ELSEVIER

Outcome of Living Donor Liver Transplantation for Glycogen Storage Disease

P.-P. Liu, V.H. de Villa, Y.-S. Chen, C.-C. Wang, S.-H. Wang, Y.-C. Chiang, B. Jawan, H.-K. Cheung, Y.-F. Cheng, T.-L. Huang, H.-L. Eng, F.-R. Chuang, and C.-L. Chen

GLYCOGEN storage diseases (GSD) are inherited disorders in which the amount and/or structure of glycogen in body tissues are abnormal.[1,2] GSD I (von Gierke disease) is caused by a deficiency of glucose 6-phosphatase activity in the liver, kidney, and intestinal mucosa with glycogen overloading in these organs. The clinical manifestations are seizures, systemic acidosis, hyperlipidemia, hyperuricemia, and growth retardation. Without effective treatment, long-term complications occur, including gout, osteoporosis, short stature, and hepatic adenomas.[3–5] GSD III (Cori disease) is caused by a deficiency of glycogen debranching enzyme activity and characterized with limit dextrin-like glycogen accumulated in both liver and muscle in most patients. Hepatomegaly, hypoglycemia, hyperlipidemia, and growth retardation are the main manifestations in children; while liver cirrhosis and /or hepatocellular carcinoma may occur later.[6,7]

Great progress in the management of GSD I and III has been made recently. For patients affected with GSD I, nocturnal nasogastric feeding of glucose or orally administered uncooked cornstarch is effective.[2,8] With early diagnosis and initiation of treatment, normal growth and development may be expected. Some patients are free of long-term complications. Treatment of GSD III consists of high-protein diet, and frequent high carbohydrate meals for patients with hypoglycemia. Nocturnal gastric feeding or cornstarch supplements comprise effective therapy. However, some patients with GSD do not respond to diet therapy and may need frequent intravenous glucose infusions and even parenteral nutrition to maintain metabolic homeostasis. Liver transplantation (LT) is considered to correct the metabolic defects and the deleterious complications of GSD. LT for GSD I and III was first reported, respectively, by Malatack et al in 198 and by Superina et al in 1989.[9,10] We present five cases of GSD (four GSD Ia; one GSD III), which were treated by living donor liver transplantation (LDLT) in our institution. These patients were unresponsive to medical therapy or developed serious complications of GSD. In this study we investigate the outcome of these children after LDLT for GSD.

PATIENTS AND METHODS

From 1996 to 2001, 78 LDLT were performed in our institution, five of which were for GSD. Four had GSD type Ia (three girls and one boy, aged from 4.3 to 14.5 years) and one GSD type III (3.8 year old girl), as diagnosed by enzyme assays. All patients were under metabolic control with frequent daytime feedings and/or nocturnal nasogastric tube feeding, while their clinical conditions did not improve. One patient (LDLT 18) suffered frequent hypoglycemic convulsions and even coma before transplantation. The GSD III patient had hepatomegaly and impaired liver function, which progressed to cirrhotic change upon biopsy. The surgical procedures were similar for all donors (five mothers) and recipients with some modifications mainly for anatomic variations. All recipients received a triple immunosuppressive regimen (cyclosporine-Neoral, corticosteroid, and azathioprine). Blood samples from all the patients were collected for biochemical studies before and regularly after liver transplantation. The surgical specimens were fixed in 10% buffered formaldehyde solution and processed for routine histological analysis. Periodic acid-Schiff stain was performed for identification of glycogen deposition.

RESULTS

The surgical procedures were similar in all patients and the type of donor hepatectomy was decided mainly on the basis of the estimated graft recipient weight ratio (GRWR) above 1% as possible. We performed two left lobectomies, one extended left lateral segmentectomy and two left lateral segmentectomies with minimal blood loss.

An adenoma was found in each explanted liver of LDLT18 ($2 \times 2 \times 2$ cm) and LDLT28 ($1 \times 1 \times 1$ cm) without malignant transformation. The histological study of liver tissue confirmed the diagnosis of GSD, and showing ballooned hepatocytes with glycogen overloaded.

Although the operative courses were generally unre-

From the Departments of Surgery and Liver Transplant Program (P-P.L., V.H.dV., Y-S.C., C-C.W., S-H.W., Y-C.C., B.J., H-K.C., Y-F.C., T-L.H., H-L.E., C.L.C.), Department of Nephrology (F-R.C), Chang Gung University and Chang Gung Memorial Hospital, Kaohsiung Medical Center, Kaohsiung, Taiwan

Address reprint requests to Dr. C. L. Chen, Department of Surgery, Chang Gung Memorial Hospital, 123, Ta-Pei Road, Niao-Sung, Kaohsiung 83305, Taiwan.

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Table 1. Anthropometry of Patients Before and After LDLT

Patients (age/sex)	Before (percentile)*	After (percentile)*
GSD III		
LDLT 5 (5.8/girl)		
Weight (kg)	17.5 (25–50th)	24.6 (50th)
Height (cm)	99 (10th)	122 (50th)
GSD Ia		
LDLT 16		
Weight (kg)	14 (<3rd)	18.3 (3–10th)
Height (cm)	93 (<3rd)	113.7 (10th)
LDLT 18		
Weight (kg)	30 (<3rd)	59 (95th)
Height (cm)	127 (3rd)	144 (3rd)
LDLT 27		
Weight (kg)	12 (<3rd)	18.3 (25th)
Height (cm)	92 (<3rd)	113 (10–25th)
LDLT 28		
Weight (kg)	19 (10th)	26 (25th)
Height (cm)	113 (<3rd)	130.3 (25th)

*Comparing the measurements of the recipients to the standard growth curve of Chinese children.

markable, there were a few manageable complications. Two of the five recipients each experienced an episode of acute cellular rejection, which was treated with pulse methylprednisolone. The response was good and there was no need to shift to FK 506. One child displayed prolonged drainage (ascites) for 1 month but no vascular complication the drainage ceased spontaneously. Two patients developed hypertension during the early postoperative period, but did not require long-term antihypertensive therapy. Mild hirsutism was noted in all patients, but it was acceptable. Hyperkalemia was observed in two cases, that responded to Neoral dose reduction and potassium ion exchange treatment. Two patients with CMV infections were treated with intravenous ganciclovir.

All patients had growth retardation despite standard diet treatment before LT. These patients showed abnormal linear growth and body weight compared to the standards for their age. Two years after LDLT all patients showed catch-up growth in both height and weight (Table 1). After LDLT the biochemical derangements improved dramatically and no further hypoglycemic episodes occurred in our recipients. Liver function tests normalized in all patients and no systemic acidosis was detected. The renal function remained normal in our patients after LDLT. Only one patient (LDLT 18) with GSD Ia had pretransplant renal involvement, which was presented as hematuria and a decreased creatinine clearance (Ccr: 44.5 ml/min). Her renal function remained adequate (Ccr: 51 ml/min) and needed no more treatment after LDLT up to 3 years. Hyperlipidemia was a serious problem but disappeared after LT in all patients (Table 2). All five patients are alive with normal liver function at follow-up periods ranging from 2.2 to 5.5 years.

Table 2. Biochemical Studies for Recipients Before and 3 Months After LDLT

Biochemical tests	Before	After
GSD Type III		
LDLT 5		
AST (U/L)	1210	48
ALT (U/L)	660	29
Lactate (mg %)	6.6	5.6
Creatinine (mg %)	0.4	0.8
Triglyceride (mg %)	193	140
GSD Type Ia		
LDLT16		
AST (U/L)	229	22
ALT (U/L)	196	9
Lactate (mg %)	24.3	6.9
Creatinine (mg %)	0.4	0.5
Triglyceride (mg %)	399	123
LDLT18		
AST (U/L)	73	23
ALT (U/L)	66	22
Lactate (mg %)	71.8	7.9
Creatinine (mg %)	0.8	0.8
Triglyceride (mg %)	1320	186
LDLT27		
AST (U/L)	39	21
ALT (U/L)	21	17
Lactate (mg %)	37.3	5.7
Creatinine (mg %)	0.4	0.5
Triglyceride (mg %)	267	190
LDLT28		
AST (U/L)	229	23
ALT (U/L)	52	19
Lactate (mg %)	20.4	5.6
Creatinine (mg %)	0.5	0.7
Triglyceride (mg %)	464	202

DISCUSSION

In the past many patients with GSD I died and the prognosis was distressing in survivors. The current management of GSD I is nocturnal, nasogastric feeding of glucose or orally administered uncooked cornstarch. Both treatments were reported to effectively sustain the measured metabolic indexes for patients with GSD I. With early initiation of treatment, the prognosis for GSD I has improved dramatically. Although the results of early aggressive nutritional support are encouraging, some patients fail to respond to the intensive regimen and/or are unable to follow strict dietary rules; some patients even require frequent hospitalizations for intravenous glucose infusions or parenteral nutrition. In such a condition LT is the option after failure of other treatments.[2,6,7] Another common indication for LT in patients with GSD I is liver adenoma with the risk of malignant transformation. Recently Matern et al published long-term result of GSD I after LT, all their patients (7 GSD Ia and 2 GSD Ib) were alive and the metabolic derangements were corrected (follow up, 0.5 to 11.3 years).[6] Faivre et al demonstrated that restoration of normal metabolic balance and improvement of the quality

of life in patients with GSD Ia but some long-term complications occur reform (follow up for 6 to 8 years).[2] The effect on growth after LT varied in different reports but growth acceleration is generally expected for patients with GSD I. In the Matern et al series, catch-up growth was observed in only two of their seven patients.[6] Kirschner et al reported that LT even corrected growth retardation and sexual immaturity in their adult patient.[11]

The occurrence of focal glomerulosclerosis, a well-recognized complication among patients with GSD I, has been attributed to the consequence of hyperfiltration due to poor metabolic control. At present it remains unclear whether reversal and /or prevention of renal disease occurs after LT. Faiver et al found in one of their patients that focal glomerulosclerosis progressed independently from the liver condition, because of an intrinsic renal enzyme defect or hyperfiltration-induced glomerular lesion. Matern et al stated that four of their seven patients with GSD I had not presented any sign of renal disease with a maximum follow-up of 6.8 years after LT.[2] While analyzing the other patients with renal involvement in their article, there was no evidence to support the theory of renal disease progression after LT.[6] One of our patients (LDLT18) with GSD I had renal involvement, which presented as hematuria and decreased creatinine clearance. Renal biopsy showed mesangial hypercellularity and periglomerular fibrosis. Her renal function remained stable and she needed no further treatment up to 3 years after LT. We propose that there are various presentations of renal involvements in GSD I, with different long-term results. GSD III is characterized by a debranching enzyme deficiency and six subtypes have been delineated. Hepatomegaly, hypoglycemia, and short stature are often present in childhood. Liver fibrosis is a common feature of GSD III and micronodular cirrhosis has been observed.[6] The main indication for LT in patients with GSD III is end-stage cirrhosis. Occasionally hepatocellular carcinoma was suspected requiring LT. Because GSD III is a multisystem disorder, the long- term success of LT for GSD III is uncertain.

In conclusion, early medical and diet treatment should improve the metabolic derangements and outcome of most patients with GSD I and III. In selected cases LT may be considered, particularly after failure of metabolic control by a diet regimen, a poor quality of life, or potential life-threatening complications. In view of our satisfactory results and favorable outcomes with LDLT, we recommend LDLT as a specific option for GSD I and III.

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