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Orthotopic Liver Transplantation for Hemochromatosis

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WE report here the use of orthotopic liver transplantation (OLT) at the University of Pittsburgh for the treatment of hereditary hemochromatosis (HC) in adults. An association between iron overload and clinical diabetes mellitus, hyperpigmentation and cirrhosis of the liver has been recognized since 1871¹; since then, cardiomyopathy has been identified as another lethal complication. In 1935, Sheldon postulated that this disease, referred to as *idiopathic hemochromatosis*, was an inborn error of iron metabolism.² With the development of percutaneous liver biopsy techniques and the ability to easily measure serum iron and ferritin levels, premortem diagnosis became possible before the development of the lethal hepatic and extrahepatic complications. HLA typing has permitted discriminating genetic studies of the disease, and the term *idiopathic hemochromatosis* has been replaced with the terms *primary hemochromatosis* or *hereditary hemochromatosis* (HC). The availability of these tests has also delineated a wide variety of other hepatic disorders (secondary hemochromatosis or hemosiderosis).³ These latter conditions include transfusional iron overload in cases with thalassemia or hereditary spherocytosis, chronic excessive iron intake, cirrhosis of any cause associated with portal systemic shunting and iron overload, and, particularly, Laennec's (alcoholic) cirrhosis.

The gene frequency for hereditary hemochromatosis (HC) is estimated to be 1 per 200 individuals with 10% of the white population thought to carry the gene,⁴ which is on chromosome 6, adjacent to the locus for the HLA antigens.^{5,6} A transferrin saturation index (TSI) of >62% can accurately predict 92% of homozygous cases.⁷ HLA antigens A3, B7, and B14 have been shown to be closely associated with the gene for HC.⁴ Five of six of our cases were of this variety. The classical complications of diabetes mellitus, bronze pigmentation, arthralgia, pseudogout, cardiomyopathy, and cirrhosis often can be forestalled by therapeutic phlebotomy if the diagnosis is made early. However, once hepatic fibrosis develops, the long-term prognosis is poor because of progressive liver failure and the frequent development of hepatocellular carcinoma.⁸

MATERIALS AND METHODS

A total of 14 adult patients were identified who had OLT between 1 January 1982 and 31 December 1988 because of hemochromatosis. Biochemical studies (ie, serum iron, serum ferritin, transferrin saturation index, total iron binding capacity) and histologic studies suggested excessive iron overload. The amount of histologic iron deposition was graded on a scale of grade I to IV as described by Scheurer et al.⁹ Hepatic iron was quantitated by

atomic absorption spectrometry. Chronic phlebotomy therapy had been tried in all cases prior to referral for transplantation.

Eight of the 14 patients were excluded from further study because the foregoing tests, and the clinical histories suggested that the iron overload was secondary to either chronic viral hepatitis (2 examples), postnecrotic cirrhosis (2), alcoholic cirrhosis (2), or hemolytic disease (2). In the other 6, the combination of clinical data, liver function tests, iron studies of serum and liver, HLA typing data, and hepatic histology were consistent with a diagnosis of hereditary hemochromatosis. All of these adults had prolonged treatment with phlebotomy and/or desferoxamine. These six patients were among 1429 liver recipients treated over the 7-year period. They were all males (Table 1). Each had classic HC with a chronic course. Variceal bleeding was the commonest symptom while ascites and jaundice were the most frequent signs. Two additional infants with perinatal acute hemochromatosis are being reported separately.

Five of the 6 patients with HC had the HLA antigens associated with HC (A3B7). HLA typing was not available for the sixth who had diabetes mellitus and clinically significant arthropathy despite a number of venesections over a 10-year period (Table 1). The mean duration of monthly phlebotomy therapy was 7 years (range of 3 to 12 years). One of these six patients had a hepatocellular carcinoma.

RESULTS

One of the six patients died soon after OLT as the result of a hepatic artery thrombosis despite an attempt at retransplantation 19 days after the initial OLT.

The five survivors are well with follow-ups ranging from 6 months to 5½ years (Table 1). All five have normal liver function. Posttransplant biopsies from 6 months to 5 years after transplantation have not shown any evidence of iron reaccumulation.

DISCUSSION

With HC, the excess iron in tissue is distributed widely. Iron deposition occurs in the parenchyma of the liver, pancreas, other endocrine glands, and heart. Such iron deposition leads to cellular injury and the classical clinical findings of diabetes mellitus, cardiomyopathy, hyperpig-

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Table 1. Clinical Features and Outcome of Patients With Hemochromatosis

Age (Years)	Sex	Clinical Symptoms/Signs	HLA Status	Serum Iron Studies	Grade or Iron Staining	Duration of Venesection	Outcome	Follow-Up Period
41	M	Diabetes, jaundice, variceal bleeding	A3B7	↑	4	7 y	Alive	4.5 y
44	M	Variceal bleeding, jaundice	A3B7	↑	4	12 y	Alive	4.3 y
61	M	Liver failure, hepatocellular CA	A3B7	↑	4	8 y	Rejection, died 19 days after re-OLT	—
52	M	Diabetes, pigmentation	ND*	↑	2	10 y	Alive	5 y
45	M	Chronic liver failure, encephalopathy, varices, arthropathy	A3B7	↑	4	3 y	Alive	4 y
44	M	Variceal bleeding, ascites, liver failure	A3B7	↑	4	6 y	Alive	0.6 y

*ND = not done.

mentation, and hepatic failure. Appropriate therapy consisting of phlebotomy can be effective if instituted early, before the development of many of these sequelae.

The commonest subtype of congenital hemochromatosis, hereditary hemochromatosis (HC), is an autosomal recessive disorder of iron metabolism with an HLA association.⁵ All six of our cases were of this variety and all were male. The precise metabolic error in HC is not established. An abnormality either in the control of gastrointestinal absorption of iron or hepatic uptake of iron are candidate possibilities.¹⁰ An incorrect affinity for iron contained in transferrin,¹¹ or a defect in the processing of iron by the reticuloendothelial system of the liver,¹² have also been considered. Most of these speculations¹³ have concerned the adult HLA-linked disorder from which five of our six patients suffered. The exact way in which iron damages cells also is hypothetical.¹³

Although we have previously mentioned our experience of OLT for HC,¹⁴ this is our first formal report on this indication for liver replacement. The observations suggest that this poorly understood defect in iron metabolism is either corrected with liver transplantation or effectively palliated for a long period, until enough iron reaccumulation can occur to injure tissues. Even if there is a recurrence and, at present, there is no evidence to suspect that this should be anticipated, death from causes other

than HC is likely to occur before the latter eventuality is reached. Based upon this experience, liver transplantation probably will play a larger role in the future in the treatment of both classical HC as well as the fulminant pediatric disorder.

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