

Congenital Hepatic Fibrosis (3 Cases Report)

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= Abstract = Congenital hepatic fibrosis is a relatively rare disease of children and young adults, that is characterized by hard hepatomegaly, portal hypertension with relative preservation of liver function and underlying architecture, and frequent renal involvement.

We report 3 cases of congenital hepatic fibrosis with quite different presentations. The first, aged 2 2/12, presented with hepatomegaly followed by splenomegaly with suspicious renal involvement. The second, aged 2 8/12, had unique feature that congenital hepatic fibrosis was associated with situs inversus, nephronophthisis and positive family history. The third, aged 9 9/12, had splenomegaly without hepatomegaly. All cases had splenomegaly, but there were no varices on esophagogram or history of hematemesis or melena.

Key Words: *Liver disease, Congenital hepatic fibrosis, Situs inversus, Nephronophthisis, Cystic disease*

INTRODUCTION

Noncirrhotic hepatic fibrosis in childhood encompasses many conditions including cystic diseases complexes syndrome group, congenital hepatic fibrosis and still undefined disease affecting portal tracts without disrupting major lobular architecture. Among these, congenital hepatic fibrosis is a relatively rare disease of children and young adults, that is characterized by stony hard hepatomegaly, portal hypertension with relative preservation of liver function and underlying architecture, and frequent renal involvement.

Since congenital hepatic fibrosis was first delineated by Kerr *et al.* in 1961, approximately 200 cases have been reported in the literature (Ghishan and Younoszai 1981). During last 5 years we have experienced 3 cases of congenital hepatic fibrosis at the Seoul National University Children's Hospital, all of which were histologically confirmed. One of 3 cases was previously published (Shin *et al.* 1981).

CASE REPORTS (Table-1,2)

Case 1. Lee Y.S.: A 2 2/12 year old girl visited the SNU Children's Hospital out-patient clinic on May 16, 1978, because of abdominal pain and

fever. The liver was palpable 4 cm below the right costal margin, and there was increased perihilar density on chest X-ray. Mantoux test was positive. She was put on antituberculous medication under the impression of tuberculosis. Thereafter fever and abdominal pain subsided, but hepatomegaly persisted. Splenomegaly was noted 4 months later. Since December 1978, polydipsia and polyuria developed. So she was admitted for further evaluation on January 11, 1979.

The past medical history revealed no previous melena, jaundice, or transfusion. Her younger brother was 1 year old and healthy.

Physical examination showed a moderately emaciated conscious girl. The heart rate was 120/min, the blood pressure 130/90 mmHg, the respiratory rate 28/min. The conjunctivae were not anemic, the sclerae were not icteric. The lungs were clear. The abdomen was distended, soft, and the liver and spleen were palpable 4 cm and 3 cm respectively below the costal margins. There was no cyanosis or edema on the extremities.

Findings from laboratory examination included the hemoglobin 13.3 gm/dl, the white-cell count 13,900/mm³, and the platelet 146,000/m³. The bleeding time, the prothrombin time and the partial

Table 1. Summary of clinical features of congenital hepatic fibrosis

	Case 1	Case 2	Case 3
Age at diagnosis(yrs)	2 2/12	2 8/12	9 9/12
Mode of presentation	hepatic form	renal form	hepatic form
Hepatomegaly	4 cm*	6 cm*	—
Splenomegaly	3 cm*	8 cm*	6 cm*
Renal involvement	suspicious	nephronophthisis	none
Varices on Esophagogram	none	none	none
Others	—	situs inversus	—

*; distance from the costal margin

Table 2. Summary of laboratory findings of 3 cases presented

	Case 1		Case 2	Case 3
	1st Adm.*	2nd Adm.*		
Hemoglobin (gm/dl)	13.3	10.1	6.7	12.9
WBC(/mm ³)	13,900	7,900	2,800	2,700
Platelet (/mm ³)	146,000	150,000	76,000	62,000
Alkaline P'tase (IU/l)	350	350	310	150 IU
Serum glutamic oxaloacetic transaminase (IU/l)	163	107	26	15
Serum glutamic pyruvic transaminase (IU/l)	83	54	19	10
Serum total protein (gm/dl)	7.4	7.0	6.7	7.5
Serum albumin (gm/dl)	4.8	3.3	3.9	4.8
Serum bilirubin (mg/dl)		3.1/1.8	0.4/0.2	1.0/
total/direct				
Blood urea nitrogen (mg/dl)	11.8		52	14
Serum creatinine (gm/dl)	0.7		3.0	0.8

*; admission

thromboplastin time were all normal. The total protein was 7.4 gm/dl, the albumin 4.8 gm/dl, the alkaline phosphatase 350 IU/l, the glutamic oxaloacetic transaminase 163 IU/dl, the glutamic pyruvic transaminase 83 IU/dl, the urea nitrogen 11.8 gm/dl, the creatinine 0.7 mg/dl. Urinalysis revealed no proteinuria or cells, but the specific gravity of first morning urine was persistently low. The urine osmolarity before and after 6 hours of water deprivation were 136 and 279 mOsm/l respectively. The intravenous pyelogram was normal, and there were no varices on esophagogram. Bone marrow examination revealed no abnormality. Liver needle biopsy showed only moderate portal fibrosis and small round cell infiltration with minimal bile duct proliferation. He was discharged on January 25, 1979, without specific diagnosis.

She was lost of follow- up till March 10, 1980, when she was readmitted because of jaundice, de-

veloped 1 month prior to the 2nd admission. She still had polyuria and polydipsia. The liver and spleen were more enlarged (6 cm and 5 cm each). The liver was hard, but not tender. There was erythema over palms and soles. The serum glutamic oxaloacetic transaminase was 107 IU/l, the glutamic pyruvic transaminase 54 IU/l, the alkaline phosphatase 350 IU/l, the total bilirubin 3.1 mg/dl, the direct reacting bilirubin 1.8 mg/dl. HBsAg was negative.

On exploratory laparotomy, the liver was grossly enlarged, hard, and finely granular. Microscopically the liver was characterized by broad bands of mature fibrous tissue with relatively normal lobular architecture in between. These fibrous septa contained numerous well-formed bile ducts and were slightly infiltrated with chronic inflammatory cells(Fig. 1,2,3).

She was discharged on March 23, 1980, fol-

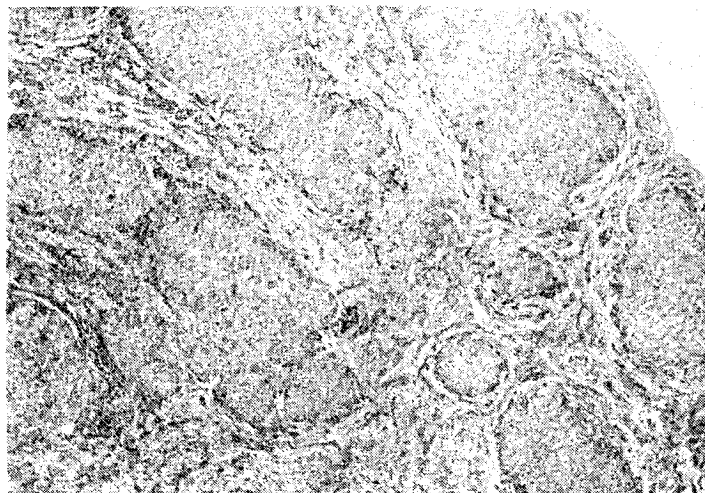


Fig. 1. Liver wedge biopsy showing islands of liver lobules surrounded by broad continuous strands of portal connective tissue. H & E, X25. Case 1.

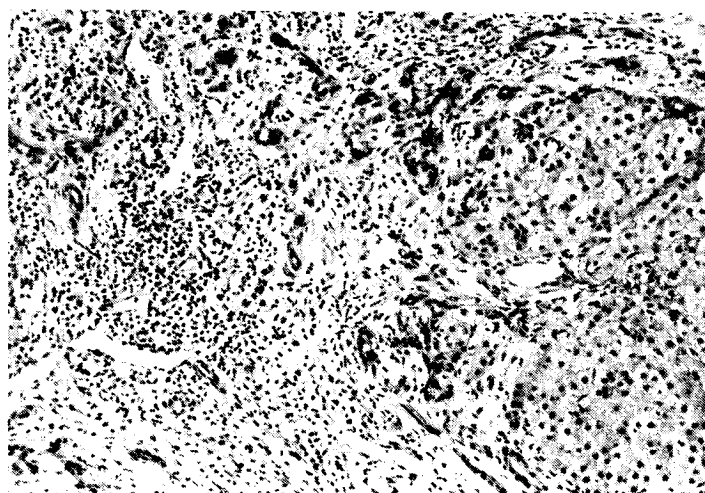


Fig. 2. Photomicrograph of the liver, showing collagen fibers running parallel in the fibrosis septa with a sharp margins to the adjacent liver tissue. Increased number of bile ducts with an area of microcystic change is seen. Note small round cell infiltration in the fibrosis bands. H & E, X100. Case 1.

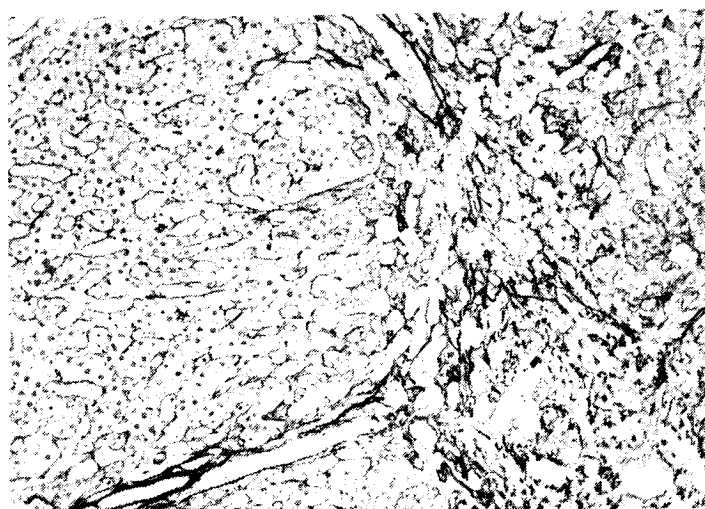


Fig. 3. Reticulum stain of the liver to show intact liver cell cords and sinusoidal structure. Reticulum stain, X100. Case 1.

lowed up till February 2, 1981, while her general condition got worse progressively with ascites formation.

Case 2. Shin S.Y. : A 2 8/12 year old boy was admitted to the SNU Children's Hospital on February 29, 1984, because of abdominal distension and dyspnea. He was born as a 2nd baby with normal term delivery. Abdominal distension was noted since birth. When 2 year old, he was admitted to a local clinic due to gastroenteritis, where he was told to have situs inversus with cardiomegaly and cardiac murmur. Since that time, tachypnea and exertional dyspnea developed. During follow-up at that clinic, dyspnea got worse and abdominal distension persisted.

His elder brother died with situs inversus, hepa-

tosplenomegaly and renal failure at the age of 2 1/2 years.

Physical examination disclosed a dark and puffy faced boy with clear consciousness. The blood pressure was 150/90 mmHg, the pulse rate 120/min, and the respiratory rate 48/min. The conjunctivae and sclerae were not anemic or icteric. There was precordial bulging on the right chest wall and grade 2/6 systolic murmur was detected at the right sternal border. The left sided liver was palpable 6 cm, and the right sided spleen was palpable 8 cm below the subcostal margins. The fingers were rather short and there was a simian line on the left hand.

Laboratory findings were as follows; The hemoglobin 6.7 gm/dl, the white-cell count 2,800/mm³, the platelet 76,000/mm³, the urine albumin (+), the red blood cell 0-1/HPF, the urine specific gravity persistently low around 1.010. The glutamic oxaloacetic transaminase was 26 IU/l, the glutamic pyruvic transaminase 19 IU/l, the alkaline phosphatase over 350 IU/l, the bilirubin total/direct 0.4/0.2 mg/dl. The BUN/creatinine were 52/3.0 mg/dl and the creatinine clearance 3.5 ml/min. There were no varices on esophagogram. The chest X-ray disclosed right sided heart with cardiomegaly (Fig.4)

During exploratory laparotomy, specimens were taken from the liver and kidney. Microscopic examination of the liver disclosed a fairly normal liver

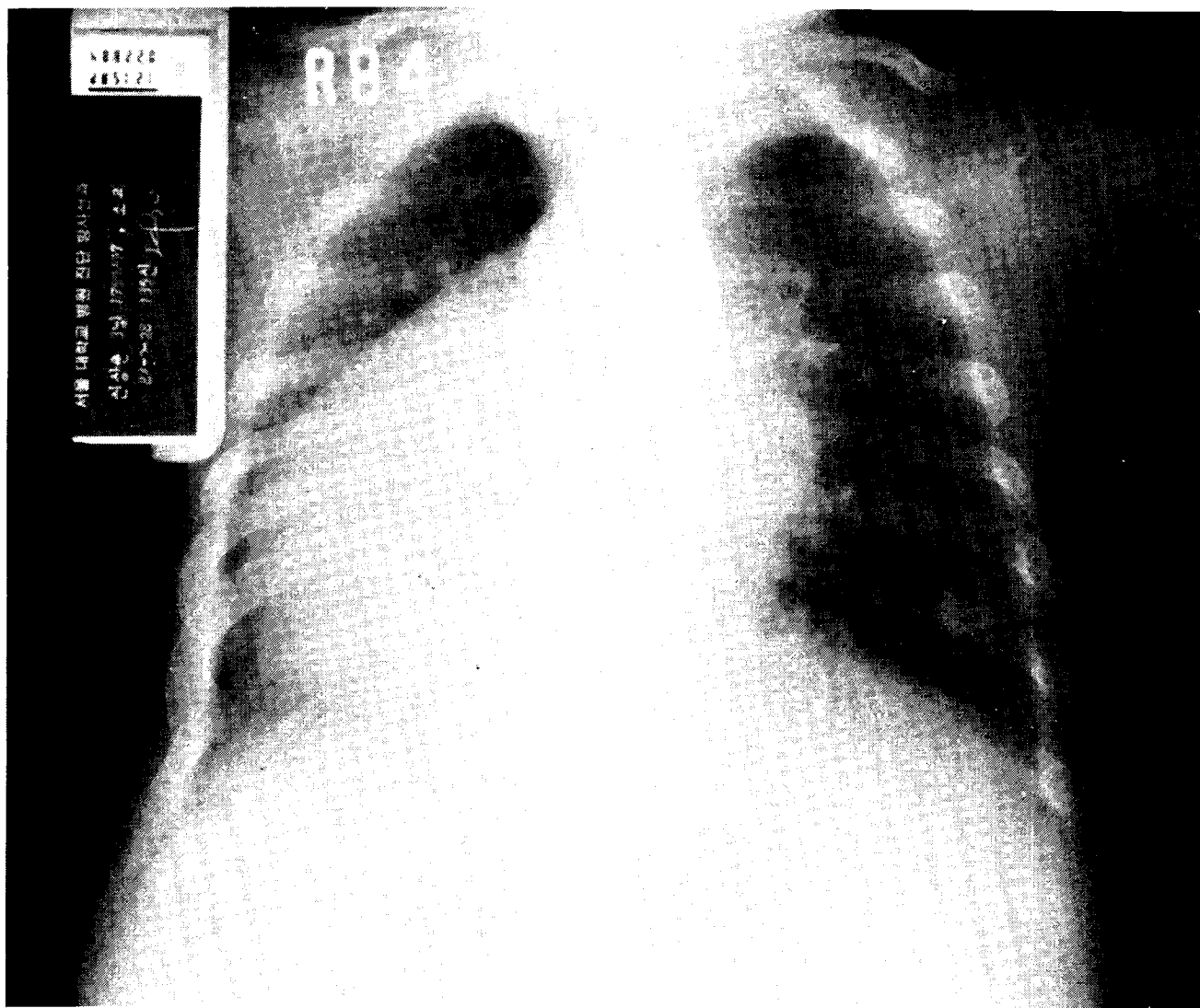


Fig. 4. Chest P-A taken with barium swallowing shows right sided heart with cardiomegaly and right sided stomach.

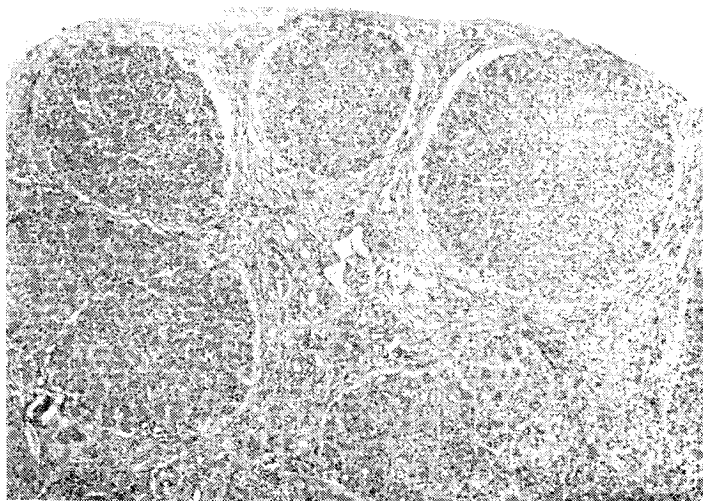


Fig. 5. Liver wedge biopsy showing round liver lobules separated by broad continuous bands of mature collagenous tissue. H & E, X25. Case 2.

parenchyma that was intersected by broad bands of fibrous tissue containing an increased number of bile ducts. One lobule or a part of a lobule was

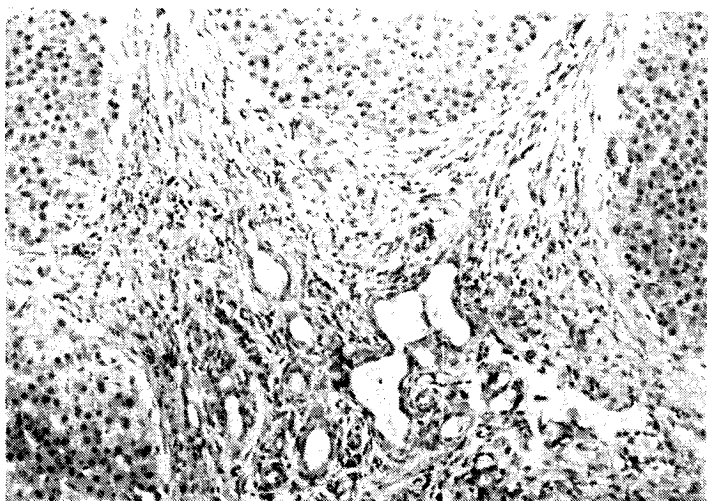


Fig. 6. Higher magnification of the liver, revealing round margin of liver lobules and mature collagenous connective tissue with minimal inflammation and cell infiltration. H & E, X100. Case 2.

enmeshed in continuous strands of mature collagen fibers. The fibrosis did not disturb lobular

architecture. Numerous uniform bile ducts were scattered in the fibrous tissue, which were slightly dilated with focal bile pluggings. On kidney sections most of the glomeruli were globally obsolescent showing periglomerular fibrosis and ischemic wrinkling of glomerular tufts. Some glomeruli revealed prominent epithelial cells with fibrocellular crescent formation. Tubules underwent focal cystic dilatation in several areas. In these areas the affected tubules were convoluted tubules and were characterized by irregular tubular ectasia lined by flat or cuboidal epithelial cells. They were surrounded by mature fibrous tissue. The lumens were characteristically empty. Moderate to marked interstitial round cell infiltration and fibrosis, hyaline arteriolar thickening were also seen (Fig. 5,6,7,8).

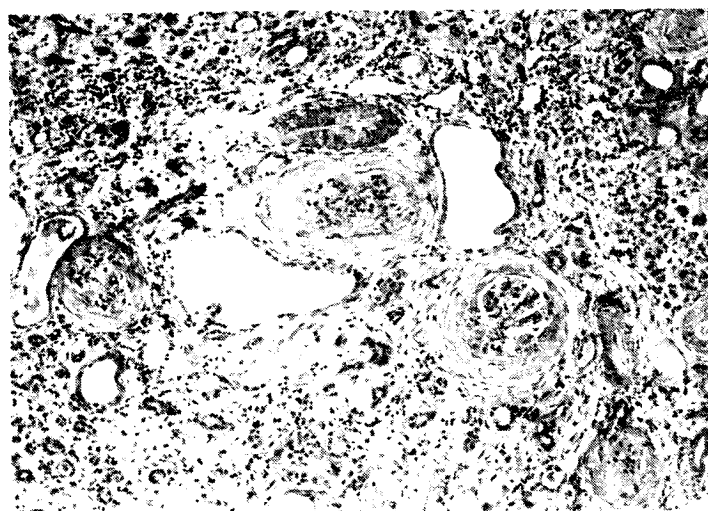


Fig. 7. Kidney biopsy, showing glomerular change, interstitial fibrosis and cystic dilation of the tubules. H & E, X100. Case.

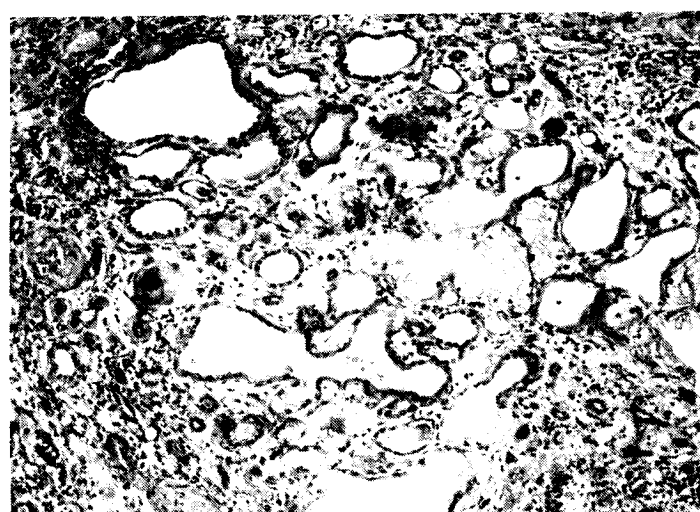


Fig. 8. Another area in the kidney, showing multiple cystic changes of the convoluted tubules together with interstitial fibrosis. H & E, X100. Case 2.

He was discharged on April 23, 1984, with the final diagnosis of situs inversus, congenital hepatic fibrosis and renal failure due to nephronophthisis. One month later, he was readmitted because of loss of consciousness and expired of superimposed acute renal failure.

Case 3. Choi, W.J.: A 9 9/12 year old boy was referred to the SNU Children's Hospital on October 18, 1985, because of splenomegaly. He had been healthy until 2 days prior to admission, when he was given a blow on left upper quadrant of the abdomen, which was followed by pain at that area. So he visited a local clinic, where huge splenomegaly was found on ultrasonic examination.

He was adopted at 3 years of age, and the past and family histories were not contributory. On physical examination, he was alert with the blood pressure of 110/70 mmHg, the heart beat of 84/min, the respiratory rate of 24/min. The sclerae were not icteric. The lungs were clear. The abdomen was slightly distended. The liver was not palpable, but the spleen was palpable 6 cm below the left subcostal margin. The extremities were normal.

Laboratory examination revealed the hemoglobin 12.9 gm/dl, the white-cell count $2,700/\text{mm}^3$ and the platelet $62,000/\text{mm}^3$. Urinalysis was normal with good concentrating ability. The blood chemistries were the albumin 4.8 gm/dl, the glutamic oxaloacetic transaminase 15 IU/l, the glutamic pyruvic transaminase 10 IU/l, the alkaline phosphatase 150 IU/l, the urea nitrogen 14 mg/dl, the creatinine 0.8 mg/dl. Splenic angiography revealed nothing abnormal except marked splenomegaly. The intravenous pyelogram was normal and varices were not demonstrated on esophagogram.

Exploratory laparotomy showed firm but not enlarged liver with somewhat irregular surface. No evidence of splenic or portal vein thrombosis was present. A liver wedge biopsy and splenectomy were done. Microscopically the liver showed well preserved lobular architecture with prominent portal and periportal fibrosis. The increased connective tissue consisted of mature collagen and showed a sharp demarcation from surrounding liver parenchyme. It contained well formed round bile ducts in the middle, associated with a mild to moderate mononuclear inflammatory cell infiltration. The bile ducts were increased in number and varied slightly in size and shape. They were lined by well formed, non-proliferating cuboidal cells, and the lumen was empty in all. No evidence of cholangitis was present. Portal vein tributaries in portal spaces were

slightly dilated but did not appear to be specially scarce. Hepatic artery branches were unremarkable. The central veins were normal. Hepatic cell plate was of single, and sinusoidal structures were all normal. The spleen weighed 600 gms. Histologically the red pulps were mostly effaced and the white pulps expanded. The sinuses were dilated and numerous myeloid cells were seen, indicating hypersplenism. The lymph nodes from mesentery were unremarkable (Fig. 9, 10).

He was discharged on November 5, 1985. Now

he is on follow-up with monthly benzathin penicillin injection.

DISCUSSION

Congenital hepatic fibrosis may occur as an isolated anomaly, but one peculiar picture of this disorder is its frequent association with diverse lesions of the kidneys, and occasional concurrence with other hepatic abnormalities (Fig. 11) and this fact has led to question whether the congenital hepatic fibrosis is a distinct entity (Murray-Lyon *et al.* 1973). Some authors assume renal involvement in as much as 100 percent (Alvarez *et al.* 1981), while by Sommerschild's review (1973) it was noted in 30-70% of cases.

Classically congenital hepatic fibrosis is known to present with hepatosplenomegaly and later gastrointestinal bleeding. But, in patients associated with polycystic kidney disease, the renal manifestations may predominate and mask the hepatic symptoms. In general the renal lesion is more important in the newborn and infants, whereas the hepatic lesion dominates the picture in older children and adolescents. But if the patient does not develop the severe renal lesions of younger childhood type, he survives and develops symptoms due to the liver lesion. Hematemesis or enlargement of the liver are the two most common initial symptoms (Kerr *et al.* 1961, Sommerschild *et al.* 1973). Portal hypertension is found in 70% of cases (Sommerschild *et al.* 1973). Classically affected patients are asymptomatic until the age of 5 years or more when portal hypertension may lead to gastrointestinal hemorrhage. In some patients the first hemorrhage from varices may be delayed until the age of 30 years (Sommerschild *et al.* 1973, Murray-Lyon *et al.* 1973). Recently, less typically manifested cases are accumulating including those with portal hypertension in neonatal period (Ghishan and Younoszai 1981), or presented as cholangitis (Alvarez *et al.* 1981, Caine *et al.* 1984).

Although our patients showed typical congenital hepatic fibrosis pathologically, the clinical presentations were quite different. Case 1 presented with clinical signs of portal hypertension as he showed hepatomegaly followed by splenomegaly in relatively early age. Later jaundice and cachexia developed, indicating hepatic dysfunction. In this patient, though not confirmed by histological examination of renal tissue, the persistently low osmolarity of the urine indicated a strong sugges-

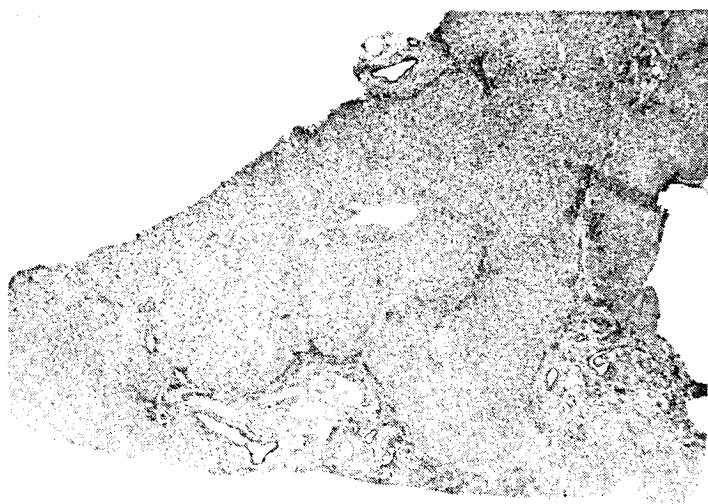


Fig. 9. Liver wedge biopsy showing punctate areas of portal widening and fine connective tissue bands extending from portal to portal tracts, associated with bile duct proliferation. H & E, X25. Case 3.

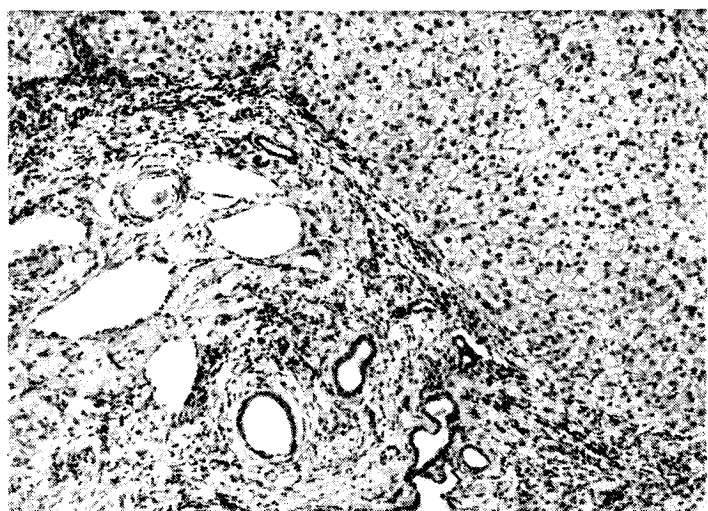


Fig. 10. Higher magnification of Fig. 9, revealing round margin of well preserved liver lobule. The portal fibrous tissue is mature and is associated with mild chronic inflammatory cells. Microcystic dilatations of vascular channels and bile ducts are also seen. H & E, X100. Case 3.

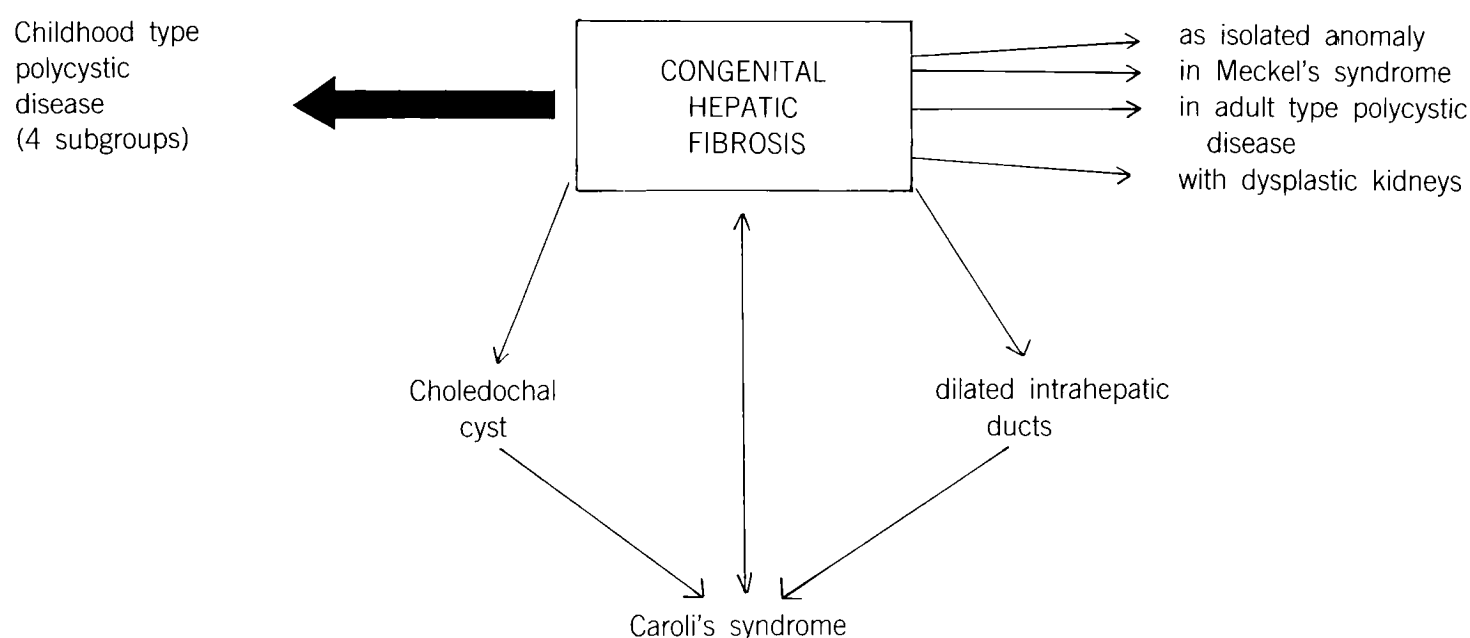


Fig. 11. Diagram illustrating the spectrum of diseases associated with congenital hepatic fibrosis and the possible relationship with Caroli's syndrome. (from Murray-Lyon *et al* 1973).

tion for coexistence of renal abnormality (Anand *et al.* 1975). Case 2 was unique that he was associated with situs inversus which has not been reported previously to be associated with congenital hepatic fibrosis. In case 3, splenomegaly was detected incidentally when examined due to abdominal pain following trauma. He didn't have a history of hepatomegaly and the liver function tests were completely normal, but he showed hepatic fibrosis on biopsy performed during exploratory laparotomy. Though there were no history of bleeding from varices and no varices on the esophagogram, the splenomegaly suggested the presence of portal hypertension.

The mechanism of portal hypertension in congenital hepatic fibrosis is not exactly known. There is a thought taht it is due to hypoplasia of the portal vein radicals of the liver (Sommerschild *et al.* 1973). The portal hypertension is presinusoidal. Biochemical evidence of hepatic failure is uncommon. Serum transaminases are usually normal or mildly elevated, but serum alkaline phosphatase is frequently elevated. But the incidence of hepatic failure increases as the length of follow-up increases, particularly after porta-caval shunt operation (Kerr *et al.* 1978). In those with splenomegaly, hematologic manifestation of hypersplenism such as thrombocytopenia with or without neutropenia may develop (Alvarez *et al.* 1981). Our three patients all had thrombocytopenia, and two, neutropenia. Patients with renal involvement may show

progressive uremia in the first year of life or may show functional impairment limited to concentrating defects and aminoaciduria (Kerr *et al.* 1961, Blyth and Ockenden 1971).

If hepato- or hepatosplenomegaly is found, the possibility of congenital hepatic fibrosis should always be considered. Alvarez *et al.* (1981) suggest that it is now feasible to get a correct diagnosis of congenital hepatic fibrosis in children using clinical, biological, and non-invasive radiological data before employing liver biopsy, particularly in early childhood when children presenting with polycystic kidney (infantile type) and hepatomegaly can probably have nothing other than congenital hepatic fibrosis. In difficult cases, more invasive tests may be necessary such as endoscopy, cholangiography or laparoscopy.

Reduction in kidney function occurs, but apart from kidney transplantation in special cases, there is little that can be done medically. A reasonable policy, as far as the management of congenital hepatic fibrosis goes, may be to treat patients under 15 or 16 years of age conservatively if possible and to consider shunt operation in patients over this age where portal hypertension has been confirmed even when the patient has never had a hemorrhage (Sommerschild *et al.* 1973). Shunt surgery gives good results in control of bleeding and hypersplenism. According to Kerr *et al.* (1978), shunt operations, performed in 18 patients, were successful in controlling hemorrhage with a low

mortality (1/18), low incidence of recurrent hemorrhage (3/18) and portal-systemic encephalopathy (3/18), but with a higher incidence of postoperative jaundice (7/18). About a third of the survivors had some evidence of hepatic dysfunction but none had chronic portal systemic encephalopathy.

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= 국문초록 =

선천성 간섬유증 3예

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선천성 간섬유증은 소아기 및 청년기에 발현하며, 간 비대, 문맥압 항진증이 있으나 간실질 및 간기능은 비교적 잘 유지되며, 신장질환이 자주 동반되는, 비교적 드문 질환이다.

저자들은 최근 발현양상이 서로현저하게 다른 3예의 선천성 간섬유증을 경험하였다. 1예는 2년 2개월된 여아로서 간비대에 이어 비의 비대로 발현하였으며, 정맥 신우촬영술은 정상 소견이었으나 뇨농축기전에 장애가 있어 신질환의 동반이 의심되었다. 또 1예는 2년 8개월된 남아로 내장 좌우 역전증, 요독성 신수질 낭성질환(uremic medullary cystic disease or nephronophthisis)이 동반되었다. 나머지 1예는 9년 9개월된 남아로 간비대없이 비장의 비대만 관찰되었다. 3예 모두 비의 비대가 있었으나 식도 조영술상 정맥류는 관찰되지 않았으며 토혈, 혈변의 병력은 없었다.