa PiZZ fenotipom, dok nije prisutno kod onih sa PiSS, PiNull i PiSZ fenotipovima tokom djetinjstva. Djeca sa simptomima imaju različite stepene oboljenja jetre; oko 25% pacijenata razvija progresivni hronični hepatitis i ranu cirozu, gdje je jedini efikasni tretman transplantacija jetre. A1AT deficijencija se sve češće otkriva kao uzrok oboljenja jetre kod odraslih, gdje čak i heterozigotno stanje (PiMZ) može povećati rizik hepatopatije, posebno u prisustvu dodatnih faktora

rizika kao što su hronični hepatitis B i C, alkoholizam, autoimunitet ili povećana rezistencija inzulina sa steatohepatitisom.

**Ključne riječi:** Alfa-1-antitripsin deficijencija, hronično oboljenje jetre, transplantacija jetre.

## INTRODUCTION AND DEFINITION

Alpha1-antitrypsin deficiency (A<sub>1</sub>ATD) is the commonest metabolic cause of chronic liver disease (CLD) in Caucasians and the leading genetic indication for liver transplantation in children (1). Furthermore, smokers with A<sub>1</sub>ATD are at risk of developing chronic obstructive lung disease in adulthood. Other complications such as vasculitis, glomerulonephritis and panniculitis have also been described.

Alpha1-antitrypsin (A<sub>1</sub>AT) is a highly polymorphic 55-kD glycoprotein, belonging to the serine protease inhibitor (serpin) superfamily (2). The Pi gene is located on chromosome 14q31-32.1. A<sub>1</sub>AT is produced at a rate of 34 mg/kg/day, primarily by hepatocytes, but also alveolar macrophages and intestinal endothelial cells (2,3). The A<sub>1</sub>AT protease inhibitor physiologically occurs in an unstable variant, which, upon activation, undergoes a structural change when its reactive centre is exposed to the attached target protease. This conformational change has the role of inactivating the protease at the end of the acute phase reaction (2). The A<sub>1</sub>AT variants other than the wild type (PiMM) appear to be less stable, leading to an increased incidence of spontaneous opening of the main sheet of the molecule, and, consequently,

abnormal folding, augmented polymerisation and retention within the hepatocytes. This has been well documented for the PiZZ and PiSS A1AT variants (4).

## EPIDEMIOLOGY

A<sub>1</sub>ATD is a condition affecting mainly Caucasians, although individuals with different variants have been anecdotally reported from other ethnicities (5). Normal serum levels of the A<sub>1</sub>AT protein are associated with the PiMM phenotypes, while A<sub>1</sub>ATD is characterized by absent or significantly reduced serum A<sub>1</sub>AT levels and phenotypic profiles PiNull, PiZ and PiS on serum isoelectric focusing. Almost one hundred genetic A<sub>1</sub>AT variants have been described to date (6). PiZ and PiS deficiency are related to 342 Glu→Lys and 264 Glu→Val point mutations, respectively (6). A<sub>1</sub>ATD is inherited in an autosomal codominant fashion; the prevalence of PiZ and PiS alleles in non-consanguineous populations of European descent is estimated to be between 0.5-2% and 1-9%, respectively (7).

## CAUSES, RISK FACTORS, DISEASE ASSOCIATIONS

PiZZ A<sub>1</sub>ATD leads to CLD in 10-20% of affected children (8). Liver disease

has also been described with rare Pi<sup>Siiyama</sup> and M<sup>malton</sup> variants of A<sub>1</sub>AT. Possible genetic modifiers leading to the development of CLD in only a minority of the affected individuals with the PiZZ phenotype are yet to be identified. Of the symptomatic PiZZ children, approximately one quarter progresses to end stage CLD and require liver replacement during childhood (1,9). Presence of fibrosis in the liver biopsies and jaundice after six months of age are associated with the highest risk of developing end stage CLD in childhood (1).

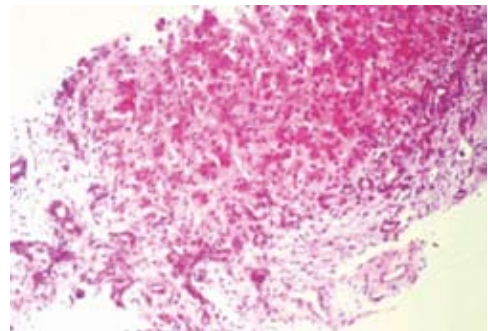
Chronic obstructive lung disease can develop in PiNull, PiZ and PiS A<sub>1</sub>ATD, albeit only in a small proportion of patients and in strong association with smoking. There is no information as yet on whether symptomatic children with liver disease are at risk of developing lung disease later in life.

## **PATHOGENESIS AND PATHOLOGY**

The mechanisms of liver and lung disease in A<sub>1</sub>ATD are different. While adults appear to develop chronic obstructive lung disease as a direct consequence of low serum levels of the A<sub>1</sub>AT protein, with consequent decreased protease inhibitory activity during inflammatory processes in the lungs, the pathogenesis of liver disease is less clear. It has been suggested that conformational changes of the unstable A<sub>1</sub>AT variants lead to retention of polymers of abnormally folded A<sub>1</sub>AT in the hepatocytes endoplasmic reticulum (4). Their presence can be demonstrated by immunoperoxidase staining in the foetal

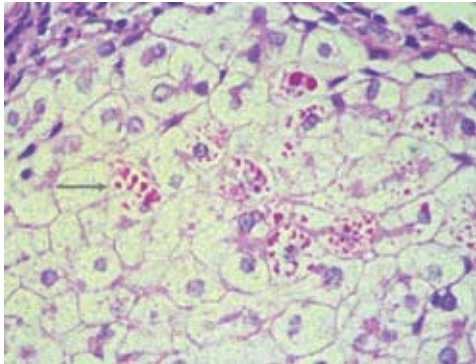
livers as early as 19 weeks post-conception (10), when exposure to triggers of acute phase response is minimal. Some early studies have suggested an increased prevalence of light-for-gestational age infants amongst PiZZ children who later require liver transplantation (11). What is relation between accumulation of Z A<sub>1</sub>AT polymers and liver injury remains unclear at present. However, these polymers are present also in the 80-85% of PiZZ A<sub>1</sub>AT-deficient individuals who do not develop clinically overt liver disease and therefore are unlikely to be major effectors of damage *per se*.

Liver histology in infancy demonstrates non-specific portal and lobular hepatitis with variable cholestasis, mild biliary features and fibrosis (Fig. 1).



*Fig. 1.: Liver biopsy from an infant with a1ATD denoting expansion of portal tract, bile duct reduplication and portal and periportal inflammation (H & E staining, x 150) (reproduced with permission from: Hadzic N. and Mieli-Vergani G. Alpha-1-antitrypsin deficiency in Weinstein WM, Hawkey CJ and Bosch J (eds) Clinical Gastroenterology and Hepatology, Elsevier Philadelphia, 2005)*

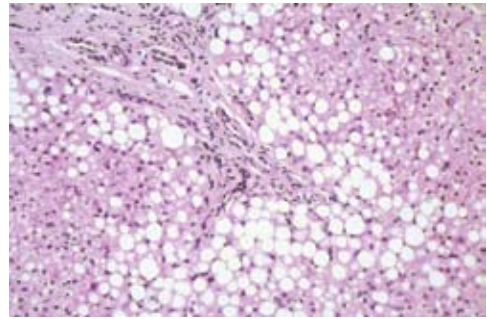
The appearances can sometimes mimic biliary atresia. Presence of periportal microvesicular fat may represent an important diagnostic clue (Fig. 2).



*Fig. 2: Liver biopsy in an infant with PiZZ A<sub>1</sub>ATD showing severe periportal deposition of macrovesicular fat and incipient portal fibrosis (H & E staining, x 150) (reproduced with permission from: Hadzic N. and Mieli-Vergani G. Alpha-1-antitrypsin deficiency in Weinstein WM, Hawkey CJ and Bosch J (eds) Clinical Gastroenterology and Hepatology, Elsevier Philadelphia, 2005)*

The demonstration of magenta-coloured A1AT deposits on periacid Schiff (PAS) stain is usually not possible within the first six months of life. Presence of PAS-positive, diastase-resistant granules and globules in the periportal hepatocytes of older children is highly suggestive of A<sub>1</sub>ATD (Fig. 3), but conventional phenotyping or genotyping is still required for the diagnosis, since these granules are seen in PiZ heterozygotes, and, at times, in hepatocellular carcinoma or alcoholic

hepatitis in adult patients with PiMM phenotype. Children with A<sub>1</sub>ATD related liver disease who present later during



*Fig. 3: Liver biopsy demonstrating retained granules and globules of A<sub>1</sub>ATD (arrow) (PASD staining, x 400) (reproduced with permission from: Hadzic N. and Mieli-Vergani G. Alpha-1-antitrypsin deficiency in Weinstein WM, Hawkey CJ and Bosch J (eds) Clinical Gastroenterology and Hepatology, Elsevier Philadelphia, 2005)*

childhood usually have inactive fibrosis or frank cirrhosis.

## CLINICAL PRESENTATION

The commonest presentation of A<sub>1</sub>ATD is with prolonged neonatal jaundice, pale stools, dark urine, elevated liver enzymes and, less frequently, vitamin K-responsive coagulopathy (9). Approximately 15% of the symptomatic PiZZ children present later during childhood with the signs of established CLD, including hepatosplenomegaly, impaired liver synthetic function and/or complications of portal hypertension. Standard biochemical indices of liver function tests

are deranged, but with no clear pattern. One study has suggested that presence of cholestasis at six months of age indicates a poor prognosis (1).

Abdominal ultrasound scan (USS) is usually unremarkable at presentation in infancy. Later, nonspecific abnormal appearances of the liver parenchyma, abnormal portal flow, splenomegaly and mild ascites, suggestive of CLD, can be observed.

Asymptomatic individuals with CLD can be detected on family screening, instituted when the diagnosis is made in the proband.

Homozygous and heterozygous forms of PiZZ A<sub>1</sub>ATD are increasingly recognised in adults with cryptogenic cirrhosis or CLD associated with alcoholism, iron overload, autoimmunity or chronic hepatitis B and C (12,13). It is conceivable that possession of a PiZ allele may represent a co-morbidity element in the "multiple hit" theory of pathogenesis of the liver injury. The liver disease can remain clinically silent for many years since there are anecdotal reports of abnormal biochemical liver indices associated with precocious emphysema as well as incidental findings of cirrhosis at *post mortem* in asymptomatic PiZZ adults.

Individuals with PiZZ A<sub>1</sub>ATD are at an increased long-term risk of developing hepatocellular carcinoma or cholangiocarcinoma (14,15). Interestingly, some of the patients with these malignancies have been non-cirrhotic and inconsistently alpha-fetoprotein positive.

PiSS A<sub>1</sub>ATD has been detected incidentally in children with various forms of liver disorders (16), in keeping with the estimated high PiS allele prevalence of 4-

10 % in Southern and Western Europe (7). Abnormal polymerisation of A<sub>1</sub>AT PiSS individuals has been demonstrated in vitro (2), but does not appear to lead to its retention in the hepatocytes and consecutive liver damage in children.

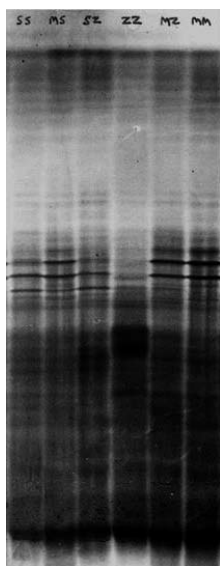
## DIFFERENTIAL DIAGNOSIS

At presentation in early infancy A<sub>1</sub>ATD must be distinguished from non-specific giant cell hepatitis, biliary atresia, neonatal sclerosing cholangitis, cystic fibrosis and Alagille syndrome. Diagnosis should be made by determining the A<sub>1</sub>AT phenotype, since blood levels of A<sub>1</sub>AT, an acute phase reactant, are often within the normal range in deficient infants with inflammatory conditions. In the less common post-infantile presentation, the diagnosis is often suggested by the presence of PAS-positive, diastase-resistant material on liver histology. Clinically, other causes of CLD in childhood such as autoimmune liver disease, Wilson disease and storage disorders need to be ruled out.

## DIAGNOSTIC METHODS

The diagnosis of A<sub>1</sub>ATD may be suspected on low serum levels of the protein or absent alpha-1 band on the agarose gel serum protein electrophoresis, particularly in older children, but the abnormal phenotype should be confirmed by isoelectric focusing on polyacrylamide gel, which is based on the different mobility of the A<sub>1</sub>AT variants (Fig. 4). Occasionally,

in the jaundiced infants differentiation between Z and S band may be difficult on isoelectric phenotyping. Genotyping by allele specific oligonucleotide probe hybridisation should be undertaken in selected cases, such as antenatal diagnosis, presence of severe jaundice or history of very recent blood transfusions. Parental testing to document their heterozygosity is mandatory for confirmation of the diagnosis.



*Fig. 4.:  $A_1AT$  phenotyping using isoelectric focusing (right to left): lane 1: PiMM – normal; lanes 2 & 5: PiMZ and PiMS heterozygous carriers; lanes 3, 4 & 6: PiZZ, PiSZ and PiSS  $A_1ATD$  (reproduced with permission from: Hadzic N. and Mieli-Vergani G. *Alpha-1-antitrypsin deficiency in Weinstein WM, Hawkey CJ and Bosch J (eds) Clinical Gastroenterology and Hepatology, Elsevier Philadelphia, 2005)**

## TREATMENT AND PREVENTION

There is no effective way of modifying the natural history of CLD in PiZZ  $A_1ATD$ . The only proven treatment for PiZZ  $A_1ATD$ -related CLD is liver transplantation. There are reports that transplanted patients with  $A_1ATD$  may be more prone to develop hypertension in the immediate postoperative period due to subclinical renal involvement (3). Overall survival rates in  $A_1ATD$  are similar to other indications for elective liver transplantation. With a successful transplant the phenotype is changed to the one of the donor. It is yet unclear whether  $A_1AT$  transplant recipients have an increased risk of developing post-transplant calcineurin inhibitor-related nephrotoxicity and whether they are protected from lung complications in adult life.

Avoidance of added risk factors such as active and passive smoking or heavy drinking is advisable in individuals with the PiZ allele, though there is no clear evidence that this always prevents liver and lung disease.

Genetic counselling is difficult because of the varying clinical severity and difficulty in predicting the prognosis. Early series have reported up to 75% concordance in severity of liver disease among siblings (9), though this should be confirmed in larger studies. Prenatal diagnosis can be made from genetic analysis after chorionic villi sampling at 8-10 weeks' gestation.

A better understanding of the pathogenesis of liver injury in  $A_1ATD$ , in particular of the role of the abnormal

folding of the PiZ variant and of the assisted export of the abnormal protein from the hepatocytes, will hopefully lead to effective treatment and/or prevention of liver damage.

## COMPLICATIONS AND THEIR MANAGEMENT

Children with severe chronic liver disease related to A<sub>1</sub>ATD can develop complications such as portal hypertension, hypoalbuminaemia and ascites at any time during childhood. Liver decompensation is more common in infancy and early puberty. Standard treatment of CLD complications, such as banding or sclerotherapy of bleeding varices, albumin supplementation and diuretics may help temporarily, but the appearance or reappearance of jaundice, hypoalbuminaemia and prolonged prothrombin time usually herald a rapid evolution to liver failure and indicate the need for urgent consideration for transplant.

## PROGNOSIS WITH AND WITHOUT TREATMENT

The prognosis of liver disease in A<sub>1</sub>ATD is related to the degree of biochemical dysfunction at presentation and severity of the histological changes, in particular to the presence of fibrosis (1). About 5% of PiZZ infants undergo rapid decompensation requiring transplantation in the first 4 years of life, but in 95% the hepatitis settles and the quality of life

is good. Of these, 25% show no further evidence of liver disease, 25% develop cirrhosis requiring transplantation before the second decade of life, and the remainder continue to exhibit biochemical and/or clinical evidence of liver disease, which may decompensate in adult life. The long-term susceptibility of children presenting with liver disease in infancy for developing chronic obstructive lung disease is yet unknown. PiZZ individuals, including non-cirrhotic ones, have slightly increased lifelong risk of developing hepatocellular carcinoma (15).

## REFERENCES

1. Francavilla R, Castellaneta SP, Hadzic N, Chambers SM, Portmann B, Tung J, et al. Prognosis of alpha-1-antitrypsin deficiency-related liver disease in the era of paediatric liver transplantation. *J Hepatol* 2000;32:986-92.
2. Carrell R, Lomas DA. Mechanisms of disease: Alpha-1-antitrypsin deficiency – a model for conformational diseases. *N Engl J Med* 2002;346:45-53.
3. Primhak RA, Tanner MS. Alpha-1 antitrypsin deficiency. *Arch Dis Child* 2001;85:2-5.
4. Lomas DA, Evans DL, Finch JT, Carrell RW. The mechanism of Z alpha1-antitrypsin accumulation in the liver. *Nature* 1992;357: 605-7.
5. de Serres FJ. Worldwide racial and ethnic distribution of alpha-1-antitrypsin deficiency. *Chest* 2002;122:1818-29.
6. Sifers RN, Finegold MJ, Woo SLC. Molecular biology and genetics of alpha-1-antitrypsin deficiency. *Sem Liver Dis* 1992;12:301-10.
7. Miravittles M. Alpha1-antitrypsin deficiency: epidemiology and prevalence. *Resp Med* 2000;94:S12-S15.
8. Sveger T. Liver disease in alpha-1-antitrypsin deficiency detected by screening of 200,000 infants. *N Engl J Med* 1976;294:1316-21.

9. Psacharopoulos HT, Mowat AP, Cook PJ et al. Outcome of liver disease associated with alpha-1-antitrypsin deficiency (PiZ). Implications for genetic counselling and antenatal diagnosis. *Arch Dis Child* 1983;58:882-7.
10. Malone M, Mieli-Vergani G, Mowat AP, Portmann B. The fetal liver in PiZZ alpha-1-antitrypsin deficiency: a report of five cases. *Pediatr Pathol* 1989;9:623-31.
11. Filipponi F, Soubrane O, Labrousse F, Devictor D, Bernard O, Valayer J, et al. Liver transplantation for end-stage liver disease associated with alpha-1-antitrypsin deficiency in children: pretransplant natural history, timing and results of transplantation. *J Hepatol* 1994;20:72-8.
12. Propst T, Propst A, Dietze O, Judmaier G, Braunsteiner H, Vogel W. High prevalence of viral infections in adults with homozygous and heterozygous  $\alpha$ 1-antitrypsin deficiency and chronic liver disease. *Ann Intern Med* 1992;117:641-5.
13. Graziadei IW, Joseph JJ, Wiesner RH, Therneau TM, Batts KP, Porayko MJ. Increased risk of chronic liver failure in adults with heterozygous  $\alpha$ 1-antitrypsin deficiency. *Hepatology* 1998;28:1058-63.
14. Zhou H, Fischer HP. Liver carcinoma in PiZ alpha-1-antitrypsin deficiency. *Am J Surg Path* 1998;22:742-8.
15. Hadzic N, Quaglia A, Mieli-Vergani G. Hepatocellular carcinoma in a 12 year-old girl with PiZZ alpha-1-antitrypsin deficiency. *Hepatology* 2006; 43:194.
16. Hadzic N, Francavilla R, Chambers SM, Castellaneta S, Portmann B, Mieli-Vergani G. Outcome of PiSS and PiSZ alpha-1-antitrypsin deficiency presenting with liver involvement. *Eur J Pediatr* 2005; 164:250-252.