Early Diagnosis and Treatment may Prevent the Development of Complications in an Adult Patient with Glycogen Storage Disease Type Ia

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Abstract

Type Ia glycogen storage disease (GSD Ia) is caused by the deficiency of glucose-6-phosphatase activity, which results in metabolic disorder and organ failure, including renal failure. GSD Ia patients are generally diagnosed at a median age of 6 months. However, we report a 20-year-old Japanese female with newly diagnosed GSD Ia. The renal disorder of GSD Ia is considered to be produced by glomerular hyperfiltration, TGF-β expression which is induced by renin-angiotensin-aldosterone system (RAS) and uric acid, and the increase in both small dense LDL and modified LDL which is characteristic of GSD Ia as well as hypertriglyceridemia. With the administration of intensive therapies, including angiotensin type 1-receptor blocker and some lipid lowering drugs, along with traditional dietary therapy, daily proteinuria of the patient improved from 2.1 g to 0.78 g. Although the patients of GSD Ia should receive an early and accurate diagnosis and effective therapies before the age of 1 year, the combination of traditional dietary therapies and intensive therapies may have therapeutic potential for the complications of adult patients. In this report, we describe the management of renal disease and the characteristic features of this metabolic disorder.

Key words: glycogen storage disease type Ia, glomerular enlargement, hyperlipidemia, intensive therapy, renal disorder

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Introduction

Type Ia glycogen storage disease (GSD Ia) was first described by von Gierke in 1929 as an autosomal recessive inborn error of carbohydrate metabolism due to the defects in the glucose-6-phosphatase (G6Pase) complex. In 1952, Coris discovered that the absence of G6Pase caused GSD Ia (1). In 1993, Lei et al. cloned and characterized the G6Pase gene, which led to the identification of a mutation on band q21 of chromosome 17 (2). G6Pase plays a central role in glycogenolysis, gluconeogenesis, and hydrolysis of glucose 6 phosphate (G6P) to glucose. Deficiency of G6Pase activity in the liver, kidney, and intestine is responsible for the accumulation of glycogen in these organs. Inadequate glucose production causes severe fasting hypoglycemia with secondary biochemical abnormalities such as a high blood lactate level, hyperuricemia, and hyperlipidemia. Further, it results

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1787
in osteopenia, growth retardation, hepatic adenoma, and renal complication. It has been reported that 70% of the over 10-year-old GSD Ia patients show renal dysfunction, and 40% of these patients develop progressive renal insufficiency. Moreover, the renal complication has been shown to adversely affect the prognosis of the patients (3). Among newborns, GSD Ia has an estimated frequency of 1 in 100,000. GSD Ia is generally recognized as a pediatric disease because it is commonly diagnosed at a median age of 6 months, and 80% of GSD patients are diagnosed before the age of 1 year. However, it has rarely been reported in adults because with the increase in age, GSD progresses to renal complication and metabolic disorders (4). The present case also showed these complications, but we were able to improve the proteinuria and metabolic disorder. Early diagnosis and treatment of this disorder facilitate the amelioration of the many complications associated with GSD. Hence, we must identify the characteristic diagnostic features of GSD Ia patients showing metabolic disorders and renal complication for preventing false diagnosis and the development of renal disorder.

**Case Report**

A 20-year-old woman was admitted to the Amagasaki Hospital for the evaluation of metabolic disorder and proteinuria (2.1 g per day). At 3 years of age, she had been diagnosed with familial type III hyperlipidemia. After the diagnosis was confirmed, she had been administered dietary therapy and some medications for lowering her serum cholesterol and triglyceride levels. At the age of 17 years, abnormal urinalysis results were obtained. She visited a physician, who referred her to our nephrology division for the management of proteinuria. Her parents were cousins. She had 2 sisters, who did not have any abnormality; however, her father had hyperlipidemia and hypertension with unknown etiology. She had a short stature (height, 152 cm; body weight, 48.8 kg). Her liver, kidney, and spleen were not palpable. Other clinical examinations were normal. She had an iron-deficiency anemia (red blood cell count, 311x10^6/mm³; hemoglobin level, 9.4 g/dL; transferrin saturation, 9.6%; ferritin level, 10.3 ng/mL). White blood cell count was 4,400/mm³, which was within the normal range. Total protein (5.9 g/dL) and albumin (3.3 g/dL) were within the normal range. Her blood urea nitrogen (21 mg/dL) and serum creatinine level (0.4 mg/dL) were within the normal range; however, the creatinine clearance rate (Ccr) (147.5 mL/min/1.73 m²) and estimated glomerular filtration rate (eGFR) (136.8 mL/min/1.73 m²) were significantly elevated. The serum uric acid level (9.5 mg/dL) and serum lactic acid level (21 mg/dL) were elevated. Fasting blood glucose level (73 mg/dL) was low. Sodium, potassium, calcium, and phosphate levels, and other immunological findings were all normal. Her venous blood gas analysis was almost normal (pH, 7.39; pCO₂, 39.3 mmHg; HCO₃⁻, 23.4 mmol/L; base excess (BE), -0.8 mmol/L, the anion-gap, 12.6 mmol/L). Urinary sediment revealed microscopic hematuria, and urinary pH was 6.5; moreover, the daily proteinuria was 2.1 g. Her urinary calcium was normal. There were significant abnormalities in her lipid profile. Her cholesterol (274 mg/dL), triglyceride (TG) (609 mg/dL), and low density lipoprotein (LDL) level (183 mg/dL) were significantly elevated, while high density lipoprotein (HDL) level (14 mg/dL) was low. Remnant lipoprotein cholesterol (RLP) level (32 mg/dL) was high, and lipoprotein (a) level (12 mg/dL) was within the normal range. Small dense LDL was detected by polyacrylamide gel electrophoresis. Capillary electrophoresis revealed increased level of modified LDL and chylomicron. Apolipoprotein (Apo) A1, Apo A2, Apo B, Apo C2, and Apo C3 levels were 37 mg/dL, 26.5 mg/dL, 222 mg/dL, 11.6 mg/dL, and 22.4 mg/dL, respectively, which were abnormal, while the Apo E level was within the normal range (7.8 mg/dL). The normal range of Apo E in our patient is inconsistent with the low level of Apo E generally observed in familial type III hyperlipidemia. The patient had an E3/E3 phenotype and e3/e3 genotype, indicating the presence of a wild-type Apo E.

A renal biopsy was performed. Histological findings of the renal tissue revealed predominant lesions, including glomerulosclerosis, with partial vacuolization and minor abnormalities in the glomeruli, which were enlarged by approximately 2-folds. In addition, severe focal interstitial fibrosis with partial proximal tubular atrophy and infiltration of lymphocytes and plasma cells were also observed (Fig. 1). Mesangial area was slightly increased (Fig. 2A). The degenerated proximal tubular epithelium had hypertrophied and had been partially eliminated; moreover, the epithelium appeared scaly (Fig. 2B, C) and showed partial nuclear vacuolization that resembled glycogen vacuolization of the liver cell nuclei, which is a characteristic feature of hepatic pathological findings of GSD Ia (Fig. 2D) (5). The results of immunofluorescent microscopy were consistent with slight granular deposition of IgA and C3 in the mesangium.

Figure 1. Light microscopic findings of a renal biopsy specimen, showing enlarged intact glomeruli with slight mesangial matrix expansion, global glomerular sclerosis, focal severe interstitial fibrosis, and tubular atrophy [periodic acid-Schiff (PAS) staining; original magnification, ×200].
Figure 2. Light microscopic findings of a renal biopsy specimen, showing (A) slight mesangial matrix expansion in the glomeruli. The proximal tubular epithelium is (B) hypertrophied and appears scaly, with (C) a partial elimination, and shows (D) partial nuclear vacuolation (arrow) [periodic acid-Schiff (PAS) staining: original magnification, A: ×400, B: ×200, C: ×600. Hematoxylin and Eosin staining: original magnification, D: ×1,000].

These findings were indicative of GSD Ia (3, 6). An abdominal non-contrast computed tomography (CT) showed hepatomegaly, splenomegaly with increased density (Fig. 3A), and renal enlargement (Fig. 3B). Moreover, an abdominal ultrasonography revealed splenomegaly, moderate hepatomegaly with increased hepatic echogenicity and deep attenuation, and renal enlargement, in which the echogenicity of the renal medullary tissue was higher than that of the renal cortex (Fig. 3C) (7). Electron microscopy showed that two-fold thickening of the glomerular basement membrane was accompanied by lamellation and irregular contour, incorporating irregular lucencies and fine granules (Fig. 3D). These findings were suggestive of GSD I. The diagnosis of GSD was confirmed by DNA analysis and glucose and glucagon tolerance tests (8). Glucose test revealed hyperglycemia and decrease in lactic acid level, and the glucagon test revealed normoglycemia (no response) and increase in lactic acid level. DNA analysis showed that the patient had a homozygous mutation (G727T). Moreover, we performed a detailed analysis of renal function and glucogenic metabolism. Fishberg test showed that the specific gravity (1.011-1.012) and urinary osmolality (483-520 mOsm/L) of our patient was lower than those of normal individuals. This finding was indicative of distal tubular dysfunction. Phenolsulfonphthalein (PSP) excretion test revealed that only 24% of PSP was excreted in 15 minutes, which indicated proximal tubular dysfunction of organic anion transport. The insulinogenic index was 0.231, and homeostasis model assessment-insulin resistance (HOMA-R) score was 0.189. Extensive dietary therapy of approximately 50 g uncooked cornstarch was used to maintain more than 70 mg/dL of fasting blood glucose level. In addition to dietary therapy, fenofibrate, probucol, tocopherol nicotinate, and icosapentate ethyl were administered to improve her lipid metabolism. Allopurinol administration reduced her serum uric acid level. Dipyridamole and losartan (a part of AT1-receptor blockers) were administered to improve renal function. Immunosuppressive therapy was not used because glucocorticoid and some immunosuppressants are generally not recommended for GSD Ia. During hospitalization, Ccr (142 mL/min/1.73 m²) and eGFR (136.1 mL/min/1.73 m²) did not change, while proteinuria decreased significantly (0.78 g per day).

Discussion

It is well known that renal disorder is frequently observed in GSD Ia patients (3). Early and accurate diagnosis and effective therapies are required to prevent the development of renal disorders in GSD Ia. There are frequent reports of cases such as ours that do not receive accurate diagnosis and
early treatment. Such cases show organ impairment. A study reported that nephrologists in the United Kingdom were unable to diagnose adult patients with newly diagnosed GSD Ia. This indicates that clinicians have difficulty in accurately diagnosing GSD in adult patients because of the lesser frequency of such patients, unlike pediatricians who diagnose GSD at a frequency of 1 in 100,000 cases (4). Therefore, it is important to understand the characteristics of GSD Ia patients. The diagnostic criteria of GSD are as follows: abnormal laboratory findings, which include a high blood lactate level, hyperuricemia, and hyperlipidemia; and abnormal imaging findings, which include organomegaly (liver, spleen, and kidney) detected by non-contrast CT and ultrasonography. In the present patient, the echogenicity of the medullary tissue was particularly higher than that of the cortex, as revealed by renal ultrasonography (7). This finding allowed us to make an accurate diagnosis.

Furthermore, obtaining accurate renal function test results are also important for early diagnosis. The renal function of our patient seemed to be normal because her Ccr and eGFR were 147.5 mL/min/1.73 m² and 136.8 mL/min/1.73 m², respectively; however, renal pathological findings indicated a progressive renal disorder. These findings suggest that Ccr and eGFR alone cannot be used to make an accurate evaluation of renal function in GSD Ia patients. We found that the amount of PSP excreted by our patient in 15 minutes was lower than that observed in normal age-matched individuals and that there was a correlation between the results of this test and the degree of renal disorder. Hence, this test may be used as a sensitive and adequate marker to evaluate the stage of renal disorder in GSD Ia patients. We believe that further studies using PSP excretion test need to be conducted to accurately evaluate renal function in GSD Ia.

Early and effective treatment of GSD Ia is also important for preventing organ failure. It has been recognized that the initiation of dietary therapy, which includes parenteral nutrition and nocturnal nasogastric infusion of glucose and uncooked cornstarch, ameliorates metabolic abnormalities, thereby preventing the exacerbation of renal function and development of malignant hepatic adenoma (9). However, a recent study indicated that traditional dietary therapy alone cannot prevent all long-term complications and in contrast it increases the risk of hepatocellular carcinoma (10). Hence, intensive therapies should be administered along with traditional dietary therapy depending on the extent of renal disorder for managing all long-term complications.

Some mechanisms underlying the development of renal disorder have been proposed. One of them is glomerular hyperfiltration. Previous reports have described that glomerular hyperfiltration has been implicated in the pathogenesis of glomerular enlargement and sclerosis (11). Although the mechanisms underlying glomerular hyperfiltration are yet unclear, a previous report has suggested the following mechanism. Within the kidney, G6Pase is expressed in the
proximal tubular epithelium. While G6Pase deficiency results in the depletion of high-energy phosphate and causes proximal tubular damage, the increase of renal plasma flow (RPF) augments the supply of oxygen and any available glucose to the renal tubules due to the decrease in intracellular energy transfer efficiency in the proximal epithelium. This results in an increased glomerular filtration rate (GFR), which ultimately causes glomerular hyperfiltration (12, 13). The regulation of hyperfiltration is the most important factor to prevent the development of renal disease; however, it is also difficult to regulate hyperfiltration because traditional dietary therapy and intensive therapies cannot fulfill the oxygen and glucose requirements of the renal tubule. However, other mechanisms underlying renal disorder can be possibly regulated by intensive therapies. It has been reported that transforming growth factor (TGF)-β expression increases in the tubular epithelial cells and is involved in the pathophysiology of renal interstitial fibrosis, which results from the increase in extracellular matrix (ECM) proteins, including collagen type I and III and fibronectin, in GSD Ia patients (13). Angiotensin-converting enzyme (ACE) inhibitors, angiotensin type 1 (AT1)-receptor blockers, and allopri- nol have been considered to be the most potential drugs to interfere with TGF-β expression because the renin-angiotensin-aldosterone system (RAS) and uric acid have been known to involved in the expression of TGF-β (14, 15). In the present case, we thought that losartan, which affects the urate excretion level by inhibiting urate transporter 1 (URAT1), was useful and effective in reducing the serum uric acid level and inhibiting TGF-β expression (16, 17), and it contributed to the reduction of proteinuria. The lipid profile of the present case suggested that the increase in both small dense LDL and modified LDL were characteristic features of GSD Ia. It has been recognized that small dense LDL and modified LDL induce the development of glomerular sclerosis and renal disorder (18). Hence, strong lipid lowering therapies are required for ameliorating renal function. The increased chylomicron level measured by capillary electrophoresis was assumed to be derived from dietary absorption. Therefore, ezetimibe (a selective cholesterol transport inhibitor) can be possibly used to effectively inhibit intestinal absorption of dietary chylomicron, and thereby reduce the levels of both small dense LDL and modified LDL in GSD Ia (19, 20).

It has been recognized that GSD I patients have severe metabolic acidosis because of the renal tubular acidosis due to distal tubular disorder and lactic acidosis associated with high blood lactate level. However, the present case did not have severe metabolic acidosis (pH, 7.39; HCO3-; 23.4 mmol/L; BE, -0.8 mmol/L; anion-gap, 12.6 mmol/L). A previous study also showed that severe metabolic acidosis (pH, 7.34±0.03) was not observed in their GSD Ia patients in spite of a high blood lactate level (21). Although the mechanism underlying metabolic acidosis is still unclear, we propose that the regulation of blood citrate level can prevent the development of severe metabolic acidosis because metabolic acidosis is known to cause an increase in the tubular citrate channel, resulting in increased citrate transport and decreased citrate excretion (22). However, we did not analyze the blood and urinary citrate levels. Further study is required to address this issue. Moreover, the low urinary citrate level probably explains the reason for the high incidence of nephrocalcinosis and nephrolithiasis in GSD Ia patients. Therefore, citrate supplementation might be expected to decrease the occurrence of metabolic disorders in GSD Ia patients (21).

Hence, the most appropriate strategy to maintain renal function is to regulate blood glucose by administering strict nutritional therapy that includes uncooked cornstarch (3, 4, 18, 21, 23, 24) and intensive therapies that include more efficacious drugs. In the present case, the combination of traditional dietary therapies and intensive therapies reduced proteinuria from 2.1 g to 0.78 g.

In 2007, induced pluripotent stem (iPS) cells were isolated from human fibroblasts (25, 26). The iPS cells derived from a patient can be used for any future treatment for that patient. A recent report suggested that the deletion of or mutation in dystrophin in the iPS cells derived from Duchenne muscular dystrophy could be corrected by using a human artificial chromosome with a complete genomic dystrophin sequence. These corrected iPS cells were allowed to differentiate in a muscle-like tissue which expressed human dystrophin (27). We think that this technique raises the possibility of developing a new therapy for GSD Ia patients. Homozygous mutation (G727T) in GSD Ia may be corrected by gene therapy using iPS cells. These cells may be allowed to differentiate into hepatic cells and the renal proximal tubular epithelium that produces G6Pase, and the differentiated cells can then be transplanted into GSD Ia patients. Further studies and discussion are required to develop new therapeutic strategies for GSD Ia patients.

Conclusion

The complete gene therapy protocol has not yet been established. Early diagnosis and treatment are important to improve the prognosis and prevent the complications in GSD Ia. Future studies should focus on understanding the mechanisms underlying the development of renal disorder in GSD Ia because adult GSD patients often develop complications of renal disease.

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