A Case of Glycogen Storage Disease Type III (Glycogen Debranching Enzyme Deficiency) with Liver Cirrhosis and Hypertrophic Cardiomyopathy

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Glycogen storage disease (GSD) type III is an autosomal recessive disorder caused by a deficiency of glycogen debranching enzyme, which leads to the storage of an abnormal glycogen with short outer chains in liver and in skeletal and heart muscle (Hers et al. 1989). Patients with GSD type III show variable clinical...
manifestations and are classified into several subtypes depending on the
differences in tissue expression of the defective enzyme (Van Hoof and Hers 1967).
In general, the prognosis of GSD type III has not been considered to be serious
(Hers et al. 1989; Coleman et al. 1992). We report here a case complicated with
liver cirrhosis and hypertrophic cardiomyopathy.

CASE REPORT

This Japanese patient was born by spontaneous vaginal delivery of term. Her
parents were healthy, but they were first cousins. Early growth and develop-
mental milestones were normal. She was admitted for evaluation of abdominal
distension at 21 months of age. She had a doll-like face and a markedly enlarged
liver (10 cm below the right costal margin) without splenomegaly. Laboratory
findings showed an elevation of serum transaminases (aspartate aminotransferase
352 IU/liter, alanine aminotransferase 400 IU/liter) and hypoglycemia (2.1 mmol/
liter) at fasting, but without any symptoms of hypoglycemia. Because of persist-
ent hepatomegaly and elevation of transaminases, a liver biopsy was performed,
which showed an accumulation of glycogen, periportal fibrosis, and regeneration
nodules (Fig. 1). She was followed as an unknown type GSD without any
enzymatic analysis, but was subsequently lost to follow-up. At 23 years of age
she had a healthy baby by cesarean delivery. She presented to Shounai Amar-
ume Hospital at 23 years of age because of a right inguinal swelling. Height was
165 cm and body weight was 66 kg. In addition to a right inguinal hernia, she
showed hepatomegaly with the liver palpable 10 cm below the right costal margin,
and splenomegaly with the spleen palpable 7 cm below the left costal margin.
Normal investigations included C-reactive protein, red blood cell count, hemoglo-

![Liver specimens biopsied at 21 months of age demonstrates enlarged hepatocytes with clear or vacuolated cytoplasm, periportal fibrosis, and regeneration nodules; hematoxylin-eosin, \times 100.](Fig.1)
A Case of Glycogen Storage Disease Type III

bin, hematocrit, serum electrolytes, blood urea nitrogen, serum creatinine, serum uric acid, blood ammonium, total protein, albumin, total cholesterol, and triglyceride. The following results were abnormal; platelet count (32,000/mm³; Normal range 125,000–375,000), white blood cell count (2,100/mm³; Normal range 5000–8500), serum aspartate aminotransferase (179 IU/liter; Normal range 9–30), serum alanine aminotransferase (122 IU/liter; Normal range 3–24), serum lactate dehydrogenase (1,292 IU/liter; Normal range 208–455), alkaline phosphatase (249 IU/liter; Normal range 70–245), γ-glutamyltransferase (89 IU/liter; Normal range 0–37), choline esterase (69 IU/liter; Normal range 180–460), creatinine phosphokinase (1181 IU/liter; Normal range 20–130), aldolase (16.1 IU/liter; Normal range 1.7–5.7), and total serum bilirubin (56, μmol/liter; Normal range 3–21). Blood glucose and lactate at fasting was 3.9 and 1.1 mmol/liter, respectively. Immunological viral studies showed no evidence of infection with hepatitis B or C virus. The value at 15 min of the indocyanine green excretion test was 32.0% (Normal range ≤10). Blood pressure was 122/64 and cardiac enlargement was not detected on x-ray. However, the ECG showed evidence of left ventricular hypertrophy (increased QRS voltage in the precordial leads), and was suggestive of myocardial damage (inverted T waves in I, aVF, and V₂–V₆). Echocardiography revealed marked thickening of the interventricular septum. Ultrasound and computed tomography of the abdomen showed hepatomegaly with an irregular surface (Fig. 2) and splenomegaly. No ascites was seen. The gastroscopy showed no esophageal varices. Enzymatic analysis of debranching enzyme in leukocytes using limit dextran as substrate (Chen et al. 1987) showed no detectable activity.

Fig. 2. Computed tomography of the abdomen at 26 year old shows hepatomegaly with irregular surface and splenomegaly.
We present a 26-year-old woman with liver type of GSD complicated with liver cirrhosis and hypertrophic cardiomyopathy. She had normal level of serum uric acid, blood lactate at fasting and phosphorylase kinase activity in leukocytes (data not shown), and was diagnosed as GSD type III (debranching enzyme deficiency) based on the enzymatic analysis and clinical manifestation. GSD type III has been usually considered to follow a mild clinical course compared with GSD type I, and progression to cirrhotic liver failure has only rarely been reported (Fellows et al. 1983; Markowitz et al. 1993). However cirrhosis has been observed in three other Japanese patients (Shimizu et al. 1982; Hibi et al. 1983; Sato personal communication). One of the reported cases (Shimizu et al. 1982) died of liver cancer. The patient reported in this paper has had no symptoms of hepatic and muscular involvement except for hepatomegaly. The histopathology, however, of the liver biopsy taken in infancy, which included extensive fibrosis and regeneration nodules, would have predicted progression to cirrhotic liver failure. The clinical manifestations of these four Japanese cases seems to be different from previous reports. Patients with GSD type III have been classified into several subtypes depending on the differences in tissue expression of the enzymes (Van Hoof and Hers 1967). Glycogen debranching enzyme has two catalytic sites, oligo-1, 4,-1, 4-glucantransferase (EC 2.4.1.25) and amylo-1, 6-glucosidase (EC 3.2.1.33) (Hers et al. 1989). In addition to the difference in tissue expression of defective enzyme, the clinical course could also be determined by the differential involvement of these two catalytic sites. Alternatively, accumulation of glycogen of abnormal structure would cause liver cirrhosis as in GSD type IV (Hers et al. 1989). Molecular analysis and in vitro expression studies should be performed to clarify the genotype-phenotype correlations.

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References


