Transplantation of a donor liver with haemochromatosis: evidence against an inherited intrahepatic defect

P C Adams, C N Ghent, D R Grant, J V Frei, W J Wall

Abstract
An iron loaded liver from a 40 year old man with occult haemochromatosis was transplanted into a 19 year old woman with acute liver failure secondary to a paracetamol overdose. Increased parenchymal hepatic iron was found in a liver specimen at biopsy undertaken because of mild rejection 30 days after transplantation. After transplantation the patient had two episodes of liver rejection confirmed by biopsy. The hepatic iron concentration fell from 161 µmol/g on day 30 after transplant to 26.5 µmol/g (normal <40) on day 210. Iron absorption, measured 45 days after transplant, was in the normal range at 12-4%. The rapid fall in hepatic iron and the normal iron absorption study result suggest that the genetic defect of haemochromatosis is not exclusively an intrahepatic defect.

Haemochromatosis is a genetic disease of unknown cause that affects approximately one in 400 of the white population. The disease is characterised by increased intestinal absorption of iron that eventually leads to parenchymal iron deposition in the liver, pancreas, and heart. Organ damage and clinical symptoms do not usually appear until the fifth decade in men and the sixth decade in women. Theories on the pathogenesis of haemochromatosis have postulated that the primary metabolic defect is in the intestinal mucosa, the reticuloendothelial system, or the liver. In this report, we describe the indirect evidence against an intrahepatic defect as the primary defect in haemochromatosis provided by inadvertent transplantation of a liver from a patient with haemochromatosis.

Patients and methods
The donor was a 40 year old Irish man who had a spontaneous cerebral haemorrhage. He had a past history of mild arthritis affecting his hands and shoulders, unexplained dyspnoea on exertion, and a two year history of impotence. There was no history of anaemia, transfusions, or alcohol abuse. Serum, tested posthumously, showed a raised serum ferritin concentration of 1436 µg/l (normal range = 15-300). The heart was not used for transplantation because it looked hypokinetic. A necropsy was not performed.

The recipient was a 19 year old woman who developed acute hepatic failure after ingesting approximately 15 g of paracetamol. She underwent emergency orthotopic liver transplantation receiving 4 U of packed red blood cells. The patient made an excellent postoperative recovery. A percutaneous liver biopsy was performed on day 30 after transplantation because of an increase in aspartate aminotransferase and alanine aminotransferase activities. The biopsy specimen confirmed a diagnosis of acute rejection. An iron stain (Perls' stain) showed 4+ iron in the hepatocytes, with minimal iron in the Kupffer cells and no fibrosis or cirrhosis (Fig 1). Hepatic iron determination by atomic absorption spectrophotometry showed a considerable increase in hepatic iron at 161 µmol/g (normal range 0-40 µmol/g dry weight). The estimated hepatic iron index (hepatic iron-age) in the donor was 4.0 which is highly suggestive of genetic haemochromatosis. Rejection was readily controlled with intravenous methylprednisolone therapy. The serum ferritin value was 2940 µg/l on day 30 and had fallen to 243 µg/l by day 570. An iron absorption study was performed on day 45 using an oral dose of 1 µCi "Fe citrate containing 10 µmol of ferrous ascorbate. The retained dose of "Fe at 14 days was calculated with a total body counter. At the time of the iron absorption study the patient had a haemoglobin concentration of 115 g/l and a transferrin saturation value of 23%. The iron absorption was 12.4%, which is within normal limits. However, iron absorption is not a diagnostic test for haemochromatosis and the wide range of values for normal volunteers and haemochromatosis patients has been previously described. The iron absorption study result in this patient is much less than would be expected for a haemochromatosis patient of this age. The patient was readmitted to hospital on day 65 and
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Orthotopic liver transplantation in human beings has provided the opportunity to study the effects of liver replacement on many inherited metabolic diseases. If the metabolic defect of haemochromatosis had been transplanted into this patient, hepatic iron would continue to accumulate as a result of the increased intestinal iron absorption associated with the disease. The rapid reduction of hepatic iron after liver transplantation with normal iron absorption in this patient suggests that the primary metabolic defect of haemochromatosis does not reside exclusively in the liver. However, inflammation in the liver associated with rejection would result in the release of iron into the circulation, redistribution of iron from the parenchyma to macrophages and may contribute to the increased serum ferritin value. Furthermore, the effects of liver transplantation on iron absorption and mobilisation of iron are not clearly understood. Experimental liver transplantation of iron loaded livers in rats has shown some reduction in hepatic iron with rejection but not to the degree seen in this patient. Experimental iron loading of animals has been shown to cause lipid peroxidation with the production of free radicals that can cause tissue damage. It is possible that the rejection in this patient hepatic rejection led to the release of free iron which further exacerbated the hepatic inflammation. The definitive proof that this patient will not develop progressive iron overload will require long term follow up with assessment of body iron stores by hepatic iron and serum ferritin determination.

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Discussion
This case documents the unusual occurrence of the transplantation of an iron loaded haemochromatosis liver. Considering the prevalence of haemochromatosis of approximately one in 400, however, it was inevitable that such a liver would eventually be transplanted inadvertently. Current organ donor procurement and preservation arrangements preclude the routine use of pretransplant liver biopsy assessments and this donor was in the precrirrhatic stage of his disease. Since liver function is clinically well preserved until the fifth or sixth decade in haemochromatosis, it is not surprising that the organ functioned well after transplantation.

The pathogenesis of haemochromatosis remains unknown. Patients with this disorder have increased intestinal absorption of iron which accumulates in the liver, pancreas, and heart causing parenchymal damage over many years. The factors that control iron absorption are poorly understood even in the normal human. A defect in the intestinal regulation of iron absorption has been postulated as the primary defect in haemochromatosis, but iron absorption does respond to body iron stores by decreasing as these increase. A generalised defect in the reticuloendothelial system has also been proposed, with the rapid release of iron by macrophages. Since haemochromatosis has major clinical sequelae in the liver, an intrahepatic lesion is another possibility. Increased hepatic iron uptake has been found in patients with haemochromatosis by scanning the liver after the infusion of radiolabelled transferrin.

Figure 2: Hepatic iron concentration of transplanted liver after transplantation (normal range 0–40 μmol/dl dry weight).

day 87 because of biochemical evidence of liver rejection which was confirmed by liver biopsy. Her hepatic iron concentrations were 68 μmol/g and 45·4 μmol/g on days 65 and 87 respectively. A biopsy specimen taken on day 210 showed that the hepatic iron had decreased to within the normal range at 26·5 μmol/g, and iron staining showed minimal iron within Kupffer cells, with no demonstrable staining of parenchymal iron. The hepatic iron concentrations, measured on four occasions, are shown in Figure 2.

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