—Case Reports—

Cholelithiasis in a Patient with Type 2 Gaucher Disease

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Abstract

Gaucher disease is an autosomal recessively inherited lysosomal storage disease in which a deficiency of glucocerebrosidase is associated with the accumulation of glucocerebroside in reticuloendothelial cells. Clinically, 3 types of Gaucher disease have been defined on the basis of the presence or absence of neurological symptoms. The frequency of gallbladder involvement is reportedly greater in patients with type 1 Gaucher disease than in healthy persons. We report a case of recurrent cholelithiasis and liver failure in a patient with type 2 Gaucher disease who showed severe progressive neurological involvement.
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Key words: Gaucher disease, cholelithiasis

Introduction

Gaucher disease is a lipidosis caused by a deficiency of glucocerebrosidase that results in the accumulation of glucocerebroside in cells of the reticuloendothelial system[1]. This disease manifests with a wide variety of symptoms, hepatosplenomegaly, anemia, thrombocytopenia, and bone involvement, and 3 types of Gaucher disease have been defined on the basis of the absence (type 1) or presence of central nervous system involvement (type 2, acute type, and type 3, subacute type)[1,2]. Enzyme replacement therapy (ERT) with modified glucocerebrosidase that targets macrophages has been established as a treatment for type 1 Gaucher disease[3]. Although ERT was not expected to affect the neurological symptoms of patients with type 2 Gaucher disease, it has been reported to prolong survival[4]. Recently, patients with type 1 Gaucher disease have been reported to be more likely to have cholecystitis[5–7]. We report on a case of recurrent cholelithiasis and liver failure in a patient with type 2 Gaucher disease.

Case Report

The patient was a 6-year-old girl in whom type 2 Gaucher disease had been diagnosed at the age of 11 months on the basis of neurological symptoms and a lysosomal enzyme activity assay with skin fibroblasts. ERT (intravenous administration of 60 U/kg of modified glucocerebrosidase every 2 weeks) was started at age 1 year. Myoclonus-like paralysis

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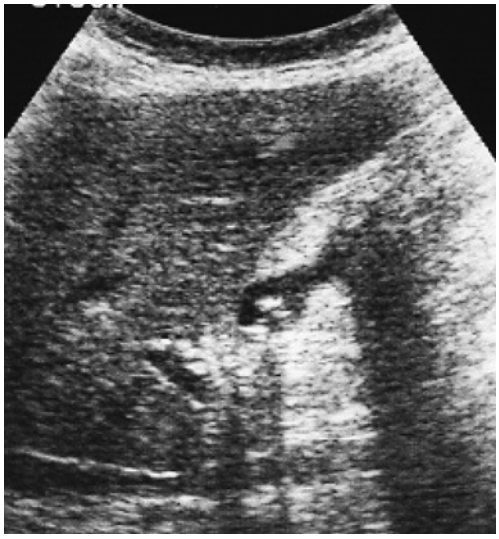

Fig. 1. Ultrasonography of the gallbladder showing gallstones, posterior shadowing, and a thickened wall.

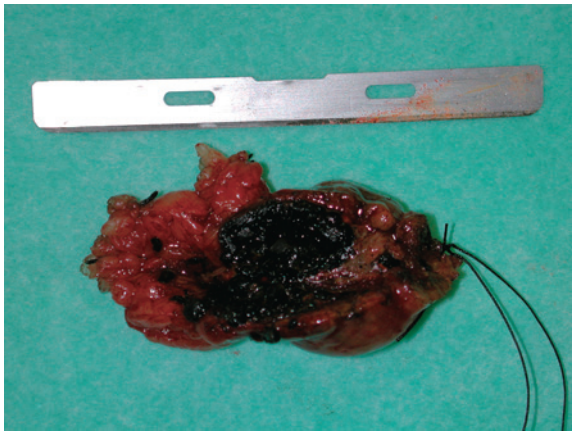

Fig. 2. The gallbladder is full of jet-black gallstones. The diameters of the gallstones range from 1 to 10 mm.

developed at the age of 1 year, and generalized tonic convulsions developed at the age of 13 months. After ERT was started, the hepatosplenomegaly improved. However, the neurological symptoms were unchanged, and the patient periodically required mechanical ventilation because of status epilepticus or pneumonia starting at the age of 22 months, and tracheostomy was performed at the age 3 years. Since the age of 5 years, the white blood cell count and levels of C-reactive protein, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, leucine aminopeptidase and γ-glutamyl transpeptidase increased as body temperature increased. Ultrasonography showed several gallstones and cholecystitis, and the gallbladder wall was hypertrophic (**Fig. 1**). The patient's father had hypercholesterolemia and asymptomatic gallstones. The patient also had higher than normal levels for her age of cholesterol (333 mg/dL) and low-density lipoprotein (LDL) cholesterol (63 mg/dL). When the patient was afebrile and in good general condition, levels of hemoglobin, total bilirubin, and haptoglobin were within the normal range. These findings showed that ERT was effective for treating systemic involvement, except for the neurological manifestations, of Gaucher disease. Elective laparoscopic choleystectomy might have been a less-invasive alternative treatment at this point. However, neurological symptoms, status epilepticus had became resistant to several kinds of anticonvulsants, and cholecystitis was controlled with antibiotics each time. Episodes of cholecystitis gradually became more frequent, and her condition deteriorated. Coagulation factors produced by hepatocytes decreased, and coagulopathy developed. Cholecystectomy was finally performed at the age of 6 years. At operation, a brownish yellow liver with a smooth surface was observed, with adhesion between the greater omentum and the hypertrophic gallbladder, suggesting frequent episodes of cholecystitis. Total cholecystectomy was performed. The gallbladder adhered widely to the liver and was full of jet-black gallstones 1 to 10 mm in diameter (**Fig. 2**). The interior of these stones was also jet-black. The composition of the stones was 76% cholesterol and 24% bilirubin calcium. Cholangiography showed a tortuous bile duct with no stones. After cholecystectomy, disseminated intravascular coagulation and multiorgan failure developed, which resulted in the patient's death at the age of 6 years 6 months. Examination of the liver at biopsy revealed chronic hepatitis with inflammation and irregular fibrosis, but significant bacterial infection was not detected. The reason coagulopathy developed after operation was unclear.

Discussion

Cholelithiasis is one of the most common

gastrointestinal diseases in adults but is rare in children. Children who have hemolytic anemia or cholecystitis (due to infection with bacteria, viruses, or parasites) or are receiving long-term hyperalimentation have an increased risk of gallstones[8]. More than 70% of gallstones in children are the pigment type, 15% to 20% are cholesterol stones, and the remainder are composed of a mixture of cholesterol, organic matrix, and calcium bilirubinate[8]. Patients with Gaucher disease are more likely to have gallstones: 21 of 66 (32%) patients had cholelithiasis at the National Institutes of Health Clinical Center in the United States, and 82 of 323 patients (25%) had gallstones in Israel[6]. The high incidence of gallstones in patients with Gaucher disease has been attributed to the high frequency of routine abdominal imaging, which would increase the likelihood that gallstones would be found. However, a cohort study has demonstrated that the prevalence of cholesterol gallstone disease is more than 5 times higher in patients with type 1 Gaucher disease than in the general population[7].

Patients with type 1 Gaucher disease have several risk factors for gallstone formation. First, increased biliary excretion of glucosylceramide predispose to gallstone formation. When hepatic secretion of bile salts and phospholipids decreases, the bile is lithogenic[9]. Second, advanced liver disease and cirrhosis also contribute to gallsones[10]. The high degree of liver involvement is significantly related to a higher risk of gallstones. Third, splenomegaly, which most patients with Gaucher disease have, is a cause of hemolysis, which increases the risk of gallstone formation[5].

In the present case, the patient's father had hypercholesterolemia and asymptomatic gallstones, and the patient also had high levels for her age of cholesterol (333 mg/dL) and LDL cholesterol (63 mg/dL). The patient's condition was good with ERT, and she had neither hepatosplenomegaly nor hemolysis. Furthermore, liver biopsy did not show severe cirrhosis. These findings suggest that the cause of gallstone formation in this case was increased biliary excretion of glucosylceramide, as mentioned by Pentchev et al[8].

In conclusion, even patients with type 2 Gaucher disease, who have the most severe neurological involvement, show improved clinical symptoms and longer survival with ERT. Thus, gallstones and cholecystitis should be considered when abdominal symptoms and liver dysfunction are seen in these patients. More studies are needed to determine the incidence and prevalence of gallstones in type 2 Gaucher disease.

Conflict of Interest: None of the authors have any conflicts of interest associated with this paper.

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