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Glycogen Storage Disease Type IV: A Case Report

Glycogen storage disease type IV (GSD-IV) is a rare autosomal recessive disease caused by deficient glycogen branching enzyme (GBE). We report a 15-month-old female patient with GSD-IV who exhibited an abdominal distension and failure to thrive for 9 months. The patient showed hepatosplenomegaly with massive ascites. The laboratory findings showed abnormal liver functions including prolongation of prothrombin time and partial thromboplastin time. The light microscopic and electron microscopic findings of the liver biopsy specimen were consistent with GSD-IV. Measurement of glycogen quantity in the red blood cells showed increased storage of glycogen in the patient and interestingly, in her mother. The GBE activity of the patient's red blood cells was undetectable. The patient's ascites, general condition, and laboratory findings have been improved with supportive treatment with diuretics and a low dose of prednisolone.

Key Words : *Glycogen storage disease type IV, 1,4-α glucan branching enzyme, Erythrocytes*

Kyung-Yil Lee, Kyung-Hee Seo, Hye-Kyung Lee*, Jong-Won Kim**

Department of Pediatrics, Department of Clinical Pathology*, Catholic University of Korea School of Medicine; Department of Clinical Pathology**, Sung Kyun Kwan University College of Medicine, Seoul, Korea

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Address for correspondence
Kyung-Yil Lee, M.D.
Department of Pediatrics, Taejon St. Mary's Hospital, Catholic University of Korea, 520-2, Taehung2-dong, Chung-gu, Taejon 301-723, Korea
Tel : (042) 220-9541, Fax : (042) 221-2925

INTRODUCTION

Glycogen storage disease type IV (GSD-IV; Anderson's disease (1), amylopectinosis, polyglucosan disease) is a rare autosomal recessive disease caused by deficient glycogen branching enzyme (GBE; 1,4-α glucan branching enzyme or amylo-1,4-1,6 transglucosidase) activity. The GBE deficiency leads to the storage of amylopectin-like abnormal glycogen deposits as polyglucosan bodies in the liver and other tissues as well as in cultured skin fibroblasts (2, 3). The classical form of GSD-IV is progressive liver cirrhosis, which begins insidiously with failure to thrive and nonspecific gastrointestinal symptoms, followed by progressive hepatosplenomegaly, portal hypertension, ascites, and hepatic failure leading to death between the ages of 2-4 years (1, 3, 4-6). On the other hand, GSD-IV is now recognized as a heterogeneous disorder with remarkable clinical variability. We report a first patient with GSD-IV in Korea.

CASE REPORT

A 15-month-old female child was admitted for progressive abdominal distension and failure to thrive for 9 months. Her development was normal. There was no family history of metabolic or liver disease. The infant weighed 8.2 kg (3-10th percentile), measured 71 cm in length (below 3rd percentile), and had a head circumference of 46 cm (25-50th percentile), a chest circumference of 43 cm (3-10th percentile), and an abdominal circumference of 53 cm. Upon a physical examination, the abdomen was distended and showed a shifting dullness which suggested ascites. The liver was palpable 10 cm below the right costal margin in the middle midclavicular line (liver span 16 cm), and the spleen was palpable 2 cm below the left costal margin in the midclavicular line. The peripheral white blood cell count was 18.7×10^9/L, with a normal differential cell count, and hemoglobin was 9.0 g/dl. The other laboratory test results were as follow: total bilirubin 2.0 mg/dl, direct bilirubin 0.8 mg/dl, total protein 5.8 g/dl, albumin 3.3 g/dl, asparate aminotransferase 477 U/L, alanine aminotransferase 210 U/L, lactic dehydrogenase 810 U/L, alkaline phosphatase 879 IU/L and γ-glutamyl transferase 144 U/L. The prothrombin time value was 15.7 seconds (control 10.9 seconds/2.3 INR), and the partial thromboplastin time was 55 seconds. Serologic tests for hepatitis B and for hepatitis C were nonreactive. An ultrasound examination of the abdomen revealed an enlarged liver with normal intrahepatic and extrahepatic ducts and spleen with marked ascites. Findings from a CT of the

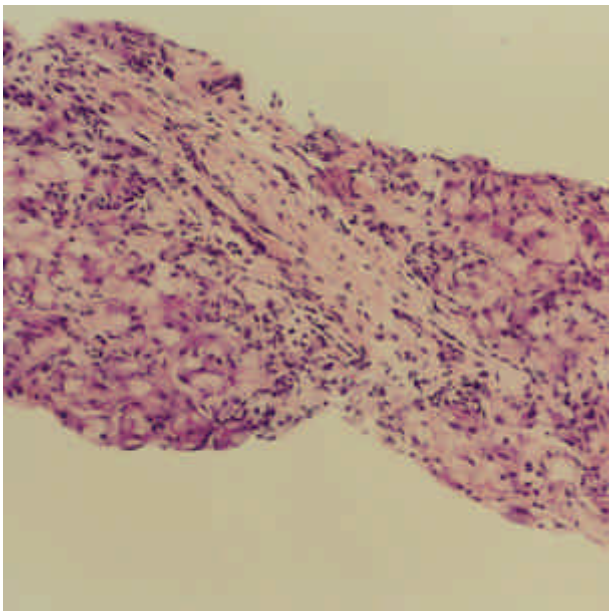

Fig. 1. Light microscopy shows eccentric pale cytoplasmic inclusions within the hepatocytes with periportal fibrosis (H&E stain, ×100).

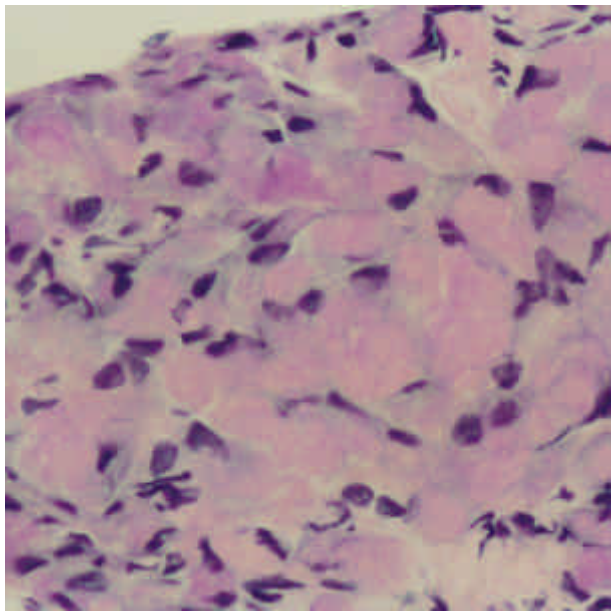

Fig. 2. PAS positive homogenous materials in hepatocytes (PAS stain, ×400).

abdomen revealed a markedly enlarged liver and spleen with massive ascites. The light microscopic finding of the percutaneous liver biopsy specimen demonstrated cirrhotic pattern with disarrayed lobular architecture and severe hepatic parenchymal cell loss replaced by fibrosis and bile ductular proliferation (Fig. 1). The hepatocytes exhibited distended cytoplasm with clear materials that were shown to be positive by periodic acid-Schiff (PAS) reaction and peripherally dislocated eccentric nucleus (Fig. 2). Electron microscopy of the liver revealed many intracytoplasmic membrane-bound or non-membrane-bound acellular homogeneous aggregations with scattered fine granular materials (Fig. 3), resembling the abnormal glycogen of type IV glycogenosis. Glycogen quantity in red blood cells showed increased storage of glycogen in the patient and her mother. The result of GBE activity

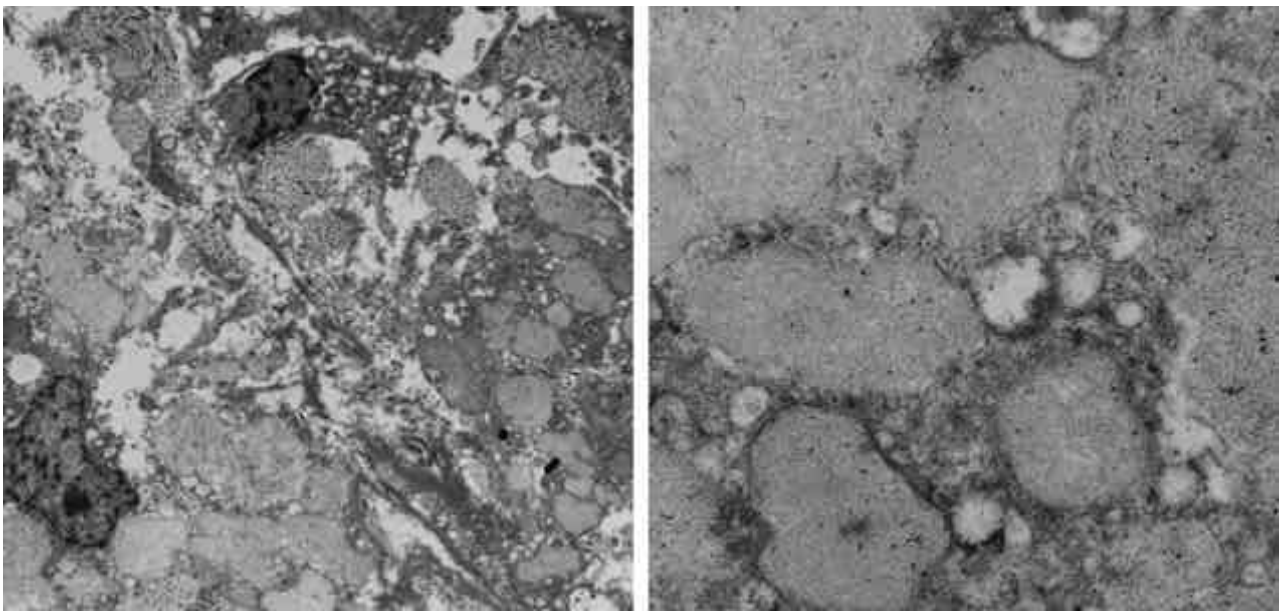

Fig. 3. EM finding shows membrane-bound or non-membrane-bound acellular homogenous amylopectin-like abnormal glycogen (×3,750 left, ×25,000).

Table 1. Gylcogen quantitation and glycogen branching enzyme (GBE) assay in red blood cells

	Glycogen (mg%)	GBE(μM/min/gHb)
Patient	20.3	undetectable
Patient's mother	20.3	13.9
Control	6.8*	38.2

*: reference range <10 mg%

was undetectable in her red blood cells and decreased in her mother (Table 1). These results were diagnostic of glycogen storage disease type IV. The patient's ascites, general condition, and the laboratory findings have been improved by supportive treatment with diuretics and a low dose of prednisolone. Since there is no specific treatment for GSD-IV, this patient is waiting for an orthotopic liver transplantation. A living-related liver donor will be one of her parents.

DISCUSSION

GBE is responsible for creating branch points in the normal glycogen molecule. In the relative or absolute absence of this enzyme, an insoluble and irritating form of glycogen, an amylopectin-like polysaccharide that resembles plant starch, accumulates in the cells. The amylopectin-like form is less soluble than normal glycogen, with longer outer and inner chains and fewer branch points.

GSD-IV shows heterogeneous clinical courses. The most common and classical form of GSD-IV is the hepatic form as previously described. There are some patients with liver dysfunction who have survived without evidence of progressive liver disease (7, 8). In addition to the hepatic form, myopathy of heart and skeletal muscles (9-11) can be present, and the involvement of the peripheral and central nervous system has also been reported (12-14). A human GBE cDNA has been cloned and the genomic GBE gene has been found to be located on chromosome 3 (15). The molecular basis of GSD-IV is not known, nor is there any known reason for the clinical variability. The difference of clinical severity and organ involvement is unlikely due to defects in tissue-specific isoenzymes encoded by different genes expressed in different tissues, since there is no clear evidence of the existence of isoforms in the branching enzyme (17, 18). In the previous study of the GBE gene in four patients with three presentations of GSD-IV, Bao et al reported that a 210 bp deletion caused by a 3' acceptor slicing site mutation was detected in a patient with a fatal neonatal neuromuscular presentation, three point mutations in two patients with classical presentation, and two point mutations in a patient with the nonprogressive hepatic form. This result suggests that the various forms of GSD-IV were caused by mutations in the same GBE gene.

The pathogenesis of tissue damage, especially liver cirrhosis, is not understood: an "irritate" role of the abnormal polysaccharide, causing fibrosis, was proposed by Anderson (1), but remains hypothetical (6). A higher concentration of the abnormal polysaccharide in the liver or the greater vulnerability of this organ to its toxic effects may explain why hepatic damage usually dominates the clinical picture. Cirrhosis is seen routinely even in patients in whom hepatic symptoms have not yet manifested (9).

GBE assays in various tissues (liver, skeletal muscles, cardiac muscles, nerve tissues, cultured skin fibroblasts, and other tissues) help to confirm the diagnosis of GSV-IV. Also, the accumulations of amylopectin-like glycogen can be shown in the liver, skeletal and heart muscles, nerve tissues, white blood cells (18), and other tissue. These materials react with PAS staining and are partially resistant to diastase digestion. In the EM study, most of patients demonstrate fibrillar aggregations that are typical of amylopectin.

We measured the glycogen quantity and GBE activity in red blood cells. In GBE assay, EDTA blood was drawn and red cells were washed and isolated. Washed red cells were 15-fold diluted. Hemoglobin concentration of the diluted red cells were determined. The reaction was carried out by incubating 50 μl samples with 50 μl of the reaction mixture pH 6.5 containing 250 mmol/L glucose-1-phosphate (Sigma, USA), 7 mmol/M adenosine monophosphate (Sigma, USA) and 1.0 U phosphorylase a (Sigma, USA). The blank was prepared by using samples which had been heat-denatured prior to the addition of the reaction mixture. After 30 min incubation at 37℃ the reaction was terminated by heating at 95℃ for 5 minutes. The activity was expressed as μmol phosphate released per min g Hb. Interestingly, the mother of the patient, who may be a carrier of GSD-IV, showed as much increased glycogen as the patient despite the fact that she had about one third of the GBE activity. The mother of the patient was healthy with a normal liver function test. Further study is necessary to evaluate the accumulation of abnormal glycogen in other tissues, including the liver in a carrier state.

No specific treatment has been shown to alter the natural course of the disease. Supportive treatment is helpful before liver transplantation.

Asymptomatic fasting-induced hypoglycemia (blood glucose <60 mg/dl), a rarely recognized complication, may be reversed by frequent feedings and corn starch supplements, and these therapies may improve the clini-

cal and laboratory findings (19). Corticosteroids may induce temporary remission (20). Our patient did not show fasting hypoglycemia the following period. Her ascites, general condition, and the laboratory findings have been improved with diuretic treatments, a low dose of prednisolone and adequate nutritional intakes.

Patients with the classic hepatic form of GSV-IV are candidates for liver transplantation. After the liver transplantation, there are some reports that various extrahepatic manifestations as well as hepatic function have not progressed or improved, because a donor liver has corrected the hepatic disease and may be a source of deficient enzyme because of systemic microchimerism (21, 22).

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