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Original Article

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Does Type I Truly Dominate Hepatic Glycogen Storage Diseases in Korea?: A Single Center Study

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Purpose: There are no studies of hepatic glycogen storage diseases (GSDs) other than type I and III in Korea. We aimed on investigating the characteristics of hepatic GSDs in Korea diagnosed and followed at a single center.
Methods: We retrospectively analyzed patients who were diagnosed as GSD and followed at Samsung Medical Center from January, 1997 to December, 2013. Clinical manifestations, laboratory results, treatment, and prognosis were investigated.
Results: Twenty-one patients were included in the study. The types of 17 patients were confirmed by enzyme activity tests and/or gene analysis. GSD Ia was diagnosed in 7 patients (33.3%), Ib in 1 patient (4.8%), III in 2 patients (9.5%), IV in 1 patient (4.8%), and IX in 6 patients (28.6%). Types other than GSD I constituted 52.9% (9/17) of the patients diagnosed with a specific type of hepatic GSD. The median age at presentation was 2 years. Hepatomegaly was observed in 95.2%, elevated liver transaminases in 90.5%, and hyperlactacidemia in 81.0% of the patients. The duration for follow-up was 77±62.0 months. Uncooked corn starch was initiated in all the patients. No mortality was observed during the follow-up period, and liver transplantation was performed in 14.3%.
Conclusion: Types other than GSD I comprised more than half of the patients diagnosed with a specific type of hepatic GSD. Clinical suspicion and thorough evaluation of hepatic GSDs in Korea should be focused not only on GSD I, but also on other types.

Key Words: Glycogen storage disease, Liver, Korea

INTRODUCTION

Glycogen storage diseases (GSDs) are a group of inherited metabolic diseases, in which excess glycogen accumulates in the liver and muscle or both due to the deficiency of enzymes that regulate glycogenolysis or gluconeogenesis. Based on the specific enzyme deficiency, GSDs are classified by over 12

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types, and the overall incidence of GSDs is approximately one out of 20,000-43,000 live births [1-3]. Types such as GSD I, III, IV, VI, IX in which glycogen primarily accumulate in the liver are known as hepatic GSDs, and present with hepatomegaly, hypoglycemia, failure to thrive, hyperlactatemia, hyperuricemia and hyperlipidemia [2,3]. The severity of these clinical and biochemical symptoms differs between hepatic GSD types. Types such as GSD I, IV have more severe and progressive features developing at early infancy, while types such as GSD III, VI, IX have more mild features with good prognosis [3]. Even within the same type, phenotypic variation exists resulting in variable clinical courses and outcomes regardless of age or treatment. Among the hepatic GSDs, GSD I is well known as the commonest most severe childhood form, representing approximately 30% of hepatic GSDs [3,4].

Despite the variability of the clinical course among hepatic GSDs, the main goal of treatment is aimed at preventing hypoglycemia to avoid hypoglycemic seizures and long-term complications such as hepatic adenomas, renal dysfunction, and growth impairment [4,5]. The basic treatment consists of frequent meals, ingestion of slow-absorption carbohydrates such as uncooked starch, and dietary restriction of fructose, galactose, sucrose and lactose which is capable of aggravating hyperlactcidemia [6,7]. When dietary control fails or long-term complications persist, liver transplantation should be considered, as it is the only curable treatment of hepatic GSDs [8,9].

Several studies regarding the treatment and prognosis of hepatic GSDs have been reported worldwide [10-14]. However, to date there are no relevant studies other than GSD I and III in Korea [15-19], and case reports of other types are also scarce in Korea. Therefore, the aim of this study was to investigate the characteristics, treatment, and prognosis of hepatic GSDs in Korea.

MATERIALS AND METHODS

This retrospective study was conducted at the Department of Pediatrics of Samsung Medical Center between January 1997 and December 2013. Electronic databases were queried to identify patients who had been diagnosed as hepatic GSDs and followed during this period. Definite diagnosis of each type of GSD (Ia, Ib, III, IV, VI, IX) was confirmed by enzyme activity test results of the liver or erythrocytes and/or identification of gene mutations corresponding to the specific type. Subjects whose types were unrevealed due to negative results on enzyme activity tests or DNA analysis despite obvious non-lysosomal glycogen accumulation on pathology reports of liver biopsy specimens were defined as "not determined". Subjects that were diagnosed with muscular GSDs, such as GSD II or V were excluded from this study.

Electronic medical records of the subjects that met the inclusion criteria were reviewed to obtain data regarding demographic characteristics, clinical symptoms, laboratory test results, treatment, and prognosis. The definitions of abnormal laboratory findings were defined as follow [3]. Hypoglycemia was defined as a fasting blood glucose level <60 mg/dL. Hyperlactacidemia was defined as a fasting blood lactate level >2.5 mmol/L, and hyperuricemia was defined as a fasting blood uric acid level >5.0 mg/dL. Hypercholesterolemia was defined as a fasting blood total cholesterol level >200 mg/dL, and hypertriglyceridemia was defined as a fasting blood total triglyceride level >250 mg/dL. Anemia was defined as a blood hemoglobin level of <9.5 g/dL in ages 3-6 months old, <10.5 g/dL in ages 6-24 months old, <11.5 g/dL in ages 2-12 years old, <13 g/dL in males >12 years old, <12 in female >12 years old. Linear growth failure was defined as <3 percentile according to the growth charts of the Center for Disease Control of Korea.

This study was approved by the institutional review board of Samsung Medical Center.

RESULTS

In this retrospective study, 24 patients were diagnosed as hepatic GSD during the study period. Three patients who showed glycogen accumulation on liv-

er biopsy specimens, but were not evaluated and were lost during follow-up were excluded from the study leaving 21 patients for inclusion in this study. Subjects with a definite diagnosis of a specific type of GSD were 7 patients of GSD Ia (33.3%), 1 patient of GSD Ib (4.8%), 2 patients of GSD III (9.5%), 1 patient of GSD IV (4.8%), and 6 patients of GSD IX (28.6%). There was no patient diagnosed as GSD VI, and the types of 4 patients were not determined (19.0%) (Table 1). Among the subjects with a definite diagnosis of a specific type, types of hepatic GSDs other than GSD I constituted 52.9% of hepatic GSDs (9/17).

The median age at presentation was 2 years (range, 10 months-9 years), and male to female sex ratio was 2 : 1. The initial chief complaints at presentation were abdominal protrusion in 12 patients (57.1%), frequent epistaxis in 3 patients (14.3%), decreased mental alertness in 2 patients (9.5%), short stature in 1 patient (4.8%), and abdominal pain in the right upper quadrant in 1 patient (4.8%). Incidentally discovered liver enzyme elevation on laboratory exams at primary clinics was the chief complaint in two patients (9.5%), who were both revealed as GSD IX. Compared to other types, the age at presentation was relatively older in GSD IX, presenting at a median age of 4.5 years. Hepatomegaly was observed in 95.2% of the subjects and linear growth failure was observed in 28.6% of the subjects. The overall clinicodemographic characteristics of the patients at presentation are shown on Table 2.

Among the laboratory exams conducted at initial presentation, elevation of aspartate aminotransferase and alanine aminotransferase was the most fre-

Table 1. Diagnosis of Hepatic Glycogen Storage Disease Patients

Patient	Sex	Age at presentation	Glycogen accumulation on liver biopsy	Enzyme activity	Genetic mutation	GSD type
1	M	4.33 y	Positive	G6Pase: decreased	Not performed	Ia
2	M	1.5 y	Positive	Amylo-1,6-glucosidase: normal	*G6PC*(−), *PYGL*(−), *PHKA2*(−)	Not determined
3	M	2.83 y	Positive	G6Pase: normal	*PYGL*(−), *PHKA2*(−)	Not determined
4	M	6.42 y	Positive	Not performed	*PYGL*(−), *PHKA2*(+)	IX
5	F	10 mo	Positive	Amylo-1,6-glucosidase: decreased	*AGL*(+)	III
6	F	1 y	Positive	Amylo-1,6-glucosidase: decreased	Not performed	III
7	M	2 y	Positive	G6Pase: decreased	*G6PC*(+)	Ia
8	M	2.42 y	Positive	G6Pase: decreased	Not performed	Ia
9	F	2.25 y	Positive	Liver PhK: decreased	Not performed	IX
10	F	5.67 y	Positive	G6Pase: decreased	*G6PC*(+)	Ia
11	M	1.42 y	Positive	Not performed	*G6PC*(+)	Ia
12	M	4.92 y	Positive	G6Pase: normal Liver PhK: normal	*G6PC*(−), *PHKA2*(+)	IX
13	M	4.08 y	Positive	Liver PhK: decreased	Not performed	IX
14	M	2 y	Positive	Liver PhK: decreased	*G6PC*(−), *PHKA2*(+)	IX
15	M	10 mo	Positive	G6Pase: normal Liver PhK: normal	*G6PC*(−), *AGL*(−), *PYGL*(−), *PHKA2*(−), *PHKG2*(−), *SLC37A4*(+)	Ib
16	F	2 y	Positive	G6Pase: decreased	*G6PC*(+)	Ia
17	M	4 mo	Positive	Not performed	*GBE1*(+)	IV
18	F	1.83 y	Positive	Not performed	*G6PC*(−), *PHKA2*(−), *PHKG2*(−)	Not determined
19	M	7 y	Positive	G6Pase: normal, Amylo-1,6-glucosidase: normal	*PHKA2*(+)	IX
20	F	1.08 y	Positive	G6Pase: decreased	*G6PC*(+)	Ia
21	M	9 y	Positive	G6Pase: normal	*G6PC*(−), *AGL*(−), *PYGL*(−), *PHKA2*(−), *PHKG2*(−)	Not determined

GSD: glycogen storage disease, M: male, F: female, G6Pase: glucose 6-phosphotase, PhK: phosphorylase kinase.

Table 2. Clinicodemographic Characterisitics of Hepatic Glycogen Storage Disease Patients at Presentation

Type	Sex (male)	Age	Hepatomegaly	Linear growth failure	Seizure	Epistaxis
Ia (n=7)	4 (57)	2 y (1.08 y-5.75 y)	7 (100)	3 (43)	1 (14)	3 (43)
Ib (n=1)	1 (100)	10 mo	1 (100)	1 (100)	0 (0)	0 (0)
III (n=2)	0 (0)	11 mo (10 mo-1 y)	2 (100)	0 (0)	0 (0)	0 (0)
IV (n=1)	1 (100)	4 mo	1 (100)	0 (0)	0 (0)	0 (0)
IX (n=6)	5 (83)	4.5 y (2 y-7 y)	6 (100)	2 (33)	0 (0)	1 (17)
ND (n=4)	3 (75)	2.33 y (1.5 y-9 y)	3 (75)	0 (0)	0 (0)	2 (50)
Total (n=21)	14 (67)	2 y (4 mo-9 y)	20 (95)	6 (29)	1 (5)	6 (29)

Values are presented median (range) or number (%).
ND: not determined.

Table 3. Laboratory Findings of Hepatic Glycogen Storage Disease Patients at Presentation

Type	Elevated AST/ALT	Fasting hypoglycemia	Hyperlactacidemia	Hyperuricemia	Hypercholesterolemia	Hypertriglyceridemia	Anemia	Neutropenia
Ia (n=7)	7 (100)	5 (71)	7 (100)	7 (100)	3 (43)	6 (86)	3 (43)	1 (14)
Ib (n=1)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (14)
III (n=2)	2 (100)	2 (100)	0 (0)	1 (50)	2 (100)	2 (100)	0 (0)	0 (0)
IV (n=1)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
IX (n=6)	5 (83)	1 (17)	6 (100)	3 (50)	1 (17)	0 (0)	0 (0)	0 (0)
ND (n=4)	3 (75)	0 (0)	3 (75)	1 (25)	3 (75)	2 (50)	0 (0)	0 (0)
Total (n=21)	19 (90)	9 (43)	17 (81)	13 (62)	10 (48)	11 (52)	4 (19)	2 (10)

Values are presented as number (%).
AST: aspartate aminotransferase, ALT: alanine aminotransferase, ND: not determined.

Table 4. Follow up and Treatment of Hepatic Glycogen Storage Disease Patients

Type	Present age (y)	Follow up period (mo)	Uncooked corn starch	Allopurinol	Statins	Liver transplantation	Hepatocyte transplantation
Ia (n=7)	8.83 (2.08-20.67)	81±64.0	7 (100)	3 (43)	1 (14)	2 (29)	1 (14)
Ib (n=1)	3	26	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
III (n=2)	12.5 (11.92-13.08)	139±11.3	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)
IV (n=1)	1.67	17	1 (100)	0 (0)	0 (0)	1 (0)	0 (0)
IX (n=6)	8.5 (4.83-19.33)	62±49.8	6 (100)	0 (0)	0 (0)	0 (0)	0 (0)
ND (n=4)	13.08 (3.25-16.17)	91±86.7	4 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Total (n=21)	8.83 (2.08-20.67)	77±61.6	21 (100)	3 (14)	1 (5)	3 (14)	1 (5)

Values are presented as median (range), mean±standard deviation, or number (%).
ND: not determined.

quently observed abnormal laboratory finding, which was observed in 19 patients (90.5%), followed by hyperlactacidemia in 17 patients (81.0%). There were no specific abnormal findings on laboratory exams other than elevation of liver transmaninases in the one patient diagnosed as GSD IV. Fasting hypoglycemia was not observed in all the four patients whose type was not diagnosed, and anemia and neutropenia were observed in only GSD Ia and Ib (Table 3).

The mean follow-up period was 77±61.6 months, and the median age at recent follow-up was 8.83 years (range, 2.08-20.67 years). Uncooked corn starch had been initiated in all patients. Eleven patients discontinued uncooked corn starch. Among these patients, 6 patients were diagnosed as GSD IX and the types of 2 patients were not determined.

Allopurinol and statins were treated only in GSD Ia patients. Liver transplantation was performed in 3 patients (14.3%), and uncooked corn starch was stopped after liver transplantation. Hepatocyte transplantation was performed in 1 patient (4.8%) (Table 4). The median age for liver transplantation was 7 years (range, 10 months-17.83 years), and the median duration from diagnosis to liver transplantation was 26 months (range, 6 months-12.67 years). The earliest liver transplantation was performed in the patient diagnosed as GSD IV, which was performed at the age of 10 months, only 6 months after initial presentation. Hepatocyte transplantation was performed at the age of 37 months in a patient diagnosed with GSD Ia, 13 month after presentation. However, fasting glucose levels after hepatocyte trans-

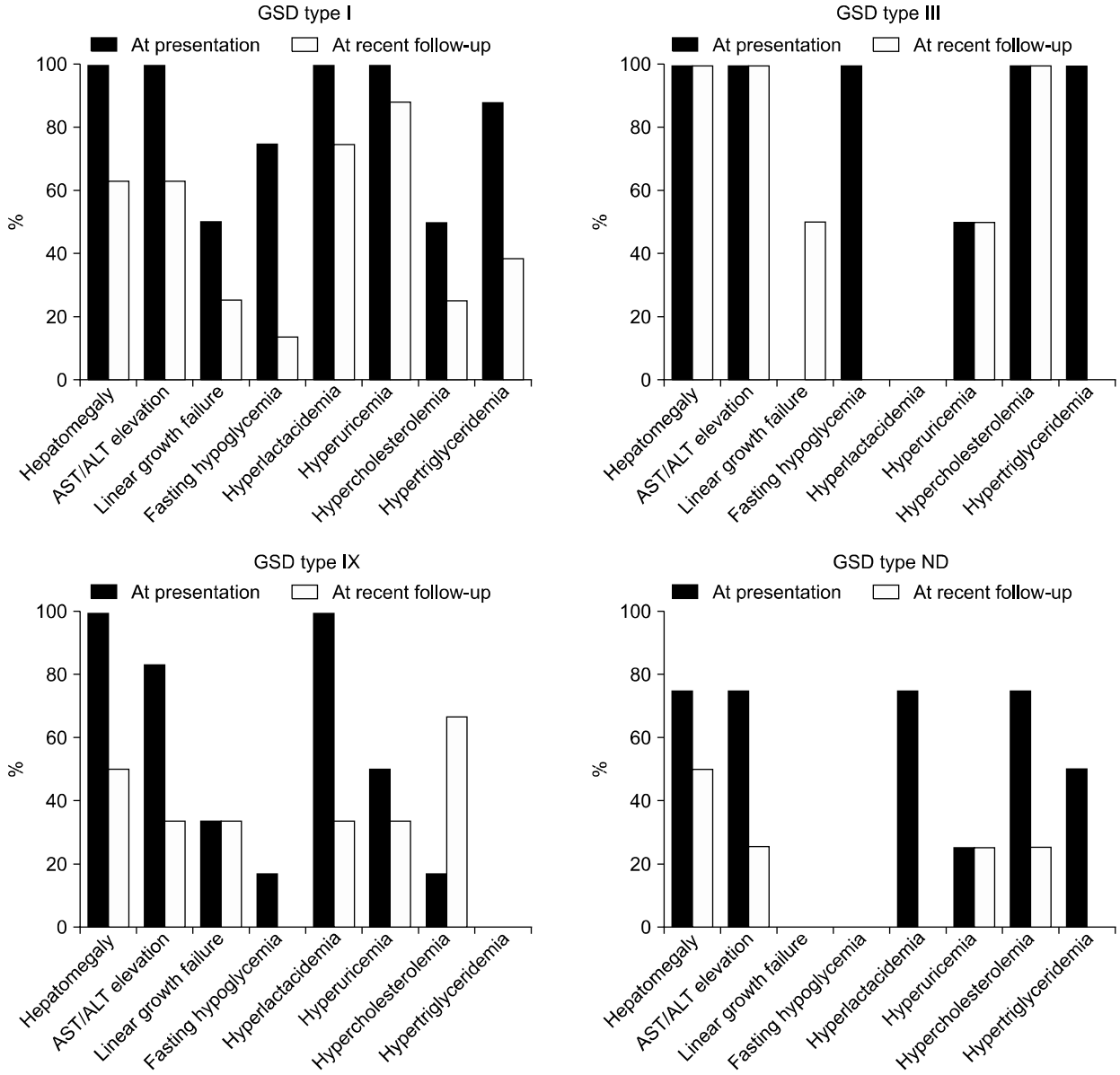

Fig. 1. Clinicolaboratory findings of hepatic glycogen strorage diseases at presentation and at recent follow up. GSD: glycogen storage disease; AST/ALT: aspartate aminotransferase/alanine aminotransferase; ND: not determined.

plantation did not normalize for 6 months, and graft loss was suspected. The patient is currently waiting for liver transplantation. According to the data at recent follow-up, most clinicodemographic abnormalities in all types showed general improvement compared to initial presentation (Fig. 1). There was no mortality during the follow-up period. However, complications such as hepatic adenoma, gout, renal dysfunction, and frequent infections were observed. Hepatic adenoma was observed in 2 patients of GSD Ia and 1 patient whose type was not determined. Gout was observed in 1 patient of GSD Ia, who also developed renal dysfunction. Frequent infection was observed in the patient diagnosed as GSD Ib.

DISCUSSION

According to our study, types of hepatic GSDs other than GSD I constituted 52.9% of the patients (9/17) diagnosed with a specific type. GSD III comprised 11.8% (2/17), GSD IV comprised 5.9% (1/17), and GSD IX comprised 35.3% of hepatic GSD patients (6/17) in which types were diagnosed. To our knowledge, this is the first study in Korea to investigate the characteristics, treatment, and prognosis of hepatic GSDs including types other than GSD I and III in Korea. Moreover, we are the first to describe the characteristics and prognosis of GSD IX in Korea.

GSD III is due to the defect in the gene *AGL*, which leads to the deficiency of the glycogen debrancher enzyme, namely, amylo-1-6-glucosidase. It accounts for approximately 24% of GSDs [2]. GSD III usually presents with symptoms of hepatomegaly, hypoglycemia, short stature, and dyslipidemia [20]. Muscle symptoms are mostly minimal at childhood. However, slowly progressive weakness and distal muscle wasting may become predominant during adulthood. Liver symptoms are likely to improve with age and may disappear after puberty, with normalization of liver enzymes [2,21]. During follow up, significant complications are observed in approximately 20% of GSD III patients and hepatic adenomas in 25% of GSD III patients [14,22,23]. Although rare, liver cirrhosis and malignant transformation have also been reported in GSD III patients [22,23]. Significant complications including hepatic adenoma or liver cirrhosis have not been observed in the two patients with GSD III in our study. However, as elevation of liver enzymes and hypercholesterolemia are shown to persist in these patients despite maintenance of normoglycemia with uncooked cornstarch supplements, further close observation is required in these patients for possible significant complications.

GSD IV is due to the defect in the gene *GBE1*, which leads to the deficiency of glycogen branching enzyme, amylo-1,4 to 1,6-transglucosidase. It accounts approximately 0.3% of GSDs [24]. Clinical manifestations of GSD IV are extremely heterogeneous, which may be due to differences in tissue involvement [25]. In the classical hepatic form, affected patients appear normal at birth. However, the disease progresses rapidly and by 18 months of age they present with failure to thrive, portal hypertension, hepatosplenomegaly, and cirrhosis [2,21]. Without liver transplantation, children will usually die by 3 to 5 years of age due to liver failure [2]. The only effective treatment for the classical hepatic form with progressive liver disease is liver transplantation. The only clinicolaboratory findings at presentation in the one patient diagnosed with GSD IX in our study (patient #17) were hepatomegaly and elevation in liver transaminases presenting at 4 months of age. However, rapid progression was observed in this patient resulting in liver cirrhosis and variceal bleeding 6 months later. Emergency liver transplantation was performed, and the patient is doing well to date. It should be kept in mind that hepatomegaly and elevation in liver transaminase may be the only findings in GSDs, but may progress rapidly into liver cirrhosis. Therefore, close observation and follow-up is required in patients, despite mild clinicolaboratory findings at presentation.

GSD IX is due to the defect in the enzyme, phosphorylase kinase, which activates glycogen phosphorylase in the muscle, liver, and other tissues. Approximately 25% of GSDs are due to phosphorylase kinase deficiency [26]. Phosphorylase kinase is

composed of 4 subunits (α, β, γ, δ), with each subunit possessing different functions. The α subunit has two isoforms, a muscle isoform and a liver isoform. They are encoded by different genes on the X chromosome (*PHKA1* and *PHKA2*), while the genes for other subunits are located on autosomal chromosomes (*PHKB* and *PHKG2*) [27]. The types involving the liver are mainly classified into the X-linked liver form (GSD IXa) and the autosomal recessive form (GSD IXb and IXc) [21]. GSD IXa, also known as X-linked liver phosphorylase kinase (alpha subunit) deficiency or *PHKA2*-related GSD IX is known as the mildest GSD, and accounts for the majority of the patients with GSD IX [2]. GSD IXa usually present between 1 and 5 years of age with hepatomegaly (92%), hypercholesterolemia (76%), hypertriglyceridemia (70%), growth retardation (68%), elevated liver transaminases (56%), delayed motor development (52%), and fasting hyperketosis (44%) [10]. The clinical course of IXa is mostly benign with these clinical and biochemical abnormalities tending to gradually disappear and asymptomatic at adult age [10]. Splenomegaly and liver cirrhosis are also known to be rare in GSD IXa. There are two types of the autosomal recessive form. One is GSD IXb, also known as the autosomal liver and muscle phosphorylase kinase (beta subunit) deficiency and the other is GSD IXc, also known as the autosomal liver phosphorylase kinase (gamma subunit) deficiency. Symptoms are generally mild or absent in GSD IXb, while symptoms are more severe with an increased risk of liver cirrhosis in GSD IXc [28,29]. The 6 patients who had been diagnosed with GSD IX in our study had initially started dietary supplementation with uncooked corn starch, as their type was not diagnosed initially. All patients consequently stopped taking uncooked corn starch after definite diagnosis as GSD IX. Both hepatic symptoms and laboratory findings did not show deterioration, even after cessation. All patients are doing well without any significant complications such as liver cirrhosis, hepatic adenomas, and renal dysfunction. As the diagnosis of 4 patients was confirmed by mutations in the *PHKA2* gene, these patients could be diagnosed as GSD IXa. Patient #9 was a female, indicating the possibility of an autosomal recessive form of GSD IX. However, genetic analysis was not performed due to financial matters of the guardians.

According to our results, the clinicolaboratory profiles of the patients whose types were not determined were relatively mild compared to other types both at initial presentation and at recent follow-up. Interestingly, all patients (patient #2, #3, #18, #21) did not show any mutations in the *PHKA2* gene, which is associated with the mildest hepatic GSD. Further evaluation of other unexamined genes of hepatic GSDs should be considered. Another interesting finding is that of patient #21. This patient presented with abdominal pain in the right upper quadrant at 9 years of age. Abdominal CT and MRI showed a 4.3 cm lobulating mass in the S8 of the liver, and biopsy results of the mass revealed liver cell adenoma with glycogen accumulation in normal parenchyme. However, evaluation including enzyme assays and analysis for mutations in genes including *G6PC, AGL, PYGL, PHKA2,* and *PHKG2* were all negative. As hepatic adenomas are known to occur in patients with GSD I or III, the negative findings of gene mutations on *G6PC* and *AGL* may indicate the presence of an unrevealed novel gene related with the pathogenesis of GSDs.

The major limitation of this study is that the number of subjects included in this study was small. Due to this limitation, we were unable to perform statistical analysis between the types of GSDs. Another major limitation of this study is that it was conducted at a single center in Korea. Therefore, our results may not represent the general population of Korea.

GSD I is known to comprise around 30% of hepatic GSDs [4]. However, according to a recent multicenter study in Japan, GSD I constituted approximately 60% of hepatic GSDs [13]. Considering the genetic similarity between Korea and Japan, there is the possibility of differences of incidence between different races and ethnicities. Still 40% of patients in that study were diagnosed with types other than GSD I. We assume that types other than GSD I con-

sist a substantial portion of hepatic GSDs in Korea, not just a minor portion. In order to predict the clinical course and to prevent or properly treat crucial complications, it is important to diagnose and clarify the types of hepatic GSDs. Therefore, clinical suspicion and evaluation of hepatic GSDs in Korea should be focused not only on GSD I, but also on other types.

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