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Alpha-1-Antitrypsin Deficiency, Mitochondrial Antibodies and Possible Primary Biliary Cirrhosis

A Case Report and Family Study

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ABSTRACT

A case of a 70-year-old woman with a history of gastric ulcer and several pneumonias is presented. She was found to have pulmonary emphysema, severe alpha-1-antitrypsin (αlAT) deficiency and raised serum mitochondrial antibodies. Surgical liver biopsy showed portal liver cirrhosis, PAS-positive, diastaseresistant globules in the hepatocytes and changes interpreted as florid duct lesion of primary biliary cirrhosis. A brother had severe αlAT deficiency. Two daughters had raised mitochondrial antibodies. One of the latter had a granulomatous hepatitis, a common finding in primary biliary cirrhosis. The association of αlAT deficiency and primary biliary cirrhosis does not seem to have been described previously.

INTRODUCTION

The association of alpha-1-antitrypsin (αlAT) deficiency with pulmonary emphysema (7) and infantile liver disease (19, 20, 21), is well known. If the liver is affected, characteristic PAS-positive, diastase-resistant globules reacting with fluorescin-conjugated antiserum to αlAT are found in the hepatocytes (17, 21). αlAT deficiency and its effect on the liver has been reviewed recently (2, 11).

Reports of liver disease in adults with deficiency of this glycoprotein are scarce but include cases of portal liver cirrhosis (1, 3, 5, 8, 13, 14, 15, 18). We here present a case of a woman with severe αlAT deficiency, emphysema, portal cirrhosis and, apparently, with florid duct lesion of chronic non-suppurative destructive cholangitis (primary biliary cirrhosis) who has a high titre of mitochondrial antibodies. This association has, to our knowledge, not been reported previously. The family of this patient has also been studied.

CASE REPORT

The patient (subject II: 7 in Fig. 1) is a 70-year-old woman (born in 1903) who at the age of 38 was hospitalised because of symptoms of gastric ulcer. Since then episodes of similar abdominal symptoms have recurred. In 1963 she had her first pneumonia and during the following 10 years she has been treated seven times for the same disease. She has been taking digitalis and diuretics for about 10 years because of slight dyspnoea and ankle oedema which, however, did not impair her normal daily activities. The past medical history included no mention of jaundice or other abnormalities indicating liver dysfunction.

The patient was admitted to the Department of Infectious Diseases, University Hospital, Uppsala in March 1973 with her third pneumonia that year. On physical examination a firm and slightly tender liver edge was palpable 4 cm below the right costal margin. The spleen was not palpable and there were no signs of ascites. The patient was not jaundiced and had no spider naevi, palmar erythema or other signs of chronic liver disease.

Serum electrophoresis showed an elevated gamma fraction and values of both IgG and IgM were high, 2880 mg/100 ml and 350 mg/100 ml respectively (upper limit of normal; 2210 and 279 mg/100 ml respectively). The alpha-1-fraction was totally absent and assay for alpha-1-antitrypsin (radial immunodiffusion, normal 150–350 mg/100 ml) showed very low values (Table I). Liver function tests including serum bilirubin, alkaline phosphatase, SGOT and SGPT were normal. Galactose tolerance test was slightly pathological with a prolonged half-time of 24.5 minutes (normal <17 min). Serum thymol turbidity test was 7.8 MacLagan units (normal <3). Latex fixation test for rheumatoid factor was positive with a titre of 1/320 but there were no clinical signs of rheumatoid arthritis. Mitochondrial antibodies measured by immunofluorescence were found in a titre of 1/400–1/800. Nuclear antibodies were not detected. Chest X-ray on admission was consistent with a right basal pneumonia. The patient responded quickly to antibiotic treatment and after 16 days the X-ray was practically normalised except for a minimal pleural effusion. Ventilatory pulmonary

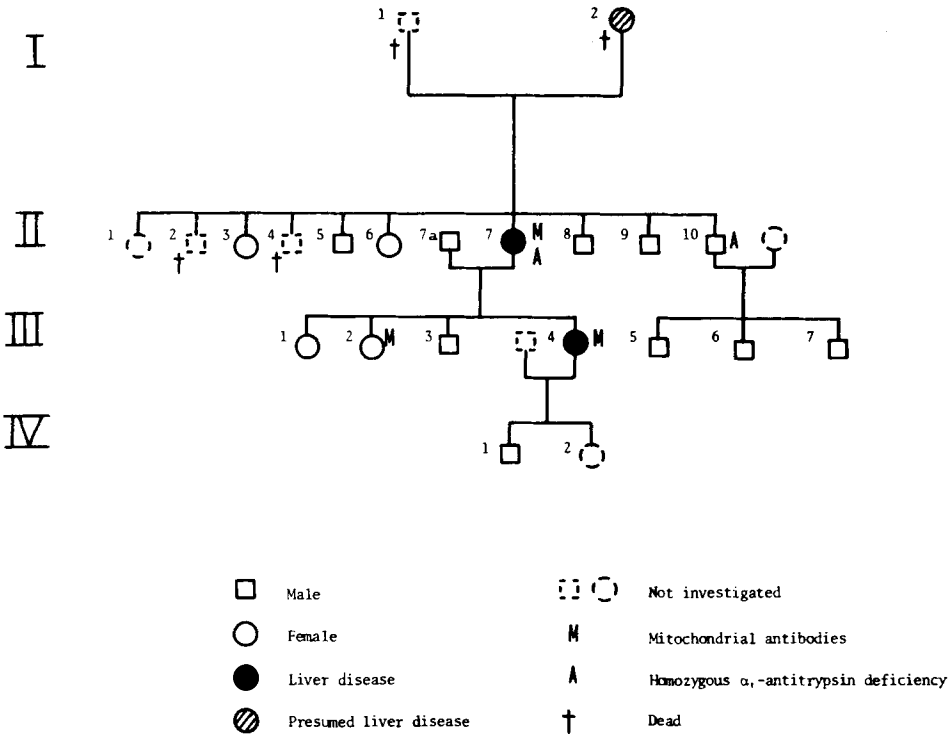

Fig. 1. Family of patient with alpha-1-antitrypsin deficiency, liver disease and mitochondrial antibodies.

function tests were consistent with a significant degree of pulmonary emphysema.

Because of the findings indicating liver disease a percutaneous liver biopsy by the Menghini technique was performed. The pieces of liver tissue were too small to permit a definite diagnosis of cirrhosis but a few portal tracts were slightly widened and fibrosed. Some parenchymal cells contained PAS-positive, diastase-resistant globules. There was no cholestasis. The interpretation of this biopsy was α1AT deficiency with suspicion of portal cirrhosis. Upper gastrointestinal X-rays revealed no oesophageal varices but there was a deformation of the duodenal bulb and the minor curvature of the stomach and a suspicion of pyloric stenosis which was confirmed by gastroscopy.

Six months later a gastroenterostomy was performed. An operative biopsy was taken from the liver which was enlarged, with a nodular surface. The biopsy showed irregular, as a rule, small noduli of liver tissue separated by irregular bands of fibrous tissue (Fig. 2). In some of the fibrous areas there was an abundance of lymphocytes and a few plasma cells together with destruction of bile ducts (Fig. 3). Most liver parenchymal cells were well preserved. Some of them contained PAS-positive, diastase-resistant globules (Fig. 4). There was no cholestasis. The histopathologic diagnosis was α1AT deficiency, portal (septal) liver cirrhosis and tentatively florid duct lesion of primary biliary cirrhosis. The patient's cirrhosis was not considered to be a manifestation of her primary biliary cirrhosis primarily because of the absence of cholestasis.

Table I. *α-1-antitrypsin assays*

Subject no.	Born	Relationship	α-1-antitrypsin mg/100 ml. Normal level: 150–350
II: 3	1883	Sister	162
II: 5	1897	Brother	162
II: 6	1900	Sister	141
II: 7*a*	1902	Husband	343
II: 7	1903	Patient	50, 43
II: 8	1905	Brother	342
II: 9	1908	Brother	354
II: 10	1914	Brother	38, 30
III: 1	1926	Daughter	180, 170
III: 2	1930	Daughter	165, 156
III: 3	1932	Son	231
III: 4	1935	Daughter	160
III: 5	1944	Brother's son	132
III: 6	1946	Brother's son	168
III: 7	1950	Brother's son	214
IV: 1	1956	Grandchild	186

FAMILY STUDY

Since α1AT deficiency is an hereditary disorder the patient's family was investigated (Fig. 1). The propositus'

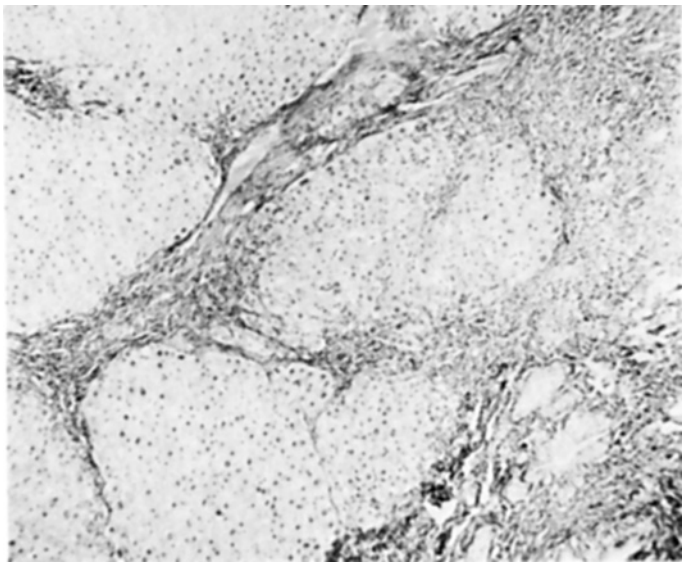

Fig. 2. Subject II:7. Portal liver cirrhosis. van Gieson, ×25.

parents are dead. Her father died aged 62 years, probably of kidney disease. Her mother had liver disease with jaundice and died at 57 years of age.

Sera were obtained for α1AT assay (listed in Table I) and liver function tests including serum bilirubin, SGOT, SGPT, alkaline phosphatase in addition to serum thymol turbidity test, from those relatives available for study. In three relatives, described below, further investigations were made because of abnormal findings.

Subject II:10 had very low α1AT. He is a 60-year-old man (born in 1914) who has had a small duodenal ulcer previously and has been treated for mild hypertension. There were no clinical signs of liver disease and liver function tests were normal. The alpha-1-band was missing in the electrophoresis, the gamma globulin level was normal. Mitochondrial and nuclear antibodies were not detected. Ventilatory pulmonary function tests were within normal limits. A percutaneous liver biopsy showed normal liver architecture. A small number of parenchymal cells contained PAS-positive diastase-resistant globules.

Subject III:2, the patient's second daughter, is a

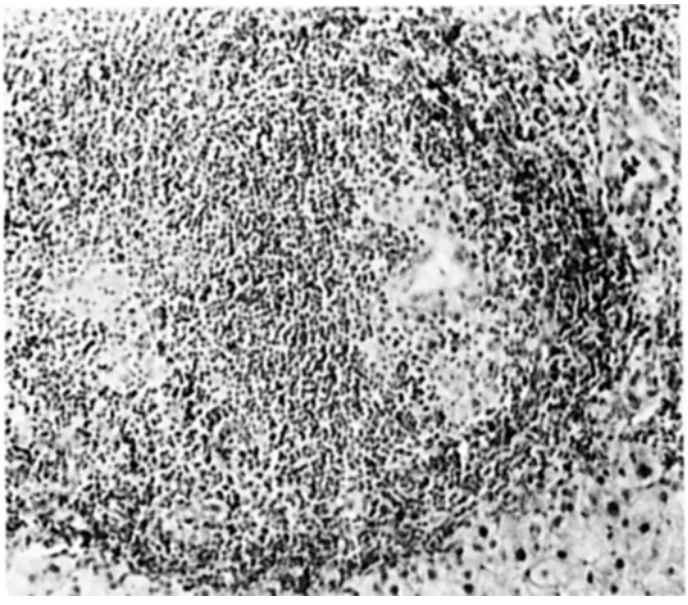

Fig. 3. Subject II:7. Internodular area with lymphocytes and bile ducts in destruction. van Gieson, ×225.

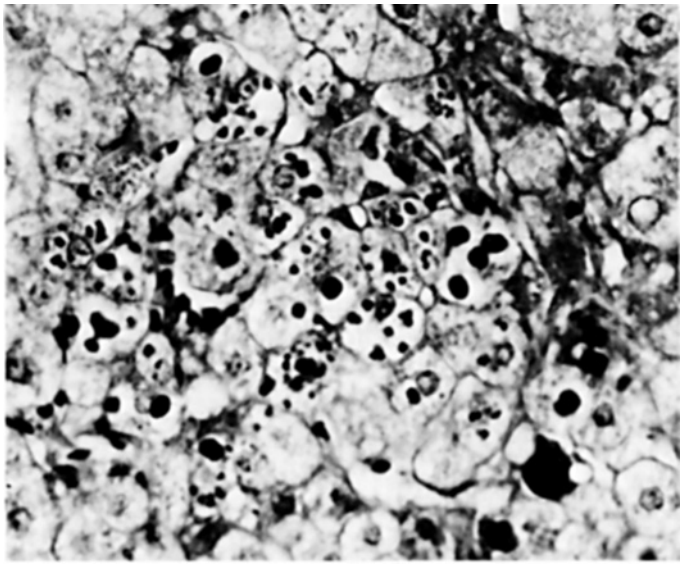

Fig. 4. Subject II:7. Liver parenchymal cells with PAS-positive globules. PAS-staining after diastase treatment. ×400.

43-year-old woman (born in 1930). In 1947, she developed arthralgia which has recurred periodically. In 1955 iridocyclitis was diagnosed and secondary cataract of both eyes has developed. She has never been aware of having gastrointestinal, pulmonary or liver disease. Routine examination was normal except for signs of cataract bilaterally, and liver function tests were normal. Thymol turbidity test was slightly elevated (5.4 MacLagan units). Serum electrophoresis showed a moderate polyclonal increase of the gamma fraction and a flattened alpha-1 peak. Her α1AT level was 165–156 mg/100 ml. Mitochondrial antibody titer was 1/100 and nuclear antibody titre 1/25. Galactose tolerance test was normal, and ventilatory pulmonary function tests revealed no signs of emphysema. Percutaneous liver biopsy showed normal liver tissue and no PAS-positive globules.

Subject III:4 is a 39-year-old woman (born in 1934) who in November 1969 was admitted to another hospital (Serafimerlasarettet, Stockholm) because of recurrent thoraco-epigastric pains. Chest X-ray and liver function tests were normal. Thymol turbidity test was 9.3 MacLagan units and serum electrophoresis showed a moderate polyclonal raise of the gamma fraction. Mitochondrial antibodies were detected in serum in a titre of 1/100. In April 1970 a cholecystography and cholegraphy were normal. A percutaneous liver biopsy was performed. We have been allowed to examine the slides from the biopsy which showed a normal liver architecture with slightly widened portal tracts containing lymphocytes and fibrocytes and in one area a granuloma (Fig. 5). The bile ductules were few and compressed. No PAS-positive globules were seen, and a diagnosis of chronic hepatitis with granuloma and paucity of bile ducts and ductules was made. The picture is compatible with primary biliary cirrhosis. The patient has been in good health except for a few episodes of transitory muscular pains. In April 1971 the mitochondrial antibody titre was 1/500, in May 1972 1/1 600, and in March 1974 1/400.

DISCUSSION

The propositus (II:7) and one of her brothers (II: 10) had no alpha-1-band in the serum electrophoresis and their α1AT values were very low representing 17–20% and 12–15% respectively of the normal mean. No Pi typing has been performed, but such low values have only been found in patients homozygous for the Pi Z gene (16) with the exception of a recently described case with no detectable α1AT (23). All the children, except one, of both the propositus and her brother (II: 10) had α1AT values about the lower limit of normal. Knowing the codominant transmission of α1AT deficiency all the children of these two patients should be heterozygotes (9). In both homozygotes, PAS-positive, diastase-resistant globules characteristic of α1AT deficiency were found in the liver.

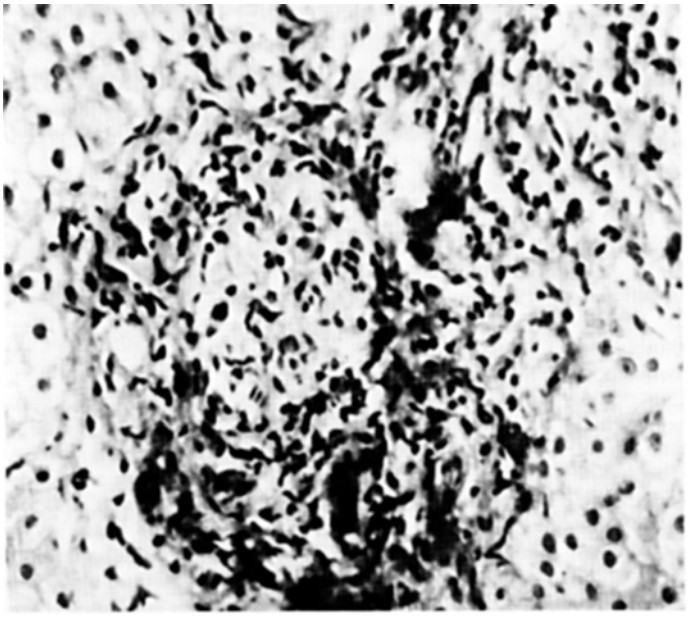

Fig. 5. Subject III:4. Slightly distended portal tract with a granuloma. Hematoxylin-eosin, ×400.

Mitochondrial antibodies is almost a constant finding in patients with primry biliary cirrhosis (22) and are also found in about 7% of healthy relatives (10, 12). These antibodies are not considered to be of any importance in the genesis of primary biliary cirrhosis, but could be a manifestation of an immunological process (6).

The propositus and two of the daughters (Fig. 1) were found to have mitochondrial antibodies. Such antibodies or other tissue antibodies have not been reported previously in patients with α1AT deficiency and liver disease. It is interesting that we also found signs of destructive cholangitis with a florid duct lesion of primary biliary cirrhosis in the propositus. She also has a cirrhosis with no signs of cholestasis, not even demonstrated by Fouchets staining method for bilirubin. Such an advanced cirrhosis, as the propositus has, should, if it was a manifestation of primary biliary cirrhosis, show cholestasis and also other signs of a biliary type of cirrhosis. We therefore interpret her cirrhosis as a portal one. It may be a sequel of her α1AT deficiency. One of her daughters with mitochondrial antibodies (III: 4) also shows liver changes compatible, though not diagnostic of primary biliary cirrhosis. Only a few familial cases of primary biliary cirrhosis have been published (4, 12, 24).

We do not know if there is any connection between α1AT deficiency and primary biliary cirrhosis. The aetiology of primary biliary cirrhosis is not known, nor is the exact mechanism by which α1AT-deficiency produces liver damage. It has been proposed that a genetic disposition to primary biliary cirrhosis could exist and we cannot exclude the possibility that both diseases may be independently inheritable in this family. Theoretically, a liver cell damage in connection with PAS-positive globules might provoke an autoimmune disease in predisposed patients.

It seems to us valuable to present this family in view of the few cases previously reported of α1AT deficiency and liver disease in adults. Biliary cirrhosis has been mentioned in some papers of α1AT deficiency (1, 13, 18), but these cases do not seem to represent primary biliary cirrhosis. Future studies will reveal if any connection exists between α1AT deficiency and primary biliary cirrhosis.

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