Case reports

Congenital hepatic fibrosis with congenital heart disease

A family study with ultrastructural features of the liver

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SUMMARY A family with congenital hepatic fibrosis (CHF) and congenital heart disease (CHD) is presented. The consanguineous healthy parents gave birth to 12 children of whom 10 survived. One son had CHF and CHD, one daughter had CHF and a second daughter had CHD. Three other siblings probably had small a ventricular septal defect and another one probably had mild pulmonary valve stenosis. Development of portal hypertension and hypersplenism necessitated performing shunt operation on both siblings suffering from congenital hepatic fibrosis. Ultrastructural findings were giant mitochondria with large laminar inclusions in hepatocytes, and excess of villi and whorls of membranes and collagen fibrils between hepatocytes.

Congenital hepatic fibrosis (CHF) is a rare recessive genetic disease that presents usually in later childhood with hepatomegaly, normal liver function tests and portal hypertension with oesophageal varices.^{1,2} Hepatic failure and ascites are rare.³ Up to 1965, 94 cases of CHF have been reported⁴ and since then about 70 additional cases have been published. Association of congenital hepatic fibrosis with cystic disease of the kidney is reported in approximately half of the cases.² Association of the disorder with dilated extrahepatic bile ducts,⁵ cystic dysplasia of the pancreas,⁶ pulmonary emphysema and fibrosis⁷ and a complex of nervous system signs⁸ have been reported as well. Review of the literature revealed only one patient who suffered from congenital hepatic fibrosis and congenital heart disease (CHD)² and only two reports of ultrastructural features of liver in congenital hepatic fibrosis.^{9,10}

The present report describes the occurrence of CHF in at least two siblings in one family with light and electron microscopic findings of the liver

in both patients. One of these two siblings and another sister have congenital heart disease proven by cardiac catheterisation. Four other siblings probably have CHD as well.

Family background (Fig. 1)

The parents of our patients are second cousins of a Druze descent. No history of liver, kidney, or heart disease in the parents' families could be elicited. Family history revealed that the eldest girl had died of chronic glomerulonephritis at the age of 19 years and the fifth sibling had died of gastroenteritis at the age of a few months. The parents and their 10 living children were examined by two of the authors (YN and NR). In order to make it easier to deal with this large family, we divided it into three groups: (1) proved liver and/or heart disease group (Fig. 1, Nos. 2, 8, and 12); (2) probable heart disease group (Fig. 1, Nos. 3, 6, 10, and 11); (3) healthy group (Fig. 1, father, mother, Nos. 4, 7, and 9).

PROVED LIVER AND/OR HEART DISEASE GROUP (Fig. 1, Nos. 2, 8, and 12).

RS (Fig. 1, No. 2)

RS was first admitted in 1964 at the age of 12 years

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Fig. 1 Pedigree of the family.

because of abdominal pain and abdominal distension of two months' duration. His past history was uneventful. On admission, abnormal findings included pallor, malnutrition, mild dyspnoea, distended and tender abdomen, a firm edge of enlarged and irregular left lobe of the liver palpable 5 cm below the right costal margin and a huge firm spleen extending to the pelvis. Blood pressure was 110/70, normal pulses 78/min regular, and a grade 3/6 holosystolic murmur was heard at the apex.

Laboratory investigation revealed the following values: haemoglobin 5.58 mmol/l (9 g/dl), reticulocyte count 2%, white blood cell count (WBC) 1000/mm³, platelet count 70 000/mm³, urinalysis normal, erythrocyte sedimentation rate (ESR) 10 mm in one hour, blood urea 3.33 mmol/l (20 mg/dl), serum bilirubin normal, prothrombin activity 55%, SGOT 10;25 IU/l (5-30 IU/l), alkaline phosphatase 38; 58 Bessey-Lowry (BL) IU/l (20-50 IU/l), total protein 71 g/l (7.1 g/dl), albumin 40 g/l (4 g/dl), cholesterol 2.64 mmol/l (102 mg/dl). No occult blood was found in stool.

Radiographic studies Radiographs of the chest revealed an enlarged cardiac silhouette. A barium swallow showed evidence of oesophageal varices. An excretory urogram (IVP) was normal.

Cardiovascular studies The electrocardiogram (ECG) presented normal sinus rhythm, left axis deviation (LAD), and left ventricular hypertrophy (LVH).

Diagnoses of portal hypertension with secondary hypersplenism and congenital heart disease were made. End-to-side splenorenal shunt was performed on 1 September 1964. A firm enlarged liver and a huge spleen weighing 4 kg were found. Surgical wedge biopsy of liver examined by light microscope revealed nodular liver tissue owing to the presence of large bands of fibrous tissue encircling large and sometimes small areas of hepatic

parenchyma, with no inflammatory changes. In these bands of fibrous tissue there were numerous bile ducts of mature appearance. Some of the larger bile ducts were dilated and seemed tortuous. Direct transformation of bile ducts from parenchymal cells was observed. All bile ducts were lined by cuboidal epithelial cells. In some areas fine strands of collagen bundles were seen extending from the fibrotic areas into the liver parenchyma, with transformation of parenchymal cells into a few small bile ducts at these sites. Portal veins in the fibrous connective tissue bands seemed normal or dilated, while in the smaller portal spaces the veins were small and sometimes absent. There was no cholestasis and the parenchymal liver cells were normal. Two additional fragments of liver tissue, obtained by needle biopsy, were available for examination, one before the shunt operation and the other 14 years later. Neither of these biopsic specimens were diagnostically conclusive.

The postoperative course was smooth. Blood count reverted to normal after splenectomy.

The patient was followed-up in the outpatient clinic and he was symptomless as far as the liver disease was concerned; his heart disease, however, slowly progressed and at the age of 22 years he was readmitted for a haemodynamic evaluation. The patient was dyspnoeic and had palpitations on mild effort. He was on digoxin and diuretic therapy. Blood pressure was 130/80, and normal peripheral pulses at a rate of 90/min, deformation of the chest wall, and biventricular impulse were noted. On auscultation, normal first sound, accentuated second sound, a third sound and a grade 3/6 holosystolic murmur at the apex, and a grade 2/6 early diastolic murmur at the left sternal border were heard. Lungs were normal. Laboratory investigation revealed normal kidney function and liver function tests except for generalised increase of gamma-globulin. ECG presented sinus rhythm with a rate

of 72/min, PR interval 0.19 s, QRS axis to the left -50° , LVH and left ventricular strain, absence of Q waves in V_5 and V_6 , and Q waves in L_3 and V_1 . Radiographs of the chest showed enlargement of heart silhouette and left atrium with signs of veno-capillary hypertension. The results of right and left cardiac catheterisations are listed in the Table. Cineangiography was performed in both ventricles and aorta. Cineangiography in the anatomic right ventricle showed a moderate left atrioventricular valve insufficiency and the aortogram showed a mild aortic regurgitation.

Table Haemodynamic data of right and left cardiac catheterisation of RS.

Site	Pressure (mean)	O ₂ saturation (%)
Superior vena cava	6	80
Right atrium	6 (a13, v7)	80
Inferior vena cava	5	79
Anatomical left ventricle	46/4	80
Pulmonary artery	22/14	81
Aorta	135/90	115
Anatomic right ventricle	140/14	94
Pulmonary vein	14	94
Left atrium	14 (a16, v18)	94

After the haemodynamic studies the following diagnoses were made: congenital corrected 1-transposition, left atrioventricular valve insufficiency (moderate), aortic insufficiency (mild), patent foramen ovale, and subpulmonary stenosis (mild).

The patient was discharged from the hospital and followed-up in our cardiac outpatient clinic.

HS (Fig. 1, No. 8)

HS was first admitted in 1970 at the age of 6 years because of abdominal pain and hepatosplenomegaly. Past history was uneventful. Physical examination revealed a pale thin girl. Liver edge was firm and palpated 3 cm below the right costal margin. Firm spleen was palpable 7 cm below the left costal margin. Otherwise, physical examination was normal. Laboratory investigation revealed the following values: haemoglobin 5.46 mmol/l (8.8 g/dl), reticulocyte count 2.2%, WBC 3400/mm³, platelet count 120 000/mm³, urinalysis normal, ESR 60 mm in one hour, blood urea 3.66 mmol/l (22 mg/dl), uric acid 0.19 mmol/l (3.2 mg/dl), creatinine 44.20 μ mol/l (0.5 mg/dl), creatinine clearance 110 ml/min, serum bilirubin normal, prothrombin activity 55%, SGOT 12 IU/l (5–30 IU/l), alkaline phosphatase 43 BL IU/l (20–50 IU/l), total protein 70 g/l (7 g/dl), albumin 39 g/l (3.9 g/dl), cholesterol 4.45 mmol/l (172 mg/dl), bromsulph-thalein retention 4% after 45 minutes and bone marrow aspirate normal.

Liver needle biopsy showed portal fibrosis with some proliferation of bile ducts. Where radiological studies were concerned those of the chest, barium swallow, and IVP were all normal. The ECG was also normal.

Congenital hepatic fibrosis was suspected and the child was followed up in our outpatient clinic.

By 10 years of age, HS was readmitted because of fatigue, anorexia, and abdominal pain of two weeks' duration. Abnormal physical findings included firm liver palpated 3 cm below the right costal

Fig. 2 HS. Liver biopsy showing a portion of portal space. Fibrous tissue is arranged concentrically around bile ducts. The latter shows tortuosity and columnar epithelial cell lining. Dilated portal vein (arrow) in the upper right-hand corner. Haematoxylin and eosin, $\times 100$ (original magnification).

margin and firm spleen palpated 11 cm below the left costal margin.

Laboratory investigation revealed haemoglobin 5.90 mmol/l (9.5 g/dl), WBC 3600/mm³, platelet count 90 000/mm³, serum bilirubin 35.91 μ mol/l (2.1 mg/dl) of which traces were direct reacting,

prothrombin activity 80%, SGOT 94 IU/l (5–30 IU/l), alkaline phosphatase 36 BL IU/l (20–50 IU/l), and bromsulphthalein retention 8% after 45 minutes. Liver needle biopsy was apparently normal.

Radiographic studies evidenced the existence of oesophageal varices and thickened mucosal folds

Fig. 3 HS. Part of a hepatocyte showing giant mitochondria which contains large lamellar inclusions (S). Arrow points to the fusion of two mitochondria. The space between hepatocytes is enlarged and cell membrane projections extend into the space (x), $\times 28\,500$ (original magnification).

in the fundus which might also be the result of varices.

The development of portal hypertension and worsening of hypersplenism (WBC dropped to $1500/\text{mm}^3$ and platelet count to $26\,000/\text{mm}^3$) led us to perform an operation for end-to-end spleno-suprarenal shunt on May 1974.

Surgical wedge biopsy of liver revealed findings identical with those observed in the liver of RS. The bands of mature connective tissue showed concentric arrangement around the larger bile ducts, which were lined by columnar epithelium and seemed tortuous (Fig. 2). Formation of new bile ducts near the limiting plates was observed as in RS. Portal veins showed the same findings as those of RS including dilatation of portal veins in the broad fibrous bands (Fig. 2).

The postoperative course was smooth and blood

count reverted to normal after splenectomy. The patient was followed-up in our outpatient clinic. Kidney function tests remained normal.

Electron-microscopic findings of RS and HS livers

The needle biopsy material of RS showed mild degenerative changes of the hepatocytes. Lobulated lipofuscin bodies were noted in the cytoplasm. The bile canaliculi were slightly dilated and the villi arranged in a disorderly fashion. The space between the hepatocytes was enlarged and the cell membrane facing this space presented irregular extensions and villi.

The needle biopsy material of HS demonstrated normal architecture of liver lobules when $1\,\mu$ thick sections from blocks embedded in Epon were examined. The ultrastructure revealed alterations of the hepatocytes and also a slight increase in

Fig. 4 HS. The enlarged space between hepatocytes contains whorls of membranes. Collagen fibrils at $0, \times 28\,500$ (original magnification).

the number of bile canaliculi. The cytoplasm of the hepatocytes showed focal accumulations of glycogen and in many areas the mitochondria was markedly enlarged and bizarre-shaped (Fig. 3). Giant, sometimes fused, mitochondria which contained large laminar inclusions were noted (Fig. 3). The interstitial space between hepatocytes was enlarged and the cell membrane was irregularly outlined and

presented finger-like extensions of varied length (Fig. 3). Frequently, whorls of membranes were noted between the cytoplasmic extensions (Figs. 3, 4). Occasionally, small amounts of collagen fibrils appeared in the enlarged space between the hepatocytes (Fig. 4).

In the wedge biopsy of HS, the increase in the number of bile canaliculi was more marked than

Fig. 5 HS. Small-sized bile ductule shows irregularly distributed microvilli. The cytoplasm contains lipofuscin bodies. Arrow points to basement lamina. A large amount of collagen fibrils is seen at 0, $\times 14\,700$ (original magnification).

in the needle biopsy material. Increase in the number of bile ducts of varied calibre was also observed. These were composed of ductal epithelial cells that rested on a continuous basement lamina

(Figs. 5, 6). Desmosomal junctions were present between ductal cells (Fig. 5). The side of the ductal cells facing the lumen presented irregularly distributed microvilli (Figs. 5, 6). Increase in the amount

Fig. 6 *HS. Bile ductule shows disorderly arrangement of microvilli. L = lipofuscin body. Arrow points to basement lamina, $\times 5700$ (original magnification).*

of collagen fibrils between hepatocytes and bile ducts was noted (Figs. 5, 6). Lipofuscin bodies and dense bodies of indefinite origin were observed in the cytoplasm of the bile duct epithelial cells (Figs. 5, 6).

MS (Fig. 1, No. 12)

MS was admitted at the age of 9 months with a history of failure to thrive. Her weight was 5700 g and height 60 cm (both less than 3rd percentile for her age). Physical examination revealed normal pulses 98/min regular, and no evidence of cyanosis or clubbing. The lungs were normal. At the left sternal border, a systolic thrill was palpated and a grade 4/6 holosystolic murmur was heard. No evidence of liver disease was demonstrated. ECG showed sinus rhythm with mild LVH. Radiograph of the chest revealed cardiac enlargement with pulmonary vascular engorgement. Right heart catheterisation disclosed a 1.6/1 left to right shunt at ventricular level with normal pressure in the pulmonary artery. The child was discharged with medical treatment and followed-up in the outpatient clinic.

PROBABLE HEART DISEASE GROUP

(Fig. 1, Nos. 3, 6, 10, and 11).

IS, SS, and WS (Fig. 1, Nos. 3, 6, and 11).

Physical examination of these asymptomatic children revealed a pansystolic murmur without a third sound or a diastolic apical murmur. ECG of all three showed a LAD of the QRS (-15° , -15° and -50° respectively) without signs of biventricular hypertrophy. Radiographs of the chest and echocardiograms were within normal limits. The most probable clinical diagnosis was small ventricular septal defect in all of them.

AS (Fig. 1, No 10)

Physical examination of AS revealed a healthy well-developed 7 year old girl with an ejection click and 2/6 ejection murmur heard in the pulmonary area. The ECG was normal. Radiograph of the chest showed a mild enlargement of the pulmonary artery. These findings were clinically compatible with mild pulmonary valve stenosis.

HEALTHY GROUP

(Father, mother; Fig. 1, Nos. 4, 7, and 9)

The father and the ninth sibling were normal on physical examination but they had QRS axis of -10° and -15° respectively. The mother and two of her siblings (Fig. 1, Nos. 4 and 7) were healthy from all points of view.

Discussion

The diagnosis of congenital hepatic fibrosis could be made in RS and HS on histological grounds because of the relative preservation of the hepatic parenchyma with abnormal bile ducts and dense fibrosis. In the absence of inflammation, the numerous bile ducts, embedded in mature collagenous tissue, are suggestive of a hamartomatous disease of the liver.^{1 4 11 12}

The aetiology of congenital hepatic fibrosis is not fully established. Some authors^{13 14} have supported the idea that portal hypertension in CHF is due to hypoplasia of intrahepatic portal vein radicles, but others^{11 15} think the more likely cause to be portal vein compression by fibrosis. In any case, the underlying liver lesion progresses very slowly.² Incidence of congenital hepatic fibrosis in more than one sibling of a family has been described^{1 2 4 16} but has not so far been reported in successive generations. Approximately half of the patients with the disorder are cases where more than one child in the same family is afflicted.¹⁷ Kidney changes were demonstrated in about 70% of the patients in the familial group and in about 30% of the cases in the group of so-called sporadic cases.¹⁷ An account of the combination of familial congenital hepatic fibrosis and familial congenital heart disease, as in this family, had not hitherto been published.

Congenital heart diseases are mostly due to interaction between genetic predisposition and environmental factors. It appears that about 8% of cases with congenital heart disease are predominantly genetic and 2% are predominantly environmental in aetiology. In the remaining 90% there is an important genetic-environmental—that is, multifactorial—interaction.¹⁸ The probability that a sibling of a child with CHD will also have a cardiac malformation varies between 1 to 4% according to the type of malformation.¹⁸ The consanguinity of the parents increases the probability that congenital heart disease in this family is either predominantly genetic or multifactorial in aetiology. Familial discordant CHD has been demonstrated in human studies and animal experiments.^{18 19} The existence of congenital hepatic fibrosis without heart disease in HS and congenital heart disease without liver disease in MS does not support a common genetic background for the occurrence of these two disorders in the same patient (RS).

The father and his ninth sibling were included in the healthy group despite QRS axis in the frontal plane of -10° and -15° respectively. It is obvious that the possibility of closure of ventricular septal defect (VSD) cannot be ruled out; especially when

the clinical findings in three other siblings (Fig. 1, Nos. 3, 6, and 11) were compatible with small VSD.

Ultrastructurally, the hepatocytes of our patients showed mitochondrial damage which was expressed by the appearance of giant mitochondria with accumulations of large laminar inclusions, as have been described by others.⁹ The aspect of hyperplastic bile ductules was similar to that described by Thaler *et al.*¹⁰ In both patients with CHF, an excess of cell membrane projections and whorls of membranes were noted in the interstitial space between hepatocytes. The interstitial membranes were sometimes intermingled with collagen fibrils and might represent a stimulating factor in the development of hepatic fibrosis. It was suggested that the excessive accumulations of connective tissue might trigger abnormal development of bile ducts.¹⁰

Finally, congenital hepatic fibrosis should be suspected in children and young adults with firm enlarged liver, portal hypertension, and well-preserved liver function tests, as these patients are excellent candidates for portacaval shunt operation, which results in relief of portal hypertension.¹⁻³

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