Table 1 Age of onset, diagnosis and definitive diagnosis of hepatic GSD patients

	Patient's age: median (minimum–maximum)	*Age at onset: median (minimum–maximum)*	*Age of diagnosis: median (minimum–maximum)*	*Enzyme activity (%)*	*Identifiable mutation (%)*	*Dead patients*	*Surviving patients*	*No. of patients*
GSD Ia	13 y 8 mo (0 d–11 y 1 mo)	9 mo (0 d–11 y 1 mo)	1 y 2 mo (0 d–11 y 2 mo)	19/65 (29%)	41/65 (63%)	2 (3%)	63 (97%)	65 Patients (male: 41, female: 24)
GSD Ib	12 y 1 mo (1 y–27 y)	3 mo (0 d–4 mo)**	5.5 mo (2 mo–6 y 6 mo)**	3/11 (27%)	6/11 (55%)	1 (9%)	10 (91%)	11 Patients (male: 7, female: 4)
GSD III	12 y (3 y 7 mo–29 y 10 mo)	10.5 mo (7 mo–2 y 3 mo)	1 y (7 mo–2 y 3 mo)	4/6 (67%)	0/6 (0%)	1 (17%)	5 (83%)	6 Patients (male: 4, female: 2)[a]
GSD IV	1 y 1 mo (2 d–14 y 2 mo)	2 mo (0 d–5 mo)*	4 mo (0 d–9 mo)*	4/4 (100%)	0/4 (0%)	3 (75%)	1 (25%)	4 Patients (male: 3, female: 1)
GSD VI	9 y 10 mo (3 y 10 mo–19 y 6 mo)	1 y 3 mo (1 mo–3 y 4 mo)	1 y 4 mo (1 mo–6 y 6 mo)	4/6 (67%)	0/6 (0%)	0 (0%)	6 (100%)	6 Patients (male: 5, female: 1)
GSD IXa	9 y 9 mo (2 y 6 mo–17 y 11 mo)	1 y 7 mo (1 mo–5 y)**	2 y (1 mo–11 y)**	29/32 (91%)	2/32 (6%)	0 (0%)	32 (100%)	32 Patients (male: 32)
Others	11 y 9 mo (11 y 9 mo–29 y 9 mo)	1 y (5 d–1y 6 mo)	1 y 8 mo (1 y 8 mo–1 y 10 mo)	1/3 (33%)	2/3 (67%)	0 (0%)	3 (100%)	3 Patients (male: 2, female: 1)
Total				64/127 (50%)	51/127 (40%)	7 (6%)	120 (94%)	127 Patients (male: 94, female: 33)

Abbreviations: d, days; GSD, glycogen storage disease; mo, months; y, years.
The category 'Others' includes the GSD IX (one patient), other than those with GSD IXa and Fanconi–Bickel syndrome (GSD XI; two patients).
*$P<0.05$.
**$P<0.01$.
[a]Includes four patients each with GSD IIIa (male, 2; female, 2) and two male patients with an unknown subtype.

One hundred percent (5/5) of the male GSD VI patients had height greater than the tenth percentile (Figure 1b). Thirty-three percent (5/15) of the female GSD Ia patients aged <18 years and 44% (4/9) of the female GSD Ia patients aged ⩾18 years had heights below the third percentile. The mean height of female GSD Ia patients aged ⩾18 years was 147.8 ± 3.80 cm ($n=9$; Figure 1d).

Long-term survival of patients with hepatic GSD

Table 1 presents the number of hepatic GSD patients who survived and died. Two patients with GSD Ia (age of death: 6 years 10 months, male; 27 years, female), a male GSD Ib patient (13 years 5 months), a female GSD IIIa patient with cardiomyopathy (24 years 8 months) and a male GSD IV patient (1 year 11 months) died because of liver failure after liver transplantation. The other two patients with GSD IV died of liver failure 2 months after birth.

The long-term survival rate of GSD Ia patients at 20 years after birth was 97% for male patients and 100% for female patients (Figure 2). The survival rate of GSD Ib patients at 20 years after birth was 80% (Supplementary Figure 1).

Treatment for hepatic GSD

Table 3 indicates the treatment received by the hepatic GSD patients. Among the patients with GSD Ia, uncooked corn starch was administered to 98% (64/65) of the patients; allopurinol, to 74% (48/65); lipid-lowering drugs, to 42% (27/65); and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, to 15% (10/65). Dietary management with restriction of the intake of galactose, fructose and saccharose was used for 63% (41/62) of the patients. Most patients were not taking the GSD formula when they were taking corn starch. Lipid-lowering drugs were administered to 66% (18/27) of the GSD Ia patients with hyperlipidemia and aged 14 years or more. The youngest patient who received lipid-lowering drugs was 5 years old.

Liver transplantation for hepatic GSD

Table 4 shows the ages at which liver transplants were performed for hepatic GSD patients. As many metabolic disorders, such as hypoglycemia, were improved in the two patients with GSD Ia who underwent successful liver transplantation, symptoms such as nasal bleeding and growth disorder were ameliorated. These two patients needed allopurinol, but not diet and corn starch treatment.

Figure 3 and Supplementary Figure 2 present the comparison between the data obtained immediately before liver transplant and 1 year after liver transplant in five patients with GSD Ib. Blood levels of uric acid, total cholesterol and triglyceride in GSD Ib patients improved after liver transplantation, but the abnormalities in the neutrophil count were not ameliorated. All the five patients received granulocyte colony-stimulating factor after liver transplants; however, the frequency of granulocyte colony-stimulating factor administration after liver transplantation was lower than that before transplantation, as was the susceptibility to infection. No patients in this study received bone-marrow transplantation.

DISCUSSION

Most patients with hepatic GSD, except for GSD VI and IXa, which were mild types, manifested symptoms before 2 years of age. Further, the age of onset for GSD Ib and IV was lower than that for the other hepatic GSDs. However, two male GSD Ia patients presented with symptoms at 11 years and 9 years, thereby indicating that GSD may be detected at any age. Enzyme activity in the erythrocytes or leukocytes was measured in patients with GSD III, VI, IXa and XI, without performing invasive liver biopsy. Genome sequencing for GSD III, VI and IXa was difficult and not likely to be performed. Among the GSD I patients, the g727t mutation of the glucose-6-phosphatase gene has been detected in almost 90% alleles of GSD Ia,[30] and the W118R mutation of glucose-6-phosphate transporter gene is highly frequent in GSD Ib patients.[31] Therefore, we performed DNA analysis rather than enzyme assay, which requires invasive liver biopsy in GSD I patients. As this study focused on GSD patients younger than 18 years, we did not include many GSDs patients older than 18 years. Thus, the exclusion of GSD patients older than 18 years and GSD III patients may have introduced a bias in the results.

We investigated the statures of patients with hepatic GSD. Among the hepatic GSDs, GSD I commonly presents with short stature. Height <3 percentile were noted in 56% of the male GSD Ia patients and 33% of female GSD Ia patients aged <18 years. Mean stature in patients with GSD Ia aged >18 years was 160.8 ± 10.6 cm ($n=14$) and 147.8 ± 3.80 cm ($n=9$) for male and female patients, respectively.

Table 2 (a) Frequent manifestations of hepatic GSD; (b) Infrequent manifestations of hepatic GSD

(a)

	Growth disorder	*Hypo- glycemia*	*Hyper- lactacidemia*	*Hyper- uricemia*	*Hyper- lipidemia*	*Hepato- megaly*	*Fatty liver*	*Liver disorder*
GSD Ia	78% (51/65)	69% (45/65)	92% (60/65)	88% (57/65)	94% (61/65)	92% (60/65)	65% (42/65)	97% (63/65)
GSD Ib	55% (6/11)	91% (10/11)	91% (10/11)	64% (7/11)	55% (6/11)	100% (11/11)	64% (7/11)	64% (7/11)
GSD III	50% (3/6)	83% (5/6)	83% (5/6)	67% (4/6)	50% (3/6)	100% (6/6)	50% (3/6)	83% (5/6)
GSD IV	25% (1/4)	50% (2/4)	25% (1/4)	0% (0/4)	0% (0/4)	50% (2/4)	0% (0/4)	50% (2/4)
GSD VI	17% (1/6)	67% (4/6)	50% (3/6)	17% (1/6)	17% (1/6)	100% (6/6)	17% (1/6)	83% (5/6)
GSD IXa	44% (14/32)	34% (11/32)	34% (11/32)	6% (2/32)	41% (13/32)	97% (31/32)	47% (15/32)	84% (27/32)
Others	67% (2/3)	0% (0/3)	0% (0/3)	0% (0/3)	0% (0/3)	67% (2/3)	0% (0/3)	33% (1/3)
Total	61%(78/127)	61% (77/127)	71% (90/127)	56% (71/127)	66% (84/127)	93% (118/127)	54% (68/127)	87% (110/127)

(b)

	Bleeding tendency	*Convulsion*	*Mental retardation*	*Gout*	*Liver tumor*	*Protein- uria*	*Renal dysfunction*	*Hyper- tension*	*Cardio- myopathy*	*Myopathy*	*Osteo- porosis*	*Increased susceptibility to infection*
GSD Ia	31% (20/65)	9% (6/65)	9% (6/65)	11% (7/65)	22% (14/65)	26% (17/65)	11% (7/65)	3% (2/65)	6%(4/65)	1.5% (1/65)	3% (2/65)	5% (3/65)
GSD Ib	18% (2/11)	36% (4/11)	27% (3/11)	9% (1/11)	18% (2/11)	9% (1/11)	0% (0/11)	9% (1/11)	9% (1/11)	0% (0/11)	0% (0/11)	100% (11/11)
GSD III	0% (0/6)	67% (4/6)	33% (2/6)	0% (0/6)	0% (0/6)	0% (0/6)	0% (0/6)	17% (1/6)	17% (1/6)	50% (3/6)	0% (0/6)	0% (0/6)
GSD IV	75% (3/4)	0% (0/4)	25% (1/4)	0% (0/4)	0% (0/4)	0% (0/4)	0% (0/4)	0% (0/4)	50% (2/4)	50% (2/4)	0% (0/4)	25% (1/4)
GSD IV	17% (1/6)	0% (0/6)	0% (0/6)	0% (0/6)	0% (0/6)	0% (0/6)	0% (0/6)	0% (0/6)	0% (0/6)	17% (1/6)	0% (0/6)	0% (0/6)
GSD IXa	0% (0/32)	0% (0/32)	0% (0/32)	0% (0/32)	0% (0/32)	6% (2/32)	3% (1/32)	0% (0/32)	0% (0/32)	3% (1/32)	0% (0/32)	0% (0/32)
Others	0% (0/3)	0% (0/3)	0% (0/3)	0% (0/3)	0% (0/3)	0% (0/3)	33% (1/3)	0% (0/3)	0% (0/3)	0% (0/3)	0% (0/3)	0% (0/3)
Total	20% (26/127)	11% (14/127)	9% (12/127)	6% (8/127)	13% (16/127)	16% (20/127)	7% (9/127)	3% (4/127)	6% (8/127)	6% (8/127)	1.6% (2/127)	12% (15/127)

Abbreviation: GSD, glycogen storage disease.

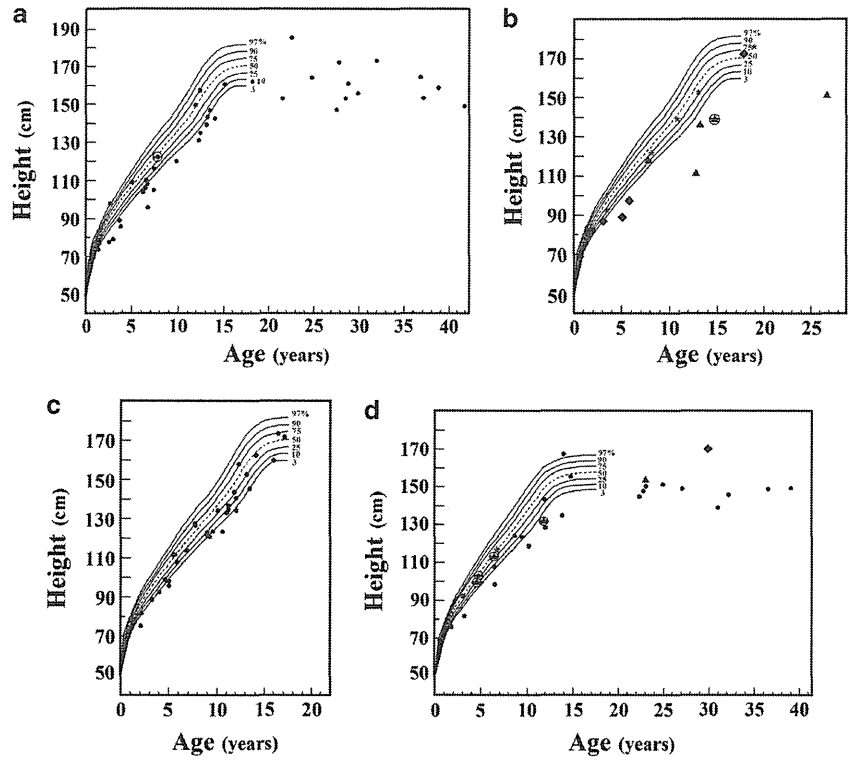

Figure 1 Stature of hepatic glycogen storage disease (GSD) patients. This figure was constructed with the age of GSD patients on the abscissa and the stature of patients with GSD on the ordinate. Percentiles are based on data from Japanese 2000 growth reports provided by the Ministry of Health, Labor and Welfare in Japan. (**a**) Stature of male patients with GSD Ia. The height of the male GSD Ia patient aged 7 years 11 months was measured after liver transplantation. ●: GSD Ia patients ($n=39$); ⊖: patients after liver transplant. (**b**) Stature of male patients with GSD Ib, GSD III and GSD VI. The heights of male GSD Ib patients aged 1 year 10 months and 14 years 10 months were measured after liver transplantation.▲: GSD Ib patients ($n=7$); ◆: GSD III patients ($n=4$); *: GSD VI patients ($n=5$); ⊖: patients after liver transplant. (**c**) Stature of male patients with GSD IXa. ●: GSD IXa patients ($n=32$). (**d**) Stature of female patients with GSD Ia, GSD Ib, GSD III and GSD VI. The heights of female GSD Ia patient aged 4 years 10 months and GSD Ib patients aged 4 years 7 months, 6 years 6 months and 11 years 11 months were measured after liver transplantation.●: GSD Ia patients ($n=24$), ▲: GSD Ib patients ($n=4$), ◆: GSD III patients ($n=1$), *: GSD VI ($n=1$), ⊖: patients after liver transplant.

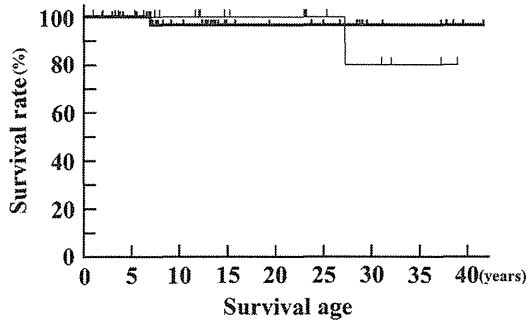

Figure 2 Long-term survival rates in patients with glycogen storage disease (GSD) Ia. The survival rates of 63 patients with different ages are shown by Kaplan–Meier survival curves. Two GSD Ia patients aged 6 years 10 months (male) and 27 years (female) died of liver failure after liver transplant. Male GSD Ia patients (black bold line), $n=41$; female GSD Ia patients (black fine line), $n=22$.

Therefore, we can expect that the final stature of patients with GSD Ia ranges from 3 to 10 percentile of the Japanese height.

Liver tumor and renal dysfunction, which are not frequently observed, are important determinants of the prognosis in patients with GSD.[1] It has been reported that liver adenomas are detected in 22 to 75% of patients with GSD Ia,[28,32] and some of these adenomas developed to hepatocellular carcinoma.[33,34] In this study, liver tumors, which have been reported to be less frequent overseas, were detected in 22% (14/65) of the patients with GSD Ia and in 18% (2/11) of patients with GSD Ib. The youngest GSD Ia patient with liver adenoma was a male patient aged 13 years 4 months, and 41% (14/34) of GSD Ia patients older than this patient had liver adenoma. Nakamura *et al.*[35] reported that 57.9% (11/19) of adult GSD Ia patients with the g727t homozygote mutation had liver adenomas, and 16% (3/19) of them had hepatocellular carcinoma. In this study, only one patient developed hepatocellular carcinoma, which was treated by percutaneous ethanol injection therapy and radiofrequency ablation, and did not recur.

Proteinuria, which is detected in many patients with GSD I, may progress to renal dysfunction or renal failure. In this study, two of the seven GSD Ia patients with renal dysfunction underwent hemodiafiltration. Chen *et al.* reported that 70% of GSD Ia patients aged >10 years presented with renal dysfunction and that 40% of GSD Ia patients with renal dysfunction developed progressive renal failure. The incidence of renal dysfunction, which was 11% (7/65) in GSD Ia patients of this study and 19% (7/36), in GSD Ia patients >10 years old, was very low.

As GSD Ia with g727t mutation is considered to be a mild type of GSD Ia, patients with the g727t mutation may develop only proteinuria but are not likely to develop renal dysfunction. It has been reported that transforming growth factor-β expression increases in the tubular epithelial cells and is involved in the pathophysiology of

Table 3 Treatment for hepatic GSD

Treatment	Dietary management	Uncooked corn starch	Sodium and potassium citrate	Allopurinol	Lipid- lowering drugs	ARB or ACE-I	Hypoglycemic medication	L- carnitine	G-CSF
GSD Ia	63% (41/65)	98% (64/65)	37% (24/65)	74% (48/65)	42% (27/65)	15% (10/65)	6% (4/65)	0% (0/65)	0% (0/65)
GSD Ib	64% (7/11)	82% (9/11)	0% (0/11)	9% (1/11)	9% (1/11)	0% (0/11)	9% (1/11)	27% (3/11)	55% (6/11)
GSD III	33% (2/6)	67% (4/6)	17% (1/6)	17% (1/6)	0% (0/6)	0% (0/6)	0% (0/6)	0% (0/6)	0% (0/6)
GSD IV	0% (0/4)	0% (0/4)	0% (0/4)	0% (0/4)	0% (0/4)	0% (0/4)	0% (0/4)	0% (0/4)	0% (0/4)
GSD VI	17% (1/6)	67% (4/6)	0% (0/6)	0% (0/6)	0% (0/6)	0% (0/6)	0% (0/6)	0% (0/6)	0% (0/6)
GSD IXa	16% (5/32)	50% (16/32)	0% (0/32)	0% (0/32)	31% (10/32)	0% (0/32)	0% (0/32)	0% (0/32)	0% (0/32)
Others	33% (1/3)	67% (2/3)	33% (1/3)	0% (0/3)	33% (1/3)	0% (0/3)	0% (0/3)	67% (2/3)	0% (0/3)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; GSD, glycogen storage disease; G-CSF, granulocyte colony-stimulating factor.

Table 4 Age at liver transplant for hepatic GSD

Age	*<1 y*	*1 y to <6 y*	*6 y to <12 y*	*12 y to <18 y*	*⩾18 y*	*Total*
GSD Ia	0	3	0	0	1	4
GSD Ib	0	4	1	2	0	7
GSD III	0	0	0	0	1	1
GSD IV	2	0	0	0	0	2
Total	2	7	1	2	2	14

Abbreviations: GSD, glycogen storage disease; y, years.

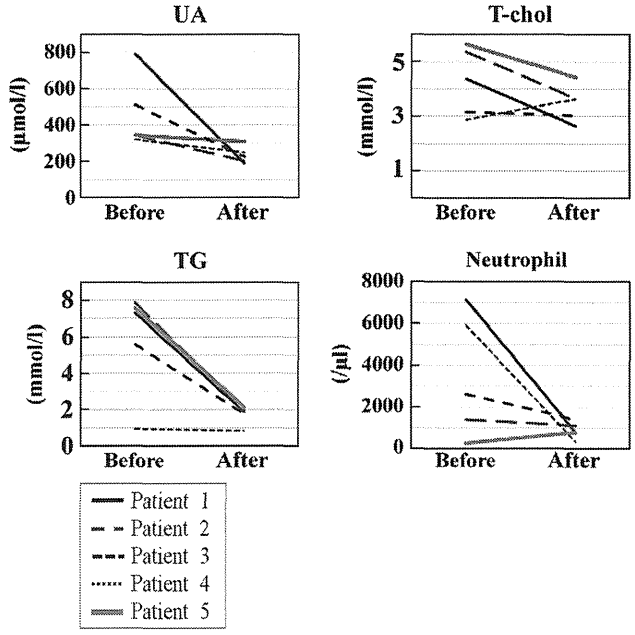

Figure 3 Comparison of data immediately before and 1 year after liver transplantation in glycogen storage disease (GSD) Ib patients. The age at liver transplantation was 1 year 1 month in patient 1 (male), 3 years 6 months in patient 2 (female), 3 years 6 months in patient 3 (male), 3 years 11 months in patient 4 (female) and 8 years 6 months in patient 5 (female). Only patient 3 received allopurinol after liver transplant. T-chol, total cholesterol; TG, triglyceride; UA, uric acid.

renal interstitial fibrosis, which results from the increase in the expression of extracellular matrix proteins in GSD I patients.[36] Angiotensin receptor blocker, angiotensin-converting enzyme inhibitor and alloprinol have been considered drugs with the highest potential of interfering with transforming growth factor-β expression because the renin angiotensin–aldosterone system and uric acid have been known to involved in the expression of transforming growth factor-β.[37,38] Moreover, it has been recognized that the small, dense low-density lipoprotein and modified low-density lipoprotein induce the development of glomerular sclerosis and renal dysfunction.[39]

Liver tumor is related to constant stimulation by hormones, such as insulin and glucagon, by persistent peripheral hypoglycemia. Therefore, the expression of renal dysfunction and liver tumor negatively correlates with metabolic control.[40] Important treatment strategies are restriction of the intake of galactose, fructose, and saccharose and blood glucose control by consumption of frequent meals and uncooked cornstarch.[40] Moreover, allopurinol, lipid-lowering drugs, and angiotensin receptor blocker or angiotensin-converting enzyme inhibitor have been reported to be significantly important in delaying the progression of kidney disease in GSD I patients.[19,39,41]

Recent reports have indicated that GSD patients may present with diabetes. Two GSD Ia patients who were brothers and had the g727t homozygote mutation developed type II diabetes and received therapy involving an α-glucosidase inhibitor and an insulin secretagogue. They monitored themselves for hypoglycemia attacks and corrected the same by consuming food or glucose. As shown in Table 1 and Figure 2, patients with hepatic GSD, except for those with GSD IV, can survive in the long term. Further, reports have also shown that GSD Ib and GSD III patients developed type II diabetes.[42,43] Therefore, physicians must pay attention to the development of obesity- and lifestyle-related diseases in GSD patients.

Table 3 indicates the treatments received by patients with hepatic GSD. As treatment after liver transplantation was recorded in Table 3, none of patients with GSD IV take dietary treatment and corn starch treatment. Use of lipid-lowering drugs has been recommended for adult GSD patients overseas.[18] Although definitive criteria for the use of lipid-lowering drugs in Japan have not yet been established, the youngest patient who received hypoglycemic medication was 5 years old.

Fourteen patients with hepatic GSD received liver transplants. According to overseas reports, the indications for liver transplantation in GSD patients are the progression of adenomatous lesions or multiple adenomas, suspicion or detection of malignant transformation of an adenoma, unresponsiveness to medical therapy, insufficient control of hypoglycemia, and growth or sexual retardation.[17,24,44] In Japan, the definitive criteria for liver transplants are controversial; many pediatricians and transplant surgeons follow the same indications reported overseas for liver transplantation. GSD I patients with uncontrolled hypoglycemia, which leads to convulsions and mental retardation, should receive liver transplants. Ninety-one

percent (10/11) of patients with GSD I received liver transplants because of insufficient control of hypoglycemia and metabolic disorders, despite medical therapy. GSD III and GSD IV patients received liver transplants because of liver failure, which was considered an indication of liver transplant, as per the pediatric end-stage liver disease scores. In this study, all GSD I patients with multiple liver adenomas underwent hepatectomy, and only one patient with GSD I received a liver transplant because of adenoma recurrence after adenoma resection. Five of 14 GSD patients died because of liver failure <2 months after liver transplantation. The other nine patients survived and improved such that they did not develop hypoglycemia without medication and showed better increase in height. The frequency of infection decreased in GSD Ib patients after transplantation, as described previously.[45] Liver transplants contributed to an improved QOL in GSD patients. We believe that liver transplants should be proactively performed in patients with GSD Ib. Although the success rate of liver transplantation for hepatic GSD in this study was lower than that reported abroad,[24,46–49] the low success rate of liver transplants may be attributed to the severe liver failure in the fatal GSD cases before transplantation.

In conclusion, we discussed the diagnosis, treatment and long-term outcome of hepatic GSDs and the present status of hepatic GSD patients in Japan. We found a characteristic genetic pattern with many GSD Ia patients presenting with the g727t mutation and GSD Ib patients showing the W118R mutation. Although patients with hepatic GSD, except for those with GSD IV, develop a variety of symptoms, they can survive in the long-term by diet therapy, corn starch treatment and supportive care. Liver transplantation is an important therapeutic strategy for hepatic GSD and can help improve the patients' QOL.

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1 Chen, Y. T., Coleman, R. A., Scheinman, J. I., Kolbeck, P. C. & Sidbury, J. B. Renal disease in type I glycogen storage disease. *N. Engl. J. Med.* **318,** 7–11 (1988).
2 Reitsma-Bierens, W. C. Renal complications in glycogen storage disease type I. *Eur. J. Pediatr.* **152** (Suppl 1), S60–S62 (1993).
3 Zangeneh, F., Limbeck, G. A., Brown, B. I., Emch, J. R., Arcasoy, M. M., Goldenberg, V. E. *et al.* Hepatorenal glycogenosis (type I glycogenosis) and carcinoma of the liver. *J. Pediatr.* **74,** 73–83 (1969).
4 Franco, L. M., Krishnamurthy, V., Bali, D., Weinstein, D. A., Arn, P., Clary, B. *et al.* Hepatocellular carcinoma in glycogen storage disease type Ia: a case series. *J. Inherit. Metab. Dis.* **28,** 153–162 (2005).
5 Parvari, R., Moses, S., Shen, J., Hershkovitz, E., Lerner, A. & Chen, Y. T. A single-base deletion in the 3'-coding region of glycogen-debranching enzyme is prevalent in glycogen storage disease type IIIA in a population of North African Jewish patients. *Eur. J. Hum. Genet.* **5,** 266–270 (1997).
6 Shen, J., Shen, J., Bao, Y., Liu, H. M., Lee, P., Leonard, J. V. *et al.* Mutations in exon 3 of the glycogen debranching enzyme gene are associated with glycogen storage disease type III that is differentially expressed in liver and muscle. *J. Clin. Invest.* **98,** 352–357 (1996).
7 Moses, S. W., Wanderman, K. L., Myroz, A. & Frydman, M. Cardiac involvement in glycogen storage disease type III. *Eur. J. Pediatr.* **148,** 764–766 (1989).
8 L'Hermine-Coulomb, A., Beuzen, F., Bouvier, R., Rolland, M. O., Froissart, R., Menez, F. *et al.* Fetal type IV glycogen storage disease: clinical, enzymatic, and genetic data of a pure muscular form with variable and early antenatal manifestations in the same family. *Am. J. Med. Genet. A* **139A,** 118–122 (2005).
9 Andersen, D. H. Familial cirrhosis of the liver with storage of abnormal glycogen. *Lab. Invest.* **5,** 11–20 (1956).
10 Selby, R., Starzl, T. E., Yunis, E., Brown, B. I., Kendall, R. S., Tzakis, A. *et al.* Liver transplantation for type IV glycogen storage disease. *N. Engl. J. Med.* **324,** 39–42 (1991).
11 Willems, P. J., Gerver, W. J., Berger, R. & Fernandes, J. The natural history of liver glycogenosis due to phosphorylase kinase deficiency: a longitudinal study of 41 patients. *Eur. J. Pediatr.* **149,** 268–271 (1990).
12 Manz, F., Bickel, H., Brodehl, J., Feist, D., Gellissen, K., Geschöll-Bauer, B. *et al.* Fanconi-Bickel syndrome. *Pediatr. Nephrol.* **1,** 509–518 (1987).
13 Bhattacharya, K., Orton, R. C., Qi, X., Mundy, H., Morley, D. W., Champion, M. P. *et al.* A novel starch for the treatment of glycogen storage diseases. *J. Inherit. Metab. Dis.* **30,** 350–357 (2007).
14 Chen, Y. T., Cornblath, M. & Sidbury, J. B. Cornstarch therapy in type I glycogen-storage disease. *N. Engl. J. Med.* **310,** 171–175 (1984).
15 Lee, P. J., Van't Hoff, W. G. & Leonard, J. V. Catch-up growth in Fanconi-Bickel syndrome with uncooked cornstarch. *J. Inherit. Metab. Dis.* **18,** 153–156 (1995).
16 Bandsma, R. H., Prinsen, B. H., van Der Velden Mde, S., Rake, J. P., Boer, T., Smit, G. P. *et al.* Increased de novo lipogenesis and delayed conversion of large VLDL into intermediate density lipoprotein particles contribute to hyperlipidemia in glycogen storage disease type 1a. *Pediatr. Res.* **63,** 702–707 (2008).
17 Rake, J. P., Visser, G., Labrune, P., Leonard, J. V., Ullrich, K. & Smit, G. P. Glycogen storage disease type I: diagnosis, management, clinical course and outcome. Results of the European Study on Glycogen Storage Disease Type I (ESGSD I). *Eur. J. Pediatr.* **161** (Suppl 1), S20–S34 (2002).
18 Rake, J. P., Visser, G., Labrune, P., Leonard, J. V., Ullrich, K. & Smit, G. P. Guidelines for management of glycogen storage disease type I - European Study on Glycogen Storage Disease Type I (ESGSD I). *Eur. J. Pediatr.* **161** (Suppl 1), S112–S119 (2002).
19 Melis, D., Parenti, G., Gatti, R., Casa, R. D., Parini, R., Riva, E. *et al.* Efficacy of ACE-inhibitor therapy on renal disease in glycogen storage disease type 1: a multicentre retrospective study. *Clin. Endocrinol. (Oxf)* **63,** 19–25 (2005).
20 Koeberl, D. D., Pinto, C., Sun, B., Li, S., Kozink, D. M., Benjamin, D. K. Jr *et al.* AAV vector-mediated reversal of hypoglycemia in canine and murine glycogen storage disease type Ia. *Mol. Ther.* **16,** 665–672 (2008).
21 Lee, Y. M., Jun, H. S., Pan, C. J., Lin, S. R., Wilson, L. H., Mansfield, B. C. *et al.* Prevention of hepatocellular adenoma and correction of metabolic abnormalities in murine glycogen storage disease type Ia by gene therapy. *Hepatology* **56,** 1719–1729 (2012).
22 Bhattacharya, N., Heaton, N., Rela, M., Walter, J. H. & Lee, P. J. The benefits of liver transplantation in glycogenosis type Ib. *J. Inherit. Metab. Dis.* **27,** 539–540 (2004).
23 Faivre, L., Houssin, D., Valayer, J., Brouard, J., Hadchouel, M., Bernard, O. *et al.* Long-term outcome of liver transplantation in patients with glycogen storage disease type Ia. *J. Inherit. Metab. Dis.* **22,** 723–732 (1999).
24 Iyer, S. G., Chen, C. L., Wang, C. C., Wang, S. H., Concejero, A. M., Liu, Y. W. *et al.* Long-term results of living donor liver transplantation for glycogen storage disorders in children. *Liver Transpl.* **13,** 848–852 (2007).
25 Matern, D., Starzl, T. E., Arnaout, W., Barnard, J., Bynon, J. S., Dhawan, A. *et al.* Liver transplantation for glycogen storage disease types I, III, and IV. *Eur. J. Pediatr.* **158** (Suppl 2), S43–S48 (1999).
26 Smit, G. P. The long-term outcome of patients with glycogen storage disease type Ia. *Eur. J. Pediatr.* **152** (Suppl 1), S52–S55 (1993).
27 Smit, G. P., Fernandes, J., Leonard, J. V., Matthews, E. E., Moses, S. W., Odievre, M. *et al.* The long-term outcome of patients with glycogen storage diseases. *J. Inherit. Metab. Dis.* **13,** 411–418 (1990).
28 Talente, G. M., Coleman, R. A., Alter, C., Baker, L., Brown, B. I., Cannon, R. A. *et al.* Glycogen storage disease in adults. *Ann. Intern. Med.* **120,** 218–226 (1994).
29 Kido, J., Nakamura, K., Mitsubuchi, H., Ohura, T., Takayanagi, M., Matsuo, M. *et al.* Long-term outcome and intervention of urea cycle disorders in Japan. *J. Inherit. Metab. Dis.* **35,** 777–785 (2012).
30 Akanuma, J., Nishigaki, T., Fujii, K., Matsubara, Y., Inui, K., Takahashi, K. *et al.* Glycogen storage disease type Ia: molecular diagnosis of 51 Japanese patients and characterization of splicing mutations by analysis of ectopically transcribed mRNA from lymphoblastoid cells. *Am. J. Med. Genet.* **91,** 107–112 (2000).
31 Hou, D. C., Kure, S., Suzuki, Y., Hasegawa, Y., Hara, Y., Inoue, T. *et al.* Glycogen storage disease type Ib: structural and mutational analysis of the microsomal glucose-6-phosphate transporter gene. *Am. J. Med. Genet.* **86,** 253–257 (1999).
32 Labrune, P., Trioche, P., Duvaltier, I., Chevalier, P. & Odievre, M. Hepatocellular adenomas in glycogen storage disease type I and III: a series of 43 patients and review of the literature. *J. Pediatr. Gastroenterol. Nutr.* **24,** 276–279 (1997).
33 Bianchi, L. Glycogen storage disease I and hepatocellular tumours. *Eur. J. Pediatr.* **152** (Suppl 1), S63–S70 (1993).
34 Nakamura, K., Tanaka, Y., Mitsubuchi, H. & Endo, F. Animal models of tyrosinemia. *J. Nutr.* **137,** 1556S–1560S, discussion 1573S-1575S (2007).
35 Nakamura, T., Ozawa, T., Kawasaki, T., Nakamura, H. & Sugimura, H. Glucose-6-phosphatase gene mutations in 20 adult Japanese patients with glycogen storage disease type 1a with reference to hepatic tumors. *J. Gastroenterol. Hepatol.* **16,** 1402–1408 (2001).
36 Urushihara, M., Kagami, S., Ito, M., Yasutomo, K., Kondo, S., Kitamura, A. *et al.* Transforming growth factor-beta in renal disease with glycogen storage disease I. *Pediatr. Nephrol.* **19,** 676–678 (2004).

37 Talaat, K. M. & el-Sheikh, A. R. The effect of mild hyperuricemia on urinary transforming growth factor beta and the progression of chronic kidney disease. *Am. J. Nephrol.* **27,** 435–440 (2007).
38 Wolf, G. Renal injury due to renin-angiotensin-aldosterone system activation of the transforming growth factor-beta pathway. *Kidney Int.* **70,** 1914–1919 (2006).
39 Keane, W. F. The role of lipids in renal disease: future challenges. *Kidney Int. Suppl.* **75,** S27–S31 (2000).
40 Wolfsdorf, J. I., Laffel, L. M. & Crigler, J. F. Jr. Metabolic control and renal dysfunction in type I glycogen storage disease. *J. Inherit. Metab. Dis.* **20,** 559–568 (1997).
41 Kalogirou, M., Tsimihodimos, V., Gazi, I., Filippatos, T., Saougos, V., Tselepis, A. D. *et al.* Effect of ezetimibe monotherapy on the concentration of lipoprotein subfractions in patients with primary dyslipidaemia. *Curr. Med. Res. Opin.* **23,** 1169–1176 (2007).
42 Oki, Y., Okubo, M., Tanaka, S., Nakanishi, K., Kobayashi, T., Murase, T. *et al.* Diabetes mellitus secondary to glycogen storage disease type III. *Diabet. Med.* **17,** 810–812 (2000).
43 Spiegel, R., Rakover-Tenenbaum, Y., Mandel, H., Lumelski, D., Admoni, O., Horovitz, Y. *et al.* Secondary diabetes mellitus: late complication of glycogen storage disease type 1b. *J. Pediatr. Endocrinol. Metab.* **18,** 617–619 (2005).
44 Lerut, J. P., Ciccarelli, O., Sempoux, C., Danse, E., deFlandre, J., Horsmans, Y. *et al.* Glycogenosis storage type I diseases and evolutive adenomatosis: an indication for liver transplantation. *Transpl. Int.* **16,** 879–884 (2003).
45 Kasahara, M., Horikawa, R., Sakamoto, S., Shigeta, T., Tanaka, H., Fukuda, A. *et al.* Living donor liver transplantation for glycogen storage disease type Ib. *Liver Transpl.* **15,** 1867–1871 (2009).
46 Davis, M. K. & Weinstein, D. A. Liver transplantation in children with glycogen storage disease: controversies and evaluation of the risk/benefit of this procedure. *Pediatr. Transplant.* **12,** 137–145 (2008).
47 Maheshwari, A., Rankin, R., Segev, D. L. & Thuluvath, P. J. Outcomes of liver transplantation for glycogen storage disease: a matched-control study and a review of literature. *Clin. Transplant.* **26,** 432–436 (2012).
48 Liu, P. P., de Villa, V. H., Chen, Y. S., Wang, C. C., Wang, S. H., Chiang, Y. C. *et al.* Outcome of living donor liver transplantation for glycogen storage disease. *Transplant. Proc.* **35,** 366–368 (2003).
49 Reddy, S. K., Austin, S. L., Spencer-Manzon, M., Koeberl, D. D., Clary, B. M., Desai, D. M. *et al.* Liver transplantation for glycogen storage disease type Ia. *J. Hepatol.* **51,** 483–490 (2009).

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新しい新生児代謝スクリーニング時代に適応した先天代謝異常症の診断基準作成と治療ガイドラインの作成および新たな薬剤開発に向けた調査研究

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