CONGENITAL HEPATIC FIBROSIS IN A FEMALE EURASIAN CHILD

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Congenital Hepatic Fibrosis is a rare condition; 94 cases have been reported in the literature (McCarthy et al., 1965). MacMahon (1929) first noticed a congenital anomaly of the liver characterised by dense, mature fibrosis and bile-duct hyperplasia, associated with congenital cystic kidneys. In 1961, Kerr et al. described 13 cases of congenital fibrosis of the liver and coined the term "Congenital Hepatic Fibrosis" to describe what is now recognised as a distinct clinico-pathological entity.

We report a case of Congenital Hepatic Fibrosis in a female Eurasian child who was first seen at the age of 17 months and found to have an unexplained hepatomegaly. The diagnosis was made at liver biopsy by one of us (TKK) and the patient was followed up till her death at the age of four years. This is the first reported case in Singapore.

CASE REPORT

S. F., a 17 month old female Eurasian child, was first admitted to General Hospital, Singapore, in September, 1963 with a three day history of fever and fits. She was found to be in good general condition. Her temperature was 102°F; her tonsils were enlarged and inflamed. The liver was enlarged four fingers' breadth below the right costal margin. No other abnormalities were detected on clinical examination. Her cerebro-spinal fluid and liver function tests (ICD 480 units; SGOT 66 units; SGPT 31 units; Serum Protein 6·8 Gm.%, Serum Albumin 4·0 Gm.% and Serum Globulin 2·8 Gm.%) were within normal limits. She was given Syrup Chloramphenicol and Paracetamol and was discharged four days later.

She was readmitted in June, 1964 for pharyngitis and fits. She improved with Tetracycline and Paracetamol.

Two weeks later she was again admitted into hospital for hyperpyrexia. She was found to be anaemic (haemoglobin 54%). The liver was still enlarged two fingers' breadth below the right costal margin. The right kidney was palpable; an I. V. P. showed bilateral enlargement of the kidneys. A needle biopsy of the liver was inconclusive, showing normal liver cells around a central vein with mild bile duct proliferation and some periportal fibrosis. Ten days after admission, she was still febrile and the liver was found to be larger (four fingers' breadth below the right costal margin) and very tender. To exclude a liver abscess, peritoneoscopy by Mr. K. T. Chan was carried out. No abscess was found; the liver was enlarged, very firm in consistency and the surface appeared mottled with red and white stipplings and furrows. The gall-bladder and both kidneys were enlarged. A liver biopsy was again done and histology showed periportal round cell infiltration, increased fibrosis, brisk bile duct reduplication and normal liver cells. A diagnosis of Congenital Hepatic Fibrosis was then made. Despite treatment with various antibiotics, the fever persisted. Blood cultures were repeatedly negative; urine culture grew *E. coli* sensitive to Chloramphenicol, Streptomycin, Neomycin and Kanamycin. The fever finally subsided after five weeks of parenteral Kanamycin.

The patient was again admitted on 24.4.65 to 30.4.65 for bronchitis and on 27.5.65 to 10.6.65, and on 13.7.65 to 16.7.65, for pharyngitis. A month later she was again hospitalised for fever and anorexia. On clinical examination, she was found to be anaemic and there was detected for the first time an enlarged spleen four fingers' breadth below the left costal margin, as well as ascites. The liver was further enlarged, down to the level of the umbilicus. Urine culture grew *A. aerogenes* and *B. proteus*. She was treated with parenteral Streptomycin, then Furadantin, and finally parenteral Colistin after which the fever subsided.

She was admitted to hospital for the last time in October, 1965 for fever and diarrhoea. The liver and spleen were about the same size as at the last admission; both kidneys were palpable, the right being larger than the left. Ascites was more marked. Serum electrophoriesis showed some abnormality:—total protein was 7·1 Gm. %, albumin 1·2 GM. %, alpha$_1$ globu-

lin 0·5 Gm. %, alpha$_2$ globulin 1·0 Gm. %, beta globulin 0·5 Gm. % and gamma globulin 4·1 Gm. %. Other liver function tests and the blood urea level were within normal limits. Urine culture grew at various times *B. proteus*, *E. coli*, *A. aerogenes*, *Staph. albus*, *Ps. pyocyaneae* and *Monilia*. Blood culture was still negative. Repeated abdominal taps were done to relieve discomfort. She was given Furadantin and Paracetamol with no effect. She was then given parenteral Kanamycin for five weeks after which the fever subsided. For the next three weeks she remained afebrile and then her fever started to swing and persisted despite treatment with various antibiotics. In may, 1966, she was noticed to be jaundiced for the first time. Her general condition continued to deteriorate and on the sixth of June, 1966, she suddenly became very dyspnoeic and drowsy and died soon after.

NECROPSY FINDINGS

The pericardial cavity contained some straw-coloured fluid and the peritoneal cavity about 4,000 c.c. of a similar fluid. There were some recent fibrinous peritoneal adhesions. The liver was markedly enlarged, weighing 1,585 gm. and on its surface there was a fibrinous deposit (Fig. 1). Very hard in consistency, the liver sectioned with difficulty revealing a densely fibrotic parenchyma with marked bile staining, dilated bile ducts, congestion and prominence of the hepatic vessels. Unlike in cirrhosis, the fibrosis was distributed haphazardly. There was an old, white, adherent thrombus, about 1·5 cm. long, in the portal vein (Fig. 2). The gall-bladder was dilated but no obstruction in the extrahepatic bile ducts was found. The spleen was also markedly enlarged, weighing 492 gm.; section showed several infarcted areas. The infarcts were mostly subcapsular, except for a string of five irregular infarcts on the medial aspect of the spleen, probably related to branches of one large vessel (Fig. 3). All lymph nodes, especially those in the porta hepatis and retroperitoneal region, were increased in size, vascular, soft and discrete. Both kidneys appeared enlarged, the left weighed 220 gm., the right 212 gm.; the capsule stripped with some difficulty revealing remnants of foetal lobulation and multiple subcapsular abscesses. The largest abscess, 3·6 cm. × 2·5 cm., was found in the right kidney. The bladder was markedly congested and showed some petechial mucosal haemorrhages. Both lungs were oedematous and congested; the left weighed 240 gm., the right 255 gm. Other systems appeared grossly normal.

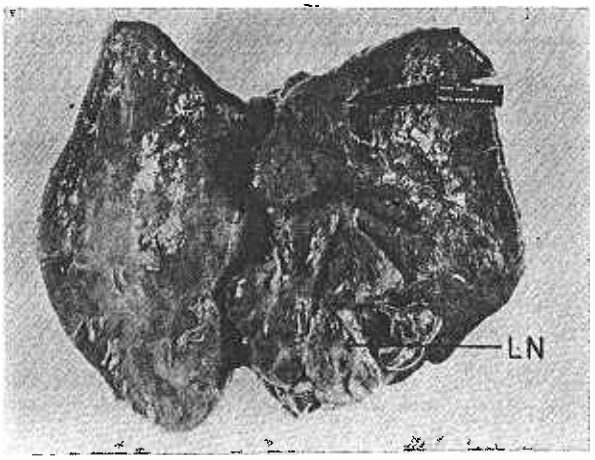

Fig. 1. Liver showing marked enlargement and surface deposits of fibrin. Note the enlarged lymph nodes in the porta hepatis (LN).

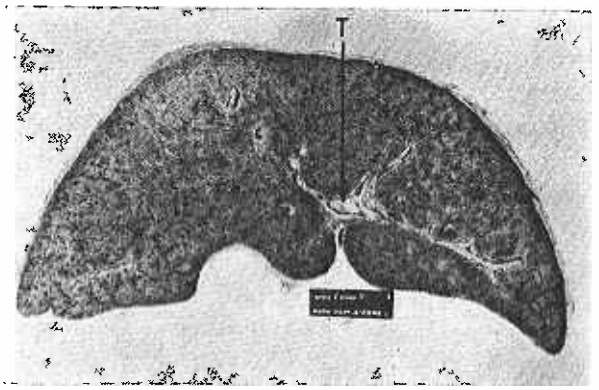

Fig. 2. Section of liver showing mottling, dilated bile ducts and hepatic vessels, and thrombus within the portal vein (T).

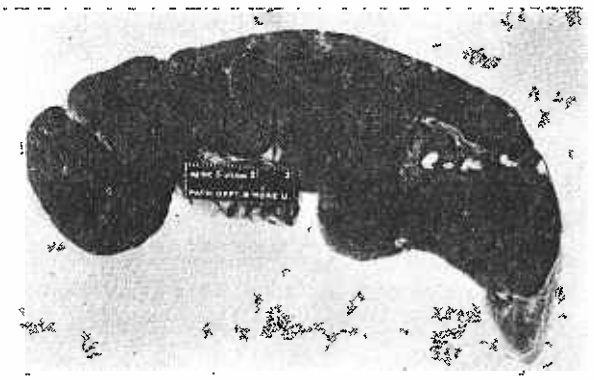

Fig. 3. Spleen showing marked enlargement and several infarcted areas, mostly subcapsular. Note string of five irregular infarcts in close relation to a large vessel at the right of the picture.

HISTOLOGICAL FINDINGS

The liver showed a vast increase in periportal connective tissue which surrounded individual liver lobules. The latter were sharply demarcated from the fibrotic bands by a limiting plate. There was no destruction of the liver architecture and no regenerating nodules of liver cells; in other words, there was no cirrhosis. The connective tissue consisted of mature

collagen fibres and within it were found briskly proliferating bile ducts, some of which were widely dilated and lined by tall columnar epithelium (Fig. 4). There was also an infiltrate of inflammatory cells, mostly polymorphs and lymphocytes, in the periportal areas and within some of the larger bile ducts (Fig. 5). No bile stasis was present. The portal vein showed an organising thrombus.

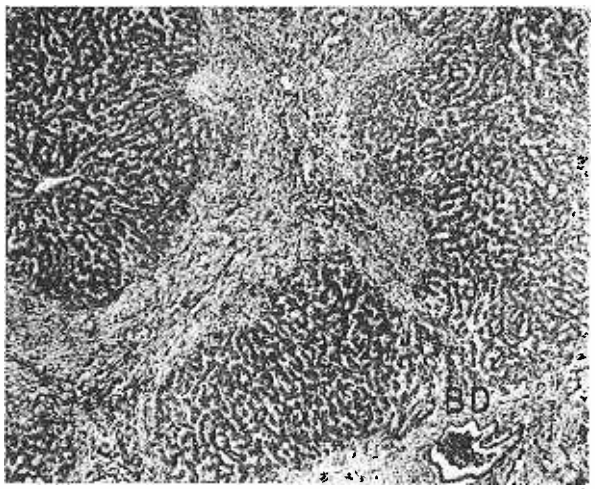

Fig. 4. Photomicrograph of the liver showing increased periportal fibrosis surrounding individual liver lobules and sharply demarcated from them by a limiting plate. One of the liver lobules shows a central vein (CV). Within the connective tissue are proliferating bile ducts, some of which are widely dilated (BD). Note the infiltrate of inflammatory cells, mostly polymorphs and lymphocytes, in the periportal areas and within the dilated bile ducts. (H & E × 45)

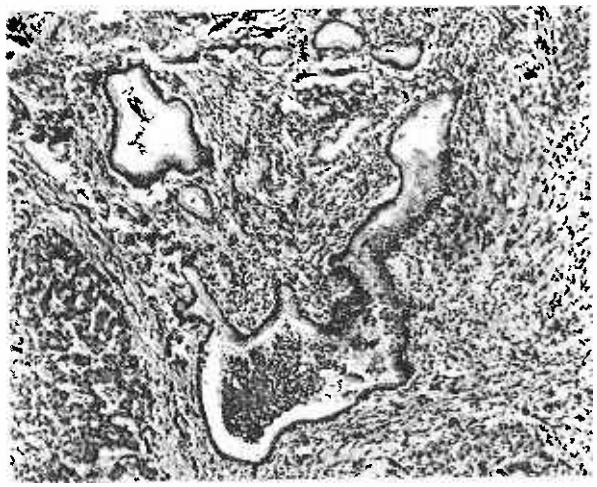

Fig. 5. Photomicrograph of the liver showing dilated bile ducts and infiltrate of polymorphs in the connective tissue and within one of the dilated bile ducts. (H & E × 75)

The spleen showed areas of infarction, and in the pulp were found numerous plasma cells and a sprinkling of polymorphs. All the lymph nodes sectioned showed reactive hyperplasia.

The kidneys showed severe infiltration by polymorphs in the interstitial tissue and within the tubules (Fig. 6). In the former situation, microabscesses were also seen. There were some "thyroidisation" of tubules and some periglomerular sclerosis. A large number of tubules showed cystic dilatation (Fig. 7). These were interpreted as ectasia rather than actual cyst formation.

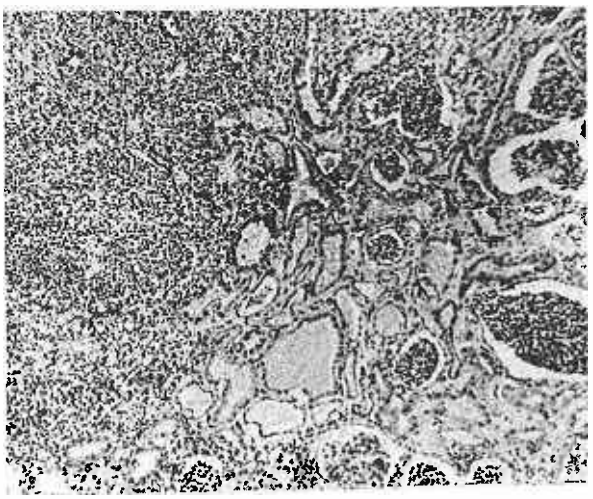

Fig. 6. Photomicrograph of the kidney showing marked infiltration of polymorphs in the interstitial tissue and within the tubules. (H & E × 75)

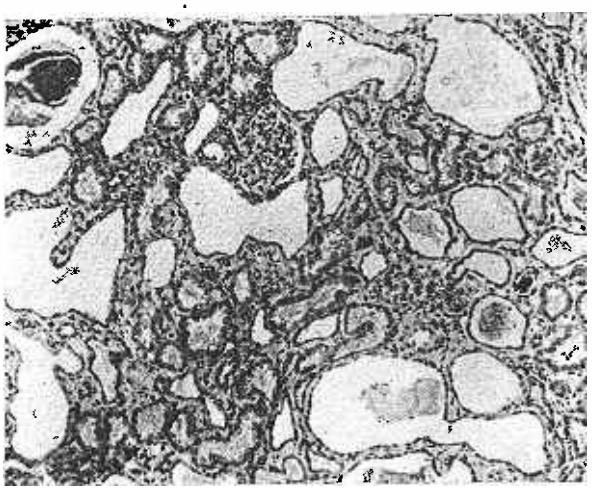

Fig. 7. Photomicrograph of the kidney showing dilated tubules some of which contain proteinaceous casts. (H & E × 75)

The pulmonary alveoli were filled with oedema fluid and some macrophages. The alveolar septae were thickened by an infiltrate of round cells, mostly lymphocytes.

In summary, the principal findings were 1) Congenital Hepatic Fibrosis 2) Portal Vein Thrombosis 3) Ascites 4) Cystic Disease of the Kidneys 5) Septicaemia and 6) Viral Pneumonia (probably terminal). Septicaemia was manifested by the presence of a) Acute-on-Chronic Cholangitis b) Acute-on-Chronic Pyelonephritis c) Septic Infarcts of Spleen and d) Reactive Hyperplasia of lymph nodes.

DISCUSSION

Histopathology

The histological picture of Congenital Hepatic Fibrosis is fairly distinct. It consists of:—

1. normal lobular architecture of the liver which may be distorted but not disrupted.
2. increased amounts of mature collagenous tissue in the portal areas. These fibrous bands completely surround the liver lobules. There is no hyalinisation or conglutination of this connective tissue such as can be found in cirrhosis.
3. the junction between liver cells and fibrous tissue is sharp. Destruction of this limiting plate is an important change in established cirrhosis.
4. within the fibrous tissues are found increased numbers of bile ducts of varying sizes. These bile ducts may be dilated but never form cysts.
5. there are no regenerating nodules of liver cells, one of the principal features of cirrhosis.
6. there is hypoplasia of the branches of the portal veins. Kerr et al. (1961) and Parker (1956) believe that this is the cause of the portal hypertension which commonly complicates this condition.

Our case meets all the above criteria, except the last. Portal hypertension was not a feature of our case except terminally and possibly the portal vein thrombosis was contributory.

Clinical Features

Congenital Hepatic Fibrosis usually manifests during the first two decades of life. The common presenting features are abdominal distension (secondary to hepatomegaly) with or without splenomegaly, and portal hypertension. The patient is usually in good general condition and has normal liver function. Sometimes, however, the alkaline phosphatase level may be raised, the cause of which is not known. Williams et al. (1964) found some anomalies of the extra-hepatic bile ducts and suggested that these are the cause of the raised alkaline phosphatase level. However, this is not a common finding. We feel that the progressive periportal fibrosis must result in death of the peripheral liver cells, thus accounting for the sporadic raised alkaline phosphatase level. Parker (1956), Campbell et al. (1958), Haas (1960) and Kerr et al. (1961) noted that these patients are very susceptible to infections. Indeed, septicaemia is a common event. Jaundice does not usually occur and its presence may indicate complications such as cholangitis (McCarthy et al., 1965), abnormality of the larger bile ducts (Kerr et al., 1961, Krainer, 1957) and cholangiocarcinoma (Parker, 1956). The latter complication is very unusual. Liver failure is rare and has only been described in two cases by Kerr et al. (1961). More usually the patient succumbs to renal failure secondary to the polycystic kidneys which are commonly associated with Congenital Hepatic Fibrosis (Parker, 1956, Hickie et al., 1962, Kerr et al., 1962), or to the complications of portal hypertension (Parker 1956, Kerr et al. 1962, Hardin 1965).

Our patient was first seen at the age of 17 months for tonsillitis; at this time hepatomegaly was noted and diagnosis was only made by a liver biopsy. She was repeatedly admitted to hospital for urinary and upper respiratory tract infections. Terminally she developed jaundice and ascites, sequelae not hitherto reported in cases of Congenital Hepatic Fibrosis. Her jaundice was due to cholangitis, and her ascites probably due to the hypoproteinaemia and portal vein thrombosis. A chronic septicaemic state with superimposed viral pneumonia finally killed her.

Associated Findings

Congenital Hepatic Fibrosis is commonly associated with polycystic kidneys and was thus once thought to be a variant of congenital cystic disease of the liver. Kerr et al. (1962) claim that this is not so in that macroscopic cysts are not found in the liver though sometimes dilated bile ducts are seen histologically. Further, the kidney lesions are different from those seen in classical polycystic disease. In our case no macroscopic cysts were seen in the liver or the kidneys. On microscopy, however, dilated bile ducts and cystically dilated renal tubules were found.

Other associated anomalies that have been described are meningocoele, cleft palate, congenital dislocation of the toes (Parker, 1956), solitary cysts of the liver (Haas 1960, Kerr et al. 1961, Kerr et al. 1962), choledochal cyst and solitary cyst of the head of the pancreas (Kerr et al., 1961), malformation of the bile ducts (Krainer, 1957, Kerr et al. 1961, Williams et al. 1964), cerebral aneurysm, laryngeal atresia, centrilobular and diffuse emphysema of the lungs (Williams et al., 1964) and cavernous portal vein (Tewarson et al., 1964).

Race, Sex and Familial Distribution

The majority of cases reported are from Western countries. Reddy et al. (1965) described three cases in India.

A review of the literature shows that there is a fairly distinct female preponderance (Morales 1965, McCarthy et al., 1965). An analysis of the papers by Parker 1956, Campbell et al. 1958, Haas 1960, Kerr at al. 1961, Hickie et al. 1962, Kerr et al. 1962, Boley et al. 1963, Tewarson et al. 1964, Morales 1965, Hardin 1965 and Reddy et al. 1965 showed that of a total of 39 cases, 25 were female. Our case is also a female.

Congenital Hepatic Fibrosis has been reported in siblings by Kerr et al. (1961), Sweetnam and Sykes (1961), Campbell et al. (1958) and Hardin et al. (1965). It has also been described in successive generations by Hickie et al. (1962). There is no family history in our patient. The presence of this condition in both males and females suggest that it is not sex-linked. Hickie et al. (1962) states that it is due to a dominant gene with variable penetrance and expressibility.

Prognosis and Treatment

Unlike cirrhosis of the liver with portal hypertension where the prognosis on the whole is very poor, patients with Congenital Hepatic Fibrosis usually respond well to shunting operations, the reason being that the liver function is normal and the portal vein usually patent. It should however, be noted that the portal vein and even the splenic and mesenteric veins may be thrombosed (Kerr et al., 1961). In our case there was portal vein thrombosis. Anderson (1966) claims that one of the factors which may contribute to the occurrence of portal vein thrombosis is swelling of the periportal lymph nodes. In our case the lymph nodes of the porta hepatis were markedly enlarged and these probably were the cause of the portal vein thrombosis.

The operative procedures that are usually done are a portocaval or a splenorenal shunt. The former has been found to be more effective and Boley et al. (1963) claim that it offers permanent cure. Hardin et al. (1965), however, believe that a superior mesenterico-caval shunt is superior in that the operation is easier to do in the presence of gross hepatomegaly, the operation field is exposed through a midline incision, bleeding is less and the collaterals already established are left undisturbed.

SUMMARY

The first Singapore case of Congenital Hepatic Fibrosis occuring in a four year old Eurasian girl is presented. The patient was first seen at the age of 17 months with tonsillitis and febrile fits and was then noted to have an enlarged liver. Diagnosis was made by a liver biopsy and the patient was followed up till her death from septicaemia at the age of four.

The clinical presentation, histopathology and treatment of this rare condition are discussed. The importance of differentiation of this treatable disease from juvenile cirrhosis is stressed.

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