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REVERSAL OF HEPATIC ALPHA-1-ANTITRYPSIN DEPOSITION AFTER PORTACAVAL SHUNT

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Summary End-to-side portacaval shunts were carried out in three children with the liver disease of alpha-1-antitrypsin deficiency and complications of portal hypertension. Their clinical courses have been stable for 3½ to almost 7 years. Postoperative liver biopsy material from two of the patients showed the typical histopathological changes caused by portal diversion, as well as an apparent reduction in the quantity of alpha-1-antitrypsin particles in the hepatocytes. The metabolic changes caused by portal diversion have apparently created a more favourable equilibrium between the synthesis and excretion of the abnormal alpha-1-antitrypsin.

Introduction

THE portacaval shunt has conventionally been used to treat the complications of portal hypertension, ascites and haemorrhage from oesophageal varices. Livers deprived by portacaval shunt of hormones, and probably other substances, in portal venous blood undergo subtle but profound changes in function.[1-4] Because these changes in hepatic function occur, portal diversion can improve the condition in two inborn errors of metabolism—glycogen storage disease[4,5] and familial hypercholesterolaemia.[4,6]

We now report a third example of metabolic engineering by end-to-side portacaval shunt in three children with liver disease associated with alpha-1-antitrypsin deficiency.

Case-reports

Patient 1

A German girl aged 4 years 8 months was referred for consideration of liver transplantation because of alpha-1-antitrypsin deficiency (PiZZ phenotype), hepatic cirrhosis, moderate ascites,

and a haemorrhage from oesophageal varices that had required five transfusions. Her sister had died of the same disease aged five years. Both children had had neonatal jaundice which subsided spontaneously. The patient's liver function test results were bilirubin 25·6 μmol/l, serum aspartate aminotransferase 150 IU/l (normal <50), serum alanine aminotransferase 260 IU/l (normal <50), alkaline phosphatase 1800 IU/l (normal <250), prothrombin time 12 s (11·5 s control), total protein 63 g/l with 33 g/l albumin, serum alpha-1-antitrypsin 300 mg/l (normal >2000), serum ammonia 58·7 μmol/l (normal <50).

End-to-side portacaval shunt was carried out on June 15, 1976. The liver was moderately enlarged and had macronodular cirrhosis. After operation the patient became jaundiced, with a peak bilirubin of 103 μmol/l, but the icterus slowly disappeared over several months. The ascites was relieved and there have been no further gastrointestinal haemorrhages. At the time of operation, the child's position on the Harvard growth curves was at the 5th weight percentile and the 50th height percentile. In the past 6¾ years, her weight and height positions have moved to the 50th and 70th percentiles, respectively. Recent liver function test results, including serum alpha-1-antitrypsin concentrations, are similar to preoperative results, with bilirubin in the range 20–30 μmol/l. Serum aminotransferase and alkaline phosphatase levels are less elevated than previously, but the serum ammonia level has risen to 58–111 μmol/l. As advised, the patient avoids a high-protein diet and has had no evidence of hepatic encephalopathy. She is a good student.

Patient 2

This girl had transient neonatal jaundice and cirrhosis later developed. Alpha-1-antitrypsin deficiency (PiZZ phenotype) was proved when she was 4½ years old. Because of repeated variceal haemorrhages and mild ascites, end-to-side portacaval shunt was carried out on March 7, 1978, when she was 6½ years old. Before operation her liver function test results were bilirubin 30·8 μmol/l, prothrombin time 13 s (11 s control), total protein 52 g/l with serum albumin 35 g/l, serum alpha-1-antitrypsin 160 mg/l and serum ammonia 29–53 μmol/l. Serum aminotransferase and alkaline phosphatase levels were 2–6 times higher than normal.

Her liver disease slowly became worse for the first 3½ years after operation, as judged mainly by serum bilirubin concentrations that reached a peak of 51–82 μmol/l in mid-1981; subsequently, total bilirubins fell to 43 μmol/l. Total protein is now 62 g/l with 40 g/l albumin. Prothrombin time is still longer than normal (12 to 13 s) and serum aminotransferase and alkaline phosphatase levels are slightly raised. Serum alpha-1-antitrypsin concentrations have not changed. Serum ammonia levels are 53–88 μmol/l on an unrestricted diet but can be kept in the normal range with a low-protein diet. The patient receives diuretics to prevent ascites but she has not had encephalopathy. She is a fair student. Her growth pattern in the 5 postoperative years has changed. Her height position has moved from the 10th to the 60th percentile on the

growth curve and her weight position from the 50th to 25th percentile.

Patient 3

A boy born in September, 1978, had neonatal jaundice for several months followed by hepatic cirrhosis and ascites. The diagnosis of alpha-1-antitrypsin (PiZZ phenotype) deficiency was established. The serum concentration of alpha-1-antitrypsin was 300 mg/l. Serum bilirubin, prothrombin time, serum albumin, and serum ammonia were normal. The aminotransferase and alkaline phosphatase levels were high, as in patients 1 and 2.

On Nov 1, 1979, when the boy was 13½ months old, an end-to-side portacaval shunt was carried out. Management of the ascites with diuretics was extremely difficult for the first few months, but not thereafter. For the 3½ years of follow-up, liver function test results have been the same as before operation except for rises in fasting serum ammonia to approximately 60 μmol/l. Mental development has been normal. The weight and height positions on the Harvard growth scale are at the 55th and 30th percentiles, respectively, about the same as before the operation.

Histopathology

We did liver biopsies on all three patients at the time of portacaval shunt. Repeat biopsy samples were obtained in patient 2 after 9 months and in patient 3 after 7, 13, and 35 months. Each specimen was divided; the larger part was fixed in buffered formalin and the smaller in glutaraldehyde. Paraffin sections were prepared and stained with a range of reagents, including periodic acid schiff (PAS), used after the section had been treated with diastase. A peroxidase-anti-peroxidase (PAP) technique with specific antibody (Dakopatts, Denmark) was used to identify alpha-1-antitrypsin. Ultra-thin sections were prepared and examined in a Phillips EM 300 electron microscope. 10 000 hepatocytes were measured in each biopsy sample by a standard morphometric technique.[1] The proportion of these hepatocytes with diastase-resistant PAS-positive granules in the cytoplasm was recorded.

The initial biopsy samples revealed macronodular cirrhosis in each patient. The livers also contained multiple, round, PAS-positive bodies in the hepatocyte cytoplasm. Most of the bodies were small and the number per cell varied considerably. They were intensely PAS-positive, resisted diastase digestion, and contained alpha-1-antitrypsin as demonstrated by the PAP technique. The bodies were more frequent at the periphery of the pseudolobules.

The biopsy sample from patient 2 taken 9 months after operation had a similar appearance, but the percentage of

hepatocytes containing alpha-1-antitrypsin globules was lower (28·5% compared with 38·2% when portacaval shunt was done), the hepatocytes were 22% smaller, and the amount of rough endoplasmic reticulum was greatly reduced.

In patient 3 the percentage of hepatocytes containing alpha-1-antitrypsin globules was 44·5% at operation and 48·2% and 38·7% 7 months and 13 months later. The hepatocytes were 15% and 20% smaller in the postoperative biopsy samples. The percentage of hepatocytes containing alpha-1-antitrypsin globules had fallen to 20·4% in the biopsy sample taken at 35 months. The hepatocytes remained 20% smaller than in the preoperative sample and the amounts of rough and smooth endoplasmic reticulum were reduced. The severity of the macronodular cirrhosis was unaltered.

Discussion

In alpha-1-antitrypsin deficiency, the liver synthesises an abnormal variant,[7-9] which apparently cannot be efficiently transported from the hepatocyte to the bloodstream and becomes concentrated near the rough endoplasmic reticulum.[10] It is thought to stimulate the fibrous reaction and eventual cirrhosis that are frequent but variable features of the disorder.[11,12] Liver transplantation has been the only decisive method of treatment; transplantation relieves hepatic failure and raises serum alpha-1-antitrypsin levels to normal, and the patients receive new protease inhibitor types.[13,14]

We have speculated previously[15] on the possibility that portal diversion might offer metabolic palliation to some of these patients at an earlier stage of disease. The stable condition of the three patients reported here for several years after portacaval shunt compared with their progressive deterioration before operation is consistent with this prediction. Similar long survival of two children after central splenorenal shunt for variceal haemorrhage has been described by Sotos et al.[16] However, the most objective evidence that the history of the hepatic disease was favourably altered came from the histopathological studies. The number of hepatocytes with cytoplasmic alpha-1-antitrypsin globules fell in both patients for whom repeat biopsy samples were available. This fall could have been due to the biopsies being unrepresentative. This explanation is, however, unlikely because the distribution of alpha-1-antitrypsin globules throughout the liver tends to be uniform, even though the location of the granules with lobules and cirrhotic pseudolobules varies. It seems unlikely that the number and

size of PAS-positive alpha-1-antitrypsin granules would decrease spontaneously. In both patient 2 and patient 3 the cirrhosis had neither progressed nor regressed.

The demonstration that portal venous blood contains hepatotrophic constituents, of which endogenous insulin is the most important,[1-4] helps to explain the consequences of portacaval shunt. In all species studied so far, including man, portal-systemic diversion of these hepatotrophic substances causes a characteristic and serious liver injury with hepatocyte atrophy, glycogen depletion, fatty infiltration, and drastic alteration of the organelles.[1-4,6] Some of these features were seen in the postoperative biopsy specimens from our patients. The reduction in hepatocyte rough endoplasmic reticulum with depletion of its polyribosomes is the most specific ultrastructural change; it provides at least a partial explanation of the depression after portacaval shunt of many biosynthetic processes,[4] including lipid and bile-acid production, the Krebs-Henseleit cycle, and activities of the microsomal mixed-function oxidase system.

Since alpha-1-antitrypsin is synthesised principally on ribosomes bound to the rough endoplasmic reticulum,[17,18] its production also should be reduced by portacaval shunt. The glycoprotein is secreted through the channels of the smooth endoplasmic reticulum and Golgi complex,[17,18] structures which are not severely damaged by portal diversion.[1-4,6] Thus, the liver damage associated with alpha-1-antitrypsin deficiency may be lessened after portal diversion by a favourable change in the equilibrium between hepatic synthesis and excretion of alpha-1-antitrypsin, without causing any change in the serum level of the glycoprotein.

Exploitation of this concept in clinical care may be exceptionally difficult. The majority of patients with alpha-1-antitrypsin deficiency do not progress to significant hepatic disease even though their livers are crammed with the abnormal glycoprotein.[11,12] At the other extreme, portacaval shunt for metabolic objectives would be futile in patients with end-stage cirrhosis. Bismuth et al[19] reported the death of a child with alpha-1-antitrypsin deficiency in whom progressive encephalopathy and hepatic failure developed after portal diversion. The patients for whom portal diversion may be suitable are those who still have good liver function and hepatopetal flow but in whom cirrhosis and portal hypertension are developing.

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