Liver transplantation (LT) may be indicated in glycogen storage disorders (GSD) when medical treatment fails to control the metabolic problems or when hepatic adenomas develop. We present our institutional experience with living donor LT (LDLT) for children with GSD. A total of 244 patients underwent primary LDLT at our institution from June 1994 to December 2005. A total of 12 (5%) children (8 female and 4 male) were afflicted with GSD and were not responsive to medical treatment. Nine patients had GSD type I and 3 had GSD type III. The median age at the time of transplantation was 7.27 yr (range, 2.4-15.7). All patients presented with metabolic abnormalities, including hypoglycemia, and lactic acidosis. In addition, 4 patients presented with growth retardation. A total of 11 patients received left lobe grafts and 1 received a right lobe graft. The mean graft-to-recipient weight ratio was 1.25 (range, 0.89-1.61). Two patients had hepatic vein stenoses that were treated by balloon dilatation; 1 patient had bile leak, which settled spontaneously. The overall surgical morbidity rate was 25%. Three patients had hepatic adenomas in the explanted liver. There was a single mortality at 2 months posttransplantation due to acute pancreatitis and sepsis. The mean follow up was 47.45 months. The metabolic abnormalities were corrected and renal function remained normal. In patients with growth retardation, catch-up growth was achieved posttransplantation. In conclusion, LDLT is a viable option to restore normal metabolic balance in patients with GSD when medical treatment fails. Long-term follow-up after LT for GSD shows excellent graft and patient survival.

sis, short stature, and hepatic adenomas with a possibility of malignant transformation. GSD type III (Cori disease) is caused by deficiency of glycogen debranching enzyme activity; and is characterized with dextrin-like glycogen accumulation in both liver and muscle in most patients. Hepatomegaly, hypoglycemia, hyperlipidemia, and growth retardation are the main manifestations in children; whereas liver cirrhosis and/or hepatocellular carcinoma may occur later. Some patients with GSD types I and III have difficulty in complying with restricted diets and sometimes need almost continuous feedings as they enter childhood; thus making them susceptible to episodes of severe hypoglycemia and seizures.

Liver transplantation (LT) is considered to correct the metabolic defects and the deleterious complications of GSD. We present our experience with living donor LT (LDLT) in children with GSD types I and III (9 GSD type I; 3 GSD type III). We believe this is the largest single-center experience with LDLT for GSD.

PATIENTS AND METHODS

A total of 244 patients underwent primary LDLT at the Chang Gung Memorial Hospital-Kaohsiung Medical Center, Taiwan, from June 1994 to December 2005. A total of 12 (5%) children (8 female, 4 male), afflicted with GSD and not responsive to medical treatment underwent LDLT from March 1996 to December 2005. Nine patients had GSD type I (5 female) and 3 girls had GSD type III. The median age at the time of transplantation was 7.27 yr (range, 2.4-15.7). All patients presented with metabolic abnormalities, which included recurrent hypoglycemia, hypertriglyceridemia, hypercholesterolemia, abnormal transaminases, and lactic acidosis (9 patients). All patients were referred for LT following failure of metabolic control with frequent daytime feedings and/or nocturnal nasogastric tube feeding. Although the median age at transplantation was 7.27 yr, all patients had been diagnosed earlier between 4 months to 24 months of age, and had been on adequate conservative treatment prior to the transplantation referral.

If on clinical presentation GSD was suspected, the diagnostic workup included serum glucose, blood pH, serum uric acid, triglycerides, cholesterol, serum creatinine, blood urea nitrogen, calcium, phosphorous, lactic acid, biochemical liver function, serum gamma glutamyltransferase, complete blood count, coagulation profile, urinalysis for aminoaciduria, proteinuria, albuminuria, uric acid, and calcium. Glucose tolerance test was performed to obtain further diagnosis and to differentiate GSD type I from type III. Further workup included mutation detection of glucose-6-phosphatase or debranching enzyme gene. However, in view of the high genotypic and phenotypic variability of the disease, the diagnosis was always confirmed with enzyme analysis (glucose-6-phosphatase or debrancher enzyme) in fresh liver biopsy prior to transplantation.

All the GSD type I patients were subtype Ia: and no GSD type I patient had persistent neutropenia or inflammatory bowel disease. Of the 3 children with GSD type III, 2 were subtype IIa based on debranching enzyme deficiency in the liver and muscle tissues. In the first GSD type III patient only liver biopsy was done. The ages of the 3 children with GSD type III at transplantation were 5.7, 2.4, and 5.4 yr, respectively. Echocardiography prior to transplantation showed normal findings in 8, trivial tricuspid regurgitation in 3, and trivial mitral regurgitation in 2 patients. Cardiomyopathy was not seen in any patient. In some children with GSD type III, the features may be indistinguishable from GSD type I. Although rare, it is possible for some GSD type III patients to persistently have metabolic problems despite frequent feedings of uncooked starch and continuous nocturnal nasogastric feeding.

In this series, 4 patients presented with growth retardation. One patient presented with decreased creatinine clearance, in which renal biopsy showed mild mesangial hypercellularity and periglomerular fibrosis. Another patient had asymptomatic bilateral nephrocalcinosis.

All patients underwent LDLT and received a triple immunosuppressive regimen (cyclosporine, prednisolone, and azathioprine). The operative technique, anesthesia management, immunosuppression, and follow-up of patients in this group were similar to that described earlier for pediatric patients in our institution. Blood samples from all patients were collected for biochemical studies before and regularly after LT.

The demographic, operative, and laboratory data were depicted as median, mean, and standard deviations. Paired t-test was used to compare pre- and post-transplantation biochemistry values. The anthropometric data (height-for-age and weight-for-age) were recorded as percentiles as compared to the normal using the growth chart for Taiwanese children. A P value of <0.05 was considered significant. Kaplan-Meier analysis was used to estimate mean survival.

RESULTS

All patients received a graft from either 1 of the parents (7 maternal, 5 paternal) and the mean donor age was 37.9 yr (range, 32.4-43.5). Seven donors were positive for hepatitis B core antibody. We performed 7 extended left lateral segmentectomy, 2 left lateral segmentectomy, 1 left lobectomy, 1 extended left lobectomy, and 1 right lobectomy with segments 5 and 8 veins reconstructed (11 left-side grafts, and 1 right-side graft). The mean graft-to-recipient-weight ratio was 1.25 (+0.24), and the mean donor blood loss was 115.8 mL (standard deviation + 78.8). There were no major postoperative complications in all donors. One donor had prolonged ileus and 1 had prolonged elevation of liver enzymes both of which settled spontaneously. All transplants were ABO-compatible and performed without venovenous bypass with preservation the inferior vena cava.

Postoperatively, prostaglandin E1 (0.01 μg/kg/hour) was routinely administered for 2 weeks. Prophylactic antibiotics included ampicillin (50 mg/kg/6 hour) and cefazidime (30 mg/kg/8 hour), or were tailored to preoperative
cultures. Oral fluconazole (4 mg/kg) was used to prevent fungal infections; and hyperimmune cytomegalovirus globulin (cytotec 1 mL/kg/week) for prophylaxis of cytomegalovirus infection was also given. Ganciclovir (5 mg/kg, twice daily) was given routinely to pediatric patients for 1 month. Patients previously vaccinated against hepatitis B whose anti-hepatitis B surface antigen titers were <1,000 IU/L received a booster(s) hepatitis B vaccine before transplantation. The donors were also vaccinated if their anti-hepatitis B virus surface antibody titers were low or negative prior to donation. The patients who received grafts from hepatitis B core antibody positive donors were given lamivudine 4 mg/kg/day postoperatively for 2 yr if their anti-hepatitis B surface antibody titers were <1,000 IU/L before transplant. Furthermore, these patients were administered hepatitis B vaccine after steroid withdrawal.

The mean operative time in the recipients was 650.9 minutes (standard deviation + 143.9), the mean blood loss was 239.9 mL (standard deviation + 400.77). Six patients underwent LDLT without perioperative blood or blood product transfusion. Three patients had liver adenomas measuring 2, 1, and 2.5 cm in maximum diameter, respectively, in the liver explants. Two patients were diagnosed preoperatively to have hepatic adenoma by diagnostic imaging. Two patients with GSD type III had liver cirrhosis on explant histology.

**Postoperative Complications**

One patient died at 2 months posttransplantation due to severe acute pancreatitis and sepsis. One child had prolonged drainage of ascitic fluid for 1 month, and 1 patient had a minor bile leak, both of which settled spontaneously. Two patients had hepatic venous outflow obstructions that were successfully managed by balloon dilatation. Two patients developed hypertension during the early postoperative period but did not require long-term antihypertensive therapy. Two patients who developed cytomegalovirus infection were treated with intravenous ganciclovir.

**Correction of Biochemical Abnormalities**

Following LDLT, the biochemical derangements improved dramatically and no further hypoglycemic episodes occurred in all patients. All patients reverted to normal diet after LDLT. The deranged transaminases improved in all surviving patients and no lactic acidosis occurred with routine fasting biochemical testing. The hypertriglyceridemia and hypercholesterolemia were not completely corrected in all patients but remarkably improved at 3 months and 1 yr postoperatively. Table 1 summarized the preoperative and postoperative biochemical parameters in the surviving patients. Hyperuricemia was seen only in 2 patients and both patients had improved values at 1 yr, postoperatively (not shown in table). The serum creatinine remained normal (including the patient with mesangial glomerulonephritis) and the deranged biochemical parameters remained controlled until the latest follow-up in all the remaining patients. Although the serum creatinine was within the acceptable normal range, significant increases in values were seen posttransplantation. The estimated creatinine clearance also showed a significant decrease at 3 months but has remained stable at 1 yr.

**Growth**

Four children presented with height less than the third percentile for age and 3 children had weights less than the third percentile for age. The children were monitored for growth posttransplantation. The mean percentile weight-for-age in these children was within nor-

### TABLE 1. Biochemical Values Pre- and Posttransplantation

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Preoperative†</th>
<th>Postoperative (3 months)†</th>
<th>Pre- and postoperative comparison (P value)</th>
<th>Postoperative (1 yr)†</th>
<th>3-month and 1-yr comparison (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate (5.7–22 U/dL)</td>
<td>34.24 (20.58)</td>
<td>6.3400 (1.03)</td>
<td>0.002</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AST (13–40 U/L)</td>
<td>272.73 (339.93)</td>
<td>34 (12.67)</td>
<td>0.036</td>
<td>46.22 (26.85)</td>
<td>0.05</td>
</tr>
<tr>
<td>ALT (16–40 U/L)</td>
<td>209.18 (292.91)</td>
<td>25.09 (14.86)</td>
<td>0.014</td>
<td>36.89 (28.56)</td>
<td>0.074</td>
</tr>
<tr>
<td>Triglyceride (30–110 mg/dL)</td>
<td>473.36 (319.52)</td>
<td>79.09 (38.76)</td>
<td>0.008</td>
<td>137.75 (54.15)</td>
<td>0.191</td>
</tr>
<tr>
<td>Cholesterol (&lt;170 mg/dL)</td>
<td>258.62 (107.5)</td>
<td>143.5 (41.11)</td>
<td>0.004</td>
<td>158.12 (45.12)</td>
<td>0.067</td>
</tr>
<tr>
<td>Creatinine (0.4–1.4 mg/dL)</td>
<td>0.463 (0.14)</td>
<td>0.609 (0.14)</td>
<td>0.001</td>
<td>0.63 (0.148)</td>
<td>0.512</td>
</tr>
<tr>
<td>Creatinine clearance (mL/minute)*</td>
<td>42.78 (9.89)</td>
<td>34.55 (10.06)</td>
<td>0.003</td>
<td>39.11 (16.51)</td>
<td>0.3</td>
</tr>
<tr>
<td>Creatinine clearance (mL/minute/1.73 m²)*</td>
<td>105.88 (21.53)</td>
<td>81.11 (19.20)</td>
<td>0.00</td>
<td>80.33 (24.65)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

**Abbreviations:** AST, alanine aminotransferase; ALT, alcoholic liver disease.

*Values in parentheses are normal laboratory ranges.

†Values in parentheses are standard deviations.

*Estimated creatinine clearance in children.20
mal range at 6 months posttransplantation (Fig. 1). The mean height-for-age was above the 10th percentile at 24 months and above the 25th percentile at 36 months (Fig. 2). All 4 patients continued to have healthy somatic growth until the latest follow-up. The remaining 7 patients who had normal weight and height pretransplantation continued to have normal posttransplantation somatic growth. All 11 patients were attending school appropriate for their age. One girl with GSD type I had delayed menarche at the age of 17 yr. In patients with GSD type III, none developed clinically progressive myopathy, muscle weakness, or cardiomyopathy.

**Follow-Up**

The mean follow up was 47.45 months (95% confidence interval, 22.87-72.03 months). Three of the 11 surviving recipients each experienced an episode of acute cellular rejection, which was treated successfully with intravenous pulse methylprednisolone. One patient was started on mycophenolate mofetil in addition to cyclosporine. None of the patients who received grafts from hepatitis B core antibody positive donors developed de novo hepatitis B infection. The mean survival using Kaplan-Meier analysis is 109.36 months (95% confidence interval, 89.29-120).

**DISCUSSION**

Characteristically, the patients with GSD types I and III have hepatomegaly, growth failure, and pubertal delay with associated biochemical abnormalities, including hypoglycemia, hyperlactatemia, hyperuricemia, and hyperlipidaemia. However, transplantation should be performed if dietary treatment with continuous overnight nasogastric feeds of glucose polymer and uncooked cornstarch fail, or if there has been malignant transformation of an adenoma. Poor metabolic control was the prime indication for LT for all our patients. LT has been reported in several patients to correct the hypoglycemia and other biochemical abnormalities, and growth impairment. Prior to surgery, good metabolic control needs to be established and glucose levels should be carefully maintained preoperatively and during surgery with intravenous dextrose.

We found 3 adenomas in this series; 2 of which were detected preoperatively. The patients with adenomas were relatively older at 9, 14, and 15 yr compared to the series median of 7.27 yr at the time of transplantation. This supports previously reported findings that the incidence of adenomas increases with age and are usually found in the second decade of life. Patients with adenomas need to be observed closely for development of hepatocellular carcinoma.

All patients in this series were relieved of recurrent hypoglycemic attacks, reduced their need for frequent and specialized diets, and thus improved their quality of life. In a report on the long-term result of GSD type I after LT by Matern et al., all of his patients (7 GSD Ia and 2 GSD Ib) were alive and the metabolic derangements were corrected (follow-up, 0.5-11.3 yr). In our series, we observed a significant reduction of hypertriglyceridemia and hypercholesterolemia, though the values did not reach normal limits posttransplantation. The lipid and lipoprotein profiles are “atherogenic,” which may raise the possibility of “atherogenic” complications in the future. The transaminases were expectedly lower posttransplantation, except during the rejection episodes in 3 patients.

Renal disease is common in patients with GSD type I. Proteinuria, renal stones, nephrocalcinosis and altered creatinine clearance, glomerular hyperfiltration, microalbuminuria, and increased renal plasma flow are also often found. With advancement of renal disease, focal segmental glomerulosclerosis and interstitial fi-
brosis are typically seen on biopsy. Two patients had mild mesangial glomerulonephritis and 1 had nephrocalcinosis. It has been suggested that the renal condition may progress independent of the liver either due to an intrinsic defect in glucose-6-phosphatase or due to progressive prolonged hyperfiltration. Both patients are on cyclosporine immunosuppression and continue to have normal creatinine levels postoperatively at the latest follow-up. However, longer follow-up is essential to establish long-term renal outcome in these patients.

Impaired growth is one of the problems encountered in patients with GSD types I and III. Dietary treatment improves growth in most patients; however, a few patients do not respond for reasons that are not clear. In the series of 9 patients with GSD type I and III by Matern et al., only 2 were reported to have catch-up growth following LT. In our series, all 4 patients with anthropometric parameters below the third percentile had catch-up growth to normal values posttransplantation. The other patients continued to have normal growth postoperatively. Puberty is frequently delayed in patients with GSD type I. Only 1 girl in this series had delayed menarche (at the 17 yr). The catch-up growth may be attributable to the good metabolic control posttransplantation.

During childhood, GSD type III may be difficult to distinguish from GSD type I as the predominant features are hepatomegaly, growth retardation, hypoglycemia, and hyperlipidemia. High liver transaminases and fasting ketosis are also common in GSD type III. Overt liver cirrhosis occurs rarely. The main indication for LT for patients with GSD type III in our series was poor metabolic control, though 2 out of 3 patients had evidence of liver cirrhosis on explant histology. Our experience with GSD shows that there are occasionally rare children with GSD type III in whom conservative treatment may fail. We emphasize the need for thorough workup, conservative treatment with frequent feeds, and continuous nocturnal feeds, and LT should be only the last resort in these children. No patient with GSD type III developed clinically progressive myopathy, muscle weakness, or cardiomyopathy. However, clinically significant myopathy and cardiomyopathy may develop only during the second decade of life or during young adulthood. Further follow-up is definitely needed.

One patient with GSD type I in this series died at 2 months posttransplantation due to severe acute pancreatitis and sepsis. Both acute and chronic pancreatitis have been described as case reports in the setting of GSD type I and have been attributed to the presence of hyperlipidemia. However, almost all patients with GSD type I have hyperlipidemia; why a few patients develop pancreatitis is unknown and the pathogenesis may be multifactorial.

In summary, our experience with LDLT for GSD types I and III shows that normal metabolic balance is restored posttransplantation. Good catch-up growth may be expected in patients with growth failure. Physical and intellectual growth is maintained, though sexual maturation is unpredictable. LDLT is a viable option for GSD I and III patients in whom medical treatment fails, with acceptable outcome and good long-term results.

REFERENCES