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■ Case report ■

A case of glycogen storage disease type Ib

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= Abstract =

We report a case of an 18-month-old girl with glycogen storage disease type Ib (GSD Ib). Her neutrophil counts had gradually decreased to less than 500/μL by the age of 3 years. However, there were no recurrent bacterial infections. Mutation analysis of the glucose-6-phosphate translocase (G6PT) gene revealed a compound heterozygous missense mutation (Ala148Val/Gly273Asp). (Korean J Pediatr 2009;52:1383-1387)

Key Words : Glycogen storage disease type Ib, Glucose-6-phosphate translocase, Neutropenia

Introduction

Glycogen storage disease type I (GSD I) is caused by inherited defects of the glucose-6-phosphatase system, resulting in excessive accumulation of glycogen in the liver, kidney, and intestinal mucosa, and leading to inadequate hepatic glucose production through normal glycogenolysis and gluconeogenesis. There are two major subtypes of GSD I: GSD type Ia (MIM232200) is caused by the deficiency of glucose-6-phosphatase (G6Pase) catalytic activity, and GSD type Ib (MIM23220) is caused by a defect in the glucose-6-phosphate translocase (G6PT)[1, 2].

G6PT controls the entry of glucose-6-phosphate (G6P) into the lumen of the endoplasmic reticulum, where it is hydrolyzed to glucose and inorganic phosphate by one of the two G6Pases: the liver-, kidney-, and intestine-restricted G6Pases-α[1, 2] or the ubiquitously expressed G6Pases-β[3, 4]. G6PT is expressed ubiquitously[2, 5]. The concerted action of GPT and G6Pases-α is required to maintain glucose homeostasis[2], and the concerted action of GPT and G6Pases-β is vital for normal neutrophil functions[4, 6].

GSD Ia and GSD Ib patients manifest a nearly identical metabolic phenotype, but GSD Ib patients also suffer from neutropenia and myeloid dysfunction, and are susceptible to recurrent bacterial infections, aphthous stomatitis, and inflammatory bowel disease[7-9]. However, neutropenia is not manifested by all GSD Ib patients[10-12]. It has been proposed that GSD Ib patients without neutropenia may have G6PT mutations that result in residual transporter activity[10].

Here, we report a case of an 18-month-old girl with GSD Ib, who had a history of frequent asthma and pneumonia, but there were no evidence of neutropenia, perianal abscess, or inflammatory bowel disease. Her neutrophil count counts gradually decreased to less than 500/uL by the age of 3 years. but no recurrent bacterial infections. Mutation analysis of the patient's SLC37A4 gene (formerly called as G6PT1) revealed compound heterozygous missense mutations.

Case report

An 18-month-old girl with nonconsanguineous parents was admitted for evaluation of hepatomegaly. On physical examination, a rounded, "doll's face" appearance and a distended abdomen with an enlarged liver over one palm length below the costal margin were observed.

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The patient's height was 77 cm (10–25th percentile), and her weight was 12 kg (75–90th percentile). Symptoms related to hypoglycemia, including cold sweats, and severe crying, were noted, and the patient had no history of seizure. She had been admitted frequently for treatment of asthma and pneumonia, but did not suffer from stomatitis, perianal abscess, or protracted diarrhea. Her birth history and family history were unremarkable.

Laboratory test results were as follows: hemoglobin level, 9.8 g/dL; hematocrit, 30.6%; white blood cell count, 4,700/μL; absolute neutrophil count, 2,650/μL; platelet count, 355,000/μL; AST/ALT, 91/93 IU/L; gamma-GTP, 37 IU/L; total bilirubin/direct bilirubin, 0.3/0.1 mg/dL; and cholesterol 113 mg/dL. Hyperlactatemia (3.25 mmol/L), hypertriglyceridemia (272 mg/dL), and hyperuricemia (10.1 mg/dL) were noted. The levels of Na, K, Ca, phosphorus, BUN, and creatinine were within the normal range. After iron administration, the patient's hemoglobin level improved to 12.1 g/dL.

Blood glucose and lactate levels in the morning (after 6 hour fast) were 59 mg/dL and 4.3 mmol/L, respectively. Although administration of a bolus of glucagon (30 μg/kg) should result in little or no increase in blood glucose in GSD I patients, the administration of glucagon resulted in a small increase in blood glucose level, and a significant increase in lactate level in this case. The 1-hour postprandial blood glucose and lactate levels were 118 mg/dL, and 2.36 mmol/L, respectively. The 2-hour postprandial blood glucose and lactate levels were 84 mg/dL and 1.5 mmol/L, respectively.

Because the sequence analysis of G6Pase revealed no mutation, a liver biopsy was performed (Fig. 1). Liver parenchyma showed hepatocytes with pale cytoplasm and conspicuous macrovesicular fatty changes in most hepatic lobules. No evidence of hepatitis nor fibrosis was present. Hepatocytes were strongly positive for PAS stain, and negative for diastase-treated PAS stain, suggesting glycogen accumulation. Glycogen deposition was also confirmed by electron microscopy. The patient was diagnosed with GSD type I.

Mutation analysis of exon 4 of the G6PT locus revealed that the patient was compound heterozygous for two different mutations (Ala148Val/Gly273Asp). The Ala148Val mutation was inherited from the patient's mother (Fig. 2A) and has been previously reported in a Korean patient with GSD Ib. The Gly273Asp mutation was inherited from the patient's father (Fig. 2B) and has not been reported before. The Gly273Asp mutation has been screened in 50 individuals with normal chromosomes and none had the same

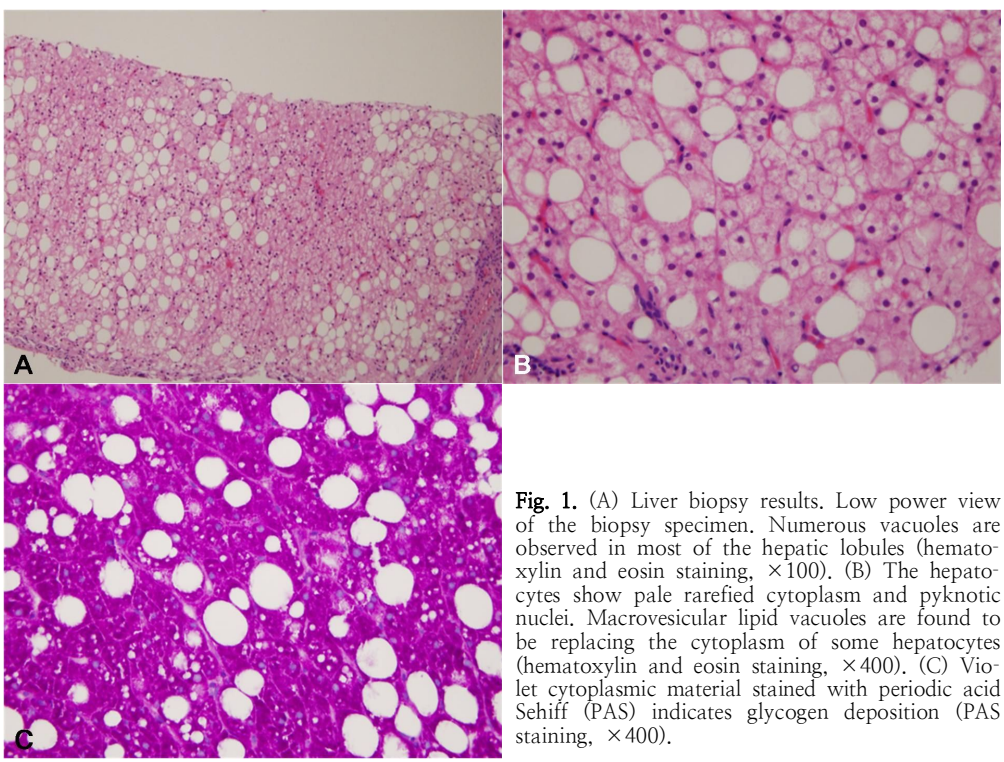

Fig. 1. (A) Liver biopsy results. Low power view of the biopsy specimen. Numerous vacuoles are observed in most of the hepatic lobules (hematoxylin and eosin staining, ×100). (B) The hepatocytes show pale rarefied cytoplasm and pyknotic nuclei. Macrovesicular lipid vacuoles are found to be replacing the cytoplasm of some hepatocytes (hematoxylin and eosin staining, ×400). (C) Violet cytoplasmic material stained with periodic acid Sehiff (PAS) indicates glycogen deposition (PAS staining, ×400).

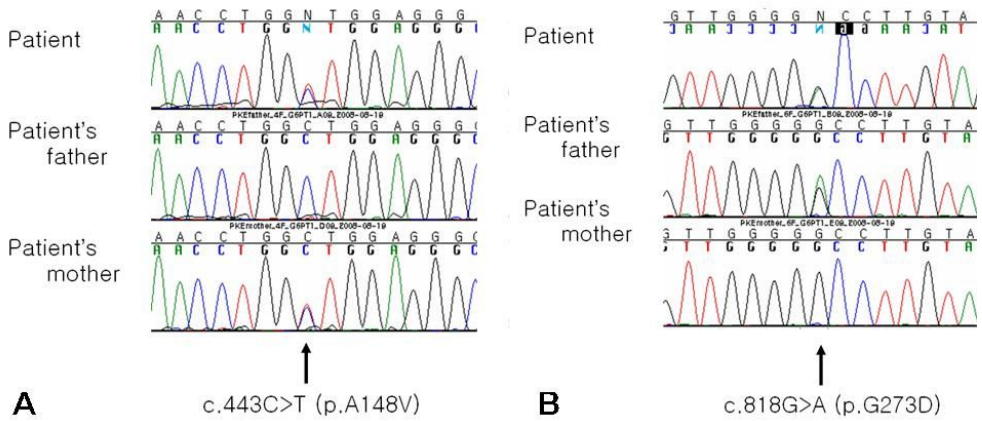

Fig. 2. Identification of SLC37A4 gene mutations. (A) Direct sequencing analysis demonstrated a heterozygous C to T transition (arrow; c.443C>T) resulting in an Ala148Val missense mutation in exon 4. (B) A heterozygous G to A transition (arrow; c.818G>A) resulting in a Gly273Asp missense mutation in exon 6.

mutation.

With dietary management and allopurinol medication, she had no recurrent bacterial infections until now. But the neutrophil count decreased (white blood cell count, 2,800/μL; absolute neutrophil count, 588/μL) at the age of 2 year 6 months. Now she is 3 years old. Her height is 96.4 cm (75th percentile), and her weight is 17 kg (95th percentile). The recent laboratory results show as follows: hemoglobin level, 13.1 g/dL; hematocrit, 37.8%; white blood cell count, 3600/μL; absolute neutrophil count, 493/μL; platelet count, 349,000/μL; AST/ALT, 21/17 IU/L; gamma-GTP, 21 IU/L; total bilirubin/direct bilirubin, 0.2/0.1 mg/dL; cholesterol, 108 mg/dL; triglyceride, 98 mg/dL; uric acid, 3.6 mg/dL.

Discussion

GSD type I is an inherited, autosomal recessive genetic condition with an incidence of 1/100,000 live births. GSD Ia is caused by mutations in the G6Pase gene (G6PC), while GSD Ib is caused by mutations in the gene encoding for glucose-6-phosphate translocase gene (SLC37A4, G6PT1). Mutations in the G6PC gene, located on chromosome 17q21, are responsible for 80% of GSD I cases, and mutations in the SLC37A4 gene, located on chromosome 11q23, are responsible for 20% of GSD I cases. Both GSD Ia and GSD Ib patients manifest phenotypic G6Pase deficiency, characterized by growth retardation, hypoglycemia, dyslipidemia, hyperuricemia, hyperlacticacidemia, and liver and kidney enlargement[1, 2].

In addition to the above findings, GSD Ib is associated with chronic neutropenia and impaired neutrophil and monocyte function. Neutropenia results in recurrent bacterial infections, and oral and intestinal mucosal ulcers[7-9]. Splenomegaly has been reported in 35% of GSD Ib patients. Splenomegaly is probably the result of extramedullary hematopoiesis and may also be a sign of frequent infections and active inflammatory bowel disease[13].

The exact pathogenesis of neutropenia and neutrophil dysfunction in GSD Ib remains unknown. Reduced intracellular G6P levels could be expected to have a major impact on the myeloid and neutrophil cell activities[2]. Recent studies[4, 6, 14] suggested that neutrophil dysfunction is related, at least in part, to endoplasmic reticulum (ER) stress and increased apoptosis. Neutrophils express the ubiquitously expressed G6PT and G6Pases-β that together transport G6P into the ER lumen and hydrolyze it to glucose. Lack of functional G6PT or G6Pases-β would be expected to impair translocation into the ER lumen and reduce G6P availability, thus resulting in disruption of endogenous glucose production in the ER, and decreased intracellular levels of NADPH and increased levels of reactive oxygen species (ROS). Activation of apoptosis in GSDIb neutrophils is due to increased production of ROS[14].

Dietary management and adjunctive pharmacotherapy for GSD Ib reduces hypoglycemia and suppresses secondary metabolic decompensation, but do not improve neutropenia, neutrophil dysfunction, or inflammatory bowel disease. Granulocyte colony-stimulating factor (G-CSF) treatment increases neutrophil count and reduces the frequency of infections and severity of inflammatory bowel disease[13].

Neutropenia may not be apparent in all GSD Ib patients [10-12] at the initial presentation, but it can develop at a later age[7, 15], as shown in this case. In a European study[7], neutropenia was documented in 64% of patients before the age of 1 year, but in 18% of patients, neutropenia was first noted between the ages of 6 and 9 years.

GSD Ib is genetically heterogeneous disorder[15, 16], several mutations predominate and vary according to population. W188R appears to be most common in Japanese patients[17], whereas two mutations, namely, G339C and 1211delCT, appear to be prevalent in Caucasian patients[18]. No correlation has been found between genotype and severity of disease[15].

In the present case, the Ala148Val mutation inherited from the patient's mother, was previously reported in a Korean GSD Ib patient with neutropenia and inflammatory bowel disease[19]. Our patient also inherited a novel variation (Gly273Asp) from her father, which we presume, is a novel mutation.

Neutropenia is not manifested by all GSD Ib patients[10-12] and some GSD Ia patients suffer from mild neutropenia [20]. In patients with clinical and biological manifestations of GSD I, even if neutropenia is not evident, analysis of both the G6PC and GPT gene should be considered.

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저자들은 생후 18개월 여아에서 당원병 Ib 형을 경험하였기에 보고하는 바이다. 진단 시에는 호중구 감소증이 없었고, 이후 점차 중성구가 감소하여 3세에 절대적 호중구수가 500/μL 미만을 보였다. 반복적인 세균 감염은 없었다. 유전자(SLC37A4) 검사에서 복합 이형접합체 과오돌연변이(Ala148Val/Gly273Asp)를 확인할 수 있었다.

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