REVIEW

Heterozygous alpha-1 antitrypsin deficiency as a co-factor in the development of chronic liver disease: a review

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ABSTRACT

Alpha-1 antitrypsin (A1AT) is an acute-phase protein that is produced in liver cells. A1AT deficiency is a hereditary disease which is defined by the hepatic production of an abnormal protein that can not be released into the plasma. This leads to deficiency of plasma A1AT and subsequently to an impaired protection against proteases, resulting in pulmonary disease. Accumulation of the abnormal protein in hepatocytes can lead to liver damage. Serum level measurement, phenotyping and liver biopsy can be used for establishing the diagnosis.

Homozygous A1AT deficiency can cause neonatal hepatitis; in adults end-stage liver disease, cirrhosis and hepatocellular carcinoma can develop. There are strong arguments to consider heterozygous A1AT deficiency as an important co-factor in the aetiology of chronic liver disease. Studies have shown that A1AT heterozygosity can be considered a modifier for hepatitis C virus, end-stage liver disease, cirrhosis and hepatocellular carcinoma. The accumulation of A1AT in the hepatocytes occurs more profoundly in a diseased liver, and as a consequence it affects the natural course of the liver disease. Therapeutic options include augmentation therapy (infusion of purified human plasma A1AT) in pulmonary disease; in end-stage liver disease liver transplantation is an option. For the future, other interventions such as gene therapy or strategies to inhibit polymerisation are promising.

KEYWORDS

Alpha-1-antitrypsin deficiency, hepatocellular carcinoma, heterozygosity, liver disease

INTRODUCTION

Alpha-1 antitrypsin (A1AT) is an acute-phase protein that is produced in liver cells. It is released into the plasma in response to an inflammatory stimulus. A1AT deficiency is a hereditary disease that is defined by the hepatic production of an abnormal protein that can not completely be released into the plasma. This leads to deficiency of plasma A1AT and subsequently to an impaired protection of the lungs against proteases. This results in pulmonary emphysema; hepatic accumulation of the abnormal protein can lead to chronic liver disease. This review gives an update of the present knowledge on partial A1AT deficiency in relation to various liver diseases.

GENETICS AND (PATHO)PHYSIOLOGY

The A1AT molecule is a serum glycoprotein acting as an acute-phase protein. It is released during inflammatory processes from the hepatocyte, which results in increased plasma concentrations. The major physiological function

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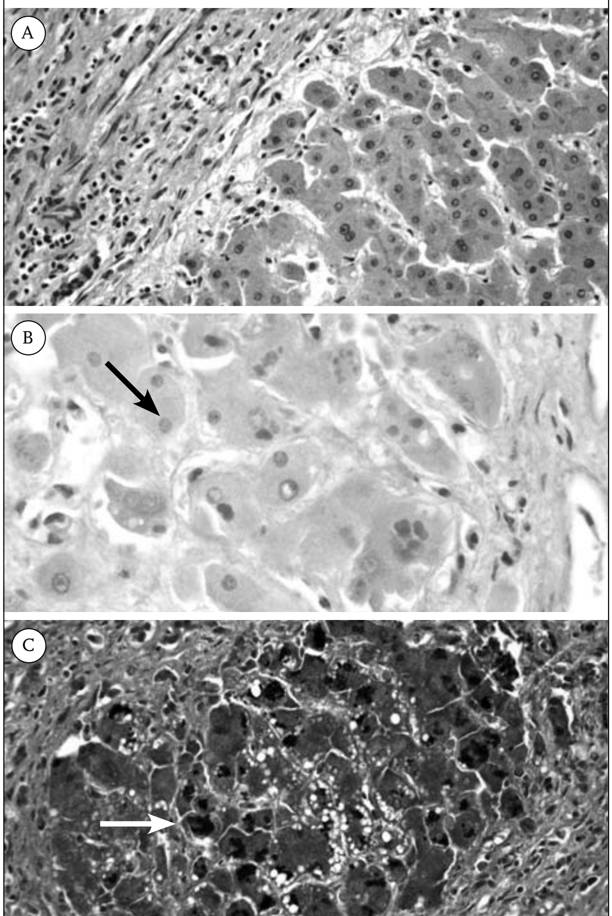
of this protein is the inhibition of destructive neutrophil elastase, thus protecting against pulmonary damage.[1]

The A1AT protein is encoded by the protease inhibitor (Pi) locus located on chromosome 14q32.1. The Pi locus is highly polymorphic, resulting in different A1AT isotypes that can be detected by electrophoresis.

The most common allele is the M allele that results in a functionally normal protein with normal serum A1AT levels. The normal A1AT protein has a tertiary structure based on a large central β-sheet, surrounded by two other sheets and a reactive centre loop. The reactive centre loop can move in and out of the large β-sheet. At higher temperatures polymerisation can occur between molecules due to insertion of the loop of one molecule into the large β-sheet of the other.

The point mutation, found in the Z variant, destabilises the loop-sheet polymerisation of the A1AT molecule, resulting in chains of polymers that are retained in the hepatocytes. These polymers accumulate in the endoplasmatic reticulum of the hepatocytes and may be recognised as PAS(+) inclusion bodies (*figure 1*). Only 15% of the Z variant of A1AT can be secreted into the plasma, the other 85% accumulates in the liver. In Pi ZZ homozygous subjects, this results in a severe deficiency of serum A1AT and in accumulation of the abnormal protein in the endoplasmatic reticulum of the hepatocyte, which can lead to chronic liver disease.

Figure 1. *Liver biopsy: cirrhosis due to alcohol abuse and heterozygosity for α1 antitrypsin (A1AT) deficiency*[33]



A. HE staining, 20x: micro nodular liver cirrhosis.
B. D-PAS staining, 40x: diastase resistant, Periodic-Schiff-Acid positive globuli, matching with A1AT accumulation.
C. A1AT antibodies, 40x: confirmation of A1AT accumulation.

The S variant of the A1AT molecule has less effect on the loop-sheet polymerisation. Formation of S polymers is slower, resulting in less retention of protein in the hepatocytes compared with the Z variant. There is a mild reduction in serum A1AT levels. When an S and a Z variant are coinherited, the two interact with the formation of polymers within the hepatocytes; this can lead to reduction in the serum A1AT level, inclusion of the polymers, accumulation and subsequently development of cirrhosis. Less frequently found variants are null alleles resulting in undetectable A1AT levels due to intracellular degradation or intracellular accumulation of the protein; this is usually associated with severe pulmonary disease, but not with liver disease (*table 1*).[2-7]

A1AT deficiency is characterised by an imbalance between the protease neutrophil elastase and the protease inhibitor A1AT. It has been suggested that neutrophil elastase might promote the development of cancer.[8] The exact carcinogenic mechanism or sequence is not known.

In a recent paper, the hypothesis was given that in A1AT deficiency, the hepatocytes in which A1AT is accumulated are inhibited in their growth, but they do express regenerative signals. Relatively normal cells, without A1AT deposits, are thereby stimulated and this chronic stimulation of regeneration may lead to the formation of neoplasmata.[9]

DIAGNOSTIC ASPECTS

To establish the diagnosis, various methods are available. The A1AT serum level can be determined by clinical chemistry. In homozygous A1AT deficiency the level is very low. However, in the heterozygous variant the A1AT level can be within the normal range, especially during an acute-phase reaction. Therefore, electrophoresis should be performed in any case of suspected A1AT deficiency in order to determine the phenotype. Liver biopsy is the

Table 1. *Characteristics of the different A1AT alleles*

Allele	Mutation	Cellular defect	Enzymatic activity
M	-	-	Normal
S	Glu264Val	Intracellular degradation	Intermediate
Z	Glu342Lys	Intracellular accumulation	Low
Null	Different mutations	Most mutations no mRNA	Null

gold standard for establishing A1AT accumulation and PAS-positive, diastase-resistant inclusions can be found. A specific immunohistochemical staining can confirm the diagnosis. It is also possible to determine the phenotype on paraffin-embedded liver slides.

EPIDEMIOLOGY

Despite the fact that A1AT deficiency is a common disorder, it is poorly recognised in clinical practice. There are probably two main reasons for this; first in patients with liver disease, the diagnosis is not always considered and second not all subjects with a deficient phenotype develop liver disease, i.e. the penetrance is low.[10]
Given this well-known underdiagnosis, the real prevalence of A1AT deficiency has mainly been determined by epidemiological methods, either using a control cohort from an epidemiological study, or through neonatal screening. The Z allele is especially prevalent in Northern Europe, while the S allele is prevalent in Southern Europe (*table 2*).[11-15]

CLINICAL ASPECTS

Pulmonary disease

A1AT deficiency is associated with less inhibition of elastase resulting in pulmonary disease. A1AT homozygosity (Pi ZZ) results in a pulmonary phenotype with early onset of emphysema, asthma and bronchiectasia. A1AT deficiency results in panacinar pathology and disproportionate emphysematous involvement of the lung bases. Tobacco smoking is the most important additional risk factor for the development of pulmonary disease. Also subjects with the Pi MZ phenotype have an increased risk of developing pulmonary disease.[7]

Neonatal/paediatric liver disease

A1AT deficiency is the most common genetic cause of liver disease in early childhood. The most common presentation is by prolonged jaundice. The stools generally contain no yellow or green pigment, indicating cholestasis and mimicking biliary atresia. All patients have hepatomegaly and about 50% also have splenomegaly. Approximately 5% of the patients present with an increased bleeding tendency. This is due to vitamin K deficiency caused by the cholestasis-induced malabsorption. Less commonly children present later in childhood with hepatosplenomegaly or with cirrhosis.[16-19]
In Sweden, between 1972 and 1974, 200,000 neonates were screened for A1AT deficiency: 120 Pi ZZ (0.06%), 2 Pi Z-, 54 Pi SZ and 1 Pi S- children were found. Only 14 of the Pi ZZ children had prolonged jaundice, nine of those had severe liver disease. All infants appeared healthy at six months of age. Infants with a Pi SZ phenotype had no signs of liver disease.
At the age of 16 years, elevated liver enzymes were found in 17% of Pi ZZ adolescents and in 8% of Pi SZ adolescents. The adults with liver disease in infancy were clinically healthy. At the age of 26 years, the Pi ZZ subjects were compared with Pi MM individuals. The Pi ZZ subjects had normal lung function; 4 to 9% of them had mild liver test abnormalities.[11,20,21] In the Province of Bozen in Northern Italy, Pi phenotyping in umbilical cord blood was performed as a routine neonatal screening. About 5% of Pi SZ children were affected by liver involvement with elevated liver enzymes and 7% of 833 Pi MZ heterozygotes had elevated liver enzymes in early childhood. At the age of 5 and 10 years, none had liver disease. The serum levels of A1AT were similar in the groups with and without liver test abnormalities; however these values had a wide range.[22,23]
Although these studies suggest a good prognosis for neonatal cholestasis due to A1AT deficiency, other studies have described children who developed severe liver disease.[16,19]

Table 2. *Epidemiology*[10-15]

Country	Frequency			Method	Year
	Pi ZZ	Pi MZ	Pi SZ		
Sweden	0.06%	-	0.03%	Neonates, phenotyping when serum A1AT <40%	1976
The Netherlands	Z allele 0.03%	-	S allele 0.04%	Neonates, phenotyping when A1AT/trans-ferrine <1,2	1980
France	0.01%	2%	0.15%	Control cohort epidemiological study	2003
Spain	0.01%	-	0.2%	Control cohort epidemiological study	2003
Italy	0.02%	2.4%	0.06%	Control cohort epidemiological study	2003
Portugal	0.02%	2.3%	0.3%	Control cohort epidemiological study	2003
Australia	0.02%	2.5%	0.12%	Control cohort epidemiological study	2003
USA	0.02%	2.7%	0.09%	Control cohort epidemiological study	2003
New Zealand	0.05%	4.3%	0.17%	Control cohort epidemiological study	2003
Canada	0.02%	2.7%	0.11%	Control cohort epidemiological study	2003

Liver disease in homozygous A1AT-deficient adults

Liver disease due to A1AT deficiency generally presents at adult age. One study reviewed adult patients with liver disease and A1AT deficiency; the mean age of the patients when liver disease became symptomatic was 58 years for the ZZ phenotype, 66 years for the SZ phenotype and 73 years for the MZ phenotype. At the time of diagnosis the liver disease was advanced, 42% of these patients died within two years.[24]

A review of autopsy data on 94 Pi ZZ homozygous A1AT deficient patients showed that cirrhotic patients survived longer compared with noncirrhotic patients. The noncirrhotic patients had more severe lung disease and died earlier.[25]

A cohort of patients who are registered in the Alpha-1 Foundation Registry (a USA foundation providing increased research and improved health for A1AT deficiency), and who had reported liver disease or jaundice (165 of the 2175 participants in the registry) completed a questionnaire. Of these patients 71% were Pi ZZ and 18% were Pi MZ, the remainder did not know what their phenotype was. Mean age at diagnosis of liver disease was 31 years (range 0 to 68 years), 30% had undergone liver transplant or were on the waiting list. Male gender and obesity were risk factors for advanced liver disease, while white race, Pi phenotype, infant jaundice, diabetes or hypercholesterolaemia were not.[26] Although this survey is the largest cohort of A1AT deficiency and liver disease in the literature, the self-selected cohort runs a risk of inclusion bias.

The natural history of the disease is not completely known. The risk of cirrhosis in adults is difficult to estimate because most available data are retrospective and derived from patients known to have A1AT-deficient lung disease or cirrhosis.[27,28]

Heterozygous A1AT deficiency and liver disease

Although the role of homozygous A1AT in liver disease is established, the association between heterozygous A1AT deficiency and chronic liver disease is still subject to ongoing investigation. Several studies, however, have shown an association between heterozygous A1AT deficiency and chronic liver disease.

In 1981 a study showed the association between Pi MZ and liver disease. About 1055 liver biopsies were screened for A1AT depositions in hepatocytes. A total of 34 patients with these inclusions were phenotyped; the prevalence of phenotype Pi MZ in the whole biopsy group was 2.4%. In liver cirrhosis, 9% had a Pi MZ phenotype. A percentage of 21% Pi MZ was found in cryptogenic cirrhosis and in chronic active hepatitis, this was significantly increased compared with other causes of cirrhosis. The prognosis of the Pi MZ cirrhotic patients was poor, most patients died within one year.[29]

More recently patients with end-stage liver disease, in work-up for liver transplantation, were investigated. Pi MZ was found in 7.3 to 8.2%, compared with 2.8% in the control population. A heterozygous phenotype was more prevalent in patients with hepatitis C, alcoholic liver disease, cryptogenic cirrhosis and hepatocellular carcinoma.[30,31]

In one study consecutive liver biopsies and autopsies were screened for Pi Z deposits. In the biopsy group 3.4% of cases were Pi MZ phenotyped, whereas in the autopsy group this was 1.8%. In biopsies from older people heterozygous for A1AT, more fibrosis and more Pi Z deposits were found; the liver involvement seems to be age-dependent. When there was another liver disease as well, the patients presented with more inflammation, more fibrosis and more Pi Z deposits than the biopsies without concomitant liver disease.[32]

We described three patients with alcoholic liver disease and a rapidly deteriorating clinical course, resulting in the patients' death. All three patients were found to be heterozygous for A1AT.[33]

To summarise, these studies showed that various liver diseases influence the A1AT accumulation and that the A1AT accumulation influences the course of the liver disease. The risk of developing liver cirrhosis is increased in patients with heterozygous A1AT deficiency, also without coexisting liver disease. The exact impact and involvement of liver disease by heterozygous A1AT deficiency are unknown. Further research is needed to give these data.

Heterozygous A1AT deficiency and coexisting hepatitis C virus infection

The role of A1AT deficiency in the severity and the course of liver disease in chronic hepatitis C virus (HCV) infection is not clear, despite the fact that several studies have analysed the association of HCV-induced liver disease and A1AT deficiency.

In Austria, 1865 patients referred for the evaluation of chronic liver disease were analysed, 9% had a deficient phenotype. From these patients with cirrhosis, 62% were HCV positive, 33% had evidence of HBV infection, 41% abuse of alcohol and 12% had features of autoimmune liver disease. Out of 53 cirrhotic A1AT-deficient patients, only five had no coexisting liver disease. These authors concluded that the risk for chronic liver disease is increased in patients with the Pi Z gene, because they may have increased susceptibility to viral infection or additional factors, necessary to induce chronic liver disease.[34]

The same authors investigated the prognosis of patients with A1AT deficiency. Some 54 patients with A1AT deficiency had evidence of chronic liver disease, 78% showed positive viral markers (hepatitis B or hepatitis C); this was compared with 106 patients with A1AT deficiency without chronic liver disease, without signs of additional viral infection. Life expectancy in A1AT-deficient patients was significantly lower in patients with chronic liver disease in comparison with patients without chronic liver disease.[35]

Patients with end-stage liver disease, in work-up for liver transplantation, were also investigated. In the HCV patients Pi MZ was found in 10 to 13%, compared with 2.8% in the control population. This suggests that an abnormal heterozygous phenotype is a co-factor in the development of chronic liver disease in HCV.[30,31]

In contrast, other studies showed no association between hepatitis C infection and A1AT deficiency.[36-38]

To conclude, the results of these studies are controversial. Some studies show a higher incidence of A1AT deficiency in HCV infection and an increased susceptibility to viral infections in A1AT deficiency and other studies do not. Different methods to determine the A1AT state were used. Further research on the influence of A1AT deficiency in the course of HCV infection and vice versa is necessary.

Heterozygous A1AT deficiency and hepatocellular carcinoma

Established risk factors for hepatocellular carcinoma include chronic hepatitis B, HCV infection and alcoholic liver cirrhosis. Several studies have investigated the correlation between A1AT deficiency and hepatocellular carcinoma.[39,40]

In 1986 it was suggested for the first time that men with A1AT deficiency may be at risk for cirrhosis and hepatocellular carcinoma (HCC). Autopsy was performed in 16 adult patients with A1AT deficiency. In five out of these 16 patients, an HCC was found.[41,42]

In 317 HCC patients, Pi Z deposits were found in 6% compared with 1.8% in the control group. In heterozygous A1AT deficiency, HCC had also developed in noncirrhotic livers and was frequently characterised by cholangiocellular differentiation. In patients with A1AT deficiency bile duct lesions were frequently found. This might reflect a predisposition for the liver tissue for developing tumours with cholangiolar differentiation in A1AT deficiency.[43,44]

In contrast to these studies, others did not show an association between A1AT deficiency and hepatocellular carcinoma, although carcinomas in noncirrhotic livers were Pi MZ associated.[45-48]

To summarise, several studies have been performed to investigate the relation between A1AT deficiency and hepatocellular carcinoma. The outcomes are not uniform. In our opinion studies with large cohorts of patients with hepatocellular carcinoma are the most reliable; these studies did find an association.

A1AT deficiency and associations with other diseases

A1AT deficiency is not only associated with liver and lung disease. Associations with panniculitis, nephrotic syndrome, intracranial aneurysm, hereditary haemochromatosis and celiac disease have been described.[49-62]

THERAPY

Most therapeutic strategies in the treatment of A1AT deficiency are directed towards the pulmonary disease. Infusion of purified pooled human plasma A1AT is known as augmentation therapy. The goal of this treatment is to raise and maintain serum A1AT concentrations above the protective threshold. Data from different studies suggest that intravenous augmentation therapy has a positive biochemical and clinical effect. The therapy is expensive (US $ 28,075 to 65,973 per year).[7] Different concepts have been studied to prevent the polymerisation and accumulation of the A1AT protein. New peptides that block the polymerisation of the Z protein have been developed.[63,64] Gene therapy by injecting adeno-associated virus carrying the human A1AT gene is another promising concept.[65] Liver transplantation is used in end-stage liver disease and results in acquisition of the donor phenotype, a rise in serum levels of A1AT and prevention of associated diseases.[66]

CONCLUSION

Alpha-1 antitrypsin deficiency is an autosomal recessive disorder that can lead to chronic pulmonary disease and liver disease. The liver disease is caused by accumulation of an abnormal, polymerised protein. Deficient phenotypes are present worldwide.

Homozygous A1AT deficiency in children can cause neonatal hepatitis. In adults homozygous patients are at risk for developing end-stage liver disease, cirrhosis and hepatocellular carcinoma. Heterozygous A1AT deficiency is probably an important co-factor in the aetiology of chronic liver disease, as several studies have shown associations with HCV, end-stage liver disease, cirrhosis and HCC.

Low-threshold screening for A1AT deficiency should therefore be carried out. A1AT serum levels may be used, but phenotyping is crucial, as serum levels may not reflect true deficiencies (as inflammation serum levels can be falsely normal). Especially in cryptogenic chronic liver disease and liver disease that deteriorates faster than may be expected, A1AT deficiency may be of clinical significance as a (co)-factor. Clinical research is needed in A1AT-related liver disease to investigate the association between heterozygous A1AT deficiency and the presentation and course of liver diseases.[67]

We believe that the current data are insufficient to decide on the pros and cons of screening on hepatocellular carcinoma in A1AT deficiency. Therapeutic options in A1AT deficiency include augmentation therapy in pulmonary disease; in end-stage liver disease liver transplantation is an option. For the future, gene therapy or strategies to inhibit polymerisation are promising.

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