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Congenital hepatic fibrosis—unusual presentations

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SUMMARY Two children with congenital hepatic fibrosis presented atypically: one with prolonged fever and hepatomegaly associated with a giant intrahepatic biliary cyst and a second with ascites at an early age despite normal serum albumin concentrations.

Congenital hepatic fibrosis usually presents within the first two decades of life, with hepatosplenomegaly and gastrointestinal bleeding due to portal hypertension and normal or near normal liver function tests. We present two children with unusual presentations of this disorder; the first with complications associated with a large intrahepatic biliary cyst and the second with ascites.

Patients

Case 1. A 9 year old Moslem boy, previously healthy, was admitted with a three month history of prolonged fever and abdominal enlargement. He had been treated elsewhere with antibiotics, with no improvement except a decrease in fever.

On examination the child was lively, without jaundice or fever. The abdomen was enlarged with increased venous markings. The liver was palpable nine cm and the spleen two cm below the costal margins with no evidence of ascites. Otherwise the physical examination was unremarkable. Laboratory tests on admission showed a moderately increased erythrocyte sedimentation rate, and a normal complete blood count. All liver function tests

were within normal limits, as were serum urea and creatinine, coagulation tests, bone marrow smears, sweat test, urine analysis, and serological screening for parasites.

Renal ultrasound study showed increased echogenicity of pyramidal regions and intravenous pyelogram showed homogenous enlargement of both kidneys with normal collecting systems. A liver-spleen technetium sulfur colloid scan showed gross enlargement of both organs, with a large round defect of the right hepatic lobe. Hepatic ultrasound showed a cystic formation with septae (Fig. 1). A HIDA (Tc-99m-dimethyl-imino-diacetic acid) biliary excretion study showed concentration of the labelled material within the cyst thus proving connection with the biliary tree (Fig. 2). Portal

Fig. 1 Ultrasound scan of the liver (case 1) showing a large septate cyst in the right lobe.

Fig. 2 HIDA biliary excretion study showing; above, accumulation of labelled material in the biliary cyst above, and below, excretion into the intestine.

angiography showed the filling defect to be avascular with no evidence of portal hypertension.

On laparotomy, a large, very hard, coarsely granular liver was found, with a large cyst 10 cm in diameter from which 100 ml of clear yellow fluid were drained. Liver biopsy showed an increased number of irregularly shaped bile ducts, with nodularity of the liver parenchyma accentuated by fibrous septae, typical of congenital hepatic fibrosis. Kidney biopsy showed tubular ectasia with formation of small cysts. The patient made an uneventful recovery and for six months was asymptomatic: he was, however, lost to long term follow up.

Case 2. A 3 year old girl of Druse origin was admitted with hepatosplenomegaly and ascites. An older brother aged 13 years had died with gastrointestinal bleeding secondary to a 'chronic liver disease'. Seven other siblings were normal. At age 16 months she had been diagnosed as having 'cirrhosis'. Except for a distended abdomen, she was otherwise healthy. Physical examination on admission disclosed a distended abdomen with noticeable ascites. The liver was very hard and palpable below the right costal margin with an 11 cm span. The spleen edge was four cm below the left costal margin. Laboratory tests showed a haemoglobin concentration of 10.3 g/dl, white blood count $3.0 \times 10^9/l$, thrombocytes $114.0 \times 10^9/l$, prothrombin time 50%, and partial thromboplastin time 61 seconds. Serum electrolytes, kidney and liver

functions, and immunological tests were normal. Paracentesis showed a transudate with normal lipid values.

Liver-spleen technecium sulfur colloid scan showed hepatomegaly with diffuse, irregular uptake and an enlarged spleen. Intravenous pyelogram was normal, and a barium study showed no oesophageal varices. Open liver biopsy showed portal areas with increased bile ducts and fibrosis. The bile ducts were irregularly shaped and covered by non-proliferating cuboidal or columnar epithelia. The fibrosis extended into the parenchyma accentuating the liver nodularity. A small number of lymphocytes were found scattered in some of the fibrous septa. A review of the brother's biopsy results from another hospital showed similar findings, all typical of congenital hepatic fibrosis. The patient remained stable for the next three years on oral diuretic treatment but was then lost to follow-up.

Discussion

Congenital hepatic fibrosis was first named and described in detail by Kerr *et al* in 1961¹ and since then approximately 150 cases have been published, with a variety of clinical pictures. Presenting usually within the first two decades of life, the patient is generally in good health, with well preserved liver function tests.^{1 2} The most common presentation is hepatosplenomegaly and later gastrointestinal bleeding with one third to one half of patients presenting as such, often many years before the development of other complications.^{1 2}

Liver function tests are usually normal, jaundice is rare, and the patient feels well. As in our case 1, the kidney is commonly affected, being present in approximately 60% of cases as infantile polycystic kidney disease or medullary sponge kidney.² Usually signs of liver disease precede clinical evidence of renal disease.² Infantile polycystic kidney disease or medullary sponge kidney, however, in the presence of portal hypertension, hepatosplenomegaly, and normal or near normal liver function tests, suggest congenital hepatic fibrosis.^{1 2}

Our first patient presented atypically with symptoms of persistent cholangitis and was noted to have hepatosplenomegaly on examination. The large cyst was found by technecium scan, and by HIDA was seen to be connected to the biliary tree. We believe this to be the first case of congenital hepatic fibrosis described with a very large solitary intrahepatic biliary cyst, although there is an association with choledochal cysts.³ Cholangitis is infrequently associated with congenital hepatic fibrosis, as opposed to Caroli's disease in which it is relatively common. It has been described previously in chil-

dren with cystic dilatation of the biliary cyst and resultant bile stasis.^{4 5} This would explain the prolonged fever and response to antibiotics.

Ascites, especially as a presenting sign, is extremely rare. It is present in only 15% of reported cases, and in these it was found only four to 29 years after the patients were first seen. Only in one other case, in the published reports known to us, has ascites associated with congenital hepatic fibrosis been described in early childhood.⁶ The mechanism of ascites in our patient is unclear, especially in the light of normal serum protein concentrations. These two patients show the varied clinical picture of congenital hepatic fibrosis while adding two further presentations to those already described.

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Plasma C peptide in hyperinsulinaemic hypoglycaemia

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SUMMARY We describe two children with hypoglycaemia due to pancreatic beta cell hyperactivity. Both had low serum insulin but raised plasma C peptide concentrations when hypoglycaemic. Measurement of C peptide is valuable in the diagnosis of hyperinsulinaemic hypoglycaemia in children.

Hyperinsulinaemia is the most common cause of hypoglycaemia presenting in the first year of life after the neonatal period.¹ Serum insulin should be undetectable during severe hypoglycaemia and this forms the basis for the diagnosis of hyperinsulinism.²

C peptide is cleaved from proinsulin in the pancreatic beta cell secretory granules in equimolar quantities to insulin. C peptide has double the half life of insulin in peripheral blood and only a small proportion of portal blood C peptide is extracted by the liver, compared with 90% of insulin.³ In addition, the radioimmunoassay of insulin in serum is relatively insensitive at concentrations of 3 mU/l or below, whereas our C peptide assay has a more sensitive detection limit of 32 to 50 pmol/l. For these reasons C peptide is more reliable than insulin as a peripheral indicator of beta cell secretory activity.

Methods

We have modified the method of Heding⁴ (available in a kit from Novo Research Institute) for the determination of plasma C peptide. We have used a double antibody radioimmunoassay and have collected samples in EDTA combined with trasylol. Fasting plasma C peptide concentration in a normal adult is between 150 and 350 pmol/l and the lower limit of detection in our laboratory is 32 to 50 pmol/l.

Case 1. A boy who weighed 2.4 kg at term presented with convulsions at age 7 months. Early morning lethargy and 'jerking' movements had been observed for two months. A blood glucose concentration of between 0.2 and 1.7 mmol/l was associated with a serum insulin value of between 8.8 and 69 mU/l. After a 95% pancreatectomy, histology and fluorescent polyclonal antibody studies showed the characteristic features of nesidioblastosis.² For three weeks postoperatively he developed temporary diabetes mellitus requiring insulin, in addition to mild steatorrhoea treated by enzyme supplements.

Seven months after the subtotal pancreatectomy he developed a recurrence of morning symptoms, although these were now intermittent. During a 24 hour fast blood glucose values ranged between 1.4