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LIVER TRANSPLANTATION FOR TYPE I GLYCOGEN STORAGE DISEASE

J. Jeffrey Malatack, David N. Finegold, Shunzaburo Iwatsuki, Byers W. Shaw Jr, J. Carlton Gartner, Basil J. Zitelli, Thomas Roe, and Thomas E. Starzl

Departments of Pediatrics and Surgery, University Health Center of Pittsburgh, Pittsburgh Pennsylvania 15261, USA; and Department of Pediatrics, University of Southern California

Summary

A 16½-year-old girl with type I glycogen storage disease was treated by orthotopic liver transplantation under cyclosporin/steroid immunosuppression. All metabolic stigmata of the disease were relieved and 1 year postoperatively she follows a normal diet and lifestyle.

Introduction

Studies of haptoglobin,^{1–3} group-specific component,^{3,4} and numerous other products of hepatic synthesis^{5–9} have shown that liver homografts permanently retain their original metabolic specificity after transplantation. Consequently, liver transplantation has been regarded for some years⁴ as a potentially decisive way to treat those inborn errors of metabolism which result partly or completely from defects in hepatic function. This objective has been realised in several different metabolic disorders.^{8,9} We report here the first use of liver transplantation for the treatment of type I glycogen storage disease, a disorder caused by glucose-6-phosphatase deficiency.

Case-report

The patient was a girl aged 16½ yr whose sibling had died in infancy of the same disease. At age 2½ yr she had had a prolonged hypoglycaemic seizure which resulted in transient blindness, hemiparesis, and a residual seizure disorder requiring therapy with anticonvulsants. She continued to have recurrent hypoglycaemia, acidosis, hyperuricaemia, hyperlipidaemia, abnormal coagulation, and epistaxes, and her growth was retarded. After an end-to-side portacaval shunt at age 8 yr,¹⁰ all these abnormalities were relieved except hypoglycaemia. The frequency of feedings necessary to avoid hypoglycaemic symptoms increased from every 4–5 h to every 2 h. Subsequently, overnight nutrient infusions were begun by nasogastric tube.¹¹

During the 2 yr before transplantation, multiple filling defects in her enlarged liver were seen on liver scans, with a dominant lesion in the right lobe. These were thought (and were later proved) to be slowly growing adenomas, but the possibility of a malignant change could not be ruled out. She had episodes of severe upper abdominal pain and liver swelling. In the year before transplantation, she had jaundice with a peak serum bilirubin concentration of 8 mg/dl (137 mmol/l) and serum alkaline phosphatase exceeding 3000 IU, encephalopathy with blood ammonia levels around 350 µg/dl (206 µmol/l), and persistent

Correspondence to: J. Jeffrey Malatack.

Correspondence should be addressed to J. J. M..

increases in serum transaminases. She was treated by protein restriction and intermittent intravenous alimentation. Her management was complicated by bacterial pseudomembranous colitis which was relieved by cholestyramine.

At the time of transplantation, she was small with normal vital signs, Tanner stage III pubertal changes, and the typical “potato face” of type I disease. She had bilateral right visual-field defects. The liver and spleen were palpable 10 and 6 cm below the right and left costal margins, respectively. There was no ascites. Orthotopic transplantation (liver replacement) was done with conventional techniques.¹² The donor was a 14-year-old boy of the same blood type. Cold ischaemia of the graft was 5 h. Detachment of the portacaval shunt, closure of the resulting defect in the inferior vena cava, and anastomosis of the portal vein to the graft portal vein were not difficult. Biliary reconstruction was with an end-to-end duct anastomosis over a T-tube stent. The T-tube was clamped at 4 wk and removed at 7 wk.

Postoperatively, a small bile leak and right subphrenic haematoma necessitated a minor drainage procedure. Immunosuppression was with cyclosporin and prednisone.⁸ After 5 wk she was discharged on daily doses of 12 mg/kg cyclosporin and 15 mg prednisone. There has been no evidence of rejection. After 1 yr, the daily cyclosporin dose is 9 mg/kg and prednisone has been reduced to 5 mg/day.

Results

The histopathological findings in the native liver, which weighed 3400 g, were consistent with type I glycogen storage disease. There were multiple hepatic adenomas. Biochemical studies of samples quick-frozen at -70°C and stored on dry ice were done by Dr Barbara Illingworth Brown, Washington University, St Louis. The findings, including absence of glucose-6-phosphatase activity, were typical of type I glycogen storage disease (table). The glycogen concentration in the liver was 8.7%.

Metabolic investigations were done 6 wk postoperatively. The oral glucose tolerance test was normal after transplantation, with no hypoglycaemia at 3 h—in contrast to the grossly aberrant findings at age 8 yr, just before the portacaval shunt (fig. 1). At age 8 yr, fasting for a brief period caused hypoglycaemia, whereas after transplantation, euglycaemia was maintained through a full day of fasting (fig. 2). Postoperatively, in either the fasting or the postprandial state, intramuscular injection of glucagon caused plasma glucose increments greater than 100% (fig. 3).

Standard liver function tests have been normal for 1 yr. Serum or plasma concentrations of lactates, lipids, and uric acid have been normal. The patient’s lifestyle has been transformed. She eats three meals a day. For the first time in her life, she can participate in the educational and social overnight activities that are part of normal teenage development.

Discussion

Type I glycogen storage disease was the first inborn error of metabolism to be classified on the basis of deficiency of a specific enzyme, glucose-6-phosphatase.¹³ This enzyme is found in the liver, kidneys, and intestine.¹⁴ Deficiency of glucose-6-phosphatase activity precludes normal breakdown of glycogen to glucose and inhibits gluconeogenesis. The consequent metabolic disturbances include growth retardation, acidosis, lactic acidemia, hyperlipidaemia, and hyperuricaemia.¹⁵ Effective treatment for the disease has been developed only within the past two decades, and our patient has participated in each step of this therapeutic evolution. The first step was the demonstration that portal-systemic diversion ameliorated all of the disease manifestations except hypoglycaemia.^{10, 16} Folkman et al¹⁷ showed that the same benefits could be achieved acutely by continuous parenteral

alimentation. In an extension of this observation, Greene et al¹¹ reported such good palliation, including control of hypoglycaemia, with round-the-clock enteral alimentation that this has become the treatment of choice. The overnight feedings have usually been by gastric tube.

Liver transplantation is a more specific option, but one which has been too dangerous to consider except for life-threatening complications such as those in our patient. However, the criteria for candidacy for this procedure will probably become less restrictive in view of the improved results with liver replacement that are being reported⁸ Although liver transplantation does not provide glucose-6-phosphatase directly for the kidneys or intestine, there has been no evidence of incompleteness of metabolic correction by the normally functioning transplanted liver.

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Addendum

About 1 yr after transplantation, the patient had an episode of melaena. Oesophageal varices were the site of the haemorrhage. Superior mesenteric artery angiography and transhepatic portography revealed extrahepatic portal vein thrombosis. Excellent collateral filling of the intrahepatic portal vein and its branches was seen, indicating that the homograft still had good hepatopetal splanchnic flow. Sclerotherapy controlled the bleeding and liver functions and carbohydrate metabolism continue normal.

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Fig. 1.
Oral glucose tolerance test at age 8 yr (before portacaval shunt) and 6 wk after transplantation.

Fig. 2.

Response of blood glucose concentrations during fasting at age 8 yr (before portacaval shunt), and 6 wk after liver transplantation.

Fig. 3.
Glucose response to 1 mg intramuscular glucagon in fasting and fed state, 6 wk after liver transplantation.

Table**LIVER ENZYME ACTIVITY OF EXCISED LIVER***

Enzyme	Patient ($\mu\text{mol/min/g liver}$)	Controls ($\mu\text{mol/min/g liver}$)
Glucose-6-phosphatase	0.08	3.7 – 14.4
Debranching enzyme	0.58	0.25 – 0.75
Phosphorylase	18.5	12.6 – 32.4
Fructose diphosphatase	9.1	4.2 – 15.5
Lysosomal α -glucosidase	2.32	0.63 – 2.85

* Analyses by Dr Barbara Illingworth Brown. The liver specimen contained 8.7% glycogen (normal <5%). Control patients had liver biopsies because of metabolic disorders, hepatomegaly, or failure to thrive. The control ranges include at least 10 different samples.