Hepatic haemangiomata: diagnosis and management

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SUMMARY Five cases of hepatic haemangioma are described, and a sixth (previously reported) is reviewed. Clinical features, investigation, and management are described to show the great variability of the complications and prognosis. Five children presented in the first 10 weeks of life with hepatomegaly; 4 developed congestive cardiac failure; 3 had cutaneous haemangiomata. One child presented at age 4 years with hepatomegaly and anaemia, and on investigation had features of chronic disseminated intravascular coagulation. Focal decrease or patchiness in hepatic uptake of technetium-99m colloid, and abnormal intrahepatic circulation was shown in all cases. In 3 children liver biopsy was performed to exclude malignant disease. In one patient there was spontaneous regression of the tumour by age 3 years. In 3 cases hepatic artery ligation was necessary to control congestive cardiac failure which had persisted despite treatment with digoxin, diuretics, and oral corticosteroids, a procedure which was without complications after up to 8 years. One infant with intractable portal hypertension, hepatic vein obstruction, and severe cholestasis died with persisting alimentary haemorrhage and intra-abdominal sepsis. One child aged 4 years showed no immediate response to hepatic artery ligation but the size of her tumour got smaller and the clinical features diminished after irradiation. These tumours cause considerable morbidity and have a high reported mortality. If congestive cardiac failure is not rapidly controlled, hepatic artery ligation should be performed.

Vascular tumours of the liver are rare in childhood and pose considerable problems in diagnosis and management. Although there can be spontaneous regression, an overall mortality of 70% has been reported.1 In half the number of patients the presenting features of hepatic haemangiomata are hepatomegaly in association with cutaneous haemangiomata; in many, high output cardiac failure occurs.2 Less common presenting features are transient obstructive jaundice,3–5 intestinal obstruction and portal hypertension,6 or intestinal bleeding from the tumour.7 Disseminated intravascular coagulation, a well recognised complication of large cutaneous haemangiomata, may also complicate the hepatic lesion.8 In the last decade, steroids,9 radiotherapy,10 surgical resection,11 and hepatic artery ligation12–13 have each been claimed to have an important place in management. The great variability in the severity and extent of these lesions and of their complications, and the occurrence of spontaneous regression makes it difficult to compare treatments. We describe in detail 5 cases and briefly report the progress of a sixth case (previously reported).13 The indications and value of the various current forms of treatment are considered.

Case histories

All children were referred to this hospital for further evaluation and each was investigated using standard techniques. Each child had been born normally at term after an uncomplicated pregnancy, and had a normal birthweight. Parents were healthy, unrelated, and without history of hepatic or cardiovascular disease. Full peripheral blood count (including platelet counts) clotting factors, plasma urea and electrolytes, serum bilirubin, aspartate transaminase (AST), alkaline phosphatase, calcium, phosphate, and serum proteins were normal, unless otherwise stated. Isotope scanning of the liver using technetium-99m colloid was performed in each.

Case 1. A girl developed dyspnoea and cyanosis at age 16 days. There were three raised cutaneous haemangiomata, hepatomegaly of 3 cm, and splenomegaly of 2 cm, and clinical evidence of cardiac failure. There was a loud precordial pansystolic murmur and a bruit over the liver. Cardiac catheterisation showed evidence of a large intra-abdominal arteriovenous shunt without an intrinsic cardiac defect. The cardiac output was 7 litres/min
per m². Angiography performed via the left femoral artery showed a grossly enlarged hepatic artery with an abnormal intrahepatic circulation consistent with an intrahepatic tumour. The iliac arteries were small. Digoxin and diuretics failed to control the cardiac failure, and further skin haemangiomata developed. When transferred at age 19 weeks she was irritable, dyspnoeic at rest, and cyanosed on crying. Her weight was 4·6 kg (<3rd centile). There were multiple cutaneous haemangiomata and diminished pulses in the left leg but the other physical signs were unchanged.

Chest x-ray film showed cardiomegaly (cardio-thoracic ratio 0·7:1) and pulmonary plethora; electrocardiogram (ECG) showed right axis deviation and right ventricular hypertrophy. The cardiac output, estimated by echocardiography, was 5·8 litres/min per m². AST was 52 IU/l. Liver scan showed filling defects in both lobes of the liver.

At laparotomy, diffuse hepatic haemangiomata were found occupying both liver lobes, with abnormal arteriovenous structures in the falciform ligament and lesser omentum. The grossly dilated hepatic artery was ligated. Transient left ventricular failure, requiring additional diuretics, occurred within 12 hours of surgery. Thereafter the condition of the child improved steadily; cardiac output (estimated by echocardiography) fell to 3·7, 3·3, and 2 litres/min per m² at 6, 14, and 48 days postoperatively. Diuretics were withdrawn on the 22nd day but poor feeding delayed discharge from hospital until the 49th postoperative day.

Treatment with digoxin was stopped at age 10 months. At 16 months the liver was impalpable and liver function tests were normal. General growth and development are currently normal (weight on 75th centile) but there is a 1 cm shortening of the left leg with a reduced left femoral artery pulse.

Case 2. An asymptomatic 9-week-old boy had hepatomegaly of 9 cm and skin pallor at routine examination. His weight was on the 50th centile. The haemoglobin (Hb) was 8 g/dl, AST 105 IU/l. A technetium liver scan showed a large filling defect in the left lobe encroaching on the right (Fig. 1) while a selenomethionine scan showed uptake in this area (Fig. 2). Coeliac axis angiography showed large hepatic arteries supplying a centrally placed vascular tumour. The histology of percutaneous liver biopsy tissue was consistent with a diagnosis of infantile haemangioma.

As the tumour was too extensive for resection and the infant was asymptomatic no treatment was given. At age 9 months cardiomegaly (cardio-thoracic ratio 0·65:1) was noted without other evidence of cardiac failure. These features remitted spon-

taneously. The liver gradually decreased in size becoming impalpable by 2·3 years, by which time the hepatic scan was normal. At 6 years growth, development, clinical examination, liver scan, and liver function tests were all normal (Fig. 3).

Case 3. A boy, whose mother drank heavily and smoked 40 cigarettes a day during pregnancy, developed skin haemangiomata at age 72 hours. Breathlessness on feeding, cough, and evidence of congestive cardiac failure were noted at age 4 weeks. A firm liver edge was palpable 3 cm below the costal

Fig. 1 (Case 2, age 10 weeks.) Technetium-99 liver scan; the white dots are markers placed on the costal margin and umbilicus. There is hepatomegaly with a filling defect (A) in the left lobe which encroaches on the right.

Fig. 2 (Case 2, age 10 weeks.) Selenium methionine scan, showing patchy uptake of isotope at the site of the filling defect shown in Fig. 1, indicating the presence within it of hepatocytes.
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Fig. 3 (Case 2, age 6 years.) Technetium-99 liver scan showing a normal-sized liver without filling defects.

Hb was 9·9 g/dl, total bilirubin 25 μmol/l (1·5 mg/100 ml), AST 78 IU/l, and alkaline phosphatase 281 IU/l. Chest x-ray film showed cardiomegaly (cardio-thoracic ratio 0·6 : 1) and pulmonary plethora; ECG showed biventricular hypertrophy. Multiple filling defects were present both on isotope and ultrasonic scans of the liver.

Transfusion, digoxin, diuretics, and prednisolone (starting at 40 mg a day, and tapered over 2 weeks) failed to reduce the size of the liver. The clinical condition was unchanged at 3 months when steroids were reintroduced and continued for a total period of 3 months. At 5 months angiography showed an enlarged hepatic artery with a prominent arteriovenous fistula in the left lobe of the liver. When aged 8 months there was a sudden episode of haematemesis and melena followed, within 48 hours, by jaundice and ascites. Liver function tests became greatly abnormal. Oesophageal varices were demonstrated.

Fig. 4 (Case 3, age 9 months.) Hepatic arteriogram (femoral approach) showing dilatation of the hepatic artery (arrowed) and diffuse haemangiomatous changes throughout the liver.
by endoscopy 5 days later and the child was referred for further evaluation.

On arrival, the infant was pale, jaundiced, and had multiple skin haemangiomata. He weighed 4·7 kg (far below 3rd centile). He had tachypnoea, tachycardia, and a short soft precordial systolic murmur. There was a firm liver edge palpable 5 cm below the costal margin, splenomegaly, an umbilical hernia, and ascites with superficial distended abdominal veins carrying blood from the umbilicus.

Hb (after transfusion) was 11·8 g/dl, total bilirubin 112 µmol/l (6·5 mg/100 ml), 80 µmol (4·6 mg/100 ml) being conjugated. AST was 131 IU/l, alkaline phosphatase 147 IU/l, and stools contained occult blood. A selective hepatic arteriogram showed multiple widespread hepatic haemangiomata and rapid retrograde filling of the portal vein without filling of the hepatic veins (Fig. 5). A review of the earlier angiogram showed that these vascular abnormalities had been present at age 5 months.

In the subsequent 3 weeks, alimentary bleeding continued requiring 10 units of blood as replacement. Laparotomy, performed in an attempt to control the bleeding, confirmed the presence of widespread haemangiomata and portal hypertension. Hepatic artery ligation failed to control portal hypertension and bleeding, so a proximal gastric transection and portoazygous disconnection of the stomach were performed with difficulty.

Postoperatively the child developed ileus, hypocalcaemia, hyponatraemia, and peritonitis; these were followed by a persistent biliary fistula. Parenteral nutrition was necessary for 6 weeks. The alimentary bleeding was much less but the child remained jaundiced and the stools became acholic. Genetic and nonpyogenic infectious causes of jaundice in this age group were excluded. A percutaneous cholangiogram at 11½ months showed patent, though narrow, tortuous intrahepatic bile ducts with multiple strictures and a free flow of contrast into the duodenum. The common bile duct and gall bladder were normal. Liver biopsy showed the histological features of periportal fibrosis without cirrhosis.

Persistent obstructive jaundice, intra-abdominal sepsis, recurrent septicemia, and cardiac failure continued. Despite many courses of antibiotics, parenteral nutrition, blood transfusions, and a great deal of devoted nursing care he died of septicemia at age 22 months. No necropsy was performed.

Case 4. A boy developed prolonged unexplained neonatal jaundice. His mother, who had quiescent untreated rheumatoid arthritis, had received hydroxy-progesterone hexanoate early in pregnancy because of threatened miscarriage. At 7 weeks the infant was found to have firm, nodular hepatomegaly and a precordial systolic bruit. A liver biopsy performed to exclude hepatoblastoma showed histological features of haemangio-endothelioma.

Fig. 5 (Case 3, age 9 months.) Hepatic arteriogram (early venous phase) showing abnormal circulation within the liver and good filling of the portal vein (arrowed) but without filling of the hepatic vein.
He also had exophthalmos with lid retraction; serum thyroxine (260 nmol/l; 19·9 mg/100 ml) and thyroid stimulating hormone (40 mU/l) were both increased. Cardiac failure, resistant to digoxin and diuretics, developed and prednisolone was then added to his treatment, initially 20 mg/day, but this dose was reduced to 15 mg/day when referred to this hospital at 5 months.

The problems then were persisting cardiac failure, poor feeding, failure to thrive, irritability, and dyspnoea at rest. The liver edge was palpable 11 cm below the costal margin, the other features being ascites, a right inguinal hernia, proptosis, and lid-lag. There were no skin haemangiomata. Chest x-ray film showed cardiomegaly (cardio-thoracic ratio 0·6:1) with pulmonary plethora. An ECG showed biventricular hypertrophy. Selective hepatic artery angiography via the femoral artery proved impossible, but injection of Conray 280 via the external jugular vein, showed a large hepatic artery supplying multiple intrahepatic haemangiomata (Fig. 6). The diameter of the aorta above the hepatic artery outflow was 8 mm but only 4 mm below it.

Because of the poorly controlled cardiac failure and failure to thrive, hepatic artery ligation was performed. At operation multiple diffuse hepatic haemangiomata were observed. After operation the cardiac and thyroid abnormalities resolved. Steroids were gradually reduced but despite this, three episodes of 'pseudotumour cerebri' occurred before steroids were eventually stopped 3 months after operation. By this time the liver had regressed in size, the edge being palpable 5 cm below the costal margin, and liver function tests were normal.

Case 5. A 4-year-old girl presented with a 5-month history of asymptomatic increase in abdominal girth. She was noted to be pale with 12 cm of firm hepatomegaly. Hb was 7·5 g/dl, the peripheral blood film showed features of iron deficiency confirmed by a low serum iron (4 μmol/l; 22·5 μg/l00 ml) and raised serum iron-binding capacity (108 μmol/l; 602 mg/100 ml). There were features of a low-grade, disseminated intravascular coagulation with a platelet count of 80 × 10^9/l, a prothrombin time of 18 seconds (control 13), partial thromboplastin time

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Fig. 6 (Case 4, age 5 months.) Hepatic arteriogram obtained by intravenous injection of Conray 280. The hepatic artery (arrowed) is dilated and tortuous, and there are widespread haemangiomatous changes throughout the liver. The aorta below the origin of the hepatic artery is narrow.
normal steroids with Treatment failure 9 weeks. his 6 months and were 1321-labelled al.'3 This et radiotherapy failed haemangiomata in tumours liver function showed (control 12), laparotomy, fluid restriction and coagulation had reduced, Case 6. and 2 she intravascular level and 6 appearances Histological 52 days. postoperatively 11, 14 and 6) had typical clinical features at presentation. Subsequent investigation in 4 were compatible with a vascular intrahepatic tumour with cardiac failure. Cutaneous lesions were present in 3 infants (Cases 1, 3, and 6) and a histological diagnosis was unnecessary. Case 3 was atypical as portal hypertension and jaundice were the major clinical problems on referral and were within the lesion. Benign lesions include focal nodular hypoplasia,14 or mesenchymal hamartoma,18 and primary lesions of the hepatic blood vessels. The last are usually termed ‘infantile haemangioendothelioma’ 16 or ‘haemangioma’.17 Haemangiomas can be single or multiple, and occur as discrete, nonencapsulated, vascular tumours which vary in diameter from a few millimetres to 15 cm. There are two distinct histological types.18 In the majority, the hepatic artery and its branches that supply the tumour are tortuous and enlarged. The tumours function as arteriovenous fistulae and cause considerable haemodynamic disturbance with cardiomegaly, increased total blood volume, and hypoperfusion of other tissues. As a result, over 80% of such patients present in the first 6 months of life with congestive cardiac failure. There is hepatic enlargement, sometimes accompanied by a palpable hepatic mass or a bruit over the liver. Many such patients die of cardiac failure, or perhaps but less frequently, of hepatic failure or haemoperitoneum. If the patient survives, spontaneous regression can occur, although there is a limited potential to develop metastases.18 Typically, liver function tests are normal, except for a raised serum bilirubin level in up to one-third of cases.16 Serum \( \alpha \)-fetoprotein concentration is normal. A technetium liver scan shows at least one area of decreased radioactivity, and ultrasonic scanning shows such spaces to be fluid filled. Coeliac angiography shows intrahepatic vascular malformation with very rapid filling of hepatic vein tributaries, tortuosity of the hepatic artery, and its branches, and occasionally additional extrhepatic vascular malformations. Angiography is desirable if surgical intervention is considered. It enables accurate identification of any vessel to be ligated. It also gives some indication on whether tumour resection is feasible. If cardiac failure is severe these advantages should be weighed against the possible disadvantages of an additional fluid load and general anaesthesia. These may preclude this investigation. Even if femoral angiography is performed in a unit experienced with this technique, there is a risk of long-term sequelae—for example, limb shortening (Case 1). In such infants an alternative approach, as in Case 5, may need to be considered. Five children (Cases 1–4, and 6) had typical clinical features at presentation. Subsequent investigation in 4 were compatible with a vascular intrahepatic tumour with cardiac failure. Cutaneous lesions were present in 3 infants (Cases 1, 3, and 6) and a histological diagnosis was unnecessary. Case 3 was atypical as portal hypertension and jaundice were the major clinical problems on referral and were Hepatic tumours in childhood, whether benign or malignant, may be accompanied by increased hepatic blood flow and abnormal vascular patterns
ultimately responsible for the child’s death. The hepatic vein was not visualised at angiography, the appearances being similar to those illustrated in a case reported by Hellikson et al.8

In 3 children (Cases 2, 4, and 5) histological confirmation of the diagnosis was necessary to exclude hepatoblastoma. Case 5 was unusual because of the late presentation, lack of haemodynamic effects, and the presence of both haemolytic anaemia and low-grade disseminated intravascular coagulation with hypofibrinogenaemia. Although haemolytic anaemia and disseminated intravascular coagulation may occur in hepatic haemangio-endothelioma,8 dysfibrinogenaemia has been reported in association with hepatoblastoma.19 A histological diagnosis was therefore necessary.

The variety of treatments used in these 6 cases illustrate the difficulties in management of this rare tumour. Apparent complete resolution occurred without any active measures in one child (Case 2). In Cases 1, 4, and 6 congestive cardiac failure, which had not responded to digoxin, diuretics, or corticosteroids, improved strikingly after hepatic artery ligation. Apart from transient exacerbation of congestive cardiac failure in Case 1, there were no sequelae to this operation, even 8 years later.

Case 3 had two additional problems—portal hypertension and severe obstructive jaundice. The portal hypertension was not controlled by hepatic artery ligation. Since there was no blood flow through the hepatic vein at angiography, an alternative approach might have been to fashion a portocaval anastomosis, a procedure which has recently been found to be useful in the treatment of the Budd-Chiari syndrome.20 The reason for the severe obstructive jaundice is unknown. The intrahepatic bile ducts looked abnormal on percutaneous cholangiography. The causes of the cholestasis are probably complex, and we would have no way of knowing whether jaundice was primarily due to biliary obstruction or to hepatocyte malfunction, as has been suggested.3–4

Hepatic artery ligation did not reduce the size of the tumour or correct the haematological abnormalities in Case 5. Whether the subsequent improvement in the child’s condition was entirely due to radiotherapy or to the decrease in hepatic blood flow is conjectural.

We suggest the following scheme of management. (1) If complications are absent, the patient should be watched carefully as even large tumours can resolve spontaneously, and five tumours that resolved in this way have been reported.21 (2) If congestive cardiac failure develops, digoxin and diuretics should be given. (3) Hepatic artery ligation to control congestive cardiac failure by reducing the hepatic blood flow is indicated in very young patients (less than 6 weeks) who develop cardiac failure. If untreated, such an infant has a mortality of up to 50% within 2 weeks of onset.12 (4) In patients presenting after 6 weeks steroids, in an initial daily dose of 2 mg/kg, should be administered, since over 70% of cases in two series,12 22 showed a good response with diminution of hepatomegaly and control of congestive cardiac failure. Angiography should be considered since hepatic artery ligation should be undertaken if there is no response in 2 weeks. Serial determination of cardiac output by echocardiography may provide a feasible noninvasive evaluation of the effectiveness of steroids. Careful observation, both during treatment with steroids and after stopping them, is essential since death from congestive cardiac failure has been reported one month after stopping steroids.

Although radiotherapy has been used successfully to hasten resolution of haemangiomata,23 its use is also associated with increased mortality.1 On balance the disadvantages of irradiation of the liver in children make it undesirable unless other forms of treatment are contraindicated.

Complete surgical resection is advisable for the management of localised tumours, particularly if complicated by intrahepatic haemorrhage.

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References

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