Histopathological features of liver disease in children with alpha-1-antitrypsin deficiency with good and bad prognosis

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Abstract

Alpha-1-antitrypsin deficiency (alpha1-ATD) is a genetic disorder associated with liver disease, mainly during infancy or childhood and with emphysema in adults. Only a small proportion of PiZZ homozygotes are at increased risk for cirrhosis and liver failure. The cause of the liver injury is still unknown. The alpha1-ATD is the most common genetic disorder in the Caucasian population. And still remains the most common metabolic disease requiring liver transplantation in children. The aim of the study was to assess histopathological findings on liver biopsies in patients with AT deficiency with good and bad prognosis.

We reviewed retrospectively 49 liver samples obtained from homozygous patients (PiZZ). All the children were divided into 2 groups: surviving longterm with no evidence of liver cirrhosis and with bad prognosis (died because of liver cirrhosis or required liver transplantation). Fibrosis, inflammation, cholestasis, D-PAS (+) globules, steatosis, cirrhosis, bile ductular proliferation and tendency for acinar formation were analyzed.

There were significantly increased fibrosis and inflammation in the group of children who were transplanted or died because of liver failure.

Key words: alpha1-antitrypsin deficiency, children, liver biopsy

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Introduction

Alpha-1-antitrypsin deficiency is a genetic disorder that predispose to chronic liver disease and chronic obstructive pulmonary disease (COPD) [2]. Alpha-1-ATD is inherited as an autosomal co-dominant disorder, for which more than 100 alleles have been identified.

The most frequent mutation that causes severe α1-antitrypsin deficiency arises in the SERPINA1 gene (formerly known as PI) and gives rise to the Z allele. The SERPINA1 gene is located on the long arm of chromosome 14 (14q31-32.3) [7]. Alpha-1-ATD is the most common inherited cause of neonatal hepatitis syndrome [10].

The first description of this deficiency was from Laurell and Eriksson in 1963. Since then much has been learned about this deficiency: the full structure of α1-antitrypsin, the mechanism of its binding to its major substrate- neutrophil elastase, the mechanism of its intrahepatic accumulation, clinical manifestations, natural history of this deficiency. But at the same time the precise mechanism of liver injury, clarification of determinants of emphysema beyond cigarette smoking and occupational risk, the role of genetic modifiers of disease expression, are not well defined.

Deficiency occurs in 1:1600–2000 live births in North American and European populations, but it is much less common with other ethnic backgrounds [8]. Only a small proportion of individuals with α1-antitrypsin deficiency (10–15%) ever develops liver disease, especially homozygous ZZ [12]. 25% of them develops cirrhosis requiring transplantation during childhood or in early adult life. To determine histological predictors of poor outcome we analyzed retrospectively liver samples obtained from children with good
and bad prognosis of alpha1-ATD.

**Methods**

Liver samples (n = 49) obtained from homozygous patients (48 PiZZ, 1 PiSS) were retrospectively analyzed. Patients were divided into two groups: group I – 38 children (12 girls, 26 boys) with no clinical features of liver cirrhosis in follow up and good prognosis; group II – 11 patients (2 girls, 9 boys) who were transplanted (n = 9) or died because of liver failure (n = 2) – with bad prognosis.

There was no difference between the groups in the age of biopsy sampling- 1.3 (0.5–2.0) y [mean (CI)] – I group vs. 2.6 (0–5.2) y – II group. The mean duration of follow up was 10.8 years (range 2–17 years). The following features were graded on a 0 to 4 scale according to increasing degree of severity: fibrosis, inflammation and on 0 to 3 scale: cholestasis and D-PAS (+) globules. Steatosis, cirrhosis, bile ductular proliferation, tendency for acinar formation were also analyzed.

Fischer’s exact test was performed to compare frequency of different histological features between the groups. The non-parametric Mann-Whitney test was used for comparison of continuous data.

**Results**

Forty eight patients had PiZZ phenotype, one had PiSS. Median age at liver biopsy was 1.3 years (range: 0.5-2 years) in the group with good prognosis and 2.6 (0.5–2 years) in the group of patients died or transplanted. Histology data concerning steatosis, tendency for acinar formation, bile ductular proliferation D-PAS (+) globules, cirrhosis are summarised in Table 1. The children with bad prognosis had higher degree of inflammation 2.1 (1.2–3) vs. 1.0 (0.6–1.4) [mean (95%CI)] (p < 0.05) and fibrosis 2.9 (2.3–3.5) vs. 1.8 (1.4–2.2) (p < 0.05) than children with good one. There was no difference in cholestasis between the groups (I vs II): 1.2 (0.8–1.6) vs 1.0 (0.2–1.8). In the group with good prognosis steatosis was mainly periportal, sometimes diffuse, present in 22 out of 38 patients, in 5–30% hepatocytes. In the II group steatosis was periportal, sometimes diffuse and focal, and was observed in 7 out of 11 children, in 5 to 40% hepatocytes. There was microvacuolar type of steatosis in 3 patients-two from group I, one died (group II). No significant differences were found between groups when analyzing steatosis and cholestasis degree, D-PAS (+) globules, bile ducts proliferation and tendency for acinar formation (Table 1).

Patients who required liver transplantation or died because of liver failure, have significantly increased fibrosis and inflammation on liver biopsy (Fig. 1 and 2).

**Discussion**

Alpha1-antitrypsin deficiency is the most common inborn error of metabolism causing liver disease and the commonest metabolic indication for liver transplantation in children [4, 9]. The course of the disease is variable – from cholestasis with potential recovery to progression to chronic liver disease. About 10-15% of PiZZ infants develop significant liver damage [12]. Histological features usually seen in pa-

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**Table 1**

<table>
<thead>
<tr>
<th>Histological features of patients with alpha1-ATD on liver biopsy</th>
<th>Group I (n=38)</th>
<th>Group II (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-PAS (+) globules</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>Steatosis</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Tendency for acinar formation</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Necrosis</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Macrophages/Kupfer cells</td>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>

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**Fig. 1.** Severe fibrosis with accompanying inflammation in explanted liver. Hematoxylin and eosin stain, original magnification 400X.

**Fig. 2.** Periportal fibrosis with tendency for fibrous septae formation in core liver biopsy specimen. AZAN stain, original magnification 200X.

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tients with alpha1-ATD are alpha1-antitrypsin deposits in cytoplasm of hepatocytes, features of neonatal hepatitis, paucity of bile ducts or bile ductular proliferation, fibrosis up to cirrhosis, inflammatory infiltrates in portal tracts, mild, usually zonal steatosis and steatohepatitis, just like in NASH [6].

Identification of histological indicators of outcome is very important. Variables associated with a poor prognosis in several previous studies are: severe bile duct proliferation and fibrosis on the initial liver biopsy [3]. According to Francavilla et al there were significantly increased frequency of cirrhosis, bridging septa, severe fibrosis and bile duct reduplication in the initial biopsy among children who required liver transplantation [3].

In our material fibrosis was also found to be an indicator of bad prognosis. Inflammation appears to be another important factor of poor outcome, that was not confirmed in other studies. Possibility of superimposed viral infection of the liver must be considered. Still, it is difficult to estimate prognosis of the disease at its early stage. Usually liver biopsy is taken in infancy, when cholestasis or chronic hepatitis develop. Our data and reports from other studies point to the important role of histological findings in making prognosis. Patients with fibrosis and severe inflammation should undergo careful follow-up to pick up any signs of deterioration of liver function.

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D-PAS-positive globules, diastase – resistant, seen in predominantly perportal hepatocytes, can not be considered fully sensitive marker of alpha1-antitrypsin deficiency. There is no relationship between the number and the size of globules and the occurrence of liver disease. They are difficult to identify in infants in the first three months of life. The globules may be observed in heterozygotes for the Z allele and even in PiM individuals [1].

In our patients there is no correlation between D-PAS – positive deposits and outcome.

Steatosis is marked by some authors as a characteristic pathology for alpha1-antitrypsin deficiency. It is usually mild and zonal, macrovacuolar or mixed [5]. This localization of steatosis was observed by Iwanicka and al. in all of 10 described patients [6]. In our study macro- and microvacuolar steatosis was observed, with periporal or diffuse location. The degree of steatosis did not exceed 40% of liver parenchyma (mild to moderate).

As we know chronic liver disease is associated with toxic effects of mutant alpha1-antitrypsin Z protein retained in the endoplasmic reticulum (ER). There is some evidence that retention of this mutant protein in ER induces mitochondrial autophagy and cell injury [13].

Further studies will be needed to compare mitochondrial changes as a prognostic factor in the groups of children with good and bad prognosis of alpha1-ATD.

References