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Liver transplantation for glycogen storage disease type Ia☆

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***Background/Aims*: Hepatocellular carcinoma (HCC) most often occurs within hepatocellular adenomas (HCAs) in glycogen storage disease Ia (GSD Ia) patients. The objective of this retrospective study is to assess outcomes after liver transplantation (LT) for GSD Ia where the principal indication for transplantation was prevention of HCC.**

***Methods*: Petitions to the United Network for Organ Sharing region 11 review board for additional model for end-stage liver disease listing points were made on behalf of GSD Ia patients. Demographics, pre-operative comorbidity, and outcomes for GSD Ia patients who underwent LT were reviewed.**

***Results*: Between 2004 and 2006, five GSD Ia patients underwent LT. Multiple HCAs with focal hemorrhage and/or necrosis but without histological evidence of malignancy were identified in all explanted specimens. Four of five patients had complications after LT, including cytomegalovirus (CMV) infections and steroid responsive allograft rejection. Hemoglobin levels and serum triglyceride, total cholesterol, blood glucose, and lactic acid concentrations improved in all patients after LT. Corn starch feeding was not required in any patient after LT. Renal function worsened in three patients despite modifications to primary immunosuppressive medications. All patients are alive at last follow-up (range 25–48 months) and all post-transplant complications have resolved.**

***Conclusions*: By removing all possible adenomatous tissue and reversing the underlying hepatic enzymatic deficiency, LT provides definitive prevention against HCC and correction of most metabolic derangements in GSD Ia patients. Renal dysfunction secondary to GSD Ia persists—underscoring the need for further studies to better understand the mechanisms of renal dysfunction in these patients.**

***Keywords*: Glycogen storage disease Ia; Liver transplantation; Hepatocellular adenoma; Hepatocellular carcinoma**

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Abbreviations: GSD Ia, glycogen storage disease type Ia; HCC, hepatocellular carcinoma; HCA, hepatocellular adenoma; LT, liver transplantation; ESGSD I, European study on glycogen storage disease type I; MELD, model for end-stage liver disease; CT, computed tomography; MRI, magnetic resonance imaging; AFP, α-fetoprotein.

1. Introduction

Glycogen storage disease type Ia (GSD Ia) is caused by a deficiency in glucose-6-phosphatase resulting in limited production of free glucose and excessive glycogen and fat accumulation in the liver, kidney, and intestinal mucosa. Subsequent metabolic derangements include hypoglycemia, lactic acidosis, hyperuricemia, and hyperlipidemia. Clinical manifestations of these metabolic dysfunctions include prolonged bleeding time due to defects in platelet aggregation; nephrocalcinosis, glomerulosclerosis, and

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interstitial fibrosis with risk of chronic renal insufficiency; growth retardation; gout; pancreatitis; and pulmonary hypertension [1,2]. Abnormal fatty acid and glycogen deposition within the liver is universal, resulting in marked steatosis and hepatomegaly [1,3,4].

Hepatocellular adenomas (HCAs) are focal liver lesions common to patients with GSD Ia and typically develop in the second or third decade of life [1–8]. Although the incidence and pathogenesis of adenoma-to-carcinoma transformation is not established, hepatocellular carcinoma (HCC) in GSD Ia patients most often occurs within pre-existing adenomatous nodules [6,9]. Lesions worrisome for malignancy on radiologic imaging include those with increasing size, number, margin effacement, or spontaneous hemorrhage [5,6,10–12].

Dietary modifications comprising nocturnal continuous enteral drip feeding to avoid fasting hypoglycemia and frequent oral uncooked corn starch intake for prolonged glucose release have improved metabolic control, enhanced growth and pubertal development, and prolonged long-term survival for GSD Ia patients [1,2,13–15]. Whereas these patients previously died at a young age due to complications of metabolic dysfunction, life expectancy has improved so that more patients suffer from longer-term GSD Ia sequelae, such as HCC [1,2,5,6,13,14]. Some studies suggest that improved metabolic control may slow the growth or prevent development of HCAs [13]; conversely, other studies demonstrate that improved metabolic control has not been associated with HCA regression or reversal of malignant transformation in GSD Ia patients [2,5,8,10,16,17]. Correspondingly, indications for liver transplantation (LT) in these patients have evolved from correction of severe metabolic derangements resulting in stunted pediatric growth and development to prevention of long-term sequelae of GSD Ia, including malignant transformation of multiple, unresectable HCAs [2,7,11,18]. Indeed, the European study on glycogen storage disease type I (ESGSD I) guidelines suggest that LT be considered in patients with unresectable and dietary unresponsive multiple HCAs [2,11]. Previously, we have reported our experience with resection of HCAs among GSD Ia patients. Because GSD Ia patients have no priority for LT on the basis of calculated model for end-stage liver disease (MELD) score [19–21], resection of suspicious HCAs was utilized as an intermediate step in the prevention of HCC. Our data demonstrated that partial hepatectomy was not a definitive preventative measure; gross adenomatous disease was present in all patients following liver resection and all living patients experienced adenomatous disease progression at a median of 23 months [22]. In contrast, LT not only eliminates the possibility of HCC development and progression, but also corrects the underlying enzymatic defect causing GSD Ia [7,11,14,18]. The objective of this study is to review the long-term impact of LT on a group of GSD Ia patients at a single center where the principal indication for transplantation for most patients was definitive prevention of HCC.

2. Patients and methods

GSD Ia patients are annually surveyed using ultrasound imaging until puberty, and thereafter by intravenous contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) for the presence of HCAs. After adenoma detection, repeat imaging studies are performed at three to six month intervals to assess for adenoma growth, increase in lesion number, margin effacement, and evidence of hemorrhage. Given our earlier experience and that of others [5,6], all GSD Ia patients were referred for management because of concern for malignant transformation on the basis of increasing adenoma size, number, and/or margin effacement. Resection of suspicious HCA lesions was performed as an intermediate step in the prevention of HCC. However because of rapid adenoma recurrence following resection, four of five patients were evaluated for LT. The primary indication for LT for these four patients was concern for malignant hepatic adenoma transformation. Based on MELD score criteria [20,21,23,24] no GSD Ia patient had sufficient priority for LT (initial MELD scores ranged from 6 to 13). Petitions to the United Network for Organ Sharing (UNOS) region 11 review board for additional MELD listing points were made prospectively. These petitions centered upon the malignant potential of several HCA lesions based on recent changes in size and margin effacement on radiologic imaging after earlier resection and the inability to biopsy each and every such lesion reliably. These applications increased MELD scores to 22–24, thereby giving high priority for LT. In contrast, justifications for appeals to regional review boards for most other patients center upon complications of portal hypertension, such as ascites, porto-systemic encephalopathy, and gastrointestinal bleeding [24].

After obtaining Institutional Review Board approval, a retrospective review of demographics, pre-operative comorbid conditions, and long-term outcomes was completed for GSD Ia patients who underwent LT from 2004 to 2006. GSD Ia patients were assigned as having poor metabolic control when they experienced repeated episodes of hypoglycemia or serum uric acid, lactate, cholesterol, and/or triglyceride concentrations that were high even for this population despite intense nutritional therapy. In addition to standard periodic follow-up done for all patients after LT, markers of renal function (blood urea nitrogen, creatinine, and microalbumin/creatinine ratio), lactic acid, cholesterol, (triglyceride, and/or lipid profiles), and uric acid levels were estimated periodically to assess metabolic control. Simple sugar restrictions were recommended for all patients post LT to prevent or abrogate renal dysfunction secondary to GSD Ia.

3. Results

From 2004 to 2006, five consecutive GSD Ia patients underwent LT (Table 1). While other metabolic derangements contributed, adenoma recurrence and progression was the principal reason for consideration of LT in four of five patients. The fifth patient (patient 2) with HCAs was granted additional priority for LT primarily on the basis of co-existent lipoprotein lipase deficiency which resulted in several life-threatening episodes of acute, pancreatitis prior to LT. Four of five patients were on oral or intra-gastric corn starch (the one remaining patient was noncompliant) and all patients were on a simple sugar intake restriction pre-transplant. Multiple HCAs without histological evidence of malignancy were identified in all explanted specimens. The largest adenoma was 6.5 cm (patient 1) and the reported greatest number of lesions was 35 (patient 2). While there was no evidence of malignant transformation, focal hemor-